The influence of the context on mobility in neurological disorders – a wearable technology approach

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Elke Warmerdam

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Erstgutachter: Prof. Dr. Burkhard Weisser
Zweitgutachter: Prof. Dr. Walter Maetzler
Drittgutachter: Prof. Dr. Tino Prell
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Chapter 1

General introduction

We are in the middle of a digital transformation. New revolutionising technologies are rising all across the world. Technologies such as artificial intelligence, Internet of Things, virtual reality, cloud computing, robotics and 3D printing are empowering many processes. The digital transformation is also finding its way into healthcare. Digital technology impacts diagnosis, prevention, monitoring and treatment of diseases. Technology assisted decisions can be made by healthcare professionals resulting in more personalized treatment.

Wearable technology to analyse movement has rapidly evolved in the last two decades. There is a growing amount of wearable sensors, apps and smartwatches available that contribute to the analysis of mobility. This wearable technology provides new options to measure people outside of the clinic in their natural environment. The data analysis has evolved from only being able to count steps to complete qualitative gait analyses. Moreover, the data can be used to track symptoms throughout the day, which can be used to optimize the treatment [1, 2]. The quantification of human movement with wearable sensors has provided new options and has high potential to further improve healthcare. Therefore, the focus of this dissertation will be on the quantification of mobility with wearable sensors.

All kinds of mobility-related activities like walking, rising from a chair and regaining balance after a perturbation require a certain amount of power to perform the action. With aging and degenerative diseases the power declines resulting in mobility limitations. Mobility limitations have a large impact on the quality of life. Healthcare professionals evaluate mobility limitations often by letting the patient answering questions about mobility and by visually observing the patient's gait pattern. The questions the patient answers provide information about the *perception* of the limitation by the patient. During the walk that is observed by the healthcare professional, it is very likely that the patient performs better than during daily living, because they are more focussed on the movement when they are aware that they are being observed. Therefore, this assessment measures *capacity*, what a patient is able to do. The healthcare professional has however not obtained any information about what the patient actually does during daily living, the *performance*. Improving the performance might be most important and relevant for the patient. Therefore, quantifying performance might need to be added to the standard clinical examination. The combined assessment of perception, capacity and performance provides a measure of the daily function of a patient [3].

Wearable sensors can easily be used to objectively quantify mobility of people by attaching one or multiple wearable sensors to the body. The wearable sensors make it possible to measure in different settings, e.g. clinic and home, indoor and outdoor,

and under different circumstances, e.g. slow walking and fast walking, single-tasking and dual-tasking, with supervision and without supervision. There is an increasing amount of literature showing that mobility might be influenced by the context it is measured in. It is however still unclear how the mobility measures obtained in different contexts relate to each other.

Aim and outline of this dissertation

The aim of this dissertation is to better understand the influence of the context on mobility in older adults and patients with neurodegenerative disorders. First, a theoretical background about mobility, the quantification of mobility and different contexts is provided (Chapter 2). To get a better understanding of how mobility parameters quantified in a supervised context (capacity) relate to similar mobility parameters quantified in an unsupervised context (performance), the existing literature was reviewed (Chapter 3). Potential reasons for the differences between supervised and unsupervised mobility parameters are discussed and suggestions for implementation of unsupervised mobility assessments in clinical care and research are provided. In Chapter 4 the development and validation of an algorithm to quantify arm swing during walking is presented. Arm swing is a mobility-relevant movement that is associated with many neurodegenerative diseases and changes with medication, as has been shown in patients with Parkinson's disease. The algorithm was validated for healthy adults and patients with Parkinson's disease. The algorithm can be used in both supervised and unsupervised environments. In Chapter 5 the arm swing algorithm is used to analyse the effect of dopaminergic medication on arm swing during walking of patients with Parkinson's disease. The effect of dopaminergic medication was assessed in different contexts. To continue the development and especially validation of algorithms that quantify mobility in different contexts, mobility data from participants in supervised instructed (reflecting capacity assessments) and uninstructed environments (reflecting daily living environment) are being collected. The study protocol is presented in Chapter 6. Both healthy participants and patients with neurological disorders are included and perform multiple walking trials with different complexity, clinical tests and movements generally performed during daily living. In Chapter 7 the main findings are summarized, the results are discussed and suggestions for future research are provided.

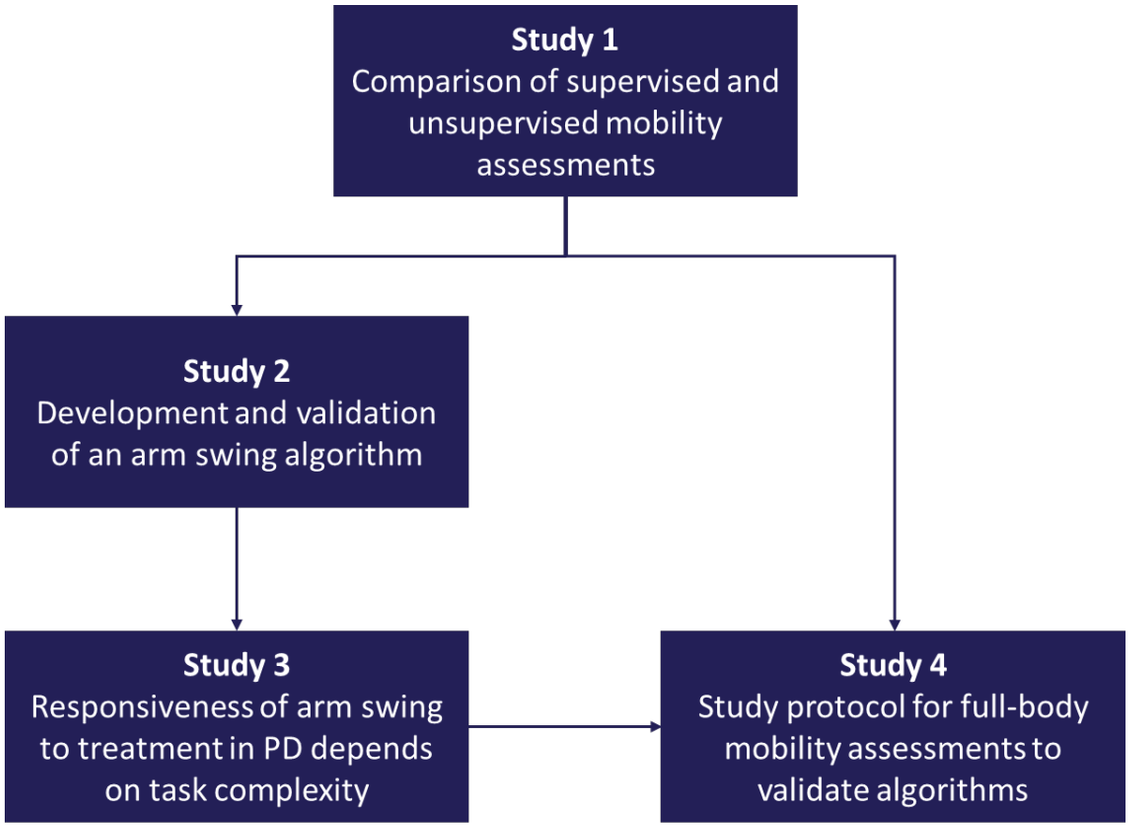

Figure 1.1: The structure of the cumulative dissertation. In study 1 the need for validated algorithms and assessments in different contexts becomes clear, which is focused on in studies 2, 3 and 4.

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Chapter 2

Theoretical background

Mobility

Mobility is defined by the international classification of functioning, disability and health model as "changing and maintaining body position" [4]. In other words, mobility is the ability to move independently or with help of assistive devices from one location or posture to another. Mobility is needed to perform activities of daily living and to engage in life [4]. A reduction in mobility is affecting independence and decreases the quality of life [5, 6], highlighting the importance of mobility. Among the most common mobility limitations are deficits in gait and balance. These deficits are associated with an increased fall risk [7, 8], hospitalization [9, 10], mortality [9, 11], anxiety [12], reduced cognitive function [13], and social isolation [14].

Gait and balance deficits are biomarkers [15, 16] and can be used to discriminate healthy adults from patients with neurodegenerative diseases [17, 18]. Moreover, gait and balance deficits can be used to differentiate between different subtypes of neurodegenerative diseases [19–21]. Gait and balance parameters also have the potential to detect neurodegenerative diseases in a preclinical stage of the disease [15, 18, 22].

Mobility in the aging population

In Germany, 28.5% of the habitants are 60 years and older [23]. The aging population is even expected to increase in the upcoming years. Aging is characterized by a cumulative decline in multiple physiological systems. A decline in the muscular, cardiovascular, visual and vestibular system can all have an effect on mobility. Especially the decline in the musculoskeletal system, which causes loss of muscle strength and power, has a large effect on mobility [24, 25].

The gait pattern of healthy older adults (>60 years) is different compared to younger healthy adults (18-40 years) [26]. This is especially visible in the spatiotemporal gait parameters. Older adults have a reduced gait speed, step length, and cadence. The temporal parameters like step time, stance time and double support time increase with age [26]. The amplitude of arm swing during walking decreases with age [27]. However, these changes in gait pattern seem to be at least partly mediated by the decrease in gait speed with aging.

Balance also changes with aging. Postural stability is an interplay between the environment and different physiological systems that decline with aging. Older adults have more static postural sway compared to younger adults (20-40 years)

[28].

Mobility in patients with Parkinson's disease

Parkinson's disease (PD) is after Alzheimer's disease the most common neurodegenerative disorder [29]. In Germany, about 797 to 961 per 100 000 people of 50 years and older have PD [30]. PD is a progressive neurodegenerative disease caused by a progressive loss of dopaminergic and other neurons in different areas of the brain, preferentially in the midbrain, resulting in a range of motor and non-motor symptoms. Motor symptoms are, for example, brady- and hypokinesia (slowness of movement), rigidity, postural instability and tremor (mainly at rest) [31, 32]. In early stages, the motor symptoms manifest mainly unilaterally [33].

Among one of the most disabling factors of PD are gait impairments, resulting in mobility limitations and an increased fall risk. Patients with PD have an impaired motor automaticity, which has an influence on the execution of sequential movements, including gait [33]. The impaired motor automaticity has also been suggested to contribute to freezing of gait. Freezing of gait is an episodic inability to generate effective steps despite the intention to walk [34, 35]. Freezing of gait occurs especially when initiating or terminating walking, when turning, or when walking through narrow passages [36].

The general gait pattern in PD also changes. Patients with PD walk slower, have shorter steps, decreased cadence and increased variability compared to age-matched healthy adults [33, 37]. The change in gait pattern can already be seen with detailed wearable sensor-based analysis about 4 years prior to diagnosis [15]. Arm swing during walking is also different in patients with PD compared to healthy adults: arm swing amplitude is decreased and the asymmetry increased [38, 39]. Patients with PD also have balance impairments. Both the static and dynamic postural stability is worse compared to healthy adults [40–42]. Since PD is a progressive disease, the mobility limitations get more severe over time.

The most common treatment for PD is based on dopaminergic medication [43]. Dopaminergic medication is highly effective in improving especially PD-related motor symptoms as measured with established clinical scales as the Movement Disorder Society revised version of the Unified PD rating scale (MDS-UPDRS) [44, 45]. Dopaminergic medication also improves some aspects of gait. Step length and gait velocity increase and the variability decreases with medication, but gait remains impaired compared to healthy controls [39, 46, 47]. Regarding balance there are contradicting results whether dopaminergic medication improves or worsens postural stability [39, 48, 49].

The sensitivity to dopaminergic medication decreases with advanced disease stages, therefore the prescribed dose often needs to be increased throughout the course of the disease [50]. With a higher dose of dopaminergic medication, the chance on negative side effects also increases. One of the most debilitating side effects of dopaminergic medication is dyskinesia, which are uncontrollable involuntary movements [43]. Almost 40% of treated PD patients develop some form of dyskinesia after about 5 years of treatment [51]. Dyskinesia is associated with a decrease in the quality of life [52, 53] and falls [54, 55]. Moreover, the uncontrollable involuntary movements can interfere with gait and balance leading to more severe mobility limitations.

Mobility in patients with multiple sclerosis

In 2015 multiple sclerosis (MS) had a prevalence of 0.32% in Germany and the prevalence is increasing [56]. MS is a neuroinflammatory and -degenerative disease resulting in a loss of myelin sheath of nerve fibers. The loss of myelin sheath comprises the conduction of action potentials leading to abnormal nerve conduction [57, 58]. Depending on the location of the demyelination symptoms like spasticity, pain, fatigue, vision problems and reduced sensation occur [59].

Patients with MS have a different gait pattern than healthy adults and PD patients. The altered nerve conduction in MS can cause spasticity or weakness of the muscles, which in combination with the reduced sensation makes it more difficult to coordinate movements. The change in gait pattern is already seen in patients with a relatively mild disease severity. Gait speed, cadence, step length, and swing time are reduced and stride time, double support time, and step width are increased in patients with MS [60].

Among one of the initial mobility limitations in patients with MS are balance problems. The slower nerve conduction due to the demyelination is an important factor for the decreased postural control, but the reduced sensation in the feet and the slower integration of motor and sensory signals also play a role [61, 62]. Patients with MS have more postural sway during quiet stance compared to healthy adults. Moreover, patients with MS have slower postural responses to perturbations [61].

The disease progression depends on the type of MS. Most patients have a relapsing and remitting variant of the disease in the early stages. In the later stages it often changes to a progressively increasing variant. A small part of the MS patients have a progressively increasing variant from the disease onset on [63]. Many disease-modifying treatments are available, mainly targeting neuroinflammation. The available treatments can reduce relapses, but generally fail to slow down the progression of the disease [58, 63].

Quantifying mobility

Clinical examinations mainly assess changes in disease-related symptoms. However, changes in symptoms do not necessarily also mean a change in the quality of life or daily function. For the assessment of quality of life there are multiple tools available [64]. However, the assessment of daily function is not clearly defined. Recently it was proposed that daily function could be captured by measuring capacity, perception and performance [3]. Capacity is often quantified by healthcare professionals with help of clinical scores. These scores, however, are subjective and even with the high standardisation of clinical tests, the interrater reliability often remains low [65]. A more objective method to quantify mobility is 3D optical motion capture. With 3D optical motion analysis, markers are adhered to the body and these markers are measured in 3D by multiple cameras (Figure 2.1). These systems are very accurate and are often used as gold standard in the field of movement analysis [66]. However, these systems are expensive and require a complex setup in a laboratory.

With the rise of mobile technology it has become possible to quantify mobility also outside of the laboratory. The type of sensor technology most frequently used for movement analysis are inertial measurement units (IMUs, Figure 2.1b) [67]. IMUs exist of tri-axial accelerometers, tri-axial gyroscopes and optionally also tri-axial magnetometers. The accelerometers measure linear accelerations, gyroscopes measure angular velocity and magnetometers measure the magnetic field (existing of

the earth magnetic field and the magnetic field from ferromagnetic materials that are nearby). These wearable sensors can be placed anywhere on the body, which makes it possible to measure all kinds of movements and symptoms [67, 68]. However, algorithms need to be developed first to transform the raw data from the wearable sensors into relevant mobility parameters. These algorithms also need to be validated to make sure they actually measure what they should measure [69, 70]. Many wearable sensors come with proprietary algorithms to extract mobility parameters. It is not known what kind of calculations are performed within these proprietary algorithms. More often there are no validation results available and even if they are available the validation has been performed with healthy adults. However, as described above, patients with neurodegenerative diseases have different movement patterns compared to healthy adults and even across different diseases [71, 72], therefore the algorithms should be validated for each patient group specifically before they can be used in healthcare.

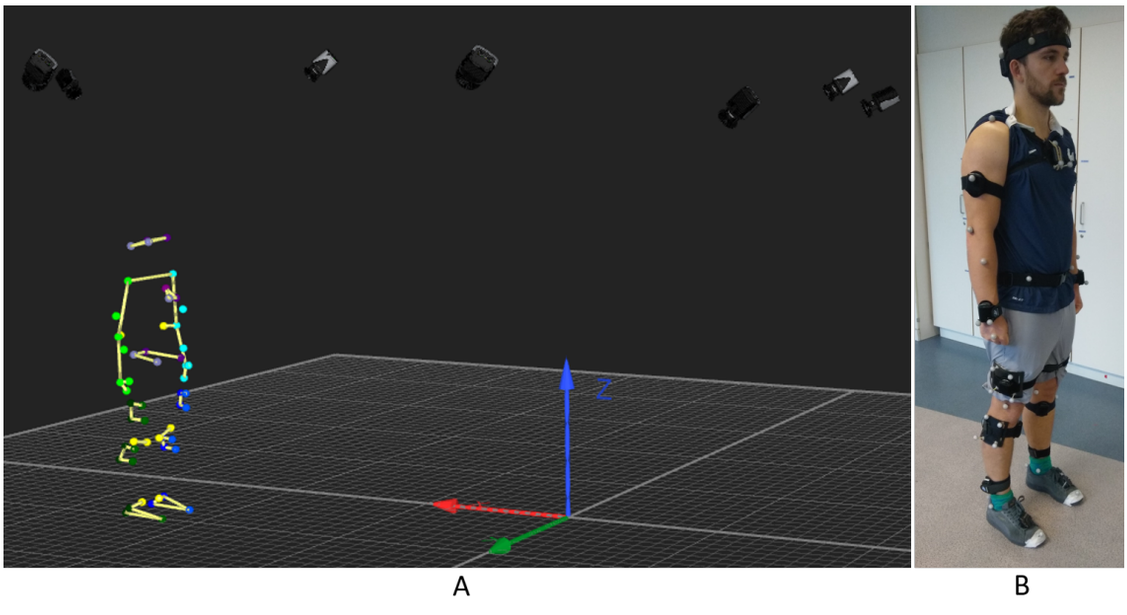

Figure 2.1: 3D optical motion capture system. A. On top the cameras hanging from the ceiling, at the left the reflective markers measured by the cameras and at the right bottom the orientation of the coordinate system. B. The participant wearing the reflective markers and also the inertial measurement units.

The combination of wearable sensors and validated algorithms can be used in the clinic to quantify the mobility-related capacity. Moreover, wearable sensors can also be used to quantify mobility in different settings and under different circumstances [68, 73, 74], enabling to quantify the mobility-related performance. The information about the mobility-related capacity and performance can help to correctly diagnose patients [17, 18], track disease progression [75, 76] and measure response to treatment [39, 77]. However, the context in which capacity and performance are measured might need to be taken into account, since this could have a substantial influence on mobility.

Mobility assessments in different contexts

Context is defined in the dictionary as "the surroundings, circumstances, environment, background or setting that determine, specify, or clarify the meaning of an event or other occurrence" [78]. The context can influence human behaviour. A well known example is the white coat effect. This white coat effect describes the phenomenon that people at home might have a normal blood pressure, but the blood pressure rises when they are at the doctor. The body responds to the presence of a healthcare professional. This phenomenon is also seen in gait. When people walk on a walkway knowing that they are being measured, they walk differently, compared to when they walk back over the same walkway thinking they are not being measured [79].

Movement analysis is most often performed in a laboratory setting, which is an open well-lit space with a regular surface and without many distractions. In contrast, movements during daily living are often performed in more cluttered environments and especially outdoors also on more irregular surfaces. It might be that patients with PD do not show any freezing of gait in the laboratory since situational demands are low. However, in more cluttered environments the demands are higher and freezing of gait might occur more frequently [80]. Moreover, freezing of gait is for example less likely to occur when crossing the road on a zebra crossing. The visual rhythmic input probably compensates for the internal automaticity and rhythm deficit in patients with PD. Rhythmic cues (visual, auditory and sensorial) are known to improve the overall gait pattern [81]. Even walking with music enhances gait parameters and arm swing [82]. The gait pattern also changes during outdoor walking on irregular surfaces. This effect is more pronounced in patients compared to healthy adults [83, 84]. Moreover, walking on different slopes changes the gait pattern and the arm swing [85, 86].

The situational demands in the laboratory can be increased by making the task more complex (e.g. circular walking) or by adding a secondary task to walking. Cognitive dual-tasks decreases the gait performance in older adults and patients with neurodegenerative diseases in the laboratory [87, 88]. Therefore, it is very likely that when older adults and patients with neurodegenerative diseases walk in a challenging environment where they cannot walk straight and need to focus on the environment as well, their walking performance will be different compared to a less challenging context. Since dual-tasking is a rather common situation in daily living, it is unclear how the (single-tasking) gait assessed in the laboratory (capacity) is associated with gait assessed in their natural environment (performance). Recent studies showed indeed that not the simple straight walking tasks, but the more complex tasks measured in the laboratory, corresponds well with the average performance in the natural environment [89, 90].

In the laboratory only movements during one short time frame are captured, whereas in a daily living context movements during the whole day, across multiple days can be captured. Gait performance measured during daily living seems to be better at discriminating between healthy adults and patients with PD compared to gait capacity measured in the laboratory [71]. Even the longer daily living walking bouts (>120 s), probably corresponding with outdoor walking, seem to be better in discriminating between healthy adults and patients with PD compared to shorter walking bouts, which probably represents indoor walking [71]. During daily living patients with PD fluctuate between OFF and ON medication states. In the laboratory, generally only the most OFF state (overnight withdrawal of medication) or

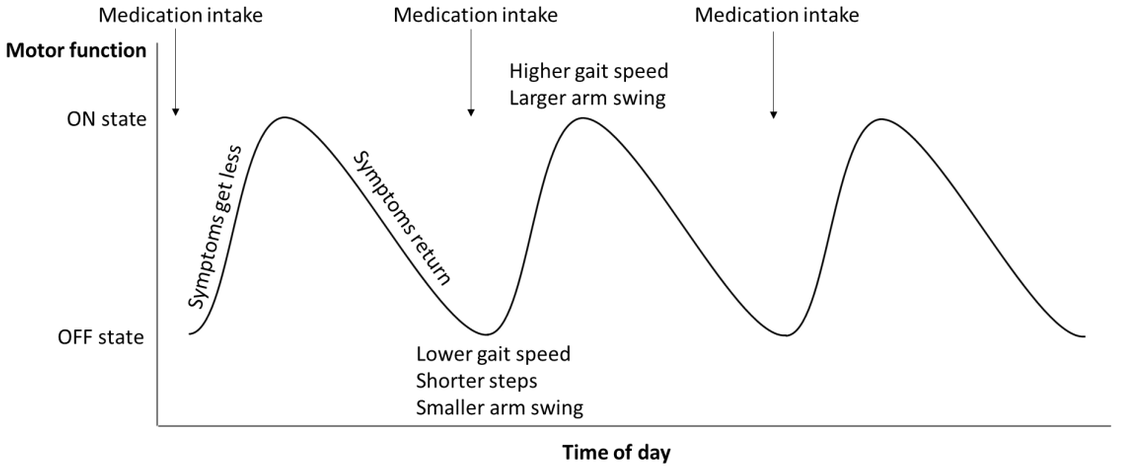

Figure 2.2: Fluctuations in motor function throughout the day.

the best ON state (approximately one hour after medication intake) is measured. In OFF state patients with PD walk slower and with shorter steps compared to ON state [39, 91, 92]. However, during daily living patients only spend a very short time in the worst OFF state and best ON state (Figure 2.2). The patients spend probably most time in the transition phase between the most OFF and ON state, on which no information is gathered during the standard laboratory assessments.

Movements performed in the laboratory are isolated standardized movements without an actual goal. The focus is directed on controlling the body to perform the requested task. Whereas movements performed in daily living are self-initiated and goal directed. The focus is on reaching the goal. This difference in focus could lead to changes in the movement patterns [93]. Moreover, the context can have an effect on psychological and physiological factors. A clinical setting can increase the blood pressure as seen with the white-coat effect [94]. Furthermore, patients can change their behaviour because they might be more motivated because they are being observed by a healthcare professional [95]. Additionally, symptoms as fatigue and pain could have a negative effect on the gait pattern and potentially increase fall risk [96, 97].

Brain activity can also differ with the context. Based on gait imagery, there is more activity in several brain areas and with better coupling between those areas during more complex walking tasks [98]. Furthermore, older adults have more activity in the cortical regions of the brain in comparison to younger adults during gait imagery [98]. Patients with PD have less activity in multiple brain areas during gait imagery of simple tasks and more activity during complex tasks compared to healthy controls [98]. The results for brain activity during real walking are not clear, since multiple studies found contradicting results [98].

The context can also have an influence on the accuracy of the mobility analysis algorithms. The type of surface has an effect on the step detection performance [99, 100]. In addition, the placement of the wearable sensors can have an influence on the accuracy. The step detection performance was lower with a wearable sensor on the lower back compared to wearable sensors on the feet [99] or on the shanks [100].

Within this dissertation the influence of the context on mobility and how different contexts (e.g., diagnosis, setting, task complexity, medication state) can affect capacity and performance measures of mobility will be analysed.

Chapter 3

Long-term unsupervised mobility assessment in movement disorders

Elke Warmerdam, Jeffrey M Hausdorff, Arash Atrsaei, Yuhan Zhou, Anat Mirelman, Kamiar Aminian, Alberto J Espay, Clint Hansen, Luc J W Evers, Andreas Keller, Claudine Lamoth, Andrea Pilotto, Lynn Rochester, Gerhard Schmidt, Bastiaan R Bloem, Walter Maetzler

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Abstract

Mobile health technologies (wearable, portable, body-fixed sensors, or domestic-integrated devices) that quantify mobility in unsupervised, daily living environments are emerging as complementary clinical assessments. Data collected in these ecologically valid, patient-relevant settings can overcome limitations of conventional clinical assessments, as they capture fluctuating and rare events. These data could support clinical decision making and could also serve as outcomes in clinical trials. However, studies that directly compared assessments made in unsupervised and supervised (e.g., in the laboratory or hospital) settings point to large disparities, even in the same parameters of mobility. These differences appear to be affected by psychological, physiological, cognitive, environmental, and technical factors, and by the types of mobilities and diagnoses assessed. To facilitate the successful adaptation of the unsupervised assessment of mobility into clinical practice and clinical trials, clinicians and researchers should consider these disparities and the multiple factors that contribute to them.

Introduction

Deficits in mobility are common in patients with neurological disorders and often affect activities of daily living, work, and socialisation [4]. These deficits predict morbidity, cognitive decline, and mortality [101–104] and negatively affect quality of life, especially in patients with movement disorders [5, 6]. For example, in patients with Parkinson's disease, health-related quality of life is strongly associated with the activities and participation components of the International Classification Of Functioning, Disability, and Health model [105]. Therefore, it is crucial for health-care professionals to obtain a full and objective evaluation of a patient's mobility as a basis for individually tailored clinical decision making and prognostication. Mobility assessments are mainly done under supervised conditions in a laboratory or hospital using standardised, mostly qualitative or semi-structured evaluations (panel) [106–108]; however, many patients do paradoxically well when they know that they are being observed. Various clinically relevant events are also difficult to capture during these snapshot observations, because they take place over long periods of time (e.g. the total amount of physical activity), are rare (e.g. falls or freezing episodes) [109], occur at night (e.g. sleep disturbances), or have complex fluctuating patterns (e.g. the response to dopaminergic treatment in Parkinson's disease). To reliably evaluate such events, it is important to measure patients unobtrusively and for longer periods of time, while they move about freely and unsupervised in their daily-living environment.

Several reviews describe the promise of unsupervised assessments of mobility using novel technologies [110, 111]. Unsupervised assessments of mobility using novel technology, although very different from other daily living acquired parameters that are already used in clinical routine (such as the Holter electrocardiogram [112, 113] and blood glucose monitoring [114]), could soon be essential for the long-term evaluation of mobility and personalised clinical decision making in neurology [110, 111]. Unsupervised assessments might save time and cost by capturing health-related data since these assessments would be largely independent of the availability of health-care services. These assessments are particularly important for patients living in rural areas or developing countries, where the number of health-care professionals is small relative to the population size [111]. Finally, unsupervised assessments offer patients an opportunity to become more actively involved by, for example, using their own devices such as smartphones and receiving feedback about their own daily living performance [115].

Unsupervised assessments of mobility can provide additional and, at least partly, complementary information compared with supervised assessments. However, differences with respect to the conventional evaluation need to be considered. In this Personal View, we summarise the evidence of the weak association between mobility assessed in the two settings and discuss potential reasons for the observed differences. We also present suggestions to facilitate the implementation of unsupervised mobility assessment in clinical care and future research.

Panel: Glossary of terms used in mobility assessment

Daily living
This term, also referred to as free living, real world, or community living, is used to distinguish testing within the normal environment of a participant from testing in a standardised setting, such as in the clinic or laboratory

Inertial measurement units
Sensors that measure acceleration or angular velocity, which can determine the quality and quantity of movement using specifically developed algorithms

Mobile health technologies
Umbrella term for wearable, portable, or domestic-integrated devices that can provide objective measures and that include digital applications, as well as body-worn (adhered to a body surface, mainly inertial measurement units) or frequently used patient-centred devices (e.g. smartphone and keyboard)

We focus on technologies that can measure the frequency and quality of movement, and mobility characteristics

Supervised assessment
Refers to the traditional, conventional mode of assessing mobility in a laboratory or clinical setting

Typically, a qualitative or semi-quantitative one-time snapshot evaluation of mobility by a trained health-care professional

Unsupervised assessment
Refers to the quantitative assessment of mobility in the home and daily living environment that is done continuously with new, mainly mobile, health technologies over relatively long periods of time

Wearables
Mobile devices worn on the body, such as inertial measurement units, smartwatches, or Holter electrocardiogram monitors

Unsupervised mobility assessment

Unsupervised assessments are usually done with mobile health technologies [110] that can measure physical activity [116–118], evaluate mobility or specific movements such as gait [71, 119, 120], or detect specific symptoms in unsupervised environments [121–123]. The potential added value of unsupervised assessments in patients with mobility deficits has been shown in several studies. For example, both predicting the risk of future falls and discriminating fallers from non-fallers in older adults (>60 years of age) [15, 124–126] and stroke survivors [127] appears to be more accurate when using data collected in the unsupervised environment. Indeed, the relevance of unsupervised mobility parameters was acknowledged by the US Food and Drug Administration [128] and the European Medicines Agency [129], both of which encourage the inclusion of para meters from unsupervised mobility assessments as exploratory endpoints in clinical trials.

We did a systematic search to compare the same features of mobility (ie, gait, turns, and postural transitions) in supervised and unsupervised assessments. 12

studies done in three different populations -adults older than 60 years, patients with Parkinson's disease, and patients with multiple sclerosis- were identified (appendix pp 1–3). Strikingly, the same mobility parameters obtained in different settings with identical participants differed from -40% (e.g. gait speed and cadence in patients with Parkinson's disease) to 180% (end turn angular velocity in healthy older adults, Figure 3.1). These differences are much larger than the effects usually measured after interventions. Thus, small and even moderate treatment effects might be buried under the variations introduced by the measurement techniques themselves if the differences between supervised and unsupervised assessments are not appropriately considered.

Differences between supervised and unsupervised assessments

Several reasons could explain the substantial differences in mobility parameters when comparing supervised with unsupervised assessments (Table 3.1). Unsupervised movements are typically self-initiated, embedded in a rich behavioural context, and goal directed. By contrast, movements in a supervised setting are usually triggered by a command and done in an isolated, standardised setting with limited ecological validity [132]. For example, self-initiated finger movements activate different brain structures compared with externally triggered movements, suggesting that the brain generates supervised movements using networks that differ from those that generate unsupervised movements [133, 134]. Moreover, with an external focus, attention is directed to the outcome of the action (e.g. leaving the room), while with an internal focus, attention is directed to controlling the body parts while executing the movement [135]. An external focus of attention results, at least sometimes, in more fluent movements [93].

Performance can be affected by several psychological and physiological processes that might differ across settings. These factors include alertness, motivation, the white-coat effect (a change [typically worsening] in a parameter because it is measured in a clinical setting), the reverse white-coat effect (a change [typically an improvement] in a clinical parameter because it is measured in a clinical setting), the Hawthorne effect (the change in behaviour of participants because of the awareness of being studied) [95], fatigue, pain, and stress. These effects might explain why patients rise from a chair with lower peak power in unsupervised assessments than during supervised assessments, even when these movements are done in an identical environment and with the same equipment [120]. Similar disparities have been identified for other gait parameters [79]. Supervised assessments seemingly provide a measure of someone's best, rather than their usual performance; that is, they capture capacity rather than performance [136, 137].

The environment is usually standardised in supervised conditions (e.g. walking in a clean and sterile environment without distractions), but much more variable in unsupervised conditions (e.g. furniture, lighting, patterns, colour of the environment, and obstacles). Unsupervised environments can induce large variability and asymmetry in mobility patterns, as shown by studies that assessed walking through busy corridors and through a city centre [100, 138]. Different types of seats and couches (e.g. firm chair or armchair) in unsupervised conditions can also partly explain the greater variability observed in postural transitions (ie, sit-to-stand and stand-to-sit movements or turning over in bed) in daily living [120, 126, 139, 140]. Moreover, asymmetry can be introduced through a constrained environment that

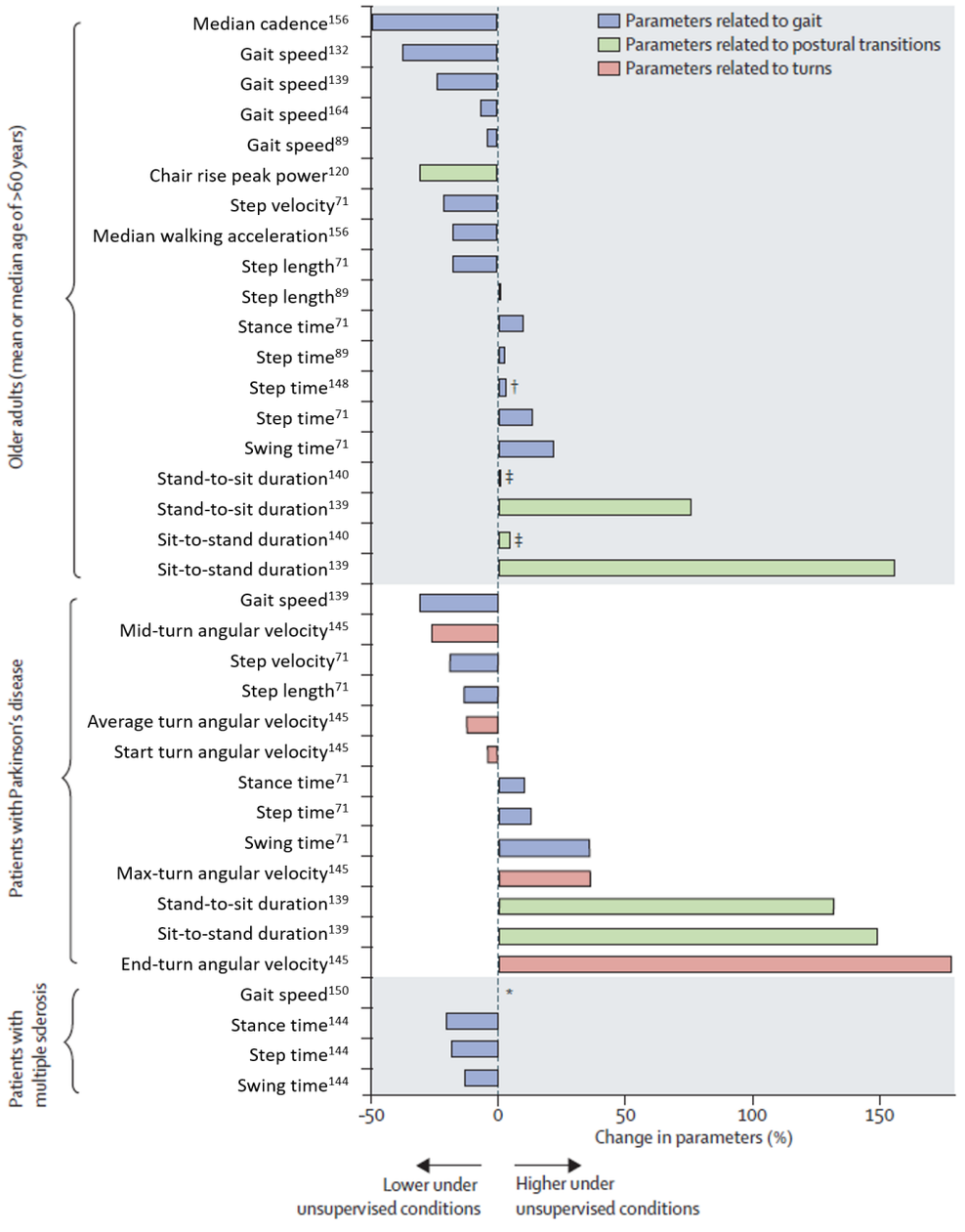

Figure 3.1: Percentage change from parameters measured under unsupervised conditions compared with supervised conditions. Data were obtained from the 12 studies identified in our systematic search (appendix pp 1–3). We did not illustrate variability and asymmetry parameters because they are especially sensitive to the environment and are probably higher for unsupervised than for supervised assessments because of the non-instructed performance and more variable physical nature of the environment [130]. Cadence is the rate at which a person steps (about 110–115 steps per min in healthy adults). Chair rise peak power is the maximum power that is exerted to lift the body's centre of mass during a sit-to-stand movement [131]. Median walking acceleration is the median of the magnitude of the acceleration during walking. Stance time is the time one leg is in contact with the surface during a step that is taken during walking. Step time is the time it takes to complete one step (ie, the time between initial contact of one foot and the initial contact of the contralateral foot). Stride time (also known as gait cycle time) is the time to complete two steps (ie, the time between initial contact of one foot and the next initial contact of the same foot). Swing time is the time one leg is not in contact with the surface during a stride that is taken during walking (in healthy young adults, swing time is about 40% of the stride time and with ageing and disease, the time spent in swing time often gets smaller). *Instructions in the supervised setting were to walk as fast as possible. †Supervised assessment was done on a treadmill with fixed speed, the unsupervised parameters used for the comparison were matched to the treadmill speed. ‡Only the best postural transitions reported were used to calculate the duration.

requires gait adaptation or turning in the same direction.

Furthermore, multitasking situations are common in unsupervised environments (e.g. walking and texting), but uncommon in supervised assessments, which could further contribute to the observed differences. Even during supervised dual-task walking, the gait quality was usually better than that during unsupervised walking [89]. The presence of a partner or caregiver can also affect mobility in unsupervised conditions. Social interactions are common during everyday walking: for example, spouses who act as an external cue to improve walking in patients with Parkinson's disease or to relieve anxiety in people with a cautious gait disorder [141].

Technical limitations might also add to the differences observed. Most algorithms have been developed and validated in supervised environments. Because the amount and variability of activities and mobility are much larger in unsupervised than in supervised environments, these algorithms might have difficulties differentiating similar movements (such as picking something up from the floor and sit-to-stand movements) that were not evaluated in the supervised assessment [142, 143]. Notably, only one study found in our systematic search used algorithms that were explicitly validated in both standardised and non-standardised settings [144]. A further bias might be introduced by the use of different device locations on the body (e.g. waist or ankle). The use of distinct mobile health technologies (e.g. hard ware or algorithms) [139, 145] could also play a part, but this aspect is limited as a change in hardware will not have a large influence on the results of a validated algorithm, because the data collected are the same (appendix p 4). The validation of algorithms for unsupervised daily living assessments brings new challenges as gold-standard references are currently absent, and urgently needed [146, 147].

Finally, the statistical approaches for the analysis of supervised assessments (e.g. means and SDs), might not be optimal for characterisation of complex data obtained from unsupervised settings. The supervised assessment typically involves one test, whereas the unsupervised evaluation might include thousands of walking bouts, turns, and transitions. It is yet to be determined how to best compare a single value with values obtained from a distribution (or histogram; Figure 3.2; appendix pp 1–3). Several studies showed that the tails of an individual's distribution correspond better to supervised assessments and therefore to clinical endpoints, such as risk of falls, limitation in activities, frailty, and supervised gait speed, compared with mean and median values [120, 132, 148].

Effect of movement type and disease on mobility

Some types of mobility (e.g. postural transitions) show seemingly larger differences than others (e.g. walking) when comparing supervised with unsupervised conditions (Figure 3.1). This difference might even depend on specific parameters. In a study of patients with Parkinson's disease, the velocity at the beginning of the turn was similar in unsupervised and supervised conditions but was lower at the middle and substantially higher at the end of turns under the unsupervised condition [145].

Notably, the type and severity of a disease might also have an effect on the differences between supervised and unsupervised assessments (Figure 3.1) [71, 149]. For example, the differences in stand-to-sit duration between both settings were smaller in older adults than in patients with Parkinson's disease [139]. Patients with multiple sclerosis showed an even more surprising pattern. Different to patients with Parkinson's disease and older adults, their performance was comparable under super-

Table 3.1: Advantages and disadvantages of supervised and unsupervised mobility assessments

	Supervised assessment	**Unsupervised assessment**
Clinometric properties (norms and test-retest reliability)	Established	In progress
Setting	Artificial	Ecologically valid (represents real-world performance)
Number of assessments	Snapshot, one-time evaluation	Multiple or even continuously performed tests can be obtained over days, weeks, and months
Sensitivity to fatigue, affect, and mood	Minimal	Yes, reflects typical performance and a range across the day and week, including best and worse behaviours
Sensitive to white-coat, Hawthorne, and related effects	Yes	Minimal
Patient centred	Not necessarily	Yes
Captures real-world challenges	Somewhat	Yes
Real-time feedback for treatment	Questionable	Yes
Interpretation of results	Easy	More challenging
Environmental influences	Minimal	Yes

vised and unsupervised assessments (gait speed) [150], while showing the opposite behaviour of what was seen in patients with Parkinson's disease and older adults (ie, for stance, step, and swing time, which were all lower in unsupervised conditions) [144]. The reasons for these observations are not yet clear, but differences in physical, attentional, and cognitive capabilities might contribute [151]. These differences between supervised and unsupervised performance might even be relevant at the subgroup level. The reported changes in turning parameters in patients with Parkinson's disease [145] differed substantially between fallers and non-fallers, with or without fear of falling. Remarkably, fallers with fear of falling showed slower turns in the supervised assessment, but faster turns in the unsupervised assessment, than did patients in other Parkinson's disease subgroups [145].

Implementation of unsupervised assessments in clinical practice and future research

As we anticipate that unsupervised assessments will become a prerequisite for future clinical decision making and clinical trials, in this section we provide directions to help move this emerging field forward (Table 3.2). Although there is still insufficient understanding of the association between supervised and unsupervised mobility when interpreting data obtained from unsupervised environments, studies suggest that any extrapolation of unsupervised mobility based on findings from supervised mobility might be substantially influenced by the type, subtype and stage of the disease, as well as type of mobility extracted from the data [139, 144, 145, 148].

Technical limitations should be also addressed, for example, by using the same mobile health technologies, located in the same place, for both supervised and unsupervised measurements. The algorithms used to calculate mobility parameters should be validated, to the highest degree possible, in both settings. Moreover, algorithms for mobility assessments should be validated separately for each type of neurological movement disorder as they might be associated with distinct movement patterns [71, 72]. Notably, even healthy people move differently at different

Table 3.2: Gaps, challenges, and steps toward a more informed use of supervised and unsupervised mobility assessments

	Gaps and challenges	**Potential resolution**
Supervised versus unsupervised mobility assessment	Weak associations might exist between the measures of these two assessments	Acknowledge the limited understanding when comparing supervised with unsupervised data and conduct more research to gain a better understanding of the interactions between these types of assessments
Algorithms	Algorithms for the assessment of unsupervised mobility are difficult to validate	Work on new approaches that can be used to validate algorithms for unsupervised mobility assessment against, or at least correlated with, clinically established parameters
Age and type of disease	Different age phases and diseases have different mobility performances, and a one-size-fits-all mobility-assessing algorithm might deliver low accuracy values in at least some cohorts	Develop and validate algorithms for the evaluation of unsupervised mobility separately per age groups and diseases
Harmonisation	Description of metadata, assessment protocol, and validation method have not yet been harmonised in the field, hindering the comparison across studies	Use standardised protocols to report, particularly concerning the description of the primary data, duration of assessments, description of the data analysis process, or reference to the algorithm and its validation
Data analysis	Statistical analysis and selection of summary measures of unsupervised data might be very different from usual statistical approaches	Explore new options for data analysis, such as the extremes of mobility performance during the day
Patient-reported outcome measures	Associations between unsupervised assessment and patient-reported outcome measures are scarcely investigated	Studies investigating either unsupervised mobility or patient-reported outcome measures should consider including the other evaluation tool and compare outcomes on an exploratory level
Behaviour	The effect of unsupervised mobility assessment on the behaviour of the user has not been investigated	Studies investigating this aspect are urgently needed; focus should be on assessment systems that provide feedback to the users
Upper body movements	Studies investigating upper body movements under supervised and unsupervised conditions are rare	More studies are necessary to see whether similar results in mobility are seen for upper body movements

ages [152, 153] and fitness levels [153]. Another requirement to increase the usefulness of unsupervised measures is harmonised reporting of parameters (e.g. as a core dataset across studies), and should include the reporting of meta-data (ie, data that accompany and describe the primary data) [154]. The duration of the unsupervised assessments should be standardised and the type of movement assessed should be reported in detail [154, 155].

Special emphasis should also be placed on more sophisticated analyses of unsupervised data. A promising approach is to consider and leverage specific episodes of mobility (e.g. turning, sit-to-stand, and stand-to-sit movements, and other movements used regularly during the day) and novel parameters, such as the distribution and extreme values of mobility parameters (Figure 3.2) [120, 132, 148, 156]. So far, these analyses have been done only for healthy older adults and not for patients with neurological disorders. An example could be the evaluation of the effects of an

experimental therapy. The effects might be measured best in the optimum state (improvement in supervised assessment and the best 10% of an individual's distribution of the unsupervised assessment), while the median and lower range of an individual's distribution might be informative of changes throughout the day (Figure 3.2). Future trials could use this information as outcomes.

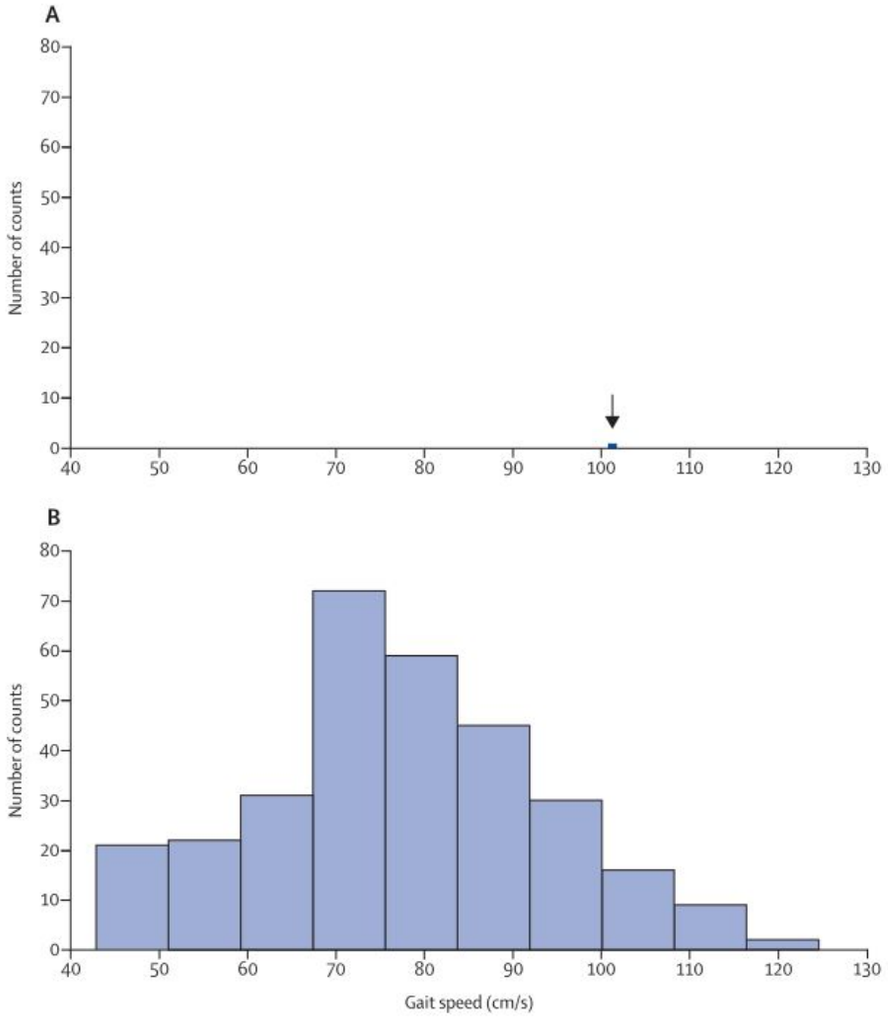

Figure 3.2: Gait speed measures based on evaluation in the laboratory and in the daily living environment in a 78-year-old woman with a history of falls. (A) The supervised testing yields a single value (101 cm/s), as indicated by the arrow. (B) By contrast, the daily living, unsupervised testing yields hundreds of tests of gait speed and a distribution of values. The daily living values are based on 30 s walking bouts from a 1-week recording [89]. Multiple measurements, in contrast to a single, one-time snapshot, might be highly valuable for the improvement of assessment protocols. In many of these unsupervised tests, gait speed is lower than that seen during supervised testing.

Variability measures can serve as a useful example of how important it is for clinicians and researchers to have a deep understanding of how their treatment and compounds influence mobility in daily life. Some variability measures (e.g. stride length variability) are highly affected by the environment and should be measured in a supervised setting, which better reflects the patient's capacity [130]. In the home environment, decreased variability with similar mean values might be a positive outcome if the goal of an intervention is to reduce motor response fluctuations in patients with Parkinson's disease. In a trial investigating patients with suboptimal treatment, a decrease in variability associated with an improvement of mean values

can indicate more consistent good performance during the day. In trials focusing on behavioural symptoms, increased variability might indicate better adaptability, more variable and enriched physical activity, and social interactions. Thus, the context is crucial for evaluating the effect of an intervention.

Whether data obtained from unsupervised environments provide relevant progression and treatment response information, rather than acting as markers of routine, fixed behaviours or trait markers, should be evaluated in future studies. Trait markers could still be good measures of progression, but appropriate interpretation is key for practical use. For example, the actions done during daily living are very different per individual, but show a surprisingly similar pattern within an individual [157].

Future statistical analyses should take advantage of the high number of repeated, specific movements occurring during long-term observation periods in unsupervised environments (Figure 3.2) [120, 145]. Deep learning, machine learning, and artificial intelligence approaches should be applied. Algorithms that learn from data have shown remarkable success in making accurate predictions for complex problems that previously depended on human skills (e.g. referral for eye diseases [158], detection of Parkinson's disease motor fluctuations) [159].

Future work should further explore the associations between objective digital measures with conventional measures of mobility, and with patient-reported outcome measures (PROMs) and caregiver-reported outcomes. Both PROMs (in this case, subjectively) and mobile health technologies (in this case, objectively) offer remote measurements in the unsupervised setting, and both approaches are potentially more ecologically valid and more meaningful to patients and their caregivers than are data acquired in the traditional clinical setting. Among the studies that we identified, only four assessed correlations with PROMs related to mobility, with contrasting findings (appendix pp 1–3).

We should keep in mind that mobile health technologies might alone cause behavioural changes, even when no feedback is provided (e.g. Hawthorne effect), but especially if feedback is provided (e.g. to induce compliance). Studies are needed to investigate if and when the performance of the user in the unsupervised setting becomes similar to that in the supervised setting, and whether the induced behavioural changes themselves might have therapeutic effects that could interfere with the evaluation. For example, patients who know that they are equipped with mobile health technologies might increase their level of physical activity, particularly when feedback about their own performance is provided.

Health-care professionals should also interpret their supervised assessments cautiously, as these findings could have limited ecological value. To improve their value, we suggest to provide natural, everyday life-like situations and instructions during supervised assessments. Explicit goals should be given to the patients, forcing them to focus on the goal instead of on the actual movements that must be performed to reach the goal [154]. For example, instructing a sitting person to walk allows for a more naturalistic observation of the sit-to-stand performance, because the person focuses more on the walking task rather than the necessary transition from sit-to-stand. Other opportunities to observe uninstructed movements occur when patients move in the waiting room or on their way to the clinician's office [160]. It is also essential to gain as much information as possible about the living environment of the person being assessed. If the person has cluttered furniture at home, health-care professionals might focus more on assessing mobility in small, crowded places instead of large, open hospital hallways. Additionally, the type of furniture, lighting,

patterns, and other environmental factors might be important [161].

Mobility differences between the supervised and unsupervised setting can also be relevant for the measurement of other symptoms and deficits. For example, deficits in upper extremity movement occur in many patients with neurological disorders [162], and several methods have been proposed to continuously assess upper limb bradykinesia in daily life [69]. However, a direct comparison of these various symptoms in supervised and unsupervised settings remains absent. One exception is a study that assessed habitual keyboard typing behaviour in patients with Parkinson's disease [163]. This study showed that various key-stroke metrics as measured in the clinic were strongly correlated with those obtained at the patient's home, suggesting that some upper extremity performances (in this case, a measure of bradykinesia) are similar under supervised and unsupervised conditions. This finding underscores the need to assess different aspects of motor functioning on a case-by-case basis.

Conclusions

There is increasing evidence that, depending on whether mobility is assessed under supervised or unsupervised conditions, the results can differ substantially [89, 120, 132, 164]. These striking differences and the importance of measurements obtained in both settings call for expanding our knowledge about unsupervised mobility (Table 3.2). Unsupervised mobility parameters could be implemented to improve clinical care and could act as primary or secondary end points in future intervention trials.

Search strategy and selection criteria

We searched PubMed, Web of Science, and Google Scholar for articles published in English, Dutch, or German between Aug 1, 2014, to Aug 1, 2019 with the search terms "environment* OR setting* OR compare", "supervised OR lab OR laboratory OR standard* OR clinic*", "unsupervised OR home OR real life OR real world OR daily life OR daily living OR free living", and "wearable sensor OR inertial sensor OR inertial measurement unit OR acceleromet* OR gyroscope OR pendant sensor", not "intervention [Title/Abstract] OR rehabilitation[Title/Abstract] OR heart rate[Title/Abstract] OR energy expenditure[Title/Abstract] OR classification[Title/Abstract]". Studies were relevant if they measured similar mobility parameters with a wearable device in a supervised and in an unsupervised setting among patients with a neurological disorder or older adults (with mean or median age of at least 60 years). Reference lists of relevant articles were screened for additional references to generate the final reference list, and the authors were asked to provide input. The final reference list was generated on the basis of the relevance of papers to the topics that are discussed in this Personal View.

Appendix

Table 3.3: Sample characteristics, parameters measured, technology used, setting, instructions, and main findings of studies comparing quantitative parameters of supervised versus unsupervised movement and mobility aspects.

Article	Number and type of participants	Mean age ± SD	Parameters measured in both settings	Technology supervised setting	Technology unsupervised setting	Location supervised setting	Location unsupervised setting	Instruction supervised assessment	Main findings
Del Din et al.[71]	47 PD 50 OA	69 ± 8 70 ± 7	Step velocity (+ var) Step length (+ var & asym) Step time (+ var & asym) Swing time (+ var & asym) Stance time (+ var & asym)	AX3 Axivity	AX3 Axivity	Laboratory with 10m walkway	Natural environment	Preferred speed	All 14 gait parameters were significantly different and low to moderate correlations were found between the supervised and unsupervised assessments.
Haertner et al.[145]	28 PD	65 ± 9	Turn duration[#] Turn angle[#] Average turn angular velocity Maximum turn angular velocity Start turn angular velocity Middle turn angular velocity End angular velocity	OPAL APDM	Rehagait Hasomed	Laboratory 7m Timed Up and Go test	Natural environment	Preferred speed	Differences in turn angular velocity were found between the supervised and unsupervised assessments. These differences changed with different phases of the turns.
Moufawad el Achkar et al.[140]	10 OA	70 ± 3	Sit to stand duration Stand to sit duration	GaitUp Physilog	GaitUp Physilog	Laboratory	Natural environment (considered only the best transitions for analysis)	Preferred speed	Transition durations in unsupervised settings are longer compared to supervised settings.
Hillel et al.[89]	150 OA	77 ± 6	Step length Gait speed Step regularity stride regularity Step time	OPAL APDM	AX3 Axivity	15m Corridor	Natural environment	Preferred speed	The gait parameters measured in a supervised setting do not reflect gait parameters measured in an unsupervised setting.
Storm et al.[144]	14 MS (moderate and severe)	55 ± 11	Stride time (+ var)[#] Step time (+ var) Stance time (+ var) Swing time (+ var)	MoveMonitor McRoberts and OPAL APDM	MoveMonitor McRoberts	Laboratory with 15m walkway	Natural environment	Preferred speed	The temporal gait parameters were shorter in unsupervised assessments compared to supervised assessments. The variability of the temporal gait parameters was higher in unsupervised compared to supervised assessments.
Supratak et al.[150]	22 MS (mild)	40 ± 9	Gait speed	AX3 Axivity	AX3 Axivity	Corridor	Natural environment	Fast speed	A high correlation was found between the maximum sustained walking speeds in unsupervised conditions and fast walking speeds in supervised conditions.

Takayanagi et al.[164]	1965 OA	70 ± 6	Gait speed	Sheet-type pressure sensor (2.4m long)	HW-100 Kao Corporation	6.4m Walkway	Natural environment	Preferred speed	Gait speed in an unsupervised setting was significantly lower compared to a supervised setting.
Toosizadeh et al.[139]	15 PD 35 OA	71 ± 6 72 ± 4	Sit to stand duration Stand to sit duration Gait speed	LEGSys and BalanSens BioSenics	PAMSys BioSenics	Clinic	Natural environment	Preferred speed	Low, non-significant, Pearson correlations were found in the measured parameters between unsupervised and supervised conditions.
Urbanek et al.[156]	51 OA	78 ± NA	Median walking acceleration Median cadence	GT3X+ ActiGraph	GT3X+ ActiGraph	20m Corridor (400m walk)	Natural environment	Fast speed	The measured parameters were on average lower in unsupervised conditions compared to supervised conditions, but significant Pearson correlations were found.
Zhang et al.[120]	25 OA	80 ± 6	Chair rise peak power	3D Accelerometer and air pressure sensor	3D accelerometer and air pressure sensor	Home	Natural environment	Preferred speed	The measured parameter was significantly lower in unsupervised conditions, but there was also a significant correlation between unsupervised and supervised assessments.

= Parameters not considered in further analyses due to lack of similarity in the parameters between settings or due to the redundancy of parameters (4th column). Asym = asymmetry. MS = Multiple sclerosis. NA = not available. OA = older adults. PD = Parkinson's disease. Var = variability

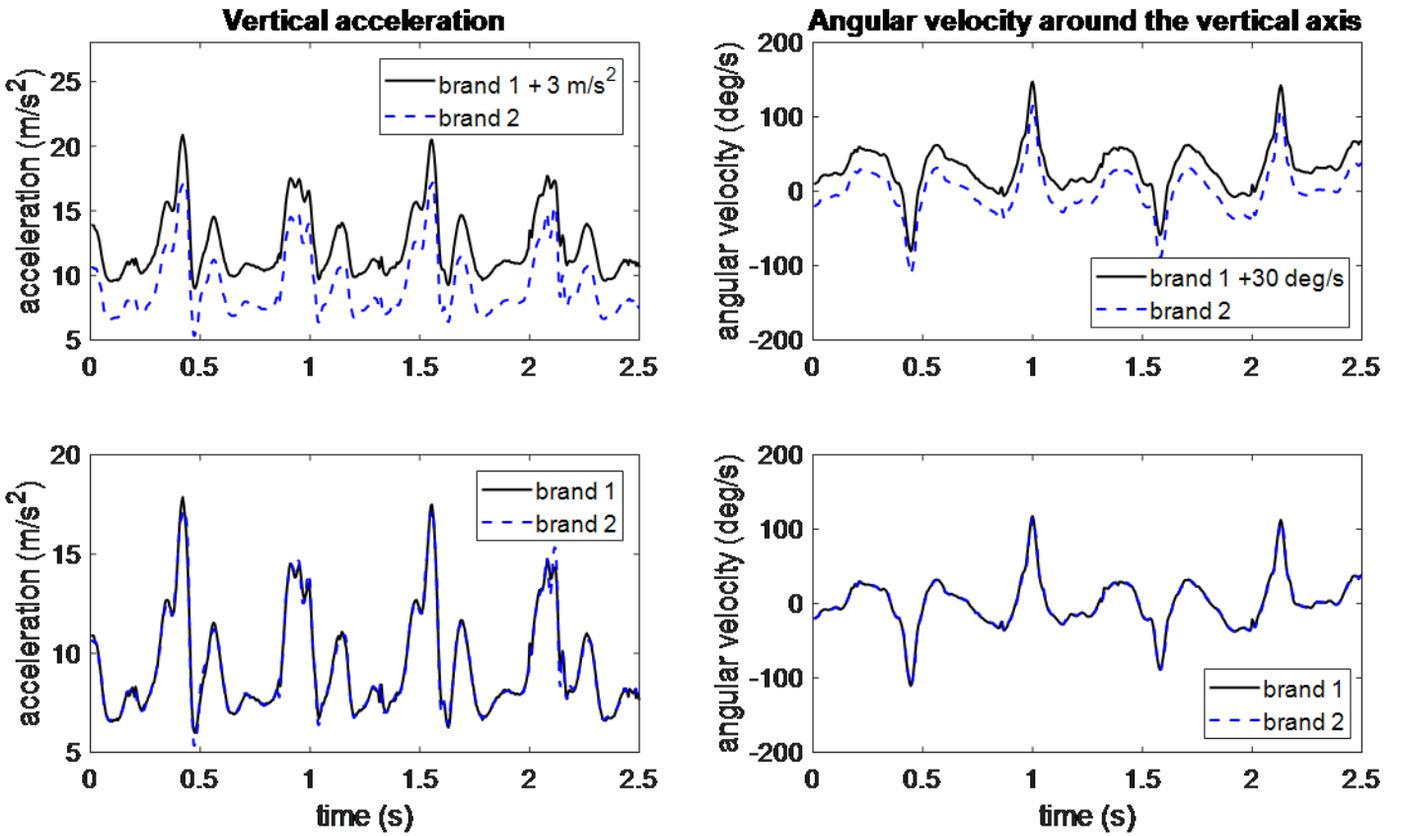

Figure 3.3: Comparison of the raw signals of two inertial measurement units (IMUs) from different brands. Two IMUs from different brands (Noraxon myomotion, brand 1, and Gait Up physilog 5, brand 2) were placed on top of each other on the lower back during a walking assessment, and then the raw data was extracted. Vertical acceleration (from the accelerometer) and angular velocity (from the gyroscope) are displayed. In the top two graphs (A and B), an offset to one of the signals was added to be able to see the different signals. In the bottom graphs (C and D), data is shown without offset (i.e. the "original" data) which demonstrates that the different IMUs collected almost the identical raw signals.

3

Chapter 4

Quantification of arm swing during walking in healthy adults and Parkinson's disease: Wearable sensor-based algorithm development and validation

Elke Warmerdam, Robbin Romijnders, Julius Welzel, Clint Hansen, Gerhard Schmidt, Walter Maetzler

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Abstract

Neurological pathologies can alter the swinging movement of the arms during walking. The quantification of arm swings has therefore a high clinical relevance. This study developed and validated a wearable sensor-based arm swing algorithm for healthy adults and patients with Parkinson's disease (PwP). Arm swings of 15 healthy adults and 13 PwP were evaluated (i) with wearable sensors on each wrist while walking on a treadmill, and (ii) with reflective markers for optical motion capture fixed on top of the respective sensor for validation purposes. The gyroscope data from the wearable sensors were used to calculate several arm swing parameters, including amplitude and peak angular velocity. Arm swing amplitude and peak angular velocity were extracted with systematic errors ranging from 0.1 to 0.5° and from −0.3 to 0.3°/s, respectively. These extracted parameters were significantly different between healthy adults and PwP as expected based on the literature. An accurate algorithm was developed that can be used in both clinical and daily-living situations. This algorithm provides the basis for the use of wearable sensor-extracted arm swing parameters in healthy adults and patients with movement disorders such as Parkinson's disease.

Keywords: Gait; Gyroscope; Inertial measurement unit; Parkinson's disease

Introduction

A distinct feature of human locomotion is the rhythmic swinging motion of the arms [165, 166]. The amplitude of the swing is associated with gait speed and cognitive loading [27, 167]. Active increase of arm swings has the potential to stabilize gait [168]. The reduction of arm swing amplitude and other alterations of the arm swing pattern, including asymmetry and irregularity, can be related to neurological pathologies. In stroke patients, the arm swing amplitude of the affected arm is smaller compared to that of the controls [169]. Patients with Parkinson's disease (PwP) also show a smaller arm swing amplitude and, in addition, more asymmetry, compared to controls [38, 170, 171]. Therefore, the arm swing is regularly evaluated in a clinical setting and has the potential to improve diagnostic accuracy [22, 170, 172] and map disease progression [22, 170]. Asymmetry in PwP might be associated with disease progression, as a study with 16 PwP in an early disease stage reported a positive correlation between asymmetry and the Hoehn and Yahr (HY) stage in an off-medication state [173]. Similar results were observed in eight mild PwP, showing a positive correlation between asymmetry and the Unified Parkinson's Disease Rating Scale (UPDRS) of the limbs [170]. However, another study analyzed 21 PwP with HY stage I and 19 PwP with HY stage II using an ultrasound-based motion analysis system, and the study found more asymmetry in the HY stage I PwP group compared to the HY stage II PwP group [171]. Levodopa intake or dopaminergic treatment has shown to improve arm swing amplitude, peak swing velocity, and asymmetry of the amplitude in 104 moderate to severe PwP [39]. This was confirmed for asymmetry in another study investigating 16 mild to moderate PwP [173].

Due to the dynamic technical development, the measurement of human movement and mobility has been revolutionized over the last decades and years. Wearable inertial systems (inertial measurement units, IMUs) are an especially attractive assessment tool for arm swings, as these techniques make it possible to measure movements during everyday life [67, 172, 174, 175]. The relevance of measuring mobility in everyday lives of patients is increasingly recognized because it is likely to differ substantially from the mobility that is performed in front of a healthcare professional [176].

This study presents, to our best knowledge for the first time, the technical development and clinical validation of a wearable sensor-based arm swing algorithm for healthy adults and PwP.

Materials and Methods

Subjects and Data Collection

There were 15 healthy adults and 14 PwP who participated in this study. The study was approved by the ethical committee of the medical faculty of Kiel University (D438/18) and performed in accordance with the Declaration of Helsinki of 1975. All subjects provided written informed consent before participating. The inclusion criterion for the healthy adults was no disorders that affect movement, and the inclusion criterion for PwP was a Parkinson diagnosis according to UK Brain Bank Criteria [177].

The healthy subjects walked at three different speeds (2, 3, and 4 km/h) on a treadmill (size: 2.2 by 0.7 m; Woodway, Weil am Rhein, Germany) for 80 s. The

PwP walked on their self-selected speed on the same treadmill for at least 60 s.

Definition of Arm Swing during Locomotion

In order to develop this algorithm, it was necessary to define the movement "arm swing" in such a way that on one hand it is coherent with existing information [165, 166], and on the other hand also addresses the characteristics of the technology used. We therefore propose the following definition:

Definition 1. *Arm swing is a rotational movement of the arm, occurring during walking and running in bipeds with a periodicity of around 1–2 Hz. The hand and arm move freely through space in opposite directions with most of the movement in the sagittal plane of the body frame (backward and forward; Figure 4.1a).*

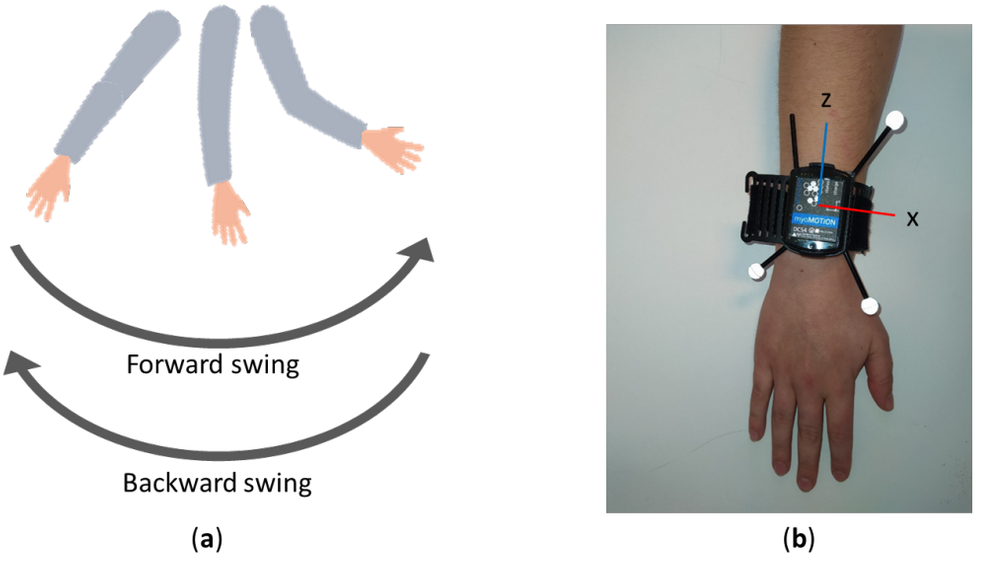

Figure 4.1: (**a**) Definition of swings. (**b**) Placement and orientation of the right-handed coordinate system of inertial measurement unit and reflective markers.

This arm swing algorithm was developed for the data collected during walking. The periodicity of an arm swing had to be between 0.3 and 3 Hz. The minimum amplitude to define an arm swing was set at 5°. Only rotations around the frontal and sagittal axis were taken into account because the wearable sensor might not always be aligned with the sagittal plane of the body frame during the swinging motion of the arms. In this way, all the rotations of the arms are measured except the longitudinal rotations, since they will also be influenced by turns of the body.

Equipment

All subjects were equipped with a cluster of three reflective markers (11 mm) and an inertial measurement unit (IMU) (Noraxon USA Inc., Scottsdale Arizona, AZ, USA) containing 3D accelerometers, 3D gyroscopes, and 3D magnetometers, on each forearm. The position of the markers was aligned with the position of the IMUs to have a similar orientation of the right-handed coordinate systems (Figure 4.1b).

The markers were captured with a 3D optical motion capture system (Qualisys AB, Göteborg, Sweden) at 200 Hz. Both systems recorded simultaneously at 200 Hz.

Data Processing

Inertial Measurement Unit Data

Only the gyroscope data of the IMU were used in this offline algorithm. The algorithm was written with MATLAB 2017a.

The gyroscope data were filtered with a zero-phase second order Butterworth low pass filter with a cut off frequency of 3 Hz to omit noise and possible tremors (ω_{filt}). A principal component analysis (PCA) was performed on the x and y component of the angular velocity. The longitudinal component (z-axis) was not taken into account for the PCA in order to remove any longitudinal rotations (such as turning) from the data. From here on, only the first component of the PCA (ω_{PCA1}) is used for the analysis. This first component represents the angular velocity in the direction of the arm swing. Extracting the angular velocity in the swing direction makes this algorithm insensitive to different wearing locations of the IMU on the forearm as long as the z-axis is aligned with the longitudinal axis of the arm. The angle (α) was calculated from the angular velocity in the swing direction (ω_{PCA1}) by numerical integration using a trapezoidal integration approximation:

$$\boldsymbol{\alpha}(t) = \int_{\tau=0}^{t} \boldsymbol{\omega_{PCA1}}(\tau) d\tau. \tag{4.1}$$

A symmetric moving average ($\hat{\mathbf{m}}_\alpha$) was calculated with a window length of $2q+1$, where q is half a second (representing a window length of 1.005 s with a sample frequency of 200). The moving average was subtracted from the angular data to remove the low frequency drift.

$$\hat{\mathbf{m}}_\alpha(n) = \sum_{j=-q}^{q} b(j)\boldsymbol{\alpha}(n+j), q < n < N-q; \tag{4.2}$$

$$\text{with } b(j) = \begin{cases} \frac{1}{4q}, & \text{if } j = \pm q \\ \frac{1}{2q}, & \text{else} \end{cases}$$

$$\boldsymbol{\alpha}_{detrend}(t) = \boldsymbol{\alpha}(t) - \hat{\mathbf{m}}_\alpha(t). \tag{4.3}$$

The frequency was extracted with a fast Fourier transform (FFT) from 3 s rectangular windows with 75% overlap. The dominant frequency was extracted from each window. The percentage of the power that was in the 0.3–3 Hz domain was calculated and used to determine whether there was a periodical movement in this specific frequency domain of arm swing motion. When this percentage was below an empirically determined threshold of 90%, this window was not taken into account for further analysis.

The local maxima and minima from the angle signal ($\boldsymbol{\alpha}_{detrend}$) were extracted. Both the positive and negative peaks needed to have a minimum peak prominence of 2° and a minimum distance of 60% of the cycle time that was extracted from the dominant frequency per window from the FFT. The overlap of the 3 s rectangular

windows for the peak detection was 50%. Peaks that were detected multiple times due to the overlapping windows were only considered once. In between two maxima, only one minimum was allowed, and in between two minima only one maximum was allowed. In case of an extra detected peak, the smallest peak was discarded. The magnitudes of a consecutive minimum and maximum or a maximum and minimum were added to each other to obtain the amplitude of the swing. The time instants of these extrema were then used to find the extrema in the angular velocity in the swing direction to obtain the peak angular velocity. When a swing took longer than twice the average cycle time, it was discarded because of the low probability of it being an actual arm swing. Any outliers (peaks that were larger than three times the 80th percentile of the peaks detected in the angle signal) were removed because those were probably other movements than the regular swinging motion during walking (e.g., scratching the head). Every swing with an amplitude below 5° or a peak angular velocity below 10°/s was removed from the data because a high detection accuracy cannot be guaranteed during such small arm movements. An overview of the main steps taken are provided in Figure 4.2.

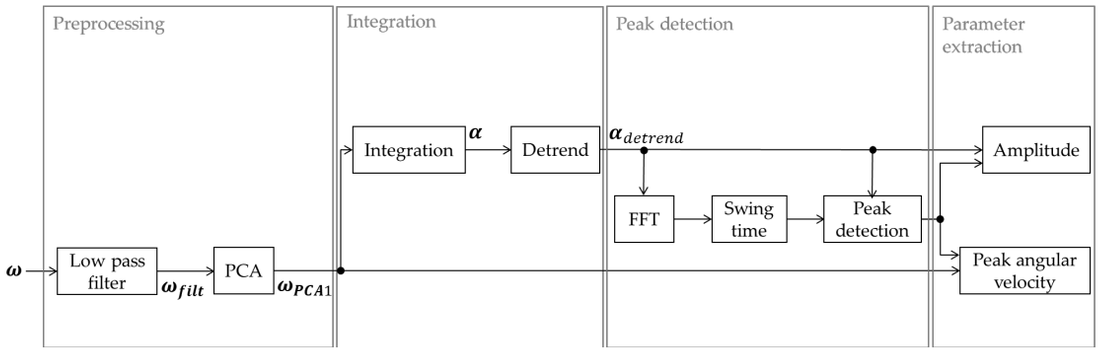

Figure 4.2: Block diagram of the arm swing algorithm

Additionally, the peak angular velocity was divided into forward and backward angular velocities, based on whether it was a minimum or a maximum in the angular velocity in the swing direction. This makes it possible to analyze potential differences caused by the direction of the movement. When there were no periodical movements of the arm or the arm movements were too small, no arm swing parameters were calculated. To understand whether the amplitude and peak angular velocity were calculated during the complete walking bout or only for a shorter period, the percentage of time in which there were swings detected in one arm during the walking bout was extracted. How frequently the arms moved was represented in the frequency as was extracted with the FFT. The similarity between neighboring swings was represented with the regularity. The regularity was calculated based on the autocorrelation of the angle [178]. The autocorrelation was extracted with a 4.5 s Tukey window with a cosine fraction of 0.3 and a 99% overlap of the windows. The maximum autocorrelation of each window was extracted, and the average of these values was taken as regularity. A regularity of 1 means that a swing is exactly similar to its neighboring swings.

When both arms were measured and the IMUs were synchronized, the percentage of simultaneously occurring arm swings in both arms was calculated. Arm swings were deemed simultaneous when a change in direction (i.e., forward to backward or backward to forward) of an arm swing in one arm was within 500 ms from a change

in direction of the arm swing in the other arm. If at least 60% of the walking episode was with simultaneously swinging arms, the asymmetry index (ASI) was calculated for the average amplitude and peak angular velocity. For the calculation of the ASI, only the phases with swings detected in both arms simultaneously were taken into account [179]:

$$ASI = \frac{(L - R)}{max(L, R)} \times 100 \tag{4.4}$$

where L is the amplitude or the peak angular velocity of the left arm and R the similar parameter of the right arm. An ASI of 0% reflects identical values of the left and right arm. The coordination between the left and right arm was calculated when during at least 60% of the walking episode, arm swings were detected in both arms simultaneously. The coordination was based on the normalized cross-correlation of which the minimum value was calculated. The absolute of this minimum was calculated for each swing during the phases where there were arm swings in both arms simultaneously, of which then the average was taken to obtain the coordination. This is a slightly adjusted version of [173], where they calculated the maximum of the absolute signal instead of the absolute minimum.

$$\mathbf{r}_{LR}(m) = \frac{\sum_{n=0}^{N-m-1} \boldsymbol{\omega}_{PCA1\_L}(n+m)\, \boldsymbol{\omega}_{PCA1\_R}(n)}{\sqrt{\sum_{n=0}^{N-m-1} \boldsymbol{\omega}_{PCA1\_L}(n)^2}\, \sqrt{\sum_{n=0}^{N-m-1} \boldsymbol{\omega}_{PCA1\_R}(n)^2}}, \tag{4.5}$$

$$coordination = \frac{1}{n} \sum |min(\mathbf{r}_{LR}(m))|. \tag{4.6}$$

with $\boldsymbol{\omega}_{PCA1\_L}$ and $\boldsymbol{\omega}_{PCA1\_R}$ the angular velocity in swing direction of the left and right arms respectively, and m ranging from 0 ± 0.5 s. A value of 1 indicates that the left and right arms swing with a similar rhythm that is exactly out of phase with each other. A value of 0 indicates that there is no coordination between the arms.

The algorithm is available online (`https://github.com/EWarmerdam/ArmSwingAlgorithm`).

Optical Data

Gaps in the optical data smaller than 250 ms were filled based on marker intercorrelations [180]. The parts of the data with gaps larger than 250 ms were discarded. A local coordinate system was calculated from the three markers on the wrist. The angular velocity was obtained from the derivative of the orientation. The orientation was also used to calculate the Cardan angles (order: zxy). The angle and angular velocity were rotated in the swinging direction based on the results from the PCA of the IMU data. From there on, the amplitude and peak angular velocity were obtained in the same way as with the IMU data.

Statistical Analysis

For the validation, the data of both arms were taken together. To compare the angle and the angular velocity between both systems, the root mean square errors (RMSe) between the IMU and the optical data were calculated. A Bland–Altman analysis was performed to extract the systematic error (average of the difference between the IMU-derived and the optical system-derived data) and the random error (95%

confidence intervals ± systematic error) of the arm swing amplitude and the peak angular velocity [181]. The average absolute error was calculated to obtain the magnitude of the error between the two systems.

For the clinical validation, the arm swing parameters of the healthy participants walking at different speeds were compared to those of the PwP group. The amplitude, peak angular velocity, percentage of walking bout with arm swing, frequency, and regularity were calculated with averaged data of the left and right arms. The percentage of the walking bout with the arm swing in both arms simultaneously, asymmetry, and coordination were calculated by comparing left versus right arm data. For the asymmetry, the magnitude was taken for the analysis. A Mann–Whitney U test was used to test for significance ($p < 0.05$).

Results

One PwP was taken out of the analysis because all amplitudes of the arm movements did not reach the 5° threshold. An overview of the remaining participants taken into the analysis is provided in Table 4.1.

Table 4.1: Demographics (mean ± standard deviation) of the subjects.

	Healthy Adults	**PD Patients**
n (male)	15 (9)	13 (5)
Age [years]	31 ± 9	71 ± 9
Body mass index [kg/m^2]	23.4 ± 2.7	28.5 ± 5.9
Hoehn and Yahr stage (1–5)	NA	2.8 ± 0.7

Healthy Adults

Fifteen healthy adults walked at three different speeds on a treadmill. The RMSe of the angle and angular velocity between the IMU- and optical system-derived signals were below 1° and below 0.05°/s, respectively (Figure 4.3, Table 4.2). The systematic errors were in the range of 0.1 to 0.5° for the amplitude and -0.1 to 0.3°/s for the peak vertical velocity of the different speeds (Figure 4.4, Table 4.2). The random error of the amplitude was between 2.2 and 2.7°, and the random error of the peak angular velocity was between 4.2 and 5.3°/s. The absolute errors ranged from 0.9 to 1.1° for the amplitude and from 1.4 to 1.9°/s for the peak angular velocity.

Patients with Parkinson's Disease

Thirteen PwP walked at their preferred speed (average 1.4 km/h) on a treadmill. The RMSe between the IMU-derived and optical system-derived data was 1.16° for the angle and 0.16°/s for the angular velocity (Figure 4.3, Table 4.2). The systematic errors were 0.2° and -0.3°/s for the amplitude and peak angular velocity, respectively (Figure 4.4, Table 4.2). The random errors were 3.8° and 6.8°/s, and the absolute errors were 1.1° and 2.0°/s for the amplitude and peak angular velocity, respectively.

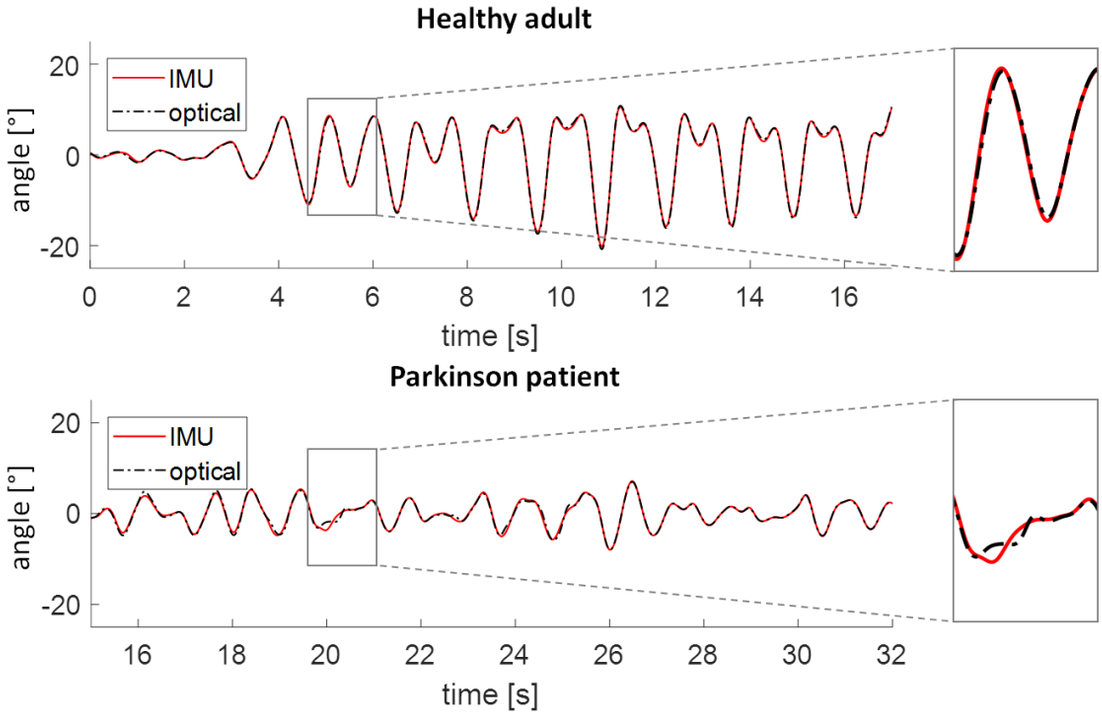

Figure 4.3: The angle of the inertial measurement unit (IMU) and optical data of a healthy participant and of a patient with Parkinson's disease.

Table 4.2: Error measures of IMU-derived arm swing data, compared to optical system-derived data.

		Healthy Adults 2 km/h	**Healthy Adults 3 km/h**	**Healthy Adults 4 km/h**	**PwP Preferred**
Angle RMSe [°]		0.83	0.91	0.72	1.18
Angular velocity RMSe [°/s]		0.03	0.03	0.03	0.16
No. of swings		3885	3788	4103	1762
Amplitude [°]	Systematic error	0.1	0.4	0.5	0.2
	Random error	2.6	2.2	2.7	3.8
	Absolute error	0.9	0.9	1.1	1.1
Peak angular velocity [°/s]	Systematic error	-0.1	-0.1	0.3	-0.3
	Random error	4.2	4.4	5.3	6.8
	Absolute error	1.4	1.6	1.9	2.0

PwP: patients with Parkinson's disease; RMSe: root mean square error.

Clinical Validation

All the arm swing parameters were extracted with the algorithm and compared between the groups. The percentage of the walk with swinging motion in one arm was the only parameter that was significantly different between the groups on all speeds. On higher speeds, more significant differences were found between the groups (Table 4.3).

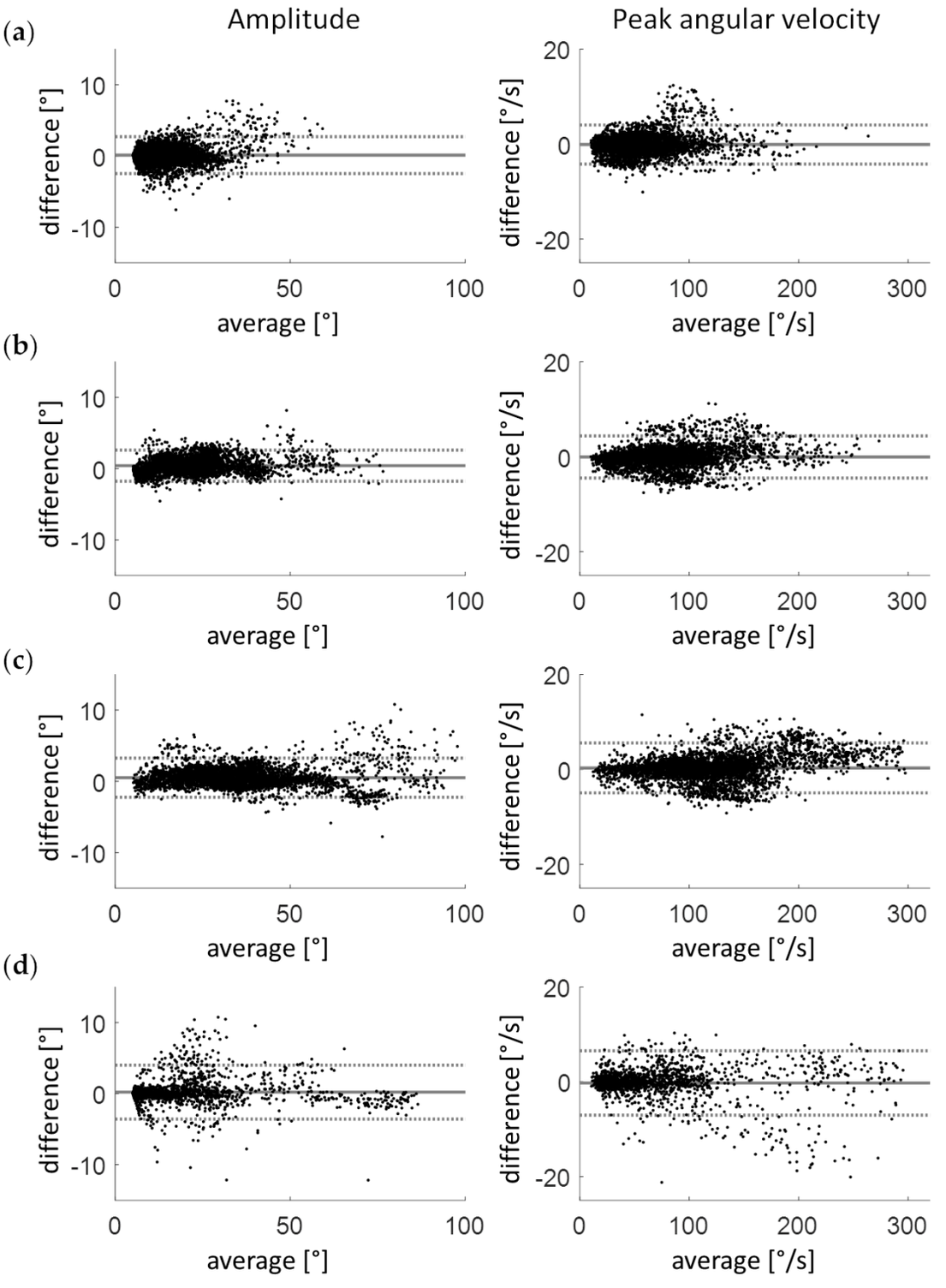

Figure 4.4: Bland–Altman plots are shown with the arm swing amplitude and peak angular velocity at 2 km/h (**a**), 3 km/h (**b**), and 4 km/h (**c**) for the healthy adults and at the preferred speed (**d**) for patients with Parkinson's disease. On the x-axes, the average of the IMU and optical results are presented, and on the y-axes the differences between IMU and optical results (IMU-optical) are presented.

Discussion

This study presents the development and the validation of an arm swing algorithm based on wearable sensors (i.e., IMUs) positioned on the wrists for healthy adults and

Table 4.3: IMU-based arm swing parameters for the healthy adults and the patients with Parkinson's disease.

	Healthy Adults 2 km/h	**Healthy Adults 3 km/h**	**Healthy Adults 4 km/h**	**PwP Preferred**
Amplitude [°]	16	23*	36*	17
Peak angular velocity [°/s]	57	84*	122*	60
Forward peak angular velocity [°/s]	59	87*	124*	60
Backward peak angular velocity [°/s]	55	80*	120*	59
Percentage of walk with swinging motion in an arm [%]	93*	99*	99*	78
Frequency [Hz]	0.9	0.9	0.9	0.9
Regularity (0–1)	0.8	0.9*	0.9*	0.7
Percentage of walk with swinging motion in both arms simultaneously [%]	90*	97*	98*	64
Absolute amplitude asymmetry index [%]	20	17	20	36
Absolute peak angular velocity asymmetry index [%]	19	18	21	33
Coordination (0–1)	0.7	0.8	0.8	0.8

*: significantly different from patients with Parkinson's disease ($p < 0.05$); see the data processing part in the methods for the calculations and interpretation of the parameters. For the asymmetry and coordination, seven PwP could be included in the analysis; the other four did not fulfil the criteria for the calculation of these parameters (see Methods section).

PwP. Based on our data, the algorithm is extremely accurate. Arm swing amplitude and peak angular velocity can all be extracted with a very small systematic error compared to the reference system.

The random errors are slightly higher for the PwP group compared to the healthy adults group. This may -at least partly- be due to the less fluent movement of the arms in PwP. It can be seen in Figure 4.3 and in the RMSe (Table 4.2) that the IMU and optical data do not overlap as well in the PwP compared to the curves derived from a healthy adult. This deviation between the IMU and optical data is especially seen around the peaks.

The healthy adults were measured at multiple speeds. Based on visual interpretation, the walking speed was not of influence on the accuracy of the algorithm. This should make the algorithm suitable for measuring arm swings in usual daily-living situations, which is particularly relevant for longitudinal and therapy studies. However, the algorithm itself cannot detect when someone is walking and might therefore include other repetitive movements of the arm that are performed throughout the day. Ideally, the arm swing algorithm should therefore be combined with a gait detection algorithm [182, 183] when used for measurements outside the lab to make sure as much as possible that arm swings are only analyzed during walking. It should also be noted that a walking bout needs to be at least 3 s for the algorithm to work. For daily-living assessments, a higher minimum walking bout length might need to be set to exclude artefacts. This can omit wrongly increased variability of the data. Users of the algorithm should also take arm swing data from longer walking bouts with a certain degree of caution, as also during such walking episodes, arm movements that are not arm swings as defined in the introduction can occur. Examples are arm movements that are not based on freely moving hands (e.g., when swinging a bag or using Nordic walking sticks) and animated movements (e.g., performed based on a given rhythm that comes from earphones of external sources).

According to the protocol of a future study or the main objectives of clinical

management that aim to integrate this algorithm in their approaches, the algorithm may be adapted to individual needs and situations. For example, in this particular study, arm swings with an amplitude below 5° were excluded. This is a very low threshold (corresponding to a horizontal displacement of 6 cm with an arm length of 70 cm), and can lead to false positive results in less strictly defined data sets (for example, it may detect movements of the arms and hands that are in the pockets during walking). Therefore, for daily-living assessments, we suggest increasing the threshold for the amplitude and combining it with a gait detection algorithm. Future studies must evaluate which thresholds have the highest accuracies, especially when recording unsupervised daily-living data. It should be mentioned again that this inaccuracy falls within the clinical and phenomenological domain and does not call into question the high technical validity of the algorithm (i.e., the compliance with the reference; see above).

For an initial clinical validation, all the parameters from the algorithm were extracted and compared between healthy adults and PwP. The percentage of the walk with swinging motion of the arms was significantly different in PwP, compared to all walking conditions performed with healthy adults. This makes a comparison of the arm swings between the groups difficult because we have to assume that in the PwP group, those arm swings are exactly the ones not included in the calculation that fall below the specified threshold of 5°. Therefore, the following qualitative comparisons must be interpreted with caution. Nevertheless, differences can be found in all group comparisons (Table 4.3).

When we compared the 4 km/h condition of the healthy adults, which comes probably closest to their preferred speed, we found significant differences in arm swings between the groups, and this finding corresponds to the literature [33, 184, 185]. Since we found less significant differences on 2 km/h, it could be that walking speed has an influence on the differences found between healthy adults and PwP, which certainly has to be investigated in future studies.

The lateralization of the disease may also have a relevant influence on arm swing parameters in PwP. A study with slow walking speeds on a treadmill only found significant differences for the amplitude between the most affected side of PwP compared to healthy adults [171]. Our results on asymmetry corroborate these preliminary results. The percentages of the walks with simultaneously performed swinging motions in both arms were substantially lower in PwP, compared to healthy adults at all measured walking speeds. We assume similarly according to our reasoning in the above paragraph that all qualitative evaluations that were performed in the PwP group may thus underestimate the real asymmetry and lack of coordination of arm swings because it is exactly those arm swings with high asymmetry and low coordination values that are excluded based on our threshold (arm swing $> 5°$). Nevertheless, it is noticeable (see also Table 4.3) that PwP have higher amplitude and peak angular velocity asymmetry indices than healthy adults. In conclusion, our preliminary clinical results indicate that the known differences in arm swing between PwP and healthy adults can be reliably and accurately detected with this algorithm, and future clinical studies may include this algorithm.

A study reporting about prodromal changes of gait in PD was recently published [15], but it did not report about arm swing behavior. The algorithm presented here can now be used to analyze such data sets with higher granularity and more exhaustive information about body movement. The algorithm can also extend the movement assessment for observational studies, clinical trials, and clinical management to the daily-living environment, an area that we have not been able to investigate

and understand in much detail so far. The evaluation of disease progression and response to treatment in PwP has a similar or even higher relevance, not only for the amplitude of arm swings but also for all other parameters presented in Table 4.3. Arm swing parameters could help to differentiate healthy adults from PwP, and they may be useful for the detection and diagnosis of additional diseases associated with impaired mobility (such as multiple sclerosis). Of course, the application of this algorithm also opens up new options in the evaluation of arm swings in the context of aging in general, with respect to the significance of arm swings in fallers, and how arm swings differ between supervised and unsupervised environments, to name a few examples.

Some aspects should be taken into account when using the algorithm in future studies. First, turns during walking in daily living have no influence on the algorithm itself, since rotations around the longitudinal axis are not taken into account. When the walking turns should be separated from the walking data, a turning algorithm should be used to detect the turns [119, 186]. Second, in general, the arm moves in phase with the contralateral leg. However, on slower speeds, the arms can swing in a 2:1 ratio with the legs instead of 1:1 [187, 188]. This in itself is no issue for the algorithm. However, during the transition phases between these two ratios (Figure 4.3, about 7 s), it depends on how fast the frequency changes and whether the swing is above the set thresholds if this swing in between is detected. When it is detected, it might influence the variance of the data, since the amplitude, peak angular velocity, and average angular velocity are smaller compared to the other swings. Third, people can be measured on one or two wrists. It is self-explanatory that in case of only one wearable device, the percentage time where there was a swing in both arms, the asymmetry, and the coordination cannot be calculated. Fourth, for some of the PwP, there were only a few arm swings detected during the walking bout because the arm movements did not exceed the 5° threshold. This is likely to happen more often in severe PwP.

The study faces the limitation that during the measurements the participants walked on a treadmill, which results in slightly different upper body movements compared to over ground walking [189]. However, we consider this a minor issue, as the main aim of the study was the validation of the IMU-derived arm swing algorithm against a reference that was assessed simultaneously. Moreover, the healthy controls were in their young adulthood and thus substantially younger than PwP. This implies that we are mapping an age effect in the clinical validation data for which we cannot correct in this data set. However, we are optimistic that we will still map a Parkinson-associated difference, as our data confirm the data from previously published studies. We are also working on a detailed representation of arm swings in existing data sets of large cohorts, including the TREND study (`https://www.trend-studie.de/`).

Conclusions

An arm swing algorithm was developed and validated for both healthy adults and PwP. The algorithm is highly accurate in a clinical environment and has high potential to be used in a daily-living environment as well.

4

Chapter 5

Arm swing responsiveness to dopaminergic medication in Parkinson's disease depends on task complexity

Elke Warmerdam, Robbin Romijnders, Clint Hansen, Morad Elshehabi, Milan Zimmermann, Florian G. Metzger, Anna-Katharina von Thaler, Daniela Berg, Gerhard Schmidt, Walter Maetzler

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Abstract

The evidence of the responsiveness of dopaminergic medication on gait in patients with Parkinson's disease is contradicting. This could be due to differences in complexity of the context gait was in performed. This study analyses the effect of dopaminergic medication on arm swing, an important movement during walking, in different contexts. Forty-five patients with Parkinson's disease were measured when walking at preferred speed, fast speed and dual-tasking conditions in both OFF and ON medication states. At preferred, and even more at fast speed, arm swing improved with medication. However, during dual-tasking, there were only small or even negative effects of medication on arm swing. Comparisons of arm swing parameters of patients with Parkinson's disease with controls suggests that the effects of both dopaminergic depletion and dopaminergic replacement are substantially influenced by the context. Assuming that dual-task walking most closely reflects real-life situations, the results suggest that the effect of dopaminergic medication on mobility-relevant movements, such as arm swing, might be small in everyday conditions. This should motivate further studies to look at medication effects on mobility in Parkinson's disease, as it could have highly relevant implications for Parkinson's disease treatment and counselling.

Keywords: Arm swing; Dual-task; Gait; Levodopa; Treatment

Introduction

Dopaminergic medication is the most common treatment for people with Parkinson's disease. It is highly effective in improving Parkinson's disease-related symptoms such as bradykinesia, rigidity and tremor, as has been shown, for example, with the unified Parkinson's disease rating scale (UPDRS), its revised version (MDS-UPDRS) and other established clinical scales [44, 45, 190, 191].

However, contradicting results were found concerning the effect of dopaminergic medication on gait deficits associated with Parkinson's disease. Only gait speed, stride length and stride velocity have consistently shown an increase with medication in multiple studies with different disease severities [39, 44, 77], study protocols [44, 46, 47, 92, 192] and measurement equipments [39, 44, 46, 91, 92, 193, 194]. The effects of dopaminergic medication on other gait parameters are not entirely clear. For example, although one relatively large study found an increased cadence (steps per minute) with dopaminergic medication [39], four others –with comparable cohort characteristics- did not [46, 92, 192, 194]. One study found a decrease in stance time [91], but another study –again with comparable cohort characteristics- did not [39]. Contradicting results were also found for double limb support (for example, one study found no significant change [39], where other studies found a decrease with medication [91, 92, 195]) and gait variability (three studies found no significant change [46, 91, 196], four studies found a decrease with medication [46, 47, 194, 196]). Similarly, there are contradicting results concerning the effect of dopaminergic medication on arm swing parameters in Parkinson's disease. For example, arm swing asymmetry only decreased with medication in one [173], but not in another study [39].

Brain activity differs with the complexity of walking tasks and with neurological pathologies [98]. We therefore hypothesize that at least some of the above-mentioned contradicting results may be explained by differences in the context where the respective walking task is performed. This hypothesis is, at least indirectly, supported by studies that found an effect of task complexity on the effect of medication on certain gait parameters (e.g., gait speed [197] and stride time variability [198]). Moreover, two studies reported a change in the difference of walking parameters between Parkinson's disease and controls, depending on the walking paradigm (between preferred and fast walking condition: gait speed, swing velocity, step time and swing time; between preferred and dual-task condition: stride length and percentage swing time [199, 200]). These differences in response of mobility patterns to different stimuli and demands could have highly relevant implications for Parkinson's disease treatment and counselling, as human behaviour depends on the use of highly diverse mobility strategies [90].

We therefore measured in this study the effect of dopaminergic medication on a specific movement, i.e., arm swing, during preferred, fast and dual-task walking. We compared the values of the patients with matched controls to analyse whether with medication the patients have comparable values as controls. We then compared the delta of medication ON minus OFF, of different arm swing parameters between the different walking conditions. We chose arm swing because arm swing (i) is relatively easy and very reliable to measure [201], (ii) is influenced by cognitive dual-tasks [27, 167, 202] that occur regularly in daily life, (iii) is influenced by Parkinson's disease (smaller arm swing amplitudes and more asymmetry compared to controls) [38, 170, 171], and (iv) is influenced by dopaminergic medication. For example, arm swing amplitude and angular velocity increase with medication [39, 173, 203].

Results

Demographics and task performance of the included Parkinson's disease patients and controls are provided in Table 5.1.

Table 5.1: Demographics and disease characteristics (mean ± standard deviation (range)) of the participants.

	Controls	Participants with Parkinson disease	
n (male)	45 (32)	45 (30)	
Age [years]	65 ± 8 (53-84)	65 ± 9 (46-84)	
Height [m]	1.70 ± 0.07 (1.55-1.88)	1.73 ± 0.11 (1.55-1.93)	
Weight [kg]	78 ± 9 (58-100)	77 ± 13 (53-107)	
MoCA (0-30)	25 ± 2 (19-29)	27 ± 2 (20-30)	
Hoehn & Yahr (1-5)		2.0 ± 0.5 (HY1 = 5, HY1.5 = 2, HY2 = 32, HY2.5 = 2, HY3 = 4)	
Disease duration [years]		5 ± 3 (1-10)	
Levodopa equivalent dose [mg]		523 ± 379 (155-1630)	
		OFF	**ON**
MDS-UPDRS III (0-132)	3 ± 5 (0-19)	34 ± 14 (11-50)	21 ± 9 (6-61)
Preferred gait speed [m/s]	1.51 ± 0.17 (1.03-1.88)	1.34 ± 0.22 (0.88-1.87)	1.39 ± 0.19 (0.95-1.78)
Fast gait speed [m/s]	1.86 ± 0.25 (1.14-2.34)	1.68 ± 0.25 (1.23-2.17)	1.75 ± 0.26 (1.26-2.52)
Dual-task gait speed [m/s]	1.57 ± 0.25 (0.94-2.13)	1.29 ± 0.27 (0.68-1.80)	1.34 ± 0.27 (0.73-2.13)
Number of arm swings in preferred condition	94 ± 14 (70-128)	87 ± 17 (51-128)	88 ± 18 (36-138)
Number of arm swings in fast condition	95 ± 18 (66-134)	86 ± 17 (36-122)	86 ± 17 (51-130)
Number of arm swings in dual-task condition	95 ± 17 (64-144)	89 ± 31 (35-231)	81 ± 16 (43-116)
Subtractions in single-task condition [n/min]	20 ± 8 (7-43)	21 ± 13 (6-60)	23 ± 13 (4-46)
Subtractions in dual-task condition [n/min]	20 ± 11 (3-59)	24 ± 12 (4-50)	22 ± 11 (9-61)
Subtraction mistakes in single-task condition [n/min]	2 ± 2 (0-8)	1 ± 2 (0-9)	1 ± 2 (0-5)
Subtraction mistakes in dual-task condition [n/min]	2 ± 3 (0-9)	2 ± 2 (0-8)	1 ± 3 (0-9)

MDS-UPDRS III = motor part of the Movement Disorders Society-sponsored revision of the unified Parkinson's disease rating scale; MoCA = Montreal cognitive assessment.

The following changes of arm swing parameters due to dopaminergic medication were significant (see also Figure 5.1 and Supplementary Table 5.4): Main amplitude and peak angular velocity increased with medication in the preferred and fast walking condition, but not in the dual-task condition. Amplitude asymmetry decreased with medication in the preferred and dual-task conditions, but not at fast speed.

Arm swing coordination only increased in the fast walking condition. Regularity improved with medication only in the preferred condition. The sideways amplitude decreased with medication during the preferred and fast walking condition, but increased during the dual-task condition.

Cognitive performance as measured with subtractions per minute improved with medication during the single-task ($P = 0.012$), but not during the dual-task. The responsiveness to dopaminergic medication was significantly different between the single-task and dual-task ($P = 0.005$; Figure 5.2). Moreover, cognitive dual-task costs were significantly different per medication state ($P = 0.027$), -29% in OFF state and -12% in ON state.

When comparing the respective arm swing parameters from patients with Parkinson's disease with control values (grey stars in Figure 5.1), then in the OFF phase during preferred speed two of the six investigated arm swing parameters (regularity and asymmetry) were significantly worse, and in the ON phase one parameter (regularity). During fast speed, five investigated arm swing parameters were significantly worse in the OFF phase than in the control group and asymmetry was significantly better than in controls. Also in the ON phase, all six investigated arm swing parameters were significantly different from the control group, but only one of them was worse (regularity), and the other five were better than the control values. During dual-task walking, one parameter (coordination) was significantly worse in both, the OFF and ON phase, than in the control group and one other parameter (asymmetry) was significantly worse in the OFF phase than in the control group.

The degree of responsiveness of respective arm swing parameters to dopaminergic medication are shown in Figure 5.2 for the 33 participants with a complete dataset. At preferred speed, the responsiveness to dopaminergic medication was moderate for amplitude asymmetry and small for all other arm swing parameters. At fast speed, the responsiveness to medication was large for main amplitude, peak angular velocity, coordination and sideways amplitude (decrease), small for amplitude asymmetry and negligible for regularity. The responsiveness to medication was small for the cognitive single-task. In the dual-task condition, the responsiveness to dopaminergic medication was moderate for amplitude asymmetry and sideways amplitude (increase), small for regularity, coordination and cognitive performance, and negligible for main amplitude and peak angular velocity.

The following responses of arm swing parameters to dopaminergic medication were significantly different across the different walking conditions in Parkinson's disease (special characters in Figure 5.2 and Supplementary Table 5.5): In the fast walking condition, main amplitude, peak angular velocity, coordination and sideways amplitude were significantly more responsive (i.e., better) and asymmetry was significantly less responsive (i.e. worse) than in the preferred walking condition. Regularity was not significantly different between these two conditions. In the dual-task walking condition, main amplitude, regularity and sideways amplitude were significantly less responsive (i.e. worse) than in the preferred walking condition. Peak angular velocity, amplitude asymmetry and coordination were not significantly different between these two conditions. In the dual-task walking condition, amplitude asymmetry was significantly more responsive (i.e., better) and main amplitude, peak angular velocity, coordination, sideways amplitude, and cognitive performance were significantly less responsive (i.e. worse) than in the fast walking condition. Regularity was not significantly different between these two conditions.

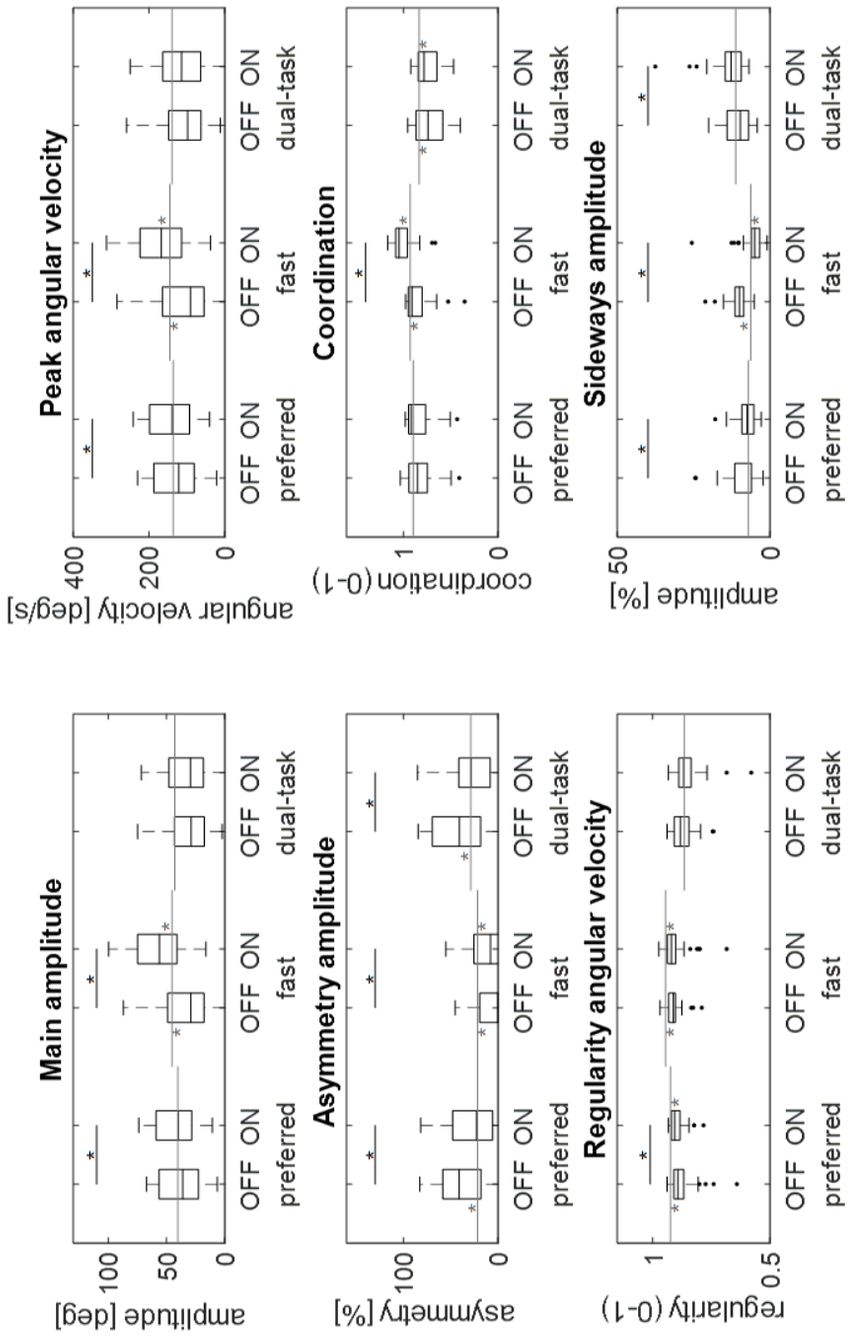

Figure 5.1: Arm swing parameters during the different medication states and different walking conditions. The grey horizontal lines indicate the values of the controls. Black * above horizontal lines, connecting different box plots = $P < 0.05$ between medication states; Grey * lateral to the box plots = $P < 0.05$ compared to controls (above grey horizontal line = higher value than controls; below grey horizontal line = lower value than controls). All data are corrected for gait speed. Center line: median; box limits: upper and lower quartiles; whiskers: 1.5 × interquartile range.

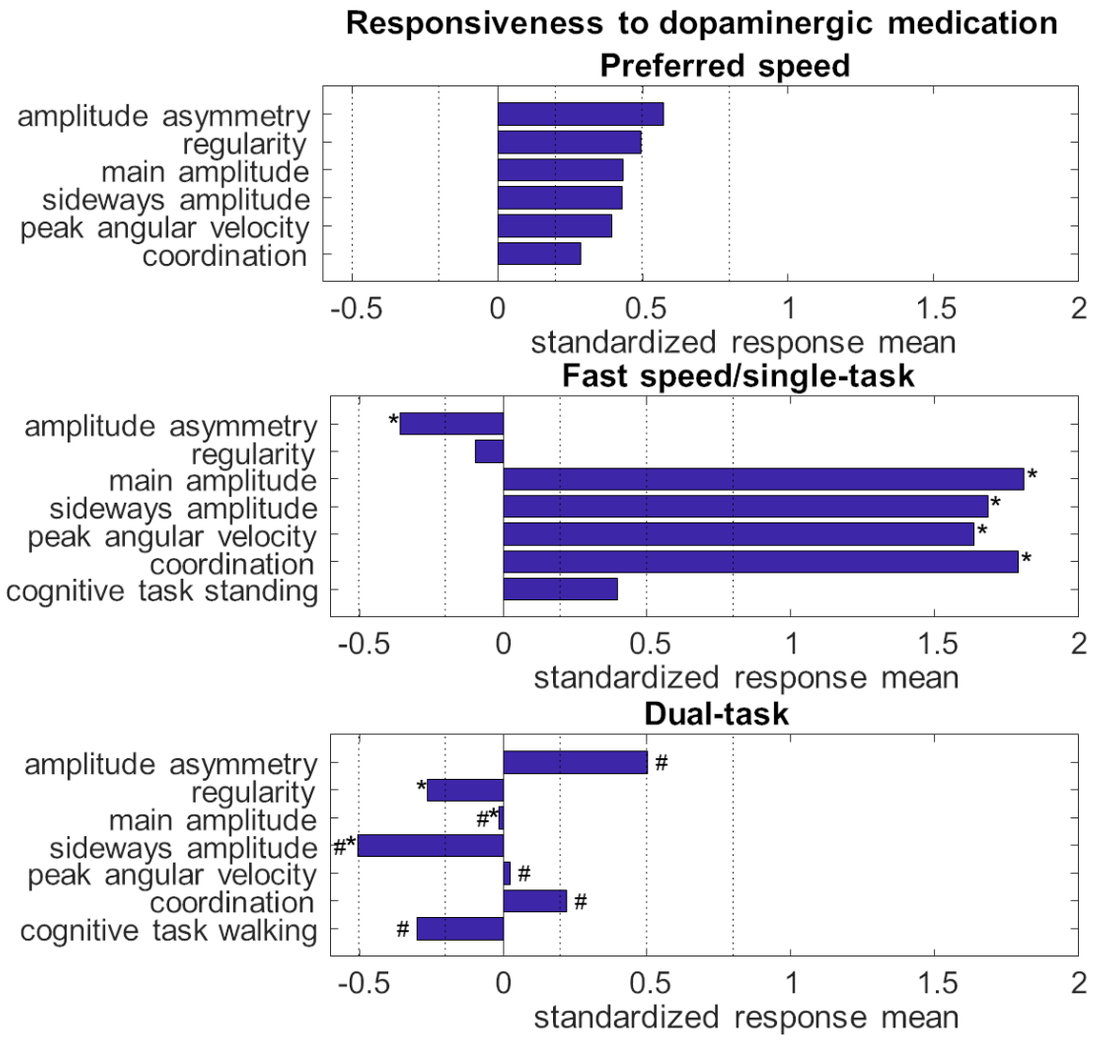

Figure 5.2: Responsiveness of the arm swing parameters and the cognitive subtraction task to dopaminergic medication. A positive standardized response mean (SRM) indicates an improvement with medication and a negative SRM a worsening with medication. $0.20 \leq SRM < 0.50$ represents a small, $0.50 \leq SRM < 0.80$ a moderate and $SRM \geq 0.80$ a large responsiveness to dopaminergic medication [39]. * = significantly different from preferred speed; # = significantly different from fast speed/single task condition.

Almost none of the ON-OFF changes in arm swing parameters correlated with any ON-OFF changes of the MDS-UPDRS (part three total score and subscores). The only exceptions were sideways amplitude and MDS-UPDRS rigidity subscore during the preferred speed condition ($P = 0.018$), as well as coordination of arm swing and postural instability and gait disorder score (PIGD) during the dual-task walking condition ($P = 0.027$; Table 5.2). Several of the ON-OFF changes in the arm swing parameters correlated with the Levodopa equivalent daily dose (LEDD). At preferred speed, main amplitude, peak angular velocity and coordination correlated with LEDD ($P = 0.005$, $P = 0.004$, $P = 0.015$, respectively; Table 5.2). At fast speed, arm swing asymmetry correlated negatively with LEDD ($P = 0.001$). However, during the dual tasking condition, none of the ON-OFF changes of the arm swing parameters correlated significantly with the LEDD.

Table 5.2: Correlation coefficients of the changes in arm swing parameters with medication and the changes in MDS-UPDRS III (subscores) with medication, and the LEDD values.

	MDS-UPDRS III total score			**MDS-UPDRS Bradykinesia subscore**			**MDS-UPDRS Rigidity subscore**			**MDS-UPDRS Tremor subscore**			**MDS-UPDRS PIGD subscore**			**LEDD**		
	Pref	Fast	Dual	Pref	Fast	Dual	Pref	Fast	Dual	Pref	Fast	Dual	Pref	Fast	Dual	Pref	Fast	Dual
n	41	41	34	41	41	34	41	41	34	41	41	34	41	41	34	43	43	36
Main amplitude	0.13	-0.16	-0.05	-0.05	0.04	-0.02	-0.07	-0.10	-0.10	0.18	-0.08	-0.19	-0.28	-0.23	-0.19	**0.42**	0.08	0.19
Peak angular velocity	0.10	-0.17	-0.05	-0.08	0.05	-0.00	-0.08	-0.14	-0.12	0.18	-0.10	-0.20	-0.29	-0.24	-0.18	**0.43**	0.15	0.16
Asymmetry	0.17	-0.02	0.29	0.22	0.08	0.28	-0.01	-0.03	-0.03	0.06	0.16	0.18	0.14	-0.01	0.26	-0.04	**-0.49**	-0.18
Coordination	0.05	0.02	-0.26	0.05	0.13	-0.27	-0.17	-0.02	-0.11	0.07	-0.03	-0.09	-0.17	-0.03	**-0.39**	**0.38**	-0.11	0.18
Regularity	-0.06	-0.18	-0.22	-0.18	-0.04	-0.26	-0.08	-0.24	-0.13	0.12	-0.01	-0.09	-0.21	-0.04	-0.06	0.13	0.11	-0.03
Sideways amplitude	0.19	0.04	-0.02	0.10	-0.10	-0.03	**0.36**	0.02	0.22	-0.08	-0.02	0.11	0.15	0.08	0.09	-0.29	0.17	-0.09

Significant correlations in bold ($P < 0.05$). Dual = dual-task walking; LEDD = Levodopa equivalent daily dose; MDS-UPDRS = Movement Disorders Society-sponsored revision of the unified Parkinson's disease rating scale; PIGD = postural instability and gait disorder; Pref = preferred speed.

Discussion

This study shows, to our knowledge for the first time, that the effect of dopaminergic medication on arm swing is substantially influenced by the context in which patients with Parkinson's disease walk. Arm swing during walking improved with dopaminergic medication at preferred walking speed, and it improved even more during fast walking at least for some parameters (main amplitude, peak angular velocity, coordination and sideways amplitude). However, the responsiveness of dopaminergic medication on arm swing changed drastically by adding a cognitive dual-task to walking compared to preferred and fast walking only, respectively. In the dual-task walking condition, the responsiveness to dopaminergic medication was low for most arm swing parameters, and sideways amplitude got even worse. Only amplitude asymmetry improved, because the amplitude of the more affected arm increased, while the amplitude of the less affected arm decreased, reducing the difference between both arms (Supplementary Figure 5.3). A different response to medication in the more and the less affected side was only seen for amplitude and peak angular velocity during the dual-task condition. We suggest that the talking out loud provides rhythmical stimulation that could have a positive effect on the coordination between both arms causing a more symmetrical arm swing pattern. The correlations between the change in arm swing parameters with dopaminergic medication and the LEDD support that the responsiveness to dopaminergic medication is influenced by the context. At preferred walking speed, three arm swing parameters correlated with LEDD values, at fast speed only one and none during dual-tasking.

The changes in main arm swing amplitude, peak angular velocity and coordination with medication at preferred speed corresponds with other studies investigating gait aspects in Parkinson's disease [39, 173, 203]. In previous studies, looking at gait parameters, it has been seen that mainly the amplitude- and velocity-based measures (step length, gait velocity, step velocity) improved with medication at preferred speed, which is comparable to our results [39, 44, 77, 92, 192]. The reduction in arm swing asymmetry found in this study corresponded with one study [173], but not with another which was probably due to the inclusion of patients with dyskinesia in that study [39]. Other studies also found effects of medication on gait parameters during more challenging (fast) walking conditions [47, 192]. Concerning more complex walking paradigms contradicting results were found [197, 198]. One study even found a larger reduction in stride time variability with medication during dual-tasking compared to single-tasking [198]. Since gait speed significantly changed between medication states and single- and dual-tasking, these effects could very well be mediated by gait speed. This issue holds also true for studies investigating arm swing. To our knowledge, none of the currently available arm swing studies controlled their results for gait speed, although it is known that arm swing is influenced by this parameter [27, 204, 205] and dopaminergic medication increases gait speed [46, 77, 91, 192]. In this study, many significant Spearman's correlations of arm swing parameters with gait speed were found, with values reaching up to 0.47 (asymmetry, fast speed) for patients with Parkinson's disease in OFF medication state, up to 0.53 (main amplitude, dual-tasking) for patients with Parkinson's disease in ON medication state and up to 0.61 (peak angular velocity, dual-tasking) for the controls. We therefore recommend to perform this gait speed correction in future studies, otherwise, there may be a risk that gait speed-associated (and not

disease state-associated) aspects are measured.

The arm swing parameters from the patients with Parkinson's disease were compared to matched controls to analyse the differences between the groups after controlling for gait speed. Moreover, to analyse whether with medication the arm swing parameters would be comparable to controls (Figure 5.1). The overall very distinct patterns of arm swing differences between patients with Parkinson's disease during OFF as well as during ON phases, compared to control values, suggest that 1) dopaminergic depletion does not "generate" a uniform movement pattern in arm swing, but this is substantially influenced by the context; 2) the compensation of this dopaminergic depletion is not equivalent to "control-like". This is especially evident during fast speed, where most of the collected arm swing parameters were even significantly "better" than those of controls; and 3) the dual-task walking condition shows relatively little differences between people with and without Parkinson's disease (only 3 out of 18 calculations were significant), suggesting that arm swing as performed in daily life may not be relevantly affected by both, dopamine depletion and dopamine replacement therapy. This is in agreement with another study that found that arm swing measured during daily living is not a very good parameter to discriminate between patients with Parkinson's disease and controls [206]. That the performance of patients with Parkinson's disease in ON medication state is in some parameters significantly better than in controls is surprising and we can only speculate about the reasons for this phenomenon. One explanation could be that patients with Parkinson‘s disease use their arm swing energy to move the body forward as soon as medication allows this (and based on the assumption that upper extremities benefit potentially more from dopaminergic medication than the lower extremities). Such a behaviour can be clinically observed in –at least some- patients with normal pressure hydrocephalus. Another reason could have to do with that sensory attenuation is affected in Parkinson's disease, and obviously influenced by dopaminergic treatment [207]. Sensory attenuation describes the phenomenon whereby sensory input elicited by self-generated actions is reduced compared to sensory input generated externally. According to recent literature [207], it could be that dopamine replacement therapy leads to increased sensory attenuation. Therefore, it is possible that this increased sensory attenuation in patients with Parkinson's disease, induced by dopaminergic medication, lead to a reduced awareness (and thus, control) of arm swing.

The cognitive performance increased with dopaminergic medication in the single-task condition, but not in the dual-task condition (Figure 5.2). This effect was accompanied by significantly more pronounced subtraction task dual-task costs in the medication OFF state compared to the ON state. We interpret these results according to already existing literature [208, 209] in that way that, when patients with Parkinson‘s disease perform a dual-task in OFF state, they prioritise the cognitive task. This prioritization of the cognitive task could have detrimental effects on the walking performance.

In the dual-task condition, the cognitive performance as well as most arm swing parameters did not improve with dopaminergic medication. A possible explanation for this could be the "levodopa overdose hypothesis" [210]. Dopaminergic medication does not target one specific brain area [198]. For example, it affects the mesocorticolimbic pathway which has a negative effect on cognitive function, including executive function that is required to control gait in patients with Parkinson's disease [198, 211, 212]. This could be a cause for the absent improvement in cognitive performance and most arm swing parameters.

Although clinical assessments are in many aspects different from daily living assessments [176], studies have shown that more complex clinical assessments correspond relatively well with the average values of daily living assessments [89, 90]. Our study shows that the effect of dopaminergic medication on arm swing is rather small or even negative during dual-tasking. This implies that dopaminergic medication might, for this specific and potentially very relevant movement [166], not be very beneficial in real life situations. For handwriting it also has been shown that dopaminergic medication had no effect on the more complex writing tasks, compared to writing down letters or one word repeatedly in patients with Parkinson's disease [213]. We can thus confirm these findings with another upper limb movement (arm swing), and contribute evidence that the effect of dopaminergic medication should not only be tested under standardised conditions, but absolutely must also be tested under daily-relevant situations. It seems possible that these medication effects differ substantially between supervised and daily-life (-relevant) conditions, and to a significant disadvantage for affected patients. The even negative effect of dopaminergic medication on sideways amplitude during dual-tasking could indicate a decrease in dynamic postural stability with dopaminergic medication, which must certainly be investigated in more detail in future studies. Nevertheless, it is possible that the difference in dopaminergic responsiveness due to different walking conditions affects not only the upper but also the lower extremities. During simple static postural stability tasks a positive effect of dopaminergic medication was found [39, 48], when more complex (eyes closed and dual-task conditions) static postural stability tasks were performed there was no effect of dopaminergic medication found [214]. During dynamic postural stability tasks there were also no effects of dopaminergic medication found and in the PIGD subgroup the postural stability even frequently deteriorated with medication [49, 190]. Therefore it seems that dopaminergic medication does not improve the postural stability during complex tasks. Interestingly, this phenomenon could also be seen in other neurotransmitter systems. During preferred speed and simple dual-task walking conditions, patients with Parkinson's disease, treated with the cholinesterase inhibitor rivastigmine, had a significantly better (reduced) step time variability compared to the placebo-treated group in a simple walking paradigm, but there were no significant differences found between the two groups during a complex dual-task walking condition [215].

None of the ON-OFF changes of arm swing parameters correlated significantly with respective changes of the total MDS-UPDRS III score. This observation strongly argues that arm swing is a movement that is largely independent of "classic" Parkinson's disease symptoms. This is all the more remarkable as there was no effect observed in any of the three different walking conditions. If this observation can also be confirmed in independent studies and cohorts, and this effect is potentially also shown in free living environments, arm swing parameters in Parkinson's disease could be used as an easily and frequently detectable complementary sign for disease progression and treatment response in clinical routine and clinical trials. Moreover, there was a positive correlation between the rigidity subscore and sideways amplitude in the preferred walking speed condition (and somewhat less pronounced and not significant in the dual-task walking condition). Rigidity causes the absence or reduction of trunk rotations. Rotations of the thorax are known to contribute to arm swing [216], therefore with decreased trunk rotations a smaller arm swing amplitude, in both main and sideways direction, was expected. This was however not the case for the sideways amplitude. It seems plausible that, due to rigidity, the trunk can contribute less to balance recovery during walking in PD.

Consequently, sideways arm swing could serve as a compensatory movement to recover from balance perturbations. To determine whether the sideways amplitude is a parameter for (limitations of) dynamic balance, further research is required. The other significant (negative) correlation observed was between PIGD items and arm swing coordination during dual-task walking. The postural instability and gait problems could cause a more unstable gait pattern and the arms might be used to compensate for any balance disturbances. Compensatory movements of the arms might negatively influence the timing between the left and right arm. The postural instability can especially be prominent during dual-tasking where patients prioritize the cognitive performance causing a decrease in postural stability according to the "posture second" strategy [208]. This significant negative correlation could speak for the usefulness of this parameter for determining the severity of (and therapy response to) PIGD symptoms, e.g. under everyday conditions [89].

This study faces limitations. First, participants performed both OFF and ON assessments on the same day and always OFF before ON, therefore fatigue is a possible confounder in this study. However, all study participants were allowed to take breaks at any time during the individual task performance. Second, only patients with mild to moderate disease severity were included, which means that the results cannot be extrapolated to more advanced disease stages.

Taken together, this study shows that the responsiveness of dopaminergic medication on arm swing in people with Parkinson's disease depends on context and task complexity. These results should motivate more granular and extensive research in the area of task complexity-influenced responsiveness of mobility aspects to dopaminergic medication in Parkinson's disease.

Methods

Participants

Forty-five patients with a diagnosis of Parkinson's disease according to the UK Brain Bank Society Criteria [177] and a Hoehn & Yahr stage between 1 and 3 (reflecting mild to moderate disease severity) were recruited at the University Hospital of Tübingen, Germany. Patients with an impaired range of motion of the shoulder due to trauma were excluded as well as patients with dyskinesia, because dyskinesia most probably has a significant and "uncontrollable" influence on gait parameters [39]. The participants were, as far as possible, age- and gender-matched to an already existing control cohort with the identical experimental setting (longitudinal observational Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND) study, 4th visit). Inclusion and exclusion criteria of the TREND study were reported elsewhere [15]. In brief, it included older adults recruited from the population concerning risk factors of age-associated neurological diseases. Exclusion criteria were, among others, signs of neurodegenerative diseases, stroke, inflammatory central nervous disease, intake of dopaminergic and antipsychotic drugs.

The ethical committee of the Medical Faculty of the University of Tübingen approved this study (715/2011B02) and also the TREND study (190/2009BO2). All participants gave a written informed consent prior to testing according to the declaration of Helsinki.

Data collection

In both studies, identical walking tasks were assessed. Participants walked a 20 m walkway up and down for 1 minute, under three conditions: (i) preferred speed ("Walk at your preferred walking speed"), (ii) fast speed ("Please walk as fast as you can, do not run, do not risk falling"), and (iii) fast speed in combination with a serial subtraction task started from a three digit number ("Please walk as fast as you can, do not run, do not risk falling, and subtract serial sevens as fast as you can from the number I will shortly tell you"). This serial subtraction task was also separately performed as single-task. Parkinson's disease participants performed the assessments first OFF medication (overnight withdrawal from dopaminergic medication) and 30 minutes to 2 hours after medication intake (based on the participant's feedback when they usually experience best ON) in ON medication condition. In both medication states the motor part of the MDS-UPDRS, part III, was assessed. The MDS-UPDRS part II was also assessed, but only assessed once. The dopaminergic medication the patients took was collected from the medical file to calculate the LEDD [217]. During the assessments, all participants wore an inertial measurement unit with tri-axial accelerometers, gyroscopes and a magnetometer (128 Hz sample frequency; Opal APDM, Portland, USA) on each wrist and one on the lower back.

Data processing

All completed straight walking phases of the 1 minute walk were extracted (turns were discarded from the data with help of a turn detection algorithm validated for patients with Parkinson's disease and healthy older adults [119]). The gait speed was calculated by dividing the 20 m walked distance by the time it took to walk those 20 m (based on the turn detection described above). The arm swing parameters from the straight walking phases were extracted with an arm swing algorithm validated for patients with Parkinson's disease and healthy adults [201]. Arm swing was defined as "a rotational movement of the arm, occurring during walking and running in bipeds with a periodicity of around 1-2 Hz. The hand and arm move freely through space in opposite directions with most of the movement in the sagittal plane of the body frame" [201]. To omit false positives, only arm swings with an amplitude of at least 5° were taken into account [201]. The first three and last three swings of the straight walking phases were excluded from the analysis so that only steady state walking phases were considered.

The arm swing algorithm extracts information from both arms, which results in the following parameters (Table 5.3): main amplitude (amplitude in main swing direction), peak angular velocity, regularity, coordination and asymmetry [201]. We also included in this analysis sideways amplitude, reflecting the amplitude of the movement during the swing in the direction orthogonal to the main swing direction (movements around the longitudinal axis are not taken into account). Sideways arm swing could be a compensatory movement to get the center of mass back above the base of support. This movement therefore may reflect, as a measure of dynamic postural stability, correction or adaptation movements during walking [218]. The parameter was calculated from the second component of the principal component analysis [201]. The dual-task costs for the cognitive serial subtraction task were calculated for both medication states [209].

Table 5.3: Description of the arm swing parameters. Exact calculations of the parameters can be found in [201].

Parameter	Description
Main amplitude [°]	The average magnitude of a swing in the main swing direction
Peak angular velocity [°/s]	The average maximal angular velocity of a swing
Asymmetry [%]	The non-directional difference in main amplitude between both arms (0% left and right arm swing on average with a similar main amplitude; 100% left and right arm swing on average with an entirely different main amplitude)
Coordination (0-1)	A measure for the timing between the left and right arm (1 if both arms move exactly out of phase, e.g. left arm at most forward point and right arm at most backward point; 0 if both arms do not move in a similar rhythm), the calculation is based on a cross-correlation
Regularity angular velocity (0-1)	The similarity of a swing with its neighbouring ipsilateral swings (1 similar; 0 not similar), the calculation is based on an auto-correlation
Sideways amplitude [% of main amplitude]	The average proportion of movement that occurs orthogonal to the main swing direction

Statistical analysis

Since arm swing is affected by gait speed [27, 204, 205], the parameters were corrected for this parameter using a linear regression between gait speed and each arm swing parameter per condition and per (medication) group. All parameters were corrected to their estimated value at 1 m/s. Wilcoxon signed rank tests were used to analyse the effects of dopaminergic medication on the arm swing parameters as well as the differences between Parkinson's values and control values. Tests were two-tailed with a significance level of 0.05.

To analyse the effect of medication on the cognitive performance during single-tasking and dual-tasking Wilcoxon signed rank tests were performed. As well as for the effect of medication on the dual-task costs.

The standardized response mean (SRM) was calculated by dividing the average of the change ($\bar{x}_{change}$) by the standard deviation of the change in a certain parameter:

$$\bar{x}_{change} = \frac{1}{N}\sum_{i=1}^{N}(x_{i,on} - x_{i,off}) \tag{5.1}$$

$$SRM = \frac{\bar{x}_{change}}{\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}|(x_{i,on} - x_{i,off}) - \bar{x}_{change}|^2}} \tag{5.2}$$

N represents the amount of participants and x_i the arm swing parameter of each participant in ON or OFF state, with $0.20 \leq SRM < 0.50$ representing a small, $0.50 \leq SRM < 0.80$ a moderate and SRM ≥ 0.80 a large responsiveness to dopaminergic medication [39].

The significances of dopaminergic medication effects between the three walking conditions were analysed with a repeated measures ANOVA. A Greenhouse-Geisser correction was performed when the assumption of sphericity was violated. $P <$

0.05 was considered significant. Post hoc testing was performed with Bonferroni corrections to control for type 1 errors.

Spearman correlations were performed to test associations between ON-OFF effects of arm swing parameters and clinical scores (total MDS-UPDRS III, and MDS-UPDRS subscores: bradykinesia (items 3.4, 3.5, 3.6, 3.8 [219]), rigidity (item 3.3), tremor (items 2.10, 3.15, 3.16, 3.17, 3.18 [220]) and PIGD (items 2.12, 2.13, 3.10, 3.11, 3.12 [221]), and LEDD. Significance of these exploratory analyses was considered when $P < 0.05$.

Data availability

The data from this study are available upon reasonable request. The TREND study (`https://www.trend-studie.de/`) is registered in the German Clinical Trials Register with number DRKS00022058. The algorithm to extract the arm swing parameters is freely available online (`https://github.com/EWarmerdam/ArmSwingAlgorithm` [201]).

Supplementary material

Table 5.4: Results from the Wilcoxon signed rank test to analyse the effect of dopaminergic medication on arm swing as well as the difference with controls.

	Preferred						**Fast**						**Dual-task**					
	OFF-ON		OFF-Controls		ON-Controls		OFF-ON		OFF-Controls		ON-Controls		OFF-ON		OFF-Controls		ON-Controls	
n	43		43		43		43		43		43		36		36		36	
	Z	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*
Main amplitude	-2.44	**0.015**	-0.83	0.405	1.04	0.299	-5.69	**<0.001**	-2.96	**0.003**	2.86	**0.004**	0.56	0.649	-1.38	0.167	-1.57	0.116
Peak angular velocity	-2.15	**0.032**	-0.95	0.340	0.74	0.461	-5.71	**<0.001**	-2.64	**0.008**	2.06	**0.039**	0.14	0.888	-1.07	0.285	-1.13	0.258
Asymmetry	3.72	**<0.001**	2.61	**0.009**	0.39	0.697	-2.78	**0.005**	-4.26	**<0.001**	-3.12	**0.002**	2.24	**0.025**	2.78	**0.005**	0.20	0.845
Coordination	-1.41	0.158	0.31	0.313	0.52	0.600	-5.45	**<0.001**	-2.00	**0.045**	3.87	**<0.001**	-1.01	0.313	-2.65	**0.008**	-2.72	**0.007**
Regularity	-3.47	**<0.001**	-4.41	**<0.001**	-3.67	**<0.001**	-0.06	0.952	-3.85	**<0.001**	-3.44	**<0.001**	1.87	0.062	0.83	0.405	-0.22	0.826
Sideways amplitude	2.50	**0.012**	0.81	0.419	-0.60	0.546	5.49	**<0.001**	5.52	**<0.001**	-2.54	**0.011**	-2.86	**0.004**	-1.38	0.167	0.97	0.330

Table 5.5: The results of the repeated measures ANOVA that compared the dopaminergic medication responsiveness per walking condition.

	Repeated Measures ANOVA			**Post hoc testing**					
				pref-fast		pref- dual		fast-dual	
	df	*F*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Main amplitude	2	42.72	**<0.001**	-6.36	**<0.001**	2.63	**0.032**	8.99	**<0.001**
Peak angular velocity	2	24.51	**<0.001**	-4.74	**<0.001**	2.09	0.120	6.83	**<0.001**
Asymmetry	1.62	12.78	**<0.001**	-3.52	**0.003**	1.38	0.521	4.90	**<0.001**
Coordination	1.58	11.61	**<0.001**	-4.06	**<0.001**	0.21	1.000	4.27	**<0.001**
Regularity	1.64	4.23	**0.026**	1.85	0.206	2.87	**0.017**	1.02	0.937
Sideways amplitude	1.55	33.99	**<0.001**	3.73	**0.001**	-4.50	**<0.001**	-8.23	**<0.001**

In bold the significant results. Post hoc testing was performed with Bonferroni correction. df = degrees of freedom; pref = preferred.

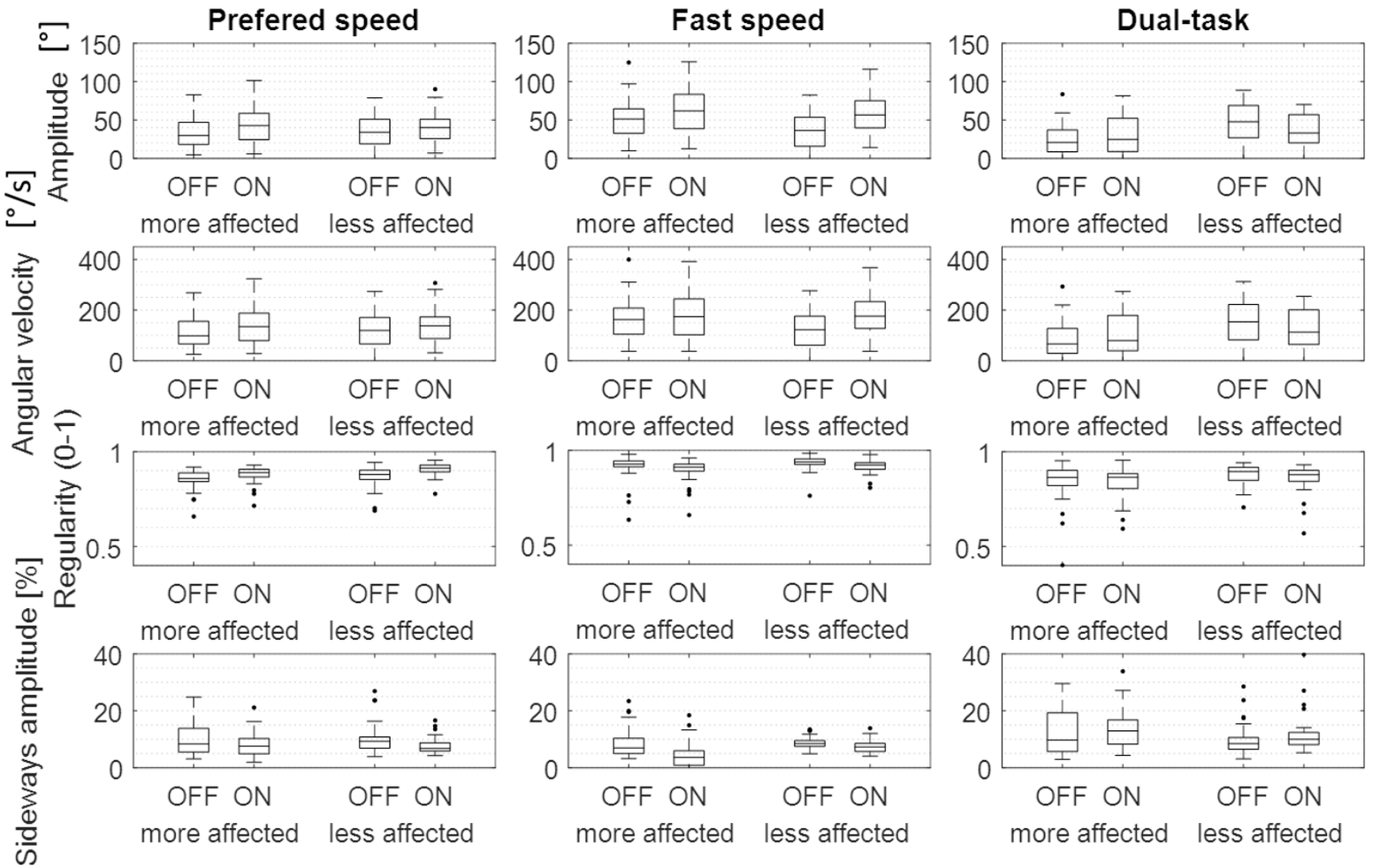

Figure 5.3: The arm swing parameters for the more and less affected side during the different medication states and different walking conditions.

Chapter 6

Mobility assessments with simultaneous full-body inertial measurement units and optical motion capture in healthy adults and neurological patients for future validation studies: Study protocol

Elke Warmerdam, Robbin Romijnders, Johanna Geritz, Morad Elshehabi, Corina Maetzler, Jan Carl Otto, Maren Reimer, Klarissa Stuerner, Ralf Baron, Steffen Paschen, Thorben Beyer, Denise Dopcke, Tobias Eiken, Hendrik Ortmann, Falko Peters, Felix von der Recke, Moritz Riesen, Gothia Rohwedder, Anna Schaade, Maike Schumacher, Anton Sondermann, Walter Maetzler, Clint Hansen

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Abstract

Healthy adults and neurological patients show unique mobility patterns over the course of their life span and disease. Quantifying these mobility patterns could support diagnosing, tracking disease progression and measuring the response to treatment. This quantification can be done with wearable technology, such as inertial measurement units (IMUs). Before the IMUs can be used to quantify mobility, algorithms need to be developed and validated. As mobility patterns differ across lifespan and between different neurological diseases, this validation must be performed in different age groups and with disease-specific datasets. We hereby present a study protocol for a full-body mobility dataset of healthy young and older participants and neurological patients. All participants will be measured simultaneously with IMUs and a 3D optical motion capture system. This study will provide a dataset that can be used to develop and validate IMU-based mobility algorithms for healthy adults and neurological patients.

This study will include healthy adults (18-60 years), healthy older adults (>60 years), and patients with Parkinson's disease (PD), multiple sclerosis (MS), with a recent symptomatic stroke and with chronic low back pain (CLBP). Specific clinical scales and questionnaires will be collected. All participants will perform standardized mobility tasks as well as non-standardized activities of daily living. During these assessments they will wear 15 IMUs and 47 reflective markers that will be captured by the optical motion capture system.

This study aims at building the largest dataset for the development and validation of IMU-based mobility algorithms for people with and without neurological diseases. It is anticipated to provide this dataset for further research use and collaboration, with the ultimate goal to use such resources effectively and to bring IMU-based mobility algorithms as quickly as possible into clinical routine and into assessment panels of clinical trials.

Keywords: Balance, Chronic low back pain, Gait, Movement analysis, Multiple sclerosis, Parkinson's disease, Stroke, Wearable sensors

Background

Healthy adults, as well as patients with neurological diseases, such as Parkinson's disease (PD), stroke and multiple sclerosis (MS) show unique mobility patterns over the course of their life span and disease. These unique mobility patterns can be used for diagnosis [17, 222], tracking disease progression [106], measuring efficacy of treatment [39] and detecting side effects of chronic medication intake [121]. In clinical routine, mobility patterns are generally evaluated by healthcare professionals during a clinical or in-praxis examination. Objective evaluation methods can provide additional and potentially more ecologically valid measures. Wearable technology, more specifically inertial measurement units (IMUs) are highly suited for objective movement analysis and can even be used to analyse mobility patterns outside the clinic and praxis, i.e. the usual environment [3, 176].

Currently, results of such mobility analyses differ substantially between different IMU devices [223, 224]. This is most likely due to multiple reasons, including lack of standardization of IMU position on the body and lack of (disease-) specific and thorough validation of the algorithms used to extract and analyse raw data. Thus, before these IMUs are used in the natural environment of the healthy adults and patients, clear information about the best position of the IMUs to calculate mobility-related parameters should be gathered and a thorough and specific validation of the used algorithms must be performed [176, 225, 226].

The accuracy of algorithms for the analysis of IMU-derived data is dependent on laborious validation studies, which cannot be performed in every laboratory and specifically for every single research question. In such validation studies, these IMU-derived algorithms need to be compared to data extracted from reference tools for the assessment of mobility, such as 3D optical motion capture systems. As mobility patterns differ across lifespan and between different neurological diseases, this validation must be performed in different age groups and in disease-specific datasets. To our best knowledge, there is currently no representative dataset available that allows for such validation by providing multiple IMU positions in a variety of neurological diseases. We present here a study protocol for a full-body mobility dataset of healthy young and older participants and neurological patients, including PD, MS, stroke and chronic low back pain (CLBP). All participants will be measured simultaneously with 15 IMUs and 47 reflective markers that are tracked with a 3D optical motion capture system. The assessment will include standardized mobility tasks as well as non-standardized activities of daily living. Specific clinical scales will be provided as anchors. The aim of the study is to provide a dataset to the research community that can be used to develop and validate IMU-based mobility algorithms for healthy adults and neurological patients.

Methods and design

Ethics

This study was approved by the ethical committee of the Medical Faculty of Kiel University (D438/18) and is in accordance with the principles of the Declaration of Helsinki. All participants will receive written and oral information about the measurements. The participants have to provide written informed consent before the start of the measurements. The study is registered in the German Clinical Trials Register (DRKS00022998).

Participants

This study will include healthy adults (18-60 years), healthy older adults (>60 years), and patients with PD (according to the UK Brain Bank Criteria [177]), MS (according to the McDonalds criteria [58]), patients with a recent (<4 weeks) symptomatic stroke and patients with CLBP, whose patients characteristics are described elsewhere [227]. Healthy adults will be recruited via flyers that will be placed in public facilities. Neurological patients will be recruited from the neurology wards and outpatient clinics of the University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Germany. Inclusion criteria are 18 years and older, and the ability to walk independently without walking aid. Exclusion criteria are a Montreal Cognitive Assessment score <15 and other movement disorders that affect mobility performance, as judged by the assessor.

Clinical and demographic data

Demographic data, including age, gender, weight, height, foot size, handedness, will be recorded. Furthermore, comorbidities of all participants will be assessed with the *Charlson Comorbidity Index* [228]. The cognitive function will be assessed with the *Montreal Cognitive Assessment* [229]. Generic health status will be assessed with the *EQ-5D-5L* [230]. Activities of daily-living will be assessed with the *Lawton Instrumental Activities of Daily Living Scale* [231] and the German *Funktionsfragenbogen Hannover* [232]. Sarcopenia will be assessed with the *SARC-F* [233]. Pain will be assessed with the *Visual Analogue Scale* [234]. Vibratory sensation will be assessed with a tuning fork (Rydel-Seiffer) [235]. Fatigue will be assessed with the *Fatigue Severity Scale* [236]. The perceived self-efficacy will be assessed with the *General Self-Efficacy Scale* [237]. The motor function of all participants will be assessed with the motor part of the *Movement Disorders Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale* (MDS-UPDRS) [106].

Disease specific scales

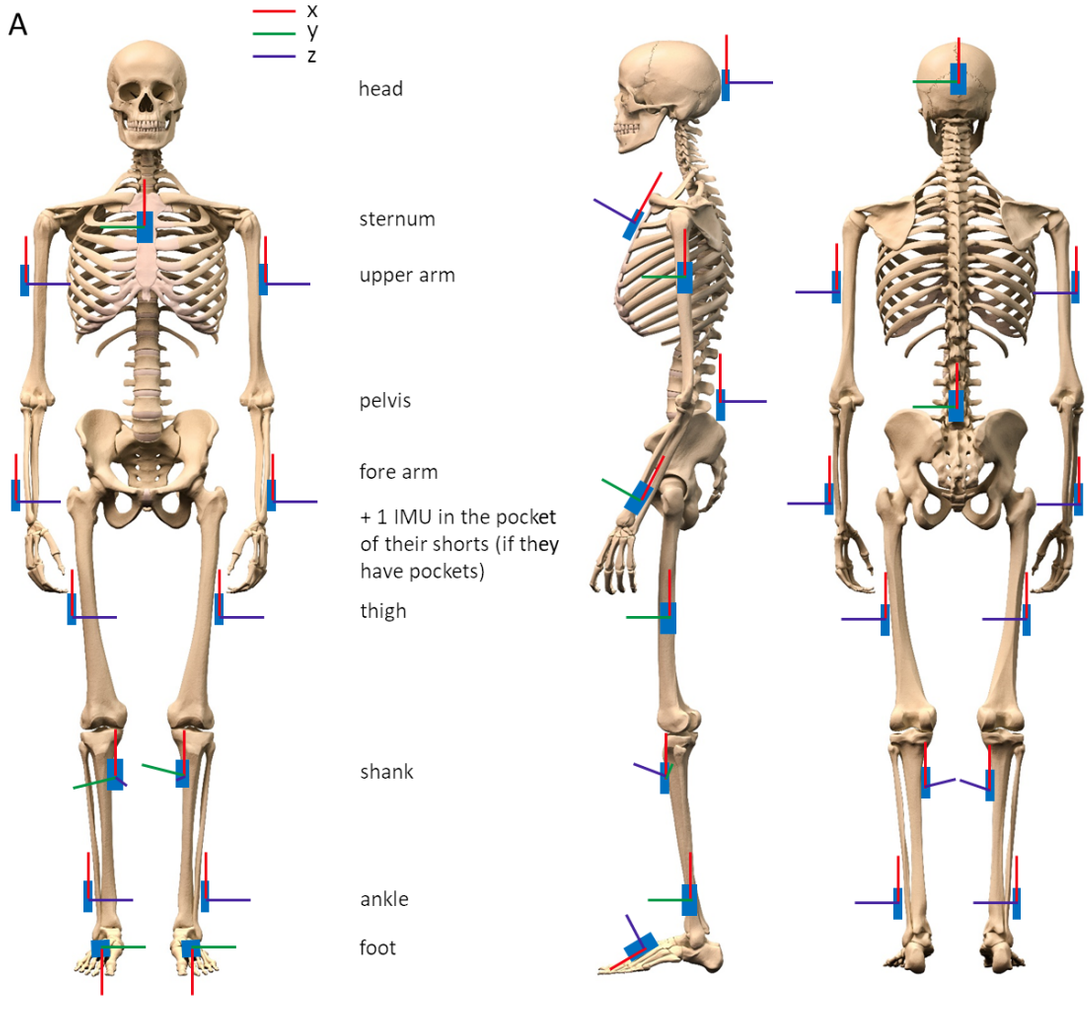
From all the patient with a neurological disorder, the diagnosis, disease duration as well as the medication (type, dose and frequency) that the patients take will be collected from the medical record. Additionally, for the PD patients the Hoehn & Yahr stage [238], for the MS patients the *Expanded Disability Status Scale* [107] and for the stroke patients the *NIH Stroke Scale* will be assessed [239].

Equipment

Participants will be measured with IMUs (Noraxon USA Inc., myoMOTION, Scottsdale, AZ, USA), containing a triaxial accelerometer (+/- 16 g), triaxial gyroscope (+/- 2000 degrees/sec) and triaxial magnetometer (+/- 1.9 Gauss). A total of 15 IMUs will be attached to different body segments (Figure 6.1A). IMUs are therefore fixed to the following body segments: head, sternum, upper arms, fore arms, pelvis, thighs, shanks (proximal), ankles and feet. The IMUs will be secured with elastic bands with a special hold for the IMU attached to it. In case the participant has pockets in the shorts, a 16^{th} IMU will be placed in the pocket. The data will be collected with a sample frequency of 200 Hz.

As reference, a twelve-camera optical motion capture system (Qualisys AB, Göteborg, Sweden) will be used to record full-body movements with 200 Hz. A total of

47 reflective markers (19 mm) will be adhered to the body (Figure 6.1B) for all movement assessments. A minimum of three markers can be found on the following body segments: head, sternum, upper arms, fore arms, hands, lower back, thighs, shanks and feet. During static calibration trials, 8 additional reflective markers (19 mm) will be placed on the body (elbows, knees and ankles) to be able to estimate joint positions (the exact positions of all the reflective markers are described in Supplementary Table 6.1). The IMU data and the optical data will be synchronized with help of a TTL signal.



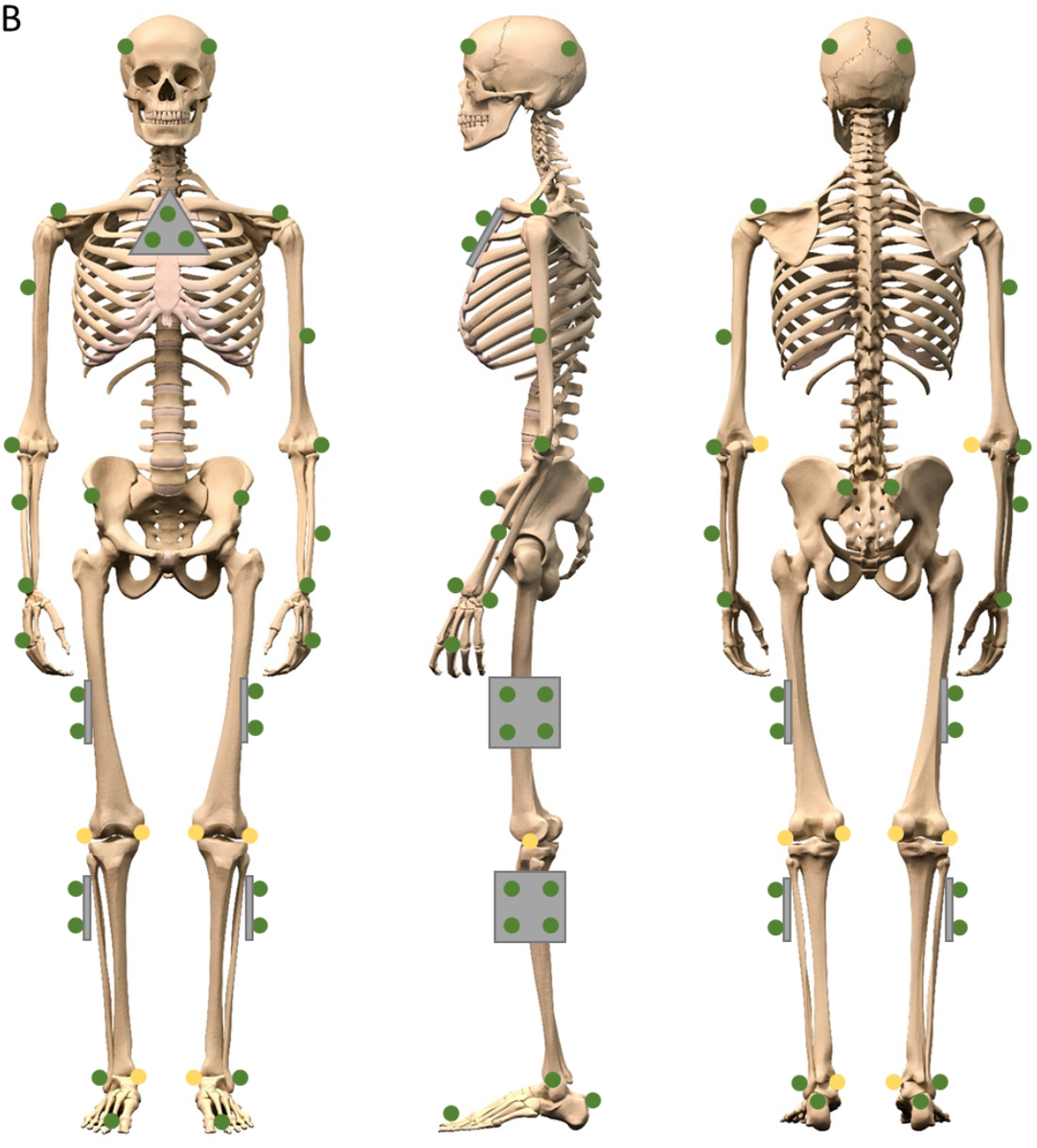


Figure 6.1: A. Placement of inertial measurement units (IMUs) including the orientation. B. Placement of the reflective markers measured by the optical motion capture system.

Two reflex light barriers (Telemecanique, photo-electronic sensor XULM06031, Rueil-Malmaison, France) standing 5 m apart will be used to measure the preferred over ground gait speed.

The over ground walking will be performed on a walkway with a width of 1 m. The start and end of the 5 m during which steady state gait is recorded will be marked by cones with reflective markers (30 mm) on top of them. For the assessment of longer gait bouts a treadmill (Woodway, Waukesha, WI, USA) of 2.10 by 0.70 m with a split belt option will be used. Dual-task assessments during over ground walking will be performed on a smartphone with a screen size of 4.5 inch (Alcatel One Touch Pop 2). A simple reaction time test and a numerical Stroop test will be used as dual-task (developed with `https://www.neurobs.com/menu_presentation/menu_features/mobile`).

The whole assessment of each participant will be videotaped by two cameras (GoPro Inc., Hero Session, San Mateo, CA, USA). The videos will be synchronized with the IMUs and optical data with help of a synchronization light that turned on and off at the start and end of each measurement.

Protocol

Patients with PD will be asked to perform the whole protocol part twice, both on and off dopaminergic medication. An overview of the protocol is given in Figure 6.2.

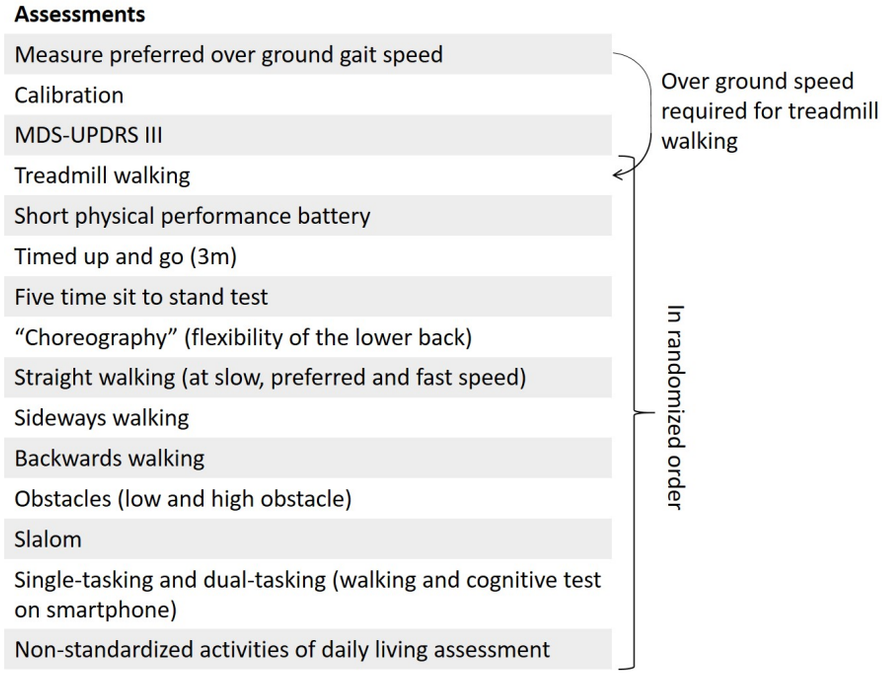


Figure 6.2: Overview of the protocol. The first three assessments will be performed in this fixed order, the remaining assessments will be performed in randomized order. An explanation of each assessment is provided in the text.

At the start, the preferred over ground speed will be measured with reflex light barriers. Participants will start walking about 2 m before the first light barrier and will stop walking about 2 m after the second light barrier. The average gait speed of five trials will be calculated and used as walking speed on the treadmill.

All trials listed below will be recorded with IMUs and the optical motion capture system.

Each assessment starts with a calibration trial where participants stand in a neutral pose (feet at hip width and arms hanging along the body). This trial will be repeated every time an IMU or marker is displaced. Next the MDS-UPDRS part III will be assessed. These trials will always be performed in this fixed order at the beginning of the measurement. Hereafter, the standardized and non-standardized mobility assessments will be performed in randomized order.

Standardized mobility assessments

During the treadmill trial, participants will start standing on a treadmill, then the speed will be gradually increased to a speed that is comfortable for the participant.

The participant will walk for 60 s at this speed. Thereafter, the speed of the treadmill will be gradually adapted to the preferred over ground walking speed which is measured at the start of the protocol. The participant will walk again 60 s at this speed.

A subset of the healthy young adults will participate in a split-belt protocol which is described in the supplementary material.

- Short physical performance battery (SPPB)
  - Side-by-side stand ("Please stand with your feet together for 10 seconds, try not to move your feet")
  - Semi-tandem stand ("Please stand with the heel of one foot touching the big toe of the other foot for 10 seconds, you can put either foot in front, try not to move your feet")
  - Tandem stand ("Please stand with the heel of one foot in front while touching the toes of your other foot, you can put either foot in front, try not to move your feet")
  - 4 m gait ("Please stand with the toes of both feet on the starting line and walk over to the end of the walkway at your normal gait speed")
  - 4 m gait ("Please stand again with the toes of both feet on the starting line and walk over to the end of the walkway at your normal gait speed")
  - Repeated chair Stand ("Please stand up straight five times in a row as fast as possible without using your arms")
- 3 m Timed up and go ("Please stand up from the chair, walk at preferred speed towards the cone, turn around it in the direction of your preference, walk back and sit down")
- Five time sit to stand test ("Please stand up straight five times in a row at your preferred speed without using your arms if possible")
- "Choreography": a series of movements related to the flexibility of the lower back (see supplementary material). The choreography contains flexion, extension and rotational movements of the back, as well as a combination of those movements ("Please perform the movements that are shown one by one on the pictures")

The following standardized walking assessments will take place on the 5 m walkway (Figure 6.3). All participants will be asked to start two steps before the start of the walkway and stop walking two steps after the end of the walkway.

- Straight walking
  - Slow speed ("Please walk half of your normal walking speed"; Figure 6.3A)
  - Preferred speed ("Please walk at your normal walking speed")
  - Fast speed ("Please walk as fast as possible, without running or falling")
- Sideways walking ("Please walk sideways, do not cross your legs during this walk")
- Backwards walking ("Please walk backwards at a speed that is comfortable for you")

- Obstacles: an obstacle with a height of 10 cm, and one with a height of 20 cm will be placed at the three meter point with reflective markers on the top of each side (Figure 6.3B), and a forward walk will be performed once for each obstacle ("Please walk at your normal walking speed and step over the obstacle")
- Slalom: cones will be placed every meter in the middle of the walkway. Each cone will have a reflective marker on top ("Please walk at your normal speed around the cones, do not step over them"; Figure 6.3C)
- Single and dual-tasking. This paradigm will be performed with two tasks with different complexity on a smartphone. The first task will be a simple reaction time test where participants will have to tap on the screen as fast as possible after a black square appears on the screen. There are six time intervals ranging from 1000 to 2000 ms (increased in steps of 200 ms), which determines the time it will take for the black square to appear on the screen. Each time interval occurs four times and the order of the 24 options is randomized. The reaction time will be recorded. The second test will be a numerical Stroop test, during this test two numbers will appear on the screen and the participants have to tap on the number that is highest in value. Within this test there are three conditions; 1. Neutral, the font size of both numbers is equal, 2. Congruent, the number highest in value has a larger font size, 3. Incongruent, the number highest in value has a smaller font size (Figure 6.4). In total 24 responses will be required, eight of each condition. The order in which the 24 options occur in the test is randomized. The reaction time as well as the accuracy will be recorded.
  - Simple reaction time task on a smartphone while standing ("Please tap on the screen as fast as possible after a black square appears on the screen")
  - Numerical Stroop task on a smartphone while standing ("On the screen will appear each time two numbers, please tap on the largest number in value, not the largest number in size")
  - Walking up and down the 5 m walkway for 30 seconds, turning direction was not instructed ("Please walk up and down the walkway at your normal speed and stay within the area marked by the cones"; Figure 6.3D)
  - Walking up and down the 5 m walkway and performing the simple reaction time test on the smartphone ("Please perform the simple reaction time test again as instructed before and walk up and down the walkway at your normal speed at the same moment")
  - Walking up and down the 5 m walkway and performing the Numerical Stroop test on the smartphone ("Please perform the numerical Stroop test again as instructed before and walk up and down the walkway at your normal speed at the same moment")

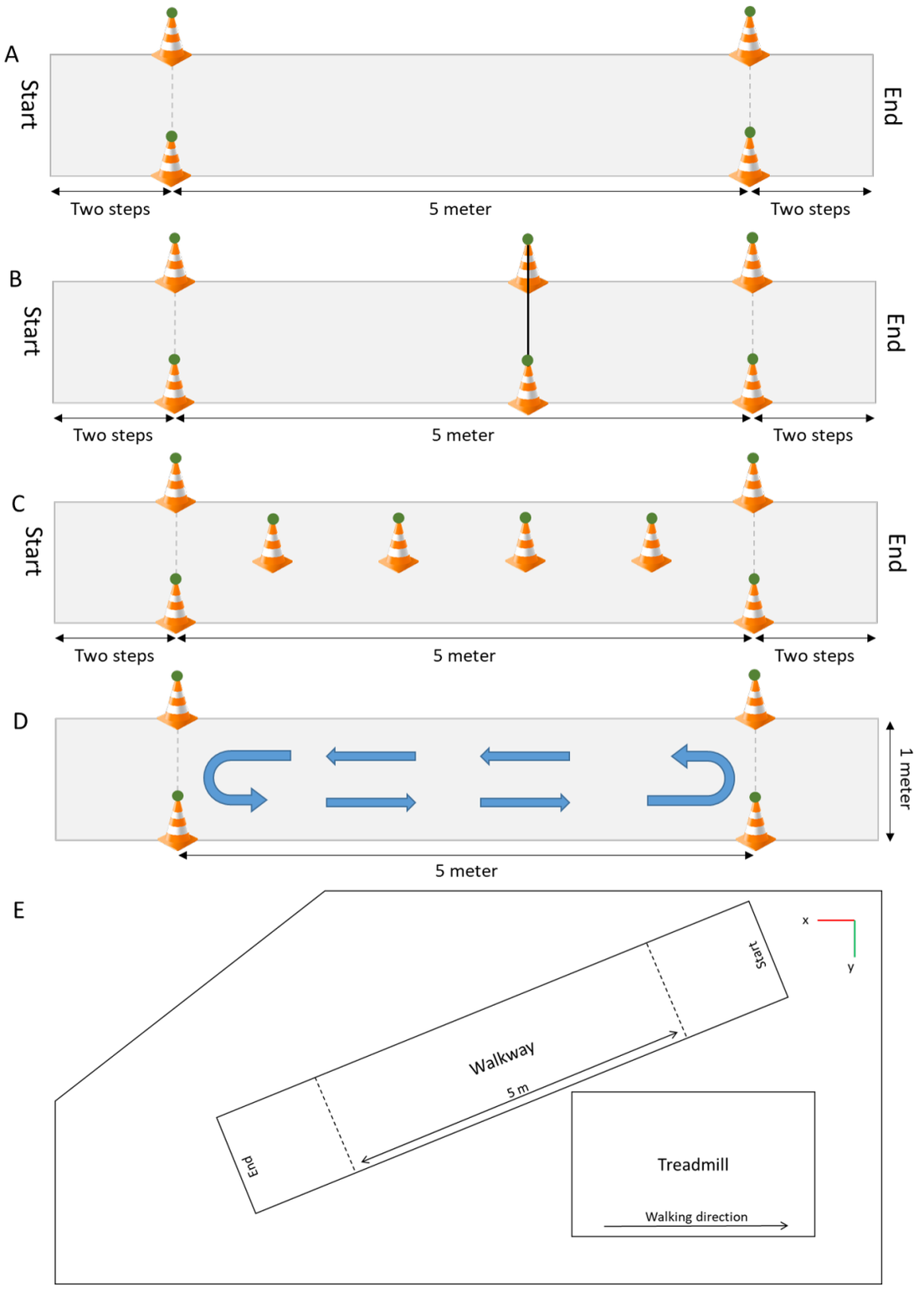


Figure 6.3: The walkway for the different over ground walking trials. A. The walkway without any extra attributes, B. The walkway with the obstacle, C. The walkway for the slalom assessment, D. The walkway for the dual-tasking assessments. The green circles represent the reflective markers captured with the optical motion capture system. E. Top view of the laboratory with the orientation of the optical motion capture system (right-handed coordinate system).

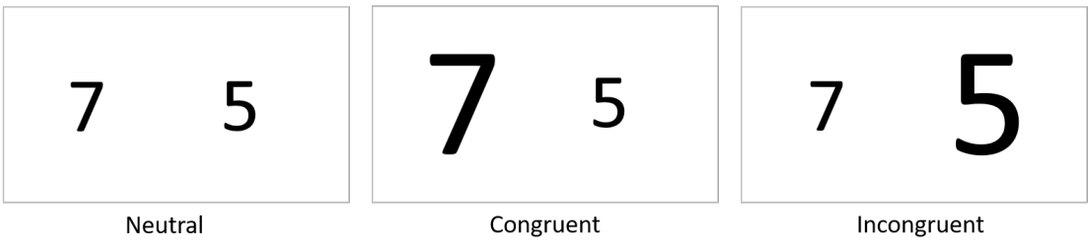


Figure 6.4: The three conditions of the numerical Stroop test that will be performed on smartphone.

Non-standardized activities of daily living assessment

The non-standardized mobility assessment consists of common daily activities that will be performed by the participants. The daily activities that will be performed are listed below. The order of the activities will not be fixed and will be decided by the researcher in the flow of this assessment.

- Setting a table (plates, cutlery, glasses)
- Eating and drinking (including opening a bottle and pouring a drink)
- Cleaning a table
- Lifting/replacing objects from different heights
- Ironing and folding a T-shirt
- Tooth brushing
- Multiple chair rises
- Sitting and reading out loud
- Sitting and talking
- Opening a cabinet and taking objects out of it

Discussion

This study will collect full-body mobility data from healthy young, older adults, and patients with PD, MS, stroke and CLBP. Each participant group will contain at least 20 participants with a maximum of 200 participants in total. All participants will be simultaneously measured with IMUs and optical motion capture. To our knowledge, this will be the first mobility dataset with full-body IMU and optical motion capture of healthy adults and multiple neurological patient groups of such size. The dataset can be used to develop and validate IMU-based algorithms for people with and without neurological diseases. With validated algorithms it will become possible to analyse mobility patterns both in the clinic and in the natural environment [176]. This objective information could help with diagnosing [17, 222], tracking disease progression [106] and measuring the response to treatment [39, 121].

Other studies with full-body IMU and optical motion capture included only young healthy participants [240–242]. Moreover, the participants performed a limited number of tasks that were not always mobility-related. Studies with full-body IMUs measuring either mobility-related tasks in older adults or symptoms in PD patients did not measure simultaneously with optical motion capture [147, 243, 244]. Other mobility related-studies that validated IMU-based algorithms against optical motion capture only measured the lower body simultaneously with both systems [245, 246]. The upper body can however also provide relevant information regarding mobility [39, 162].

The data that will be collected within this study will contain full-body IMU and optical motion capture data from a range of mobility-related tasks performed by both healthy participants and multiple neurological patient groups. Therefore, new and valuable information will be added to already existing datasets.

A large amount of standardized mobility assessments will be performed. There will be short (5 m) walking trials with different types of walking (straight, backwards, slalom, obstacle, sideways, dual-tasking). This will make it possible to test the accuracy of algorithms during straight walking and more complex walking assessments, which are likely to influence gait patterns [87, 247, 248]. To analyse the performance of algorithms during longer walks, there will be treadmill data collected. The split-belt treadmill walking data (speed reduction of 25% on one side [249]) can be used to analyse how well an algorithm deals with gait asymmetry. The SPPB, timed up and go and five chair rise test are well known assessment tools that are frequently performed in the clinic [250–252]. More information from these tests can be extracted by adding one or a few IMUs [253, 254]. The non-standardized assessment part with activities of daily living can be used to develop and validate algorithms for the analysis of the performance in the natural environment of the patients. The different movements performed throughout all the assessments and the IMUs on different body parts make it also possible to define which IMU position is the most accurate to quantify a certain movement.

With the data from the different groups, disease-specific mobility patterns can be extracted and compared between diseases. These disease-specific mobility patterns could help to correctly diagnose patients [17, 222]. It will also be possible to analyse how these mobility patterns change during the courses of the diseases, since the PD and MS groups will include patients with different disease stages [255]. All PD patients that consent in conducting assessments during ON and OFF dopaminergic medication states, will be measured in both conditions. This data will help assessing the effect of novel mobility algorithms and parameters to measure effect of treatment [39].

With the data from the different assessments it will be possible to analyse mobility in different circumstances. With the dual-task assessments it will, for example, be possible to measure how much the mobility deteriorates with an easy and a more complex dual-task. The walk with a low and a high obstacle will provide information about the obstacle negotiation performance, which could indicate whether the individual has an increased risk of falling [256, 257]. Moreover, the clinical scores and questionnaires can be related to the mobility performance during the different assessments [258, 259].

This study will have some limitations. The laboratory where the assessments will be performed is relatively small. Therefore, only 5 m of steady state walking can be captured on the over ground walkway and the distances covered during the non-standardized activities of daily living will also not exceed the 5 m. The

measurements will last about three hours because of the many assessments that will be performed. It is possible that not every participant will be able to perform all assessments due to fatigue or loss of motivation, and that only a subset of the data can therefore be collected for those participants.

In conclusion, this study aims at building the largest currently available database for future development and validation of IMU-based mobility algorithms. It will include representative numbers of healthy adults over a large age range, as well as patients with diverse neurological diseases. The combined analysis of demographic and clinical data with full-body IMU and optical motion capture data should stimulate highly efficient research in this area, to eventually catalyse the implementation of accurate mobility parameters in clinical routine and assessment panels of clinical trials.

Supplementary material

Table 6.1: Information about the placement of the reflective markers and the corresponding name in the data files. See also Supplementary Figure 6.5.

Abbreviation used in the data files	Location	Exact description of the location
Head		
l/rf_hd	front of the head	Located approximately over the temple
l/rb_hd	back of the head	Placed on the back of the head, roughly in a horizontal plane of the front head markers
Torso		
m_ster1	sternum	Placement mid of sternum, just caudal of SC joints
m_ster2	sternum	Caudal and to the left of ster1
m_ster3	sternum	Caudal and to the right of ster1
Arm		
l/r_sho	shoulder	Placed on the acromio-clavicular joint
l/r_ua	upper arm	Placed between elbow and shoulder (left side closer to elbow, right side closer to shoulder)
l/r_elbl	elbow	Placed on lateral epicondyle approximating elbow joint axis
l/r_st_hem	humerus epicondylus medialis	Placed on top of humerus epicondylus medialis
l/r_frm	forearm	Placed between wrist and elbow (left side closer to wrist, right side closer to elbow)
l/r_wrr	wrist, radial side	On IMU above the radial styloid
l/r_wru	wrist, ulnar side	On IMU above the ulnar styloid
l/r_hand	dorsal side of hand	Dorsum of the hand just proximal of the head of the second metacarpal
Pelvis		
l/r_asis	anterior superior iliac spine	Placed directly on top of anterior superior iliac spine
l/r_psis	posterior superior iliac spine	Placed directly on top of posterior superior iliac spine
Leg		
l/r_th	thigh	Marker cluster on lateral side of thigh, contains four markers
l/r_st_fem	femur epicondylus medialis	Placed on the medial epicondyle of the knee
l/r_st_fel	femur epicondylus lateralis	Placed on the lateral epicondyle of the knee
l/r_sk	shank	Marker cluster on lateral side of shank, contains 4 markers
l/r_st_mm	malleolus medialis	Placed on the malleolus medialis
l/r_ank	ankle	Placed on the malleolus lateralis
l/r_heel	heel	Placed on the calcaneous
l/r_toe	toe	Placed on the shoe around the 2nd middle phalanx

IMU = inertial measurement unit; l/r = marker is placed both on the left and right side; m = marker is placed around the midline of the body; st = indicates that this is a static marker that is only on the body during the static calibration trials.

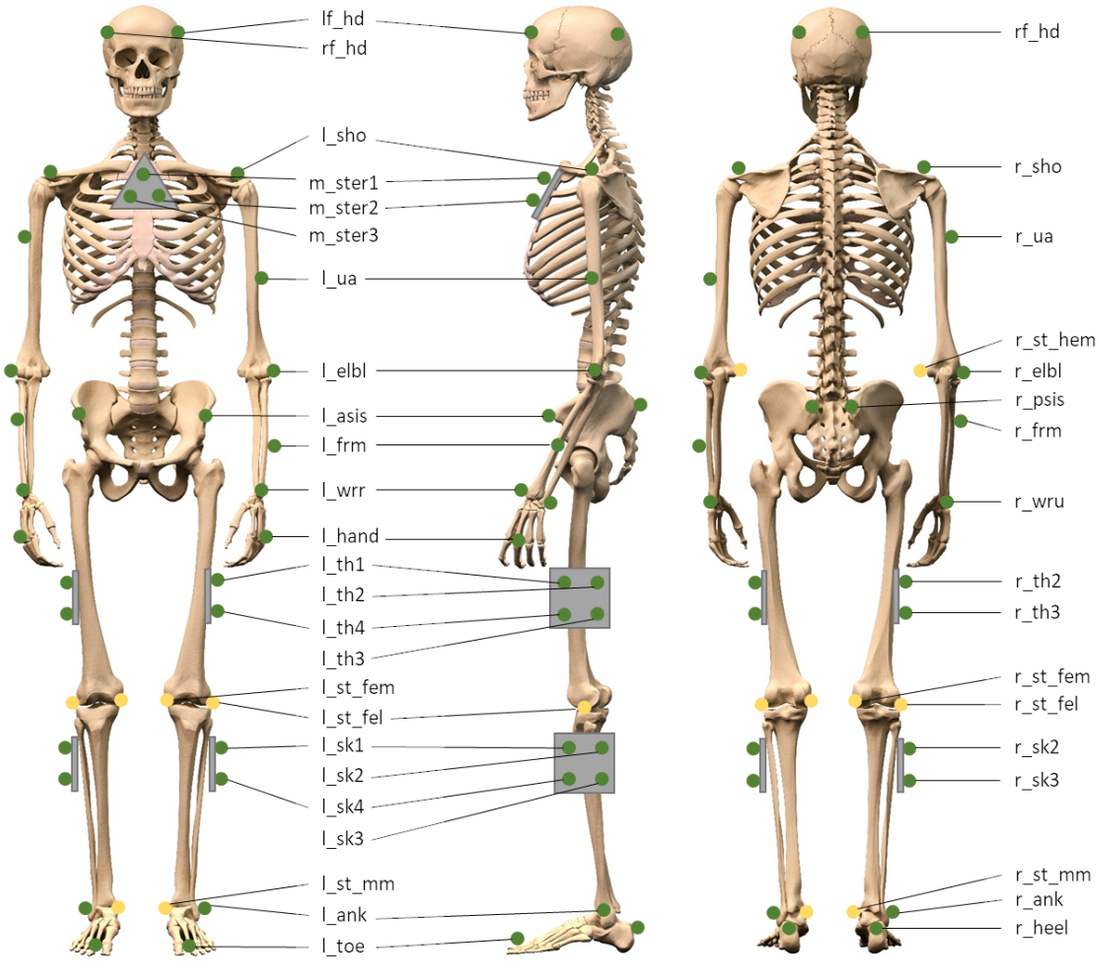


Figure 6.5: Placement of the reflective markers and the corresponding name in the data files. Full names and descriptions can be found in Supplementary Table 6.1.

Treadmill split-belt protocol

A subset of the healthy young adults will be asked to participate in two split-belt trials. The speed of the treadmill will be set to the comfortable walking speed from the first part of the first treadmill trial at which the participant will walk for 60 s. Then the speed of one of the two belts will be reduced with 25% for 120 s. This will be followed by another 60 s with both belts at the same comfortable walking speed. This trial will then be repeated with a speed reduction of the other belt. The order in which belt the speed was reduced first will be randomized.

Choreography assessment

The choreography assessment will exist of a series of movements related to the flexibility of the lower back. The participants will first perform a full flexion and extension of the back. Second, a right and left rotation of the back will be performed, which will be followed by a right and left lateral flexion of the back. Thereafter, the participants will pretend to lift an object from the floor (which is located in front and slightly to the right of the participant), they will lift this above the head and put it back on the floor (in front and slightly to the left of them). This is a

movement that combines flexion and rotation of the back. Lastly, the participants will sit down and lift up the right leg while keeping it bended and pretend to put on a sock, which will then be repeated with the left leg.

Chapter 7

General discussion

The evaluation of mobility of patients with neurodegenerative diseases is crucial for healthcare professionals to tailor individual treatments and track disease progression. More individualized treatment has high potential to improve the quality of life, improve mobility and decrease fall risk. Nowadays mobility is mainly assessed during clinical examinations. However, with the rise of digital wearable technology, it has become possible to quantify mobility objectively in different settings. It is however unclear how mobility data collected in different settings, or more general different contexts, are associated with each other. Therefore, the aim of this dissertation was to understand the influence of context on mobility in older adults and patients with neurodegenerative disorders.

Main findings

Chapter 3 focused on the systematic evaluation of studies that compared the same mobility parameters measured in supervised and unsupervised contexts with each other. This evaluation revealed differences ranging from -40% to 180% change between the two contexts. The type of movement and the type of diagnosis as well as psychological, physiological, cognitive, environmental and technical factors influenced these differences. Because of the influence of context, the unsupervised performance assessments provide complementary information to the supervised capacity assessments. For the implementation of unsupervised performance assessments in clinical practice and research, a few factors need to be considered. Data analysis of unsupervised performance data should make use of the high amount of movement repetitions measured. Moreover, the algorithms to extract mobility-related parameters should be validated in both contexts as far as possible. The mobility-related parameters obtained from the algorithms should be analysed to see which parameters are relevant disease progression and treatment response markers.

In Chapter 4, the development of an algorithm to quantify arm swing during walking from wearable sensor data from a wrist-worn IMU was described. The algorithm was validated for healthy adults and patients with PD. The algorithm was highly accurate as well as sensitive enough to detect differences in arm swing between healthy adults and patients with PD.

Subsequently, as described in Chapter 5, this arm swing algorithm was used to analyse the effect of dopaminergic medication on arm swing in patients with PD during tasks with different complexity. Arm swing showed moderate improvements with dopaminergic medication at preferred walking speed. Large improvements with

medication were found for several arm swing parameters at fast walking speed. However, the responsiveness of arm swing to medication during dual-tasking was small or even negative. It was concluded that, since dual-tasking most closely resembles the average real-life performance, the effect of dopaminergic medication on arm swing during real life might be limited.

In Chapter 6, a study protocol was introduced for the collection of full-body wearable sensor data as well as full-body optical motion capture data from mobility performed under standardized conditions (reflecting the typical assessment in the clinical and laboratory environment) and non-standardized conditions (reflecting daily life performance). It describes the protocol of a, to our best knowledge, unique dataset worldwide of this extent and granularity that can be used by the research community to validate mobility algorithms. Data will be collected from healthy adults (18-60 years), healthy older adults (>60 years), PD patients, MS patients, stroke patients and patients with low back pain caused by orthopaedic issues. In more detail, this dataset can be used to continue the research regarding the influence of the context on mobility, as well as the development and validation of wearable sensor-based algorithms that can quantify mobility in different contexts.

Performance assessments

The performance measures provide complementary information to the capacity measures that are commonly quantified during clinical examinations (Chapter 3). This is for a large part because of the different contexts they are measured in. In real life, where the performance measures are captured, there is no supervision from healthcare professionals, the environment is more cluttered and contains more obstacles, the movements that are performed are self-initiated and goal-directed, and movements are more frequently part of multi-tasking actions.

Improvements in capacity do not automatically indicate an improvement in performance. Since patients spend most of their time in their own environment and not in the clinic, it is more relevant for the patients to improve their performance. Therefore, performance assessments should be implemented into clinical practice and as outcome in clinical trials to be able to quantify changes in performance. With the implementation of regular performance assessments, healthcare professionals can monitor the patient from distance and less clinical visits will be required. This can be beneficial particularly in rural areas where distances to the clinic can be large [111]. Less clinical visits and remote monitoring of mobility could have been especially beneficial during the recent COVID-19 pandemic, which increased the need for telemedicine [260, 261].

Although performance might be the most relevant measure for the patient, it still remains important to regularly measure the capacity in a standardized setting due to different reasons. First, information about how well someone can do specific tasks provides information about the general capacity of a patient. Second, parameters obtained in standardized settings are more stable than performance measures, simply because one can control better for influencing factors.

The influence of the context on the association between capacity and performance

Capacity and performance are two different measures that are associated with each other [262, 263]. It is known that capacity-related measures of mobility are influenced by the context they are measured in. The task complexity, medication status, diagnosis and many more factors can influence capacity. It is also known that the mobility-related performance is influenced by the context. The walking setting, indoor versus outdoor or even versus rough surface or flat versus inclined surface, can all affect the walking performance. A few studies showed that the capacity of older adults measured during simple tasks correlate best with the more extreme performance values (close to the maximum performance measured) [120, 132, 148]. On the other hand, complex capacity tasks are probably more associated with the average performance values, since these more complex tasks better represent real life situations [89, 90] (Figure 7.1). Therefore, we recommend healthcare professionals to add a dual-task assessment to the clinical examination. This dual-task assessment might give the healthcare professional a better indication of how patients move during real life.

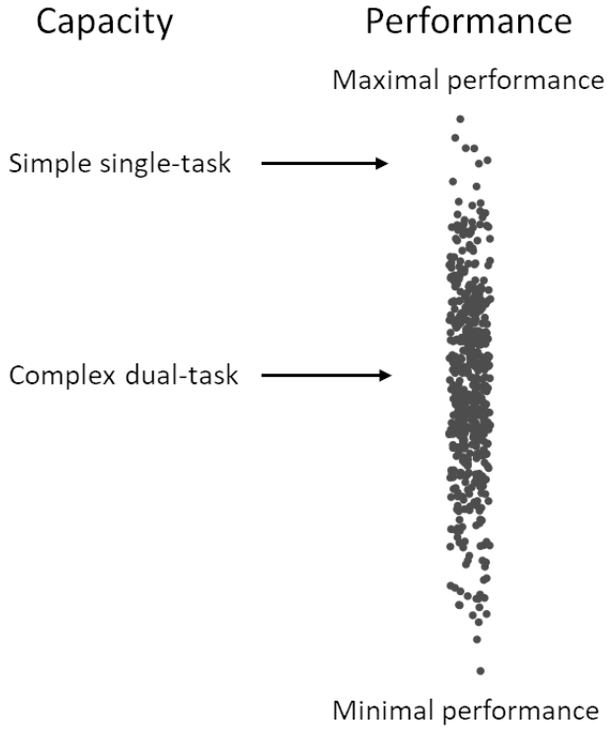


Figure 7.1: The association between capacity and performance with different task complexity (simulated data).

As discussed in Chapter 1, measuring capacity, performance and perception could provide information about the daily function of patients [3]. However, with the research presented in this dissertation it has become clear that the context affects capacity and performance measures and the association between those two measures. Therefore, the association between capacity, performance and perception is more complex as previously described (Figure 7.2 A) [3]. In this dissertation, a new version of the daily function assessment is proposed to which an extra level was added to

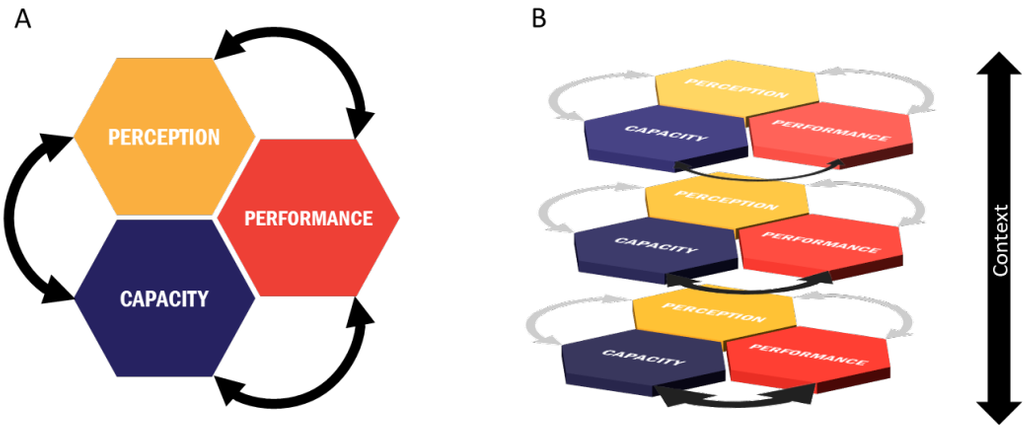


Figure 7.2: A. The daily function assessment as it was originally proposed [3]. B. The new proposed version of the daily function assessment. With a change in context the association between capacity and performance changes (indicated by the different thickness of the arrows). The associations with perception are in grey, because no information is available about the influence of the context on perception.

represent the influence of the context (Figure 7.2 B). This version is however still incomplete since it is unknown what the influence of the context is on mobility-related perception.

The influence of the context on treatment effect

Treatment of neurodegenerative disorders should have an effect on all three measures of the daily function assessment model: capacity, performance and perception. However, the effect of treatment can change between different contexts. In Chapter 5, it was shown that during simple tasks, dopaminergic medication had moderate to large positive effects on arm swing of PD patients. However, during dual-tasking medication had either small or negative effects on arm swing. Another study also showed that gait did improve with dopaminergic medication during simple tasks, but not during dual-tasking [197]. Moreover, the effect of dopaminergic medication on postural stability also seems to be influenced by the task complexity. Two studies found an improvement in several sway parameters during 30 s quite stance with the eyes open, which is a relatively easy task [39, 48]. Another study that added also an eyes closed and dual-task condition to the simple quite stance task did not find improvements in postural sway with dopaminergic medication [214]. A study that provided perturbations during quite stance by rotating the platform the PD patients were standing on, which is also a more complex task, did not find improvements of dopaminergic medication either [190]. Since more complex tasks represent daily living more closely, it could be that dopaminergic medication is not beneficial during daily living. To understand the effect of treatment during daily living, a first step would be to additionally assess the capacity during tasks with a higher complexity. In the future, the performance assessments should also be implemented to be able to directly assess the effect of treatment on the performance.

It is clear that treatments like physiotherapy or resistance training can improve

capacity [264, 265]. However, it is unclear how well this transfers to the real life performance. It is known from research in sports that for example, resistance training improves muscle strength, but that this does not always directly improve their sport performance [264]. Training needs to be more sport specific to achieve improvements in the sport performance. This could also be the case for movement-related therapies in patients with neurodegenerative diseases. It has already been shown that healthy young adults that trained a specific balance task, rapidly improved their performance on this task, but did not improve their performance in other balance task [266]. Therapies might therefore need to be more context specific. This can only be explored by implementing performance measurements in the future.

Recommendations for the implementation of performance measurements

Complex tasks can be added relatively easy to the clinical examination to improve the capacity measures. There are however multiple steps that need to be taken before we can really implement the performance measurements in routine clinical care. Performance measures are starting to be used more often in research [267, 268]. Moreover, the European Medicines Agency and the US Food and Drug Administration encourage the use of performance measures as exploratory endpoints in clinical trials. This is necessary to continue exploring the association between capacity and performance measures and for trying out new data analysis methods to see how we can benefit most from the performance assessments. With the information provided in this dissertation we are taking a step forward, but a few more steps need to be taken.

To measure all possible movements and symptoms during daily living, patients have to be equipped with many wearable sensors. This is not feasible during daily living and the amount of devices that need to be worn for performance assessments should be minimal to keep the adherence of the users high. How many wearable sensors need to be worn will depend on the type of movement and symptoms that are most interesting to be quantified [122]. This will be disease-dependent and might even be subtype- and severity-dependent. For many movements and symptoms, it is not clear yet which sensor location can be used best. This can in the future be explored in more detail with the dataset that was introduced in Chapter 6. Ideally the sensor data from smartwatches and smartphones are also used (these contain the similar type of sensors as IMUs), since these are devices that the patients might already have and wear. These might therefore be the least obtrusive and it has already been shown that they are feasible for assessing mobility [269]. When additional wearable sensors are used, it should be made sure that the battery has a long lifetime, because having to charge the wearable sensors could also affect the adherence [270, 271].

The amount of algorithms that is available to analyse performance data from wearable sensors is limited. More open source algorithms should be developed and especially validated for the different diseases and for use in daily living, like the arm swing algorithm introduced in Chapter 4 and other mobility-related algorithms [100, 119, 272]. For the analysis of performance data, we should take advantage from the high amount of repetitions of movements, since single occurrences could be largely influenced by changes in context. The distribution should for example be taken into account. The effect of a treatment might be best evaluated by looking at

changes in the top and maybe even bottom 10% of the distribution [120, 132, 148]. Detecting changes in the overall distribution could be used to analyse fluctuations over time. Other methods to analyse the data, like artificial intelligence and machine learning algorithms should also be explored. These methods have already been shown to perform well on data from clinical examinations [273, 274], and are starting to be tested with performance data [275]. These methods can deal well with the large quantity of data from performance assessments. However, care should be taken with these methods because they lack transparency [276]. The contribution of specific parameters or data features to the classification is often not known in much detail, making it hard to clinically interpret the analysis.

The outcomes from the analyses and algorithms need to be validated before they can be used in routine clinical care. We recommend that algorithms that detect or classify specific movements should be validated with datasets that have at least video data from patients [147]. Algorithms that measure the quality of movements should be compared to gold standard/reference systems, such as optical motion capture or force plate data [277]. The detection of symptoms and fluctuations in performance and symptoms should be compared to clinical scores and patient-reported outcome measures [278, 279]. The test-retest reliability should be tested for all outcome parameters as well as the sensitivity and the minimal clinically relevant change [110, 280].

From the available validated outcome measures it should be explored which parameters are the relevant biomarkers to detect or track a certain disease, progression aspects of the disease and treatment responses. What the relevant biomarkers are will be disease and biomarker type-dependent and might even depend on disease subtypes and disease severity [16, 49, 280]. Per biomarker should then be explored how often and for how long the performance should be measured to obtain a reliable result for the respective question [281].

This scenario can even be developed further: The collected biomarker data needs to be managed and visualised to be able to track the progression over time. The results can be linked to the digital health record and should then be accessible to the patient and, when the patients grants them access, to the healthcare professional and other people involved in (the treatment of) the disease [282]. This feedback on the biomarker data could improve the long-term adherence to using wearable sensors. Wearable sensors are in general well accepted by users/patients [283, 284], but long-term adherence can be an issue [285, 286]. However, feedback could also influence the behaviour of the patients, which might not always be wanted especially in clinical trials investigating new compounds and other treatments where this behaviour could be part of the outcome parameters.

Limitations

Both mobility and context are broad terms containing many different aspects. Within this dissertation only a limited amount of mobility-related and context-related aspects were discussed. Especially regarding the type of diseases, only PD and MS were taken into account. For the comparison of supervised and unsupervised assessments (Chapter 3), no research was available for other diseases. However, with the dataset introduced in Chapter 6 the research regarding the influence of the context on mobility can now also be extended to patients with a stroke and with structural lower back pain problems.

Wearable sensors in combination with algorithms can be used to quantify

performance-related mobility, but interpreting the results remains difficult. For example, a decrease in step length during a walking bout could be an indication for one of the PD-related symptoms bradykinesia (a reduction in speed and amplitude of repetitive movements), but can also be due to fatigue, fear of falling or a change in the slope of the walking surface. It might be easier to interpret the data by adding more wearable sensors. With data from multiple body parts, the data interpretation will become easier, but wearing many sensors might not be feasible for the patients and might not be good for the adherence.

In this dissertation, only one type of sensor was taken into account, the inertial measurement unit. There are more wearable sensors available that measure mobility-related aspects like EMG (electromyography) and insoles with pressure sensors. Moreover, ambient motion sensors are starting to be used more often in research [287]. Ambient motion sensors are sensors located in a fixed place in a space that can track e.g. movements of persons in that space [288]. Since these sensors always measure in the same setting, the influence of context on the mobility will be smaller.

Outlook

As discussed above in the section with recommendations for the implementation of performance assessments, there are still many factors that need to be explored before the performance assessments can become part of routine clinical care. When performance assessments are part of clinical care, patients can besides discussing their problems with a healthcare professional, also share their objective performance data with them. Together with the clinical examination, the healthcare professional has then information about the capacity, performance and perception at their disposal. This way the healthcare professional has a more complete view on the health problems and it will become easier to correctly diagnose patients in an earlier disease stage. This might make it possible to start treatment earlier and potentially slow down the progression of the disease in an earlier stage. This will increase the quality of life of patients and reduce healthcare costs.

Performance assessments can be used to objectively track the disease progression by regularly assessing the patients. With the regular performance data, healthcare professionals gain more insight on which activities and symptoms cause the most problems during daily living. This information can be used to individually tailor the treatment and thereafter to measure the response to treatment. Performance assessments can also be processed in real-time to measure the immediate effect of treatment. This could for example be used in patients with PD to indicate when a new dose of dopaminergic medication should be taken, e.g. when the symptoms seem to get worse again.

Smartphones and smartwatches cannot only be used to measure the performance, but they could also be used to measure the perception. Apps are being developed where patients can regularly answer a few questions related to their health [175]. In this way, additional, e.g. non-motor symptoms can be tracked, as most of them cannot be measured directly with wearable sensors. These electronic patient-reported outcomes can provide more regular perception data since they can be assessed frequently in between clinical visits. A next step in the development of these digital tools for the assessment of daily life of the patients will thus be to increase the number of validated diaries for the assessment of symptom perception, and to associate these digital perception and performance data consequently with each other. The

digital perception and performance data should then also be associated with the capacity data to gain a more complete understanding from daily function.

With the performance and perception assessments, patients can effectively monitor themselves and the healthcare professional will eventually be able to monitor the patient mainly from distance. The healthcare professional can decide to schedule clinical visits based on changes in the performance and perception data. The regular performance and perception assessments make it possible to detect problems early on. During the scheduled clinical visit, these changes can be discussed and the capacity can be measured to check whether this has changed as well. Based on these results from different contexts the treatment can be adjusted to keep the quality of life as good as possible.

Conclusion

This dissertation contributed to our understanding of the influence of the context on mobility. The first study (Chapter 3) revealed that supervised capacity and unsupervised performance measures can substantially differ from each other. Consequently, both measures provide complementary information that can be used to gain a better understanding of daily function. During both, supervised and unsupervised assessments, context plays a substantial, and currently not well understood role. This is demonstrated, as an example, in Chapter 5: The effect of dopaminergic medication on arm swing in patients with PD is influenced by medication state and task complexity. We therefore highly recommend to assess patients in different contexts to get a better understanding of the effect of treatment or the disease progression. More validated algorithms, like the arm swing algorithm in Chapter 4, are required to analyse the wearable sensor data from different contexts. With the dataset introduced in Chapter 6, an indefinite number of additional movement and mobility algorithms can be developed and validated. The development and validation of these algorithms can further move our understanding of the influence of context on mobility forward.

Chapter 8

Summaries

Deutsche Zusammenfassung

Der Einfluss des Kontexts auf die Mobilität bei neurologischen Erkrankungen - ein tragbarer Technologie-Ansatz

Allgemeine Einführung

Wir befinden uns mitten in einer digitalen Transformation, die große Auswirkungen auf das Gesundheitswesen mit sich bringt. Digitaler Fortschritt und neue Technologien beeinflussen die Diagnose, Prävention, Überwachung und Behandlung von Krankheiten. Medizinisches Fachpersonal kann technologiegestützte Entscheidungen treffen, was zu einer stärker personalisierten Behandlung führen kann. Es gibt eine wachsende Anzahl von tragbaren Technologien, die zur Analyse von Mobilität beitragen. Solche tragbaren Sensoren ermöglichen es, die Mobilität auch außerhalb der Klinik und über längere Zeiträume zu messen und auszuwerten. Diese Informationen haben ein hohes Potenzial, die Gesundheitsversorgung weiter zu verbessern.

Mobilitätsbezogene Aktivitäten erfordern einen gewissen Kraftaufwand. Mit steigendem Alter und dem Auftreten von Alters-assoziierten Erkrankungen nimmt die Kraft ab, was häufig zu Einschränkungen der Mobilität führt. Mobilitätseinschränkungen haben einen großen Einfluss auf die Lebensqualität. Medizinisches Fachpersonal bewertet Mobilitätseinschränkungen häufig mittels Fragebögen und der Beurteilung von einer kurzen Gehstrecke im Rahmen der klinischen Untersuchung. Die Fragen, die die Patientin bzw. der Patient beantwortet, liefern Informationen über die eigene Wahrnehmung (perception). Das Testen von Gehen im klinischen Kontext liefert (vornehmlich) Informationen über die Kapazität (capacity), d.h. was die Patientin bzw. der Patient in der Lage ist zu tun. Was sich damit aber schlecht darstellen lässt, ist was die Patientinnen und Patienten im täglichen Leben können. Dies wird in dieser Arbeit als Performance bezeichnet. Die Verbesserung der Performance dürfte für viele Patientinnen und Patienten wichtiger sein als die Verbesserung der Kapazität, da sie relevanter für die Alltagsbewältigung sein dürfte. Es ist auch davon auszugehen, dass die kombinierte Bewertung von Wahrnehmung, Kapazität und Performance ein sehr realistisches Maß für die Mobilität im Alltag (Alltagsfunktion) einer Patientin oder eines Patienten liefert [3].

Diese Arbeit befasst sich mit dem Einfluss von Kontext auf Mobilität, welche mit tragbaren Sensoren erfasst wird. Diese Sensoren lassen eine objektive Erfassung der Mobilität in verschiedenen Umgebungen und unter verschiedenen Umständen zu. Diese Arbeit soll zeigen, dass der Kontext in der Mobilität gemessen wird,

bei älteren Erwachsenen und Patientinnen und Patienten mit neurodegenerativen Erkrankungen von entscheidender Bedeutung für die Ergebnisse ist.

Theoretischer Hintergrund

Mobilität bezeichnet die Fähigkeit, sich selbstständig oder mit Hilfe von Hilfsmitteln von einem Ort zu einem anderen, oder von einer Körperposition in eine andere zu bewegen. Einschränkungen der Mobilität führen zu einer Verminderung von Selbständigkeit und Lebensqualität [5, 6]. Zu den häufigsten Mobilitätseinschränkungen gehören Defizite in Gang und Gleichgewicht, die wiederum mit einem erhöhten Sturzrisiko [7, 8], Krankenhausaufenthalten [9, 10], Mortalität [9, 11], Angstzuständen [12], Einschränkungen der kognitiven Funktionen [13] und sozialer Isolation [14] verbunden sind. Gang- und Gleichgewichtsdefizite lassen eine Unterscheidung zwischen gesunden Erwachsenen und Patientinnen und Patienten mit neurodegenerativen Erkrankungen [17, 18] und zwischen verschiedenen Subtypen von neurodegenerativen Erkrankungen zu [19–21] und erfüllen damit die Kriterien von Biomarker [15, 16]. Weiter haben sie das Potenzial, neurodegenerative Erkrankungen in einem präklinischen Stadium erkennbar zu machen [15, 18, 22].

Während sich das physiologische Altern allein bereits negativ auf die Mobilität auswirkt [24, 25], haben neurodegenerative Erkrankungen wie Morbus Parkinson und Multiple Sklerose einen noch stärkeren Einfluss auf die Mobilität [33, 37, 60]. Morbus Parkinson ist eine neurodegenerative Erkrankung, die durch einen fortschreitenden Verlust von dopaminergen und anderen Neuronen in verschiedenen Bereichen des Gehirns, bevorzugt im Mittelhirn, verursacht wird und zu einer Reihe von motorischen und nicht-motorischen Symptomen führt [31, 32]. Einer der prominentesten Faktoren des Morbus Parkinson sind Gangstörungen, die zu Einschränkungen der Mobilität und einem erhöhten Sturzrisiko führen [33]. Da es sich bei Morbus Parkinson um eine progressive Erkrankung handelt, werden die Mobilitätseinschränkungen mit der Zeit immer gravierender. Die Erkrankung wird in der Regel mit dopaminergen Medikamenten behandelt [43]. Sie sind hochwirksam, insbesondere bei der Verbesserung motorischer Symptome [44, 45]. Dopaminerge Medikamente verbessern auch einige Aspekte des Gangs, welcher jedoch im Vergleich zu gesunden Kontrollpersonen meist auch unter optimaler Therapie beeinträchtigt bleibt [39, 46, 47]. Multiple Sklerose ist eine neuroinflammatorische und -degenerative Erkrankung, die zu einem Verlust der Myelinscheiden der Nervenfasern und damit zu einer abnorm veränderten Nervenleitung führt [57, 58]. Je nach Lokalisation der Schädigungen kann die Krankheit z.B. zu Spastik, Schmerzen, Müdigkeit, Sehstörungen und verminderter Sensibilität führen [59]. Die Spastik, oft in Kombination mit der verminderten Sensibilität, macht es für die Patientinnen und Patienten schwieriger, Bewegungen zu koordinieren. Die Veränderung des Gangbildes ist bereits bei Patientinnen und Patienten mit einem relativ geringen Krankheitsschweregrad zu beobachten. Die verfügbaren Behandlungen können die Schübe reduzieren, aber oft das Fortschreiten der Krankheit nicht substantiell verlangsamen [58, 63].

Mit Hilfe von tragbaren Sensoren lässt sich die Mobilität innerhalb und außerhalb des Labors quantifizieren. Die Art von Sensorik, die häufig zur Quantifizierung von Bewegung verwendet wird, sind Inertialmesseinheiten (inertial measurement units, IMUs) [67]. Die Rohdaten dieser Sensoren (Beschleunigungs- und Gyroskopdaten) werden mit Algorithmen analysiert, um bewegungsbezogene Parameter zu extrahieren [67, 68]. Die tragbaren Sensoren in Kombination mit validierten Algorith-

men können in der Klinik zur Quantifizierung der Kapazität und in der natürlichen Umgebung zur Quantifizierung der Performance eingesetzt werden. Allerdings muss der Kontext, in dem Kapazität und Performance gemessen werden, berücksichtigt werden, da dieser einen erheblichen Einfluss auf die Mobilität haben kann.

Der Kontext wird im Wörterbuch definiert als "die Umgebung, die Umstände, das Umfeld, der Hintergrund oder das Setting, welche(r) die Bedeutung eines Ereignisses oder eines anderen Vorgangs bestimmen, spezifizieren oder klären" [78]. Der Kontext kann das menschliche Verhalten beeinflussen. Allein das Wissen, dass die eigenen Bewegungen analysiert werden, verändert die Mobilität bereits mit großer Sicherheit. Außerdem ist ein gut beleuchteter offener Raum ohne viele Störfaktoren während einer klinischen Untersuchung nicht mit Bewegungen vergleichbar, wie sie im täglichen Leben üblich sind. Selbst innerhalb klinischer Untersuchungen lassen sich Unterschiede zwischen Single- und Dual-Task-Aufgaben [87, 88] sowie Medikationsstatus [39, 91, 92] feststellen. Im Rahmen dieser Dissertation wird der Einfluss des Kontexts auf die Mobilität analysiert. Speziell wird untersucht, wie sich der Kontext (z. B. Diagnose, Setting, Aufgabenkomplexität, Medikationsstatus) auf Kapazität und Performance der Mobilität bei älteren Gesunden und Personen mit neurodegenerativen Erkrankungen auswirkt.

Langzeit-Mobilitätsbeurteilung bei Bewegungsstörungen

Mobilitätsdefizite sind bei neurologischen Patientinnen und Patienten weit verbreitet und beeinträchtigen z.B. die Aktivitäten des täglichen Lebens, die Arbeit und die sozialen Aktivitäten [4]. Mobilitätsdefizite sind auch Prädiktoren für erhöhte Morbidität, eingeschränkte kognitive Leistungsfähigkeit und erhöhte Mortalität [101–104]]. Sie wirken sich negativ auf die Lebensqualität aus, insbesondere bei Patientinnen und Patienten mit neurologischen Bewegungsstörungen [5, 6]. Daher ist es für das medizinische Fachpersonal von entscheidender Bedeutung, eine vollständige und objektive Bewertung der Mobilität einer Patientin bzw. eines Patienten als Grundlage für eine individuell zugeschnittene klinische Entscheidungsfindung und Prognose zu erhalten. Derzeit werden Mobilitätsbeurteilungen hauptsächlich beaufsichtigt in einem Labor oder Krankenhaus mit standardisierten, meist qualitativen oder halbstandardisierten Tests durchgeführt [106–108]. Viele Patientinnen und Patienten zeigen jedoch (paradoxerweise, unbewusst und ungewollt) gute Leistungen, wenn sie wissen, dass sie beobachtet werden. Darüber hinaus sind verschiedene klinisch relevante Symptome während dieser Momentaufnahme schwer zu erfassen, entweder weil sie über lange Zeiträume stattfinden (z. B. Umfang der körperlichen Aktivität), selten sind (z. B. Stürze), nachts auftreten (z. B. Schlafstörungen) oder komplexe fluktuierende Muster aufweisen (z. B. die Reaktion auf eine dopaminerge Behandlung). Um solche Ereignisse zuverlässig zu bewerten, ist es notwendig, Patientinnen und Patienten über längere Zeiträume zu messen, während sie sich frei und unbeaufsichtigt in ihrem täglichen Lebensumfeld bewegen. Dies kann mit tragbaren Sensoren geschehen [110, 111]. Die Langzeit Mobilitätsbeurteilung kann im Vergleich zur klinischen Beurteilung zusätzliche und teilweise ergänzende Informationen liefern. Dabei sind jedoch Unterschiede zur herkömmlichen klinischen Untersuchung zu beachten.

Die erste in der Dissertation vorgestellte Arbeit ist ein systematisches Review, welches die (schwache) Assoziation zwischen standardisierten (d.h. im klinischen Kontext) und nicht-standardisierten (d.h. im häuslichen Umfeld) Assessments von Mobilität aufzeigt. Dabei wird auch aufgezeigt, dass verschiedene Kontexte die

erhobenen Mobilitätsdaten substantiell beeinflussen können. Es werden Vorschläge zur Implementierung von Langzeit-Mobilitätserfassungen in die klinische Versorgung und die zukünftige Forschung erarbeitet.

Im Detail fanden sich folgende Ergebnisse: Wenn die selben Mobilitätsparameter von identischen Teilnehmerinnen und Teilnehmer (ältere Erwachsene, Patientinnen und Patienten mit Morbus Parkinson und Patientinnen und Patienten mit Multiple Sklerose) zwischen standardisierten und nicht-standardisierten Bedingungen verglichen wurden, zeigten sich Unterschiede von -40% bis 180% (Abbildung 8.1). Diese Unterschiede sind deutlich größer als die, die nach Interventionen beobachtet werden. Somit können kleine und moderate Behandlungseffekte durch Variation von Kontext im Rauschen untergehen und damit unbeobachtet bleiben.

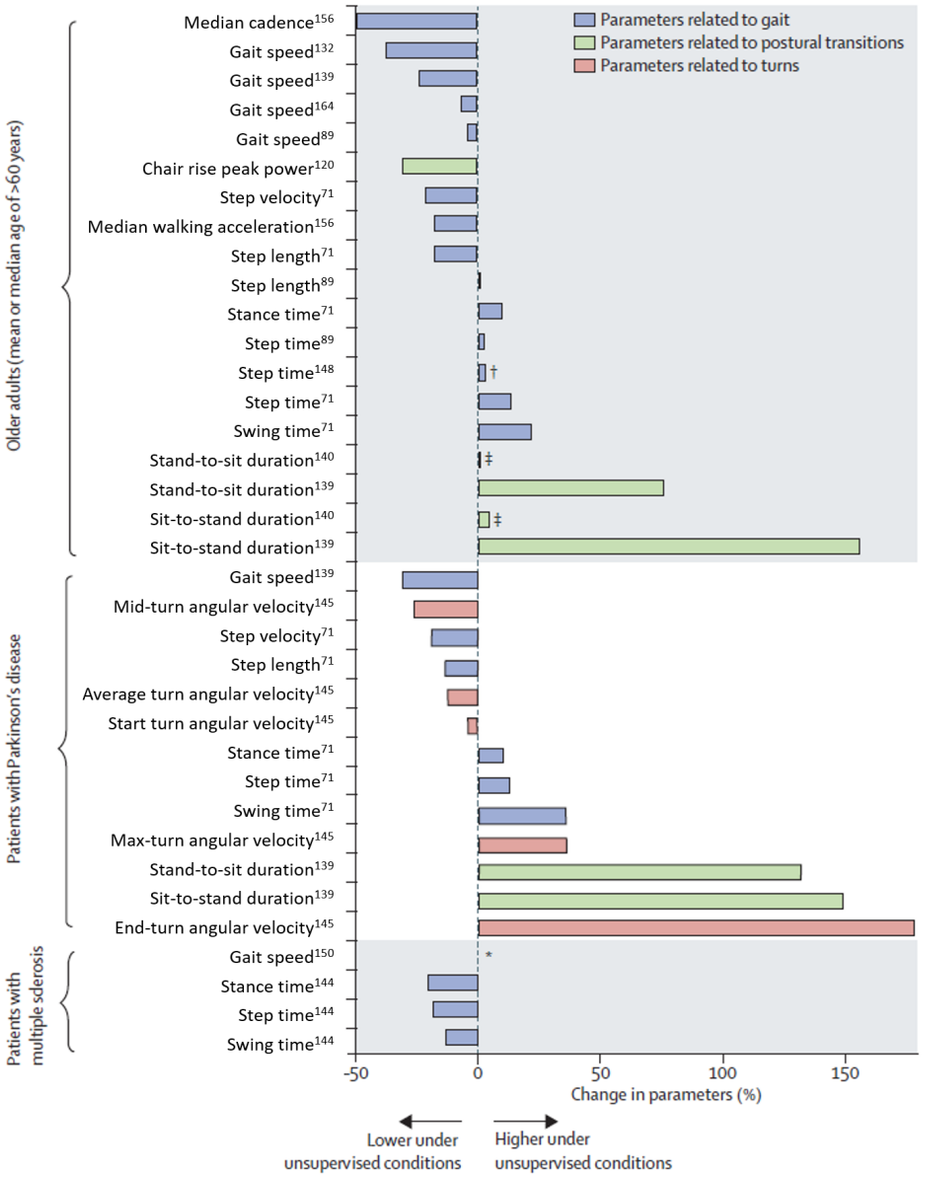


Abbildung 8.1: Prozentuale Änderung von Parametern, die unter nicht-standardisierten Bedingungen gemessen wurden, im Vergleich zu standardisierten Bedingungen. Für weitere Informationen siehe Kapitel 3.

Wir gehen davon aus, dass eine Langzeit-Mobilitätsbeurteilung in Zukunft Voraussetzung für klinische Studien und die klinische Entscheidungsfindung sein wer-

den. Es gibt jedoch noch einige Aspekte, die angegangen werden müssen, bevor die Langzeit-Mobilitätsbeurteilung in die klinische Routineversorgung implementiert werden kann. Die Algorithmen, die zur Berechnung der Mobilitätsparameter verwendet werden, sollten so weit wie möglich sowohl unter standardisierten als auch unter nicht-standardisierten Bedingungen validiert werden. Besonderes Augenmerk muss auf eine differenziertere Datenanalyse von nicht-standardisierten Daten gelegt werden. Neue Analysemethoden sollten erforscht werden und wir müssen evaluieren, ob relevante Maße aus den Daten extrahiert werden können. Um die klinische Relevanz von Ergebnissen der Langzeit-Mobilitätsbeurteilung besser zu verstehen, sollten zukünftige Arbeiten die Beziehung zwischen diesen objektiven digitalen Messwerten untersuchen und mit Ergebnissen von Fragebögen (sowohl für Patientinnen und Patienten wie auch deren Betreuende) in Zusammenhang bringen.

Quantifizierung des Armschwungs beim Gehen bei gesunden Erwachsenen und Patientinnen und Patienten mit Morbus Parkinson: Entwicklung und Validierung eines Algorithmus auf Basis eines tragbaren Sensors

Eine schwingende Bewegung der Arme charakterisiert den Gang. Eine Verringerung oder Asymmetrie des Armschwungs wird häufig bei Patientinnen und Patienten mit Morbus Parkinson beobachtet [38, 170, 171] und könnte damit auch ein potenzieller Prodromal- und Progressionsmarker für Morbus Parkinson sein [22, 170]. Dies unterstreicht den Bedarf an einem genauen Beurteilungsinstrument für Armschwung. Ziel dieser zweiten Arbeit war es, einen Algorithmus zu entwickeln und zu validieren, der den Armschwung bei Patientinnen und Patienten mit Morbus Parkinson während des Gehens quantifiziert und der sowohl in der Klinik als auch im Alltag eingesetzt werden kann, und damit eine Testung des Einflusses von Kontext auf den Armschwung ermöglichen kann.

Von 13 Patientinnen und Patienten mit Morbus Parkinson wurden mit Hilfe eines Laufbands Gangdaten bei bevorzugter Geschwindigkeit erhoben, und von 15 gesunden Teilnehmerinnen und Teilnehmern bei drei verschiedenen Geschwindigkeiten. Jeweils ein IMU und drei reflektierende Marker (optisches Bewegungserfassungssystem, das als Referenzsystem dient) wurden an den Handgelenken der Teilnehmenden angebracht. Aus den Rohdaten der IMUs wurden Hauptamplitude, Spitzenwinkelgeschwindigkeit, Seitwärtsamplitude, Regelmäßigkeit, Koordination und Asymmetrie des Armschwungs berechnet. Eine Hauptkomponentenanalyse wurde durchgeführt, um die Parameter in der Hauptschwungrichtung zu berechnen und den Algorithmus robust gegenüber unterschiedlichen Trageposition am Unterarm zu machen. Die Maxima der ersten Hauptkomponente wurden detektiert, um die Spitzenwinkelgeschwindigkeit zu erhalten. Die Daten wurden integriert und mit einem gleitenden Mittelwertfilter gefiltert, um den Winkel zu erhalten, der für die Berechnung der Amplitude verwendet wurde. Die Regelmäßigkeit des Armschwungs wurde auf der Grundlage der Autokorrelation der Winkelgeschwindigkeit berechnet, was ein Maß für die Ähnlichkeit zwischen aufeinanderfolgenden Armschwüngen darstellt. Die Koordination zwischen linkem und rechtem Arm basiert auf einer normalisierten Kreuzkorrelation, die Informationen über den zeitlichen Versatz der linken und rechten Armschwünge liefert. Die Asymmetrie zwischen beiden Armen wurde aus der durchschnittlichen Armschwungamplitude jedes Arms extrahiert.

Die Ergebnisse des Algorithmus wurden mit den Ergebnissen des optischen Bewegungserfassungssystems verglichen. Die systematischen Fehler für gesunde Erwachsene und Patientinnen und Patienten mit Morbus Parkinson lagen im Bereich von 0,1

bis 0,5° für die Amplitude und -0,3 bis 0,3°/s für die Spitzenwinkelgeschwindigkeit der verschiedenen Geschwindigkeiten. Der Zufallsfehler der Amplitude lag zwischen 2,2 und 3,8° und der Zufallsfehler der Spitzenwinkelgeschwindigkeit zwischen 4,2 und 6,8°/s. Die absoluten Fehler lagen bei 0,9 bis 1,1° für die Amplitude und 1,4 bis 2,0° für die Spitzenwinkelgeschwindigkeit. Damit sind die Ergebnisse des Algorithmus, die auf den IMU-Daten beruhen, sehr gut vergleichbar mit den Ergebnissen vom Referenzsystem. Der IMU-basierte Algorithmus kann daher als sehr akkurat bezeichnet werden. Armschwungamplitude und Spitzenwinkelgeschwindigkeit können alle mit einem sehr kleinen systematischen Fehler im Vergleich zum Referenzsystem extrahiert werden. Die zufälligen Fehler sind bei der Parkinson-Gruppe etwas höher als bei der Gruppe der gesunden Erwachsenen. Dies kann - zumindest teilweise - auf die weniger fließende Bewegung der Arme bei Patientinnen und Patienten mit Morbus Parkinson zurückzuführen sein.

In einem vorläufigen Vergleich wurden die Armschwungparameter aus dem Algorithmus zwischen gesunden Erwachsenen und Patientinnen und Patienten mit Morbus Parkinson verglichen. Es zeigten sich signifikante Unterschiede in den Armschwungparametern zwischen den Gruppen, was darauf hindeutet, dass der Algorithmus sensitiv genug ist, um Gruppenunterschiede zu erkennen.

Der Armschwungalgorithmus liefert zusätzliche Informationen zur klassischen Ganganalyse, die typischerweise nur Bewegungen des unteren Körpers misst. Der Algorithmus kann sowohl in der Klinik als auch im häuslichen Umfeld angewendet werden, ein Bereich, den wir bisher noch nicht sehr detailliert untersuchen und verstehen konnten. Dann sollte er aber mit einem Gangerkennungsalgorithmus kombiniert werden [182, 183].

Ansprechen des Armschwungs auf die dopaminerge Medikation bei Morbus Parkinson hängt von der Komplexität der Aufgabe ab

Das Ansprechverhalten dopaminerger Medikation auf Gangparameter bei Patientinnen und Patienten mit Morbus Parkinson ist widersprüchlich [39, 46, 92, 192, 194]. Nur Ganggeschwindigkeit, Schrittlänge und Schrittgeschwindigkeit zeigen eine Verbesserung durch die Medikation [39, 44, 77]. Der Medikationseffekt auf andere Gangparameter ist jedoch weiterhin ungeklärt. Es ist bekannt, dass sich die Gehirnaktivität sowohl bei der Komplexität von Gangaufgaben als auch bei neurologischen Pathologien unterscheidet [98]. Daher stellten wir für die dritte Arbeit dieser Dissertation die Hypothese auf, dass das Ansprechen von Armschwungparametern auf dopaminerge Medikation durch die unterschiedliche Komplexität der Gehaufgaben beeinflusst werden kann.

Bei 45 Patientinnen und Patienten mit Morbus Parkinson (alle ohne Dyskinesien) wurde der Armschwung beim Gehen mit bevorzugter Geschwindigkeit, mit schneller Geschwindigkeit und beim Gehen mit einer kognitiven Dual Task-Aufgabe (Subtraktion in 7er-Schritten) analysiert. Die Teilnehmerinnen und Teilnehmer gingen eine Minute lang 20 Meter in einem Korridor auf und ab. Alle Teilnehmerinnen und Teilnehmer führten diese Gangparadigmen sowohl ohne als auch mit dopaminerger Medikation durch. Eine Gruppe von Kontrollpersonen (gematcht nach Alter und Geschlecht) führte die gleichen Gangparadigmen einmalig über eine Strecke von 20 Metern durch. Während der Untersuchung trugen die Teilnehmerinnen und Teilnehmer jeweils einen tragbaren Sensor an beiden Handgelenken. Der validierte, öffentlich verfügbare Algorithmus, der in der zuvor erwähnten Arbeit vorgestellt wurde, wurde hier verwendet, um die Armschwungparameter zu extrahieren. Die

Armschwungparameter wurden für die Gehgeschwindigkeit korrigiert, da bekannt ist, dass die Ganggeschwindigkeit den Armschwung beeinflusst [27, 204, 205].

Bei bevorzugter Geschwindigkeit, und noch mehr bei schneller Geschwindigkeit, verbesserten sich die Armschwungparameter mit der Medikation (Abbildung 8.2). Allerdings war der Effekt der dopaminergen Medikation auf die meisten Armschwungparameter während der Dual Task-Aufgabe deutlich reduziert. Bei bevorzugter Geschwindigkeit und bei der Dual Task-Aufgabe waren die Unterschiede zwischen den Patientinnen und Patienten mit Morbus Parkinson und den Kontrollen relativ gering. Bei schneller Geschwindigkeit unterschieden sich jedoch alle Parameter signifikant zwischen den Patientinnen und Patienten mit Morbus Parkinson mit und ohne Medikation im Vergleich zu der gesunden Kontrollgruppe. Interessanterweise waren die medikamentenbedingten Veränderungen des Armschwungs nicht relevant mit den Veränderungen von klinischen Skalen für die Erfassung von dopaminerger Wirkung korreliert.

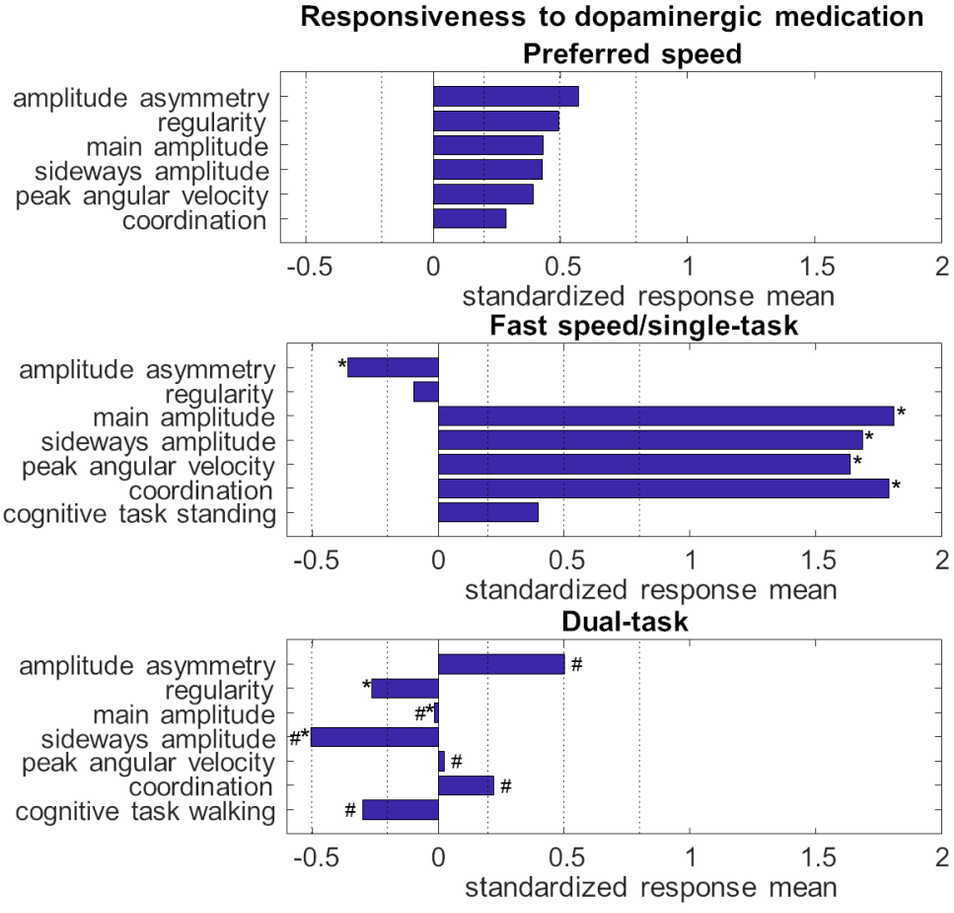


Abbildung 8.2: Ansprechbarkeit der Armschwungungparameter und der kognitiven Subtraktionsaufgabe bei dopaminerger Medikation. Ein positiver standardisierter Response-Mittelwert (SRM) zeigt eine Verbesserung mit Medikation und ein negativer SRM eine Verschlechterung mit Medikation an. $0.20 \leq SRM < 0.50$ steht für ein geringes, $0.50 \leq SRM < 0.80$ für ein moderates und $SRM \geq 0.80$ für ein großes Ansprechen auf dopaminerge Medikation [39]. * = signifikant verschieden von bevorzugter Geschwindigkeit; # = signifikant verschieden von schneller Geschwindigkeit/Einzelaufgabenbedingung.

Diese Arbeit konnte damit zeigen, dass das Ansprechen des Armschwungs auf

die dopaminerge Medikation bei Morbus Parkinson wesentlich durch den Kontext beeinflusst wird. Weiter führte die dopaminerge Medikation nicht dazu, dass die Armschwünge der Patientinnen und Patienten mit Morbus Parkinson sich jenen der Kontrollgruppe stark annäherten (also dass der Armschwung "normal" wurde). Es kam vielmehr dazu, dass während des schnellen Gehens unter Medikation die Patientinnen und Patienten mit Morbus Parkinson bessere Werte aufwiesen als die Kontrollgruppe. Dies könnte dadurch erklärt werden, dass Patientinnen und Patienten mit Morbus Parkinson die Energie des Armschwungs nutzen, um den Körper vorwärts zu bewegen. Es könnte möglicherweise auch dadurch erklärt werden, dass durch eine erhöhte sensorische Dämpfung, die bei Patientinnen und Patienten mit Morbus Parkinson verändert ist und durch die dopaminerge Medikation verstärkt wird [207], eine reduzierte Wahrnehmung (und damit Kontrolle) des Armschwungs eintritt. Die Gangaufgabe mit zusätzlicher kognitiver Aufgabe zeigte relativ geringe Unterschiede zwischen den Kontrollen und Patientinnen und Patienten mit Morbus Parkinson. Letztendlich lässt diese Arbeit vermuten, dass die dopaminerge Medikation für den Armschwung im Alltag nicht sehr vorteilhaft ist. Weitere Studien müssen diese Ergebnisse bestätigen und, falls sie sich bestätigen lassen, untersuchen ob dieser (fehlende) Effekt auch bei anderen alltagsrelevanten Bewegungen zu beobachten ist. Dies hätte potentiell nachhaltigen Einfluss auf die Gestaltung der Therapie insbesondere beim fortgeschrittenen Parkinsonsyndrom.

Detaillierte Mobilitätsmessungen mit Inertialmesseinheiten (IMUs) und optischer Bewegungserfassung bei gesunden Erwachsenen und neurologischen Patientinnen und Patienten für zukünftige Validierungsstudien: Ein Studienprotokoll

Gesunde Erwachsene und neurologische Patientinnen und Patienten zeigen einzigartige Mobilitätsmuster im Laufe ihres Lebens bzw. ihrer Erkrankungen. Die Quantifizierung dieser Bewegungsmuster könnte die Diagnose [17, 222], den Krankheitsverlauf [106] und die Messung des Ansprechens auf eine Behandlung [39, 121] unterstützen. Diese Quantifizierung kann mit tragbarer Technologie, wie IMUs, durchgeführt werden. Bevor die IMUs zur Quantifizierung der Mobilität verwendet werden können, muss immer ein Algorithmus entwickelt und validiert werden, welcher die Rohdaten entsprechend "interpretiert". Da sich Mobilitätsmuster über die Lebensspanne und zwischen verschiedenen neurologischen Erkrankungen unterscheiden, muss diese Validierung in verschiedenen Altersgruppen und mit krankheitsspezifischen Datensätzen durchgeführt werden. Diese vierte Arbeit stellt ein Studienprotokoll für einen "Ganzkörper-Mobilitätsdatensatz" von gesunden jungen und älteren Teilnehmerinnen und Teilnehmer und neurologischen Patientinnen und Patienten vor. Alle Teilnehmerinnen und Teilnehmer werden gleichzeitig mit multiplen IMUs, verteilt über den gesamten Körper, und einem optischen 3D-Bewegungserfassungssystem gemessen. Diese Studie soll einen bis dato in diesem Ausmaß nicht erhältlichen Datensatz liefern, der für die Entwicklung und Validierung von IMU-basierten Mobilitätsalgorithmen für gesunde Erwachsene und neurologische Patientinnen und Patienten entscheidende Impulse setzen kann.

Die Studie wird gesunde jüngere Erwachsene (18-60 Jahre), gesunde ältere Erwachsene (>60 Jahre), Patientinnen und Patienten mit Morbus Parkinson, Patientinnen und Patienten mit Multiple Sklerose, Patientinnen und Patienten mit einem kürzlich erlittenen Schlaganfall und Patientinnen und Patienten mit chronischen Schmerzen im unteren Rückenbereich umfassen. Spezifische klinische Skalen

und Fragebögen über die kognitive Funktion, Aktivitäten des täglichen Lebens, Müdigkeit und Lebensqualität werden zusätzlich erhoben. Alle Teilnehmerinnen und Teilnehmer werden sowohl standardisierte Mobilitätsaufgaben als auch nicht-standardisierte Aktivitäten des täglichen Lebens durchführen. Die standardisierten Mobilitätsaufgaben umfassen Gehen unter Single- und Dual Tasking Bedingungen, das Überschreiten eines Hindernisses, Drehbewegungen, Transferbewegungen vom Sitzen zum Stehen und vom Stehen zum Sitzen sowie Gleichgewichtsübungen. Die nicht-standardisierten Assessments umfassen das Decken eines Tisches, Bewegungen beim Essen und Trinken, das Reinigen eines Tisches, Bügeln, Lesen, Heben und Auswechseln von Gegenständen. Während der standardisierten und nicht-standardisierten Bewegungsanalyse tragen alle Teilnehmerinnen und Teilnehmer mindestens 15 IMUs und 47 reflektierende Marker, die vom optischen System erfasst werden.

Die gesammelten Daten können zur Entwicklung und Validierung von Algorithmen für verschiedene Bewegungen und Symptome in unterschiedlichen Alters- und Krankheitsgruppen verwendet werden. Die standardisierten komplexeren Gehaufgaben und die nicht standardisierten Aktivitäten des täglichen Lebens können insbesondere zur Entwicklung und Validierung von Algorithmen für die Analyse der Performance in der natürlichen Umgebung der Patientin bzw. des Patienten verwendet werden. Die vielen IMUs, die an verschiedenen Körperteilen positioniert sind, werden es auch möglich machen, zu definieren, welche IMU-Position die beste ist, um eine bestimmte Bewegung zu quantifizieren.

Mit den Daten aus den verschiedenen Gruppen wird es potentiell auch möglich sein, krankheitsspezifische Bewegungsmuster zu analysieren und diese zwischen den Gruppen zu vergleichen. Außerdem kann damit analysiert werden, wie sich die Mobilitätsmuster mit dem Schweregrad der Erkrankung oder mit der Medikation verändern. Insgesamt können die Daten genutzt werden, um Algorithmen zu entwickeln, die die Mobilität innerhalb und außerhalb der Klinik objektiv quantifizieren können, um letztlich den Krankheitsverlauf besser verfolgen und eine individuellere Behandlung anbieten zu können.

Allgemeine Diskussion

Das Ziel dieser Dissertation war es, den Einfluss des Kontextes auf die Mobilität bei älteren Erwachsenen und Patientinnen und Patienten mit neurodegenerativen Erkrankungen besser zu verstehen. Ein systematisches Review (Kapitel 3) konnte zeigen, dass unterschiedliche Kontexte bei Kapazität und Performance unterschiedliche Ergebnisse bei Mobilitätsparametern liefern können. Verbesserungen im Kapazitätsbereich deuten nicht automatisch auf einer Verbesserung im Performancebereich hin. Das ist eine wichtige Beobachtung, insbesondere da die Patientinnen und Patienten die meiste Zeit im häuslichen Umfeld und nicht in der Klinik bzw. einer klinischen Untersuchung verbringen. Daher sollten Performance-Assessments in Zukunft in die klinische Praxis und in die Assessment-Panels von klinischen Studien implementiert werden.

Kapazität und Performance sind zwei unterschiedliche Maße, die allerdings auch miteinander in Verbindung stehen [262, 263]. Sowohl Kapazität als auch Performance werden durch den Kontext beeinflusst. Die mit einfachen klinischen Tests gemessene Kapazität älterer Erwachsener korreliert -wenig überraschend- am besten mit den oberen Bereichen der Performancewerte [120, 132, 148]. Auf der anderen Seite scheinen komplexe Kapazitätsaufgaben eher mit den Performancewerten um

den Bereich des Mittelwertes / Medians zu korrelieren. Diese komplexeren Kapazitätsaufgaben bilden möglicherweise reale Lebenssituationen besser ab [89, 90]. Es könnte daher im Rahmen der klinischen Untersuchung sinnvoll sein, eine komplexere Untersuchung von Mobilität durchzuführen, die z.B. auch kognitive Elemente beinhaltet. Dies könnte dem medizinischen Personal zumindest eine grobe Vorstellung davon geben, wie sich Mobilität im realen Alltag der Patientin bzw. des Patienten abbildet.

Für die Behandlung von neurodegenerativen Erkrankungen sollte Mobilität als ein Grundpfeiler des menschlichen Seins konsequent erfasst werden, und am besten mit Kapazitäts-, Wahrnehmungs- und Performanceparametern [3]. Dabei sollte darauf geachtet werden, dass für den Kontext, in dem die Untersuchungen durchgeführt werden, so gut wie möglich kontrolliert wird. Darauf deuten v.a. die in der dritten Arbeit vorgestellten Ergebnisse hin: Für den Armschwung ergaben sich bei komplexen, jedoch nicht bei einfachen Aufgaben geringe und manchmal sogar negative Effekte der dopaminergen Medikation bei Patientinnen und Patienten mit Morbus Parkinson (Kapitel 5). Ähnliche Ergebnisse wurden bereits für Gleichgewichtsparameter berichtet [39, 48, 190, 214]. Da wir im täglichen Leben kaum "einfache" Aufgaben durchführen, könnte es daher z.B. sein, dass im Alltag die dopaminerge Medikation bei Patientinnen und Patienten mit Morbus Parkinson viel weniger Vorteile bietet, als dies unter standardisierten Bedingungen, wie sie in einer Klinik vorherrschen, gemessen wird. Diese Schlussfolgerung muss sicherlich, wie schon oben erwähnt, mit zukünftigen prospektiven Studien kritisch überprüft werden.

Es ist wiederholt überzeugend nachgewiesen worden, dass Behandlungen wie Physiotherapie und Krafttraining Kapazitätsparameter bei Patientinnen und Patienten mit hier untersuchten Erkrankungen verbessern können [264, 265]. Es ist jedoch weitgehend unklar, wie gut sich dies auf Performancewerte überträgt. Im Sport muss das Training der jeweiligen Disziplin angepasst sein, damit Verbesserungen in der sportlichen Leistung erreicht werden können [264]. Wettkampfnahe Trainingssituationen sind der Schlüssel für erfolgreiche sportliche Leistungen. Dies könnte auch für Patientinnen und Patienten mit neurodegenerativen Erkrankungen gelten: spezifische bewegungsbezogene Therapien könnten helfen, die Performance im Alltag zu verbessern. Die Trainingssituationen in der Klinik stimmen oftmals nicht mit der tatsächlichen Umgebung im häuslichen Umfeld überein. Somit ist es wichtig, dass die Kontextinformationen mit in die Therapie eingebunden werden. So sollten z.B. Türschwellen, geschlossene Türen oder enge unübersichtliche räumliche Verhältnisse in Therapiekonzepte mit einbezogen werden.

Die Anzahl an Algorithmen, die zur Analyse von Performancedaten von tragbaren Sensoren zur Verfügung steht, ist begrenzt. Es müssen mehr Open Source Algorithmen entwickelt und speziell für die verschiedenen Krankheiten und für den Einsatz im täglichen Leben validiert werden, bspw. wie der in Kapitel 4 vorgestellte Armschwung-Algorithmus und andere mobilitätsbezogene Algorithmen [100, 119, 272]. Für die Analyse von Performancedaten kann man sich die hohe Anzahl von Wiederholungen von Bewegungen zunutze machen, da viele der zu messenden Bewegungen sehr oft am Tag / während der Woche etc. auftreten. Dabei kann und sollte z.B. auch die Verteilung der Bewegungen insgesamt und der quantitativen Parameter dieser Bewegungen berücksichtigt werden. Andere Methoden zur Analyse der Daten, wie künstliche Intelligenz und maschinelle Lernalgorithmen sollten ebenfalls intensiv getestet werden. Selbstverständlich müssen die Ergebnisse der Algorithmen ausführlich validiert werden, bevor sie in der klinischen Routineversorgung eingesetzt werden können. Aufbauend auf diesen Ergebnissen sollte

untersucht werden, welche Parameter als Biomarker fungieren können, die eine bestimmte Krankheit, Aspekte des Krankheitsverlaufs oder das Ansprechen auf die Behandlung am besten messen können. Es ist sehr unwahrscheinlich, dass ein Parameter all diese verschiedenen Aspekte erfüllen kann, selbst innerhalb eines bestimmten Mobilitätsmaßes [15]. In Zukunft sollte auch darüber nachgedacht werden, wie die gesammelten Daten nicht nur dem medizinischen Personal, sondern auch (und möglicherweise vor allem) den Patientinnen und Patienten präsentiert werden können, sodass diese die Daten entsprechend interpretieren und daraus relevante Schlüsse ziehen können. Die Ergebnisse sollten z.B. mit der (potentiell bald umfassend zur Verfügung stehenden) elektronischen Gesundheitsakte verknüpft werden können [282]. Sobald Performancedaten Teil der klinischen Versorgung sind, können Patientinnen und Patienten diese nicht nur im Rahmen von Visiten mit dem medizinischen Personal verwenden, sondern auch mit anderen Gruppen teilen.

Es ist festzuhalten, dass Interpretationen von mobilitätsbezogenen Performancedaten aktuell vorsichtig vorgenommen werden sollten, da der Kontext praktisch alle Parameter substantiell beeinflussen kann, und wir bis heute noch nicht wissen, inwieweit wir "Kontext" bereits adäquat und umfassend verstanden und definiert haben. Zum Beispiel könnte eine über eine gewisse Zeitspanne beobachtete Reduktion der Schrittlänge während des Gehens ein Hinweis auf ein Prodromalstadium eines Morbus Parkinson sein [15], kann aber auch auf (chronische) Müdigkeit, Sturzangst aufgrund eines erstmalig aufgetretenen Sturzes, Umzug in eine andere Gegend / Wohnung, anderes soziales Umfeld (z.B. hat der Partner eine Erkrankung, und die regelmäßigen gemeinsamen Spaziergänge fallen damit langsamer aus), Berentung, etc. zurückzuführen sein.

In dieser Dissertation sind nur IMUs zum Einsatz gekommen, um mobilitätsbezogene Aspekte zu messen. Es ist gut denkbar, dass auch andere Sensorsysteme Mobilität im Bereich Performance adäquat erfassen können. Ein Beispiel sind stationäre Sensoren (Sensoren, die sich an einem festen Ort in einem Raum befinden und z. B. Bewegungen von Personen in diesem Raum verfolgen können) [287, 288]. Da diese Sensoren immer in der gleichen Umgebung messen, verringert sich der Einfluss des Kontexts auf die Mobilität.

Smartphones und Smartwatches können zur Messung der Performance, aber auch zur Messung der Wahrnehmung eingesetzt werden. Applikationen werden entwickelt, bei denen Patientinnen und Patienten regelmäßig Fragen zu ihrer Gesundheit beantworten können [175]. Auf diese Weise können zusätzliche, z.B. nicht-motorische Symptome verfolgt werden, da die meisten von ihnen nicht direkt mit IMUs gemessen werden können. Der Zusammenhang zwischen diesen digitalen Fragebögen, von Kapazitäts- und von Performanceparametern sollte weiter detailliert untersucht werden, um ein vollständigeres Verständnis der Alltagsfunktion zu erhalten.

Zusammenfassend lässt sich sagen, dass verschiedene Kontexte, wie Diagnose, Umgebung, Aufgabenkomplexität und Medikamentenstatus einen Einfluss auf die Mobilität in den hier untersuchten Gruppen haben. Daher sollte die Mobilität in verschiedenen Kontexten beurteilt werden, um mehr Informationen über die Alltagsfunktion zu erhalten. Diese Informationen können für eine individuellere Behandlung verwendet werden.

English summary

The influence of the context on mobility in neurological disorders – a wearable technology approach

The current digital transformation is changing healthcare rapidly. There is a growing amount of wearable technology available that contribute to the analysis of mobility. Mobility can be used to discriminate healthy adults from patients with neurodegenerative diseases [17, 18], to differentiate between different subtypes of neurodegenerative diseases [19–21] and have potential to detect neurodegenerative diseases in a preclinical stage [15, 18, 22]. Mobility limitations have a large impact on the quality of life. Healthcare professionals evaluate mobility limitations often by letting the patient answering questions about their mobility limitations (perception) and by taking a qualitative look at how the patient walks. The walk provides information about the capacity, what a patient is able to do (generally close to their maximal ability when performed under supervision). The healthcare professional has however not obtained any information about what the patient actually does during daily living, the performance. The combined assessment of perception, capacity and performance provides a measure of the daily function of a patient [3].

Wearable sensors can be used to objectively quantify mobility in different settings and under different circumstances. There is an increasing amount of literature that shows that mobility might be influenced by the context (surroundings, circumstances, environment or setting) it is measured in. It is however still unclear how the mobility measures obtained in different contexts relate to each other. The aim of this dissertation is to better understand the influence of the context on mobility in older adults and patients with neurodegenerative disorders.

A systematic evaluation of studies that compared the same mobility parameters measured in supervised and unsupervised contexts with each other in older adults, patients with Parkinson's disease (PD) and multiple sclerosis (MS) revealed -40% to 180% change between the two contexts. These differences are much larger than the effects usually measured after interventions. Thus, small and even moderate treatment effects might be buried under the variations introduced by the measurement techniques themselves if the differences between supervised and unsupervised assessments are not appropriately considered.

A swinging motion of the arms characterizes gait. A reduction or asymmetry in the swinging motion is often seen in patients with PD [38, 170, 171] and could be a potential prodromal and progression marker of PD [22, 170]. In Chapter 4, the development of an algorithm to quantify arm swing during walking from wearable sensor data from the wrist was described. The algorithm was validated for healthy adults and patients with PD. The algorithm is highly accurate. In a preliminary analysis, arm swing parameters were compared between healthy adults and patients with PD. Significant differences in arm swing parameters were found between the groups, indicating that the algorithm is sensitive enough to detect differences between healthy adults and patients with PD.

The arm swing algorithm was used to analyse the effect of dopaminergic medication on arm swing in patients with PD during walking tasks with different complexity. Arm swing during straight walking at preferred speed, at fast speed and during dual-tasking was analysed both OFF and ON dopaminergic medication. Arm swing showed moderate improvements with dopaminergic medication at preferred

walking speed. Large improvements with medication were found for several arm swing parameters at fast walking speed. However, the responsiveness of arm swing to medication during dual-tasking was small or even negative. Arm swing parameters could be used in PD as an easily and frequently detectable marker for disease progression and treatment response in clinical routine and clinical trials.

To continue the development and validation of mobility-related algorithms in different contexts, a study protocol for a full-body wearable sensor dataset with simultaneously recorded optical motion capture data was introduced. Mobility data will be collected under standardized conditions (reflecting the typical assessment in the clinical and laboratory environment) and non-standardized conditions (reflecting daily life performance). Data will be collected from healthy adults (18-60 years) and healthy older adults (>60 years), as well as PD, MS, stroke and chronic low back pain patients. Specific clinical scales and questionnaires will be collected about the cognitive function, activities of daily living, fatigue and quality of life. This study protocol will result, to our best knowledge, in a unique dataset worldwide of this extent and granularity that can be used by the research community to validate mobility algorithms in different contexts.

Unsupervised performance assessments provide complementary information to the supervised capacity assessments. Improvements in capacity measured in the laboratory might not automatically indicate an improvement in performance. Since improvements in performance might be most relevant to patients, performance assessments should be implemented into clinical practice and as outcome in clinical trials. It remains important to regularly measure the capacity in a standardized setting, where you can control for influencing factors like the context.

The context has an influence on both capacity and performance measures. Simple tasks to measure the capacity seem to correspond best with the more extreme performance values during daily living [120, 132, 148]. Whereas the capacity measures of more complex tasks correspond better with the average performance [89, 90].

The response to treatment is also affected by the context. During simple tasks, there is a positive effect of dopaminergic medication on mobility in patients with PD. However, during more complex tasks, there were only small and sometimes even negative effects of dopaminergic medication. This is seen in arm swing (Chapter 5), gait [197] and balance [39, 48, 190, 214]. Since more complex tasks represent daily living more closely, it could be that dopaminergic medication is not beneficial during daily living. To understand the effect of treatment during daily living, a first step would be to additionally assess the capacity during tasks with a higher complexity. In the future, the performance assessments should also be implemented to be able to directly assess the effect of treatment on the performance. For the implementation of unsupervised performance assessments in clinical routine and research, a few factors need to be taken into account. More mobility-related algorithms should be developed and validated in both settings as far as possible. Data analysis of unsupervised performance data should make use of the high amount of movement repetitions measured, e.g. by taking the distribution into account and not only average values. The mobility-related parameters obtained from the algorithms should be analysed to see which parameters provide relevant disease progression and treatment response markers.

When performance assessments become part of clinical care, patients can besides discussing their problems with a healthcare professional, also share their objective performance data with them. Together with the clinical examination, the healthcare professional has then information about the capacity, performance and perception

at their disposal. With this information, it will become easier to correctly diagnose patients in an earlier disease stage, track the disease progression and response to treatment. This will make it possible to provide more individualized treatment and increase the quality of life of patients.

Chapter 9

References

[1] D. Johansson, A. Ericsson, A. Johansson, A. Medvedev, D. Nyholm, F. Ohlsson, M. Senek, J. Spira, I. Thomas, J. Westin, and F. Bergquist, "Individualization of levodopa treatment using a microtablet dispenser and ambulatory accelerometry," *CNS Neuroscience and Therapeutics*, vol. 24, no. 5, pp. 439–447, 2018.

[2] C. H. Kuo, G. A. White-Dzuro, and A. L. Ko, "Approaches to closed-loop deep brain stimulation for movement disorders," *Neurosurgical Focus*, vol. 45, no. 2, 2018.

[3] W. Maetzler, L. Rochester, R. Bhidayasiri, A. J. Espay, A. Sánchez-Ferro, and J. M. van Uem, "Modernizing Daily Function Assessment in Parkinson's Disease Using Capacity, Perception, and Performance Measures," *Movement Disorders*, vol. 36, no. 1, pp. 76–82, 2021.

[4] World Health Organization, *International Classification of Functioning, Disability and Health.* 2001.

[5] J. Shafrin, J. Sullivan, D. P. Goldman, and T. M. Gill, "The association between observed mobility and quality of life in the near elderly," *PLoS ONE*, vol. 12, no. 8, 2017.

[6] J. C. Davis, S. Bryan, L. C. Li, J. R. Best, C. Liang Hsu, C. Gomez, K. A. Vertes, and T. Liu-Ambrose, "Mobility and cognition are associated with well-being and health related quality of life among older adults: a cross-sectional analysis of the Vancouver Falls Prevention Cohort," *BMC Geriatrics*, vol. 15, no. 75, 2015.

[7] A. F. Ambrose, G. Paul, and J. M. Hausdorff, "Risk factors for falls among older adults: A review of the literature," *Maturitas*, vol. 75, no. 1, pp. 51–61, 2013.

[8] S. H. Park, "Tools for assessing fall risk in the elderly: a systematic review and meta-analysis," *Aging Clinical and Experimental Research*, vol. 30, no. 1, 2018.

[9] N. Kutner, R. Zhang, Y. Huang, and P. Painter, "Gait Speed and Mortality, Hospitalization, and Functional Status Change Among Hemodialysis Patients: A US Renal Data System Special Study," *Am J Kidney Dis.*, vol. 66, no. 2, pp. 297–304, 2015.

[10] L. P. Fried, C. M. Tangen, J. Walston, A. B. Newman, C. Hirsch, J. Gottdiener, T. Seeman, R. Tracy, W. J. Kop, G. Burke, and M. A. McBurnie, "Frailty in older adults: Evidence for a phenotype," *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, vol. 56, no. 3, pp. 146–157, 2001.

[11] T. Abe, A. Kitamura, Y. Taniguchi, H. Amano, S. Seino, Y. Yokoyama, M. Nishi, M. Narita, T. Ikeuchi, Y. Fujiwara, and S. Shinkai, "Pathway from gait speed to incidence of disability and mortality in older adults: A mediating role of physical activity," *Maturitas*, vol. 123, no. November 2018, pp. 32–36, 2019.

[12] R. Feldman, S. Schreiber, C. G. Pick, and E. Been, "Gait, balance, mobility and muscle strength in people with anxiety compared to healthy individuals," *Human Movement Science*, vol. 67, no. September, p. 102513, 2019.

[13] S. K. Darweesh, S. Licher, F. J. Wolters, P. J. Koudstaal, M. K. Ikram, and M. A. Ikram, "Quantitative gait, cognitive decline, and incident dementia: The Rotterdam Study," *Alzheimer's and Dementia*, vol. 15, no. 10, pp. 1264–1273, 2019.

[14] L. Li and B. P. Loo, "Mobility impairment, social engagement, and life satisfaction among the older population in China: a structural equation modeling analysis," *Quality of Life Research*, vol. 26, no. 5, pp. 1273–1282, 2017.

[15] S. Del Din, M. Elshehabi, B. Galna, M. A. Hobert, E. Warmerdam, U. Suenkel, K. Brockmann, F. Metzger, C. Hansen, D. Berg, L. Rochester, and W. Maetzler, "Gait analysis with wearables predicts conversion to parkinson disease," *Annals of Neurology*, vol. 86, no. 3, pp. 357–367, 2019.

[16] S. Lotankar, K. S. Prabhavalkar, and L. K. Bhatt, "Biomarkers for Parkinson's Disease: Recent Advancement," *Neuroscience Bulletin*, vol. 33, no. 5, pp. 585–597, 2017.

[17] R. Z. U. Rehman, S. Del Din, Y. Guan, A. J. Yarnall, J. Q. Shi, and L. Rochester, "Selecting Clinically Relevant Gait Characteristics for Classification of Early Parkinson's Disease: A Comprehensive Machine Learning Approach," *Scientific Reports*, vol. 9, no. 1, pp. 1–12, 2019.

[18] A. Dalton, H. Khalil, M. Busse, A. Rosser, R. van Deursen, and G. ÓLaighin, "Analysis of gait and balance through a single triaxial accelerometer in presymptomatic and symptomatic Huntington's disease," *Gait and Posture*, vol. 37, no. 1, pp. 49–54, 2013.

[19] R. Mc Ardle, S. Del Din, B. Galna, A. Thomas, and L. Rochester, "Differentiating dementia disease subtypes with gait analysis: feasibility of wearable sensors?," *Gait and Posture*, vol. 76, no. August 2019, pp. 372–376, 2020.

[20] M. Prime, J. L. Mckay, A. Bay, A. Hart, C. Kim, A. Abraham, and M. E. Hackney, "Differentiating Parkinson Disease Subtypes Using Clinical Balance Measures," *J Neurol Phys Ther*, vol. 44, no. 1, pp. 34–41, 2020.

[21] D. Orcioli-Silva, R. Vitório, E. Lirani-Silva, P. C. R. Santos, V. S. Beretta, and L. T. B. Gobbi, "Objective measures of unobstructed walking and obstacle avoidance in Parkinson's disease subtypes," *Gait and Posture*, vol. 62, no. February, pp. 405–408, 2018.

[22] A. Mirelman, H. Bernad-Elazari, A. Thaler, E. Giladi-Yacobi, T. Gurevich, M. Gana-Weisz, R. Saunders-Pullman, D. Raymond, N. Doan, S. Bressman, K. Marder, R. Alcalay, A. Rao, D. Berg, K. Brockmann, J. Aasly, B. Waro, E. Tolosa, D. Vilas, C. Pont-Sunyer, A. Orr-Urtreger, J. Hausdorff, and N. Giladi, "Arm Swing as a Potential New Prodromal Marker of Parkinson's Disease," *Mov Disord.*, vol. 31, no. 10, pp. 1527–1534, 2016.

[23] Statista, "Population of Germany as of December 31, 2019, by age group," 2020.

[24] T. M. Manini and B. C. Clark, "Dynapenia and aging: An update," *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, vol. 67 A, no. 1, pp. 28–40, 2012.

[25] F. Lauretani, C. R. Russo, S. Bandinelli, B. Bartali, C. Cavazzini, A. Di Iorio, A. M. Corsi, T. Rantanen, J. M. Guralnik, and L. Ferrucci, "Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia," *Journal of Applied Physiology*, vol. 95, no. 5, pp. 1851–1860, 2003.

[26] N. Herssens, E. Verbecque, A. Hallemans, L. Vereeck, V. Van Rompaey, and W. Saeys, "Do spatiotemporal parameters and gait variability differ across the lifespan of healthy adults? A systematic review," *Gait and Posture*, vol. 64, pp. 181–190, 2018.

[27] A. Mirelman, H. Bernad-Elazari, T. Nobel, A. Thaler, A. Peruzzi, M. Plotnik, N. Giladi, and J. M. Hausdorff, "Effects of Aging on Arm Swing during Gait: The Role of Gait Speed and Dual Tasking," *PLOS ONE*, vol. 10, no. 8, 2015.

[28] D. Goble and H. Baweja, "Normative Data for the BTrackS Balance Test of Postural Sway: Results from 16,357 Community- Dwelling Individuals Who Were 5 to 100 Years Old," *Physical Therapy*, vol. 98, pp. 779–785, 2018.

[29] Y. Hou, X. Dan, M. Babbar, Y. Wei, S. G. Hasselbalch, D. L. Croteau, and V. A. Bohr, "Ageing as a risk factor for neurodegenerative disease," *Nature Reviews Neurology*, vol. 15, no. 10, pp. 565–581, 2019.

[30] M. Nerius, A. Fink, and G. Doblhammer, "Parkinson's disease in Germany: prevalence and incidence based on health claims data," *Acta Neurologica Scandinavica*, vol. 136, pp. 386–392, 2017.

[31] W. Dauer and S. Przedborski, "Parkinson's disease: Mechanisms and models," *Neuron*, vol. 39, pp. 889–909, 2003.

[32] A. Samii, J. G. Nutt, and B. R. Ransom, "Parkinson's disease dementia," *The Lancet*, vol. 363, pp. 1783–1793, 2004.

[33] A. Mirelman, P. Bonato, R. Camicioli, T. D. Ellis, N. Giladi, J. L. Hamilton, C. J. Hass, J. M. Hausdorff, E. Pelosin, and Q. J. Almeida, "Gait impairments in Parkinson's disease," *The Lancet Neurology*, vol. 18, no. 7, pp. 697–708, 2019.

[34] J. G. Nutt and B. R. Bloem, "Freezing of gait: moving forward on a mysterious clinical phenomenon," *Lancet Neurol*, vol. 10, no. 8, pp. 734–744, 2011.

[35] N. Giladi and A. Nieuwboer, "Understanding and treating freezing of gait in Parkinsonism, proposed working definition, and setting the stage," *Movement Disorders*, vol. 23, no. SUPPL. 2, pp. 423–425, 2008.

[36] A. Cucca, M. C. Biagioni, J. E. Fleisher, S. Agarwal, A. Son, P. Kumar, M. Brys, and A. Di Rocco, "Freezing of gait in Parkinson's disease: from pathophysiology to emerging therapies," *Neurodegenerative disease management*, vol. 6, no. 5, pp. 431–446, 2016.

[37] M. W. Creaby and M. H. Cole, "Gait characteristics and falls in Parkinson's disease: A systematic review and meta-analysis," *Parkinsonism and Related Disorders*, vol. 57, no. July, pp. 1–8, 2018.

[38] M. D. Lewek, R. Poole, J. Johnson, O. Halawa, and X. Huang, "Arm Swing Magnitude and Asymmetry During Gait in the Early Stages of Parkinson's Disease," *Gait and Posture*, vol. 31, no. 2, p. 256, 2010.

[39] C. Curtze, J. G. Nutt, P. Carlson-Kuhta, M. Mancini, and F. B. Horak, "Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease," *Movement Disorders*, vol. 30, no. 10, pp. 1361–1370, 2015.

[40] B. Debû, C. De Oliveira Godeiro, J. C. Lino, and E. Moro, "Managing Gait, Balance, and Posture in Parkinson's Disease," *Current Neurology and Neuroscience Reports*, vol. 18, no. 5, 2018.

[41] F. Doná, C. C. Aquino, J. M. Gazzola, V. Borges, S. M. Silva, F. F. Ganança, H. H. Caovilla, and H. B. Ferraz, "Changes in postural control in patients with Parkinson's disease: a posturographic study," *Physiotherapy (United Kingdom)*, vol. 102, no. 3, pp. 272–279, 2016.

[42] B. Aktar, B. Donmez Colakoglu, and B. Balci, "Does the postural stability of patients with Parkinson's disease affect the physical activity?," *International Journal of Rehabilitation Research*, no. 3195, pp. 41–47, 2020.

[43] M. T. Hayes, "Parkinson's Disease and Parkinsonism," *American Journal of Medicine*, vol. 132, no. 7, pp. 802–807, 2019.

[44] K. Rosqvist, M. Horne, P. Hagell, S. Iwarsson, M. H. Nilsson, and P. Odin, "Levodopa effect and motor function in late stage Parkinson's disease," *Journal of Parkinson's Disease*, vol. 8, no. 1, pp. 59–70, 2018.

[45] H. Zach, M. Dirkx, J. W. Pasman, B. R. Bloem, and R. C. Helmich, "The patient's perspective: The effect of levodopa on Parkinson symptoms," *Parkinsonism and Related Disorders*, vol. 35, pp. 48–54, 2017.

[46] L. Rochester, K. Baker, A. Nieuwboer, and D. Burn, "Targeting dopa-sensitive and dopa-resistant gait dysfunction in Parkinson's disease: Selective responses to internal and external cues," *Movement Disorders*, vol. 26, no. 3, pp. 430–435, 2011.

[47] M. S. Bryant, D. H. Rintala, J. G. Hou, A. L. Charness, A. L. Fernandez, R. L. Collins, J. Baker, E. C. Lai, and E. J. Protas, "Gait variability in Parkinson's disease: influence of walking speed and dopaminergic treatment," *Physiology and behavior*, vol. 33, no. 9, pp. 959–964, 2011.

[48] A. Beuter, R. Hernández, R. Rigal, J. Modolo, and P. J. Blanchet, "Postural sway and effect of levodopa in early Parkinson's disease," *Canadian Journal of Neurological Sciences*, vol. 35, no. 1, pp. 65–68, 2008.

[49] P. H. Pelicioni, M. A. Brodie, M. D. Latt, J. C. Menant, H. B. Menz, V. S. Fung, and S. R. Lord, "Head and trunk stability during gait before and after levodopa intake in Parkinson's disease subtypes," *Experimental Gerontology*, vol. 111, pp. 78–85, 2018.

[50] D. W. Brodell, N. T. Stanford, C. E. Jacobson, P. Schmidt, and M. S. Okun, "Carbidopa/levodopa dose elevation and safety concerns in Parkinson's patients: A cross-sectional and cohort design," *BMJ Open*, vol. 2, no. 6, pp. 1–6, 2012.

[51] J. E. Ahlskog and M. D. Muenter, "Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature," *Movement Disorders*, vol. 16, no. 3, pp. 448–458, 2001.

[52] S. Montel, A. M. Bonnet, and C. Bungener, "Quality of life in relation to mood, coping strategies, and dyskinesia in parkinson's disease," *Journal of Geriatric Psychiatry and Neurology*, vol. 22, no. 2, pp. 95–102, 2009.

[53] S. Chapuis, L. Ouchchane, O. Metz, L. Gerbaud, and F. Durif, "Impact of the motor complications of Parkinson's disease on the quality of life," *Movement Disorders*, vol. 20, no. 2, pp. 224–230, 2005.

[54] B. Lindholm, F. Eek, Ö. Skogar, and E. E. Hansson, "Dyskinesia and FAB score predict future falling in Parkinson's disease," *Acta Neurologica Scandinavica*, vol. 139, no. 6, pp. 512–518, 2019.

[55] O. Rascol, S. Perez-Lloret, P. Damier, A. Delval, P. Derkinderen, A. Destée, W. G. Meissner, F. Tison, and L. Negre-Pages, "Falls in ambulatory non-demented patients with Parkinson's disease," *Journal of Neural Transmission*, vol. 122, no. 10, pp. 1447–1455, 2015.

[56] J. Holstiege, A. Steffen, B. Goffrier, and J. Bätzing, "Epidemiology of multiple sclerosis – a population-based , Germany-wide study," *Versorgungsatlas*, no. 9, 2017.

[57] J. Correale, M. I. Gaitán, M. C. Ysrraelit, and M. P. Fiol, "Progressive multiple sclerosis: from pathogenic mechanisms to treatment," *Brain*, vol. 140, no. 3, pp. 527–546, 2017.

[58] A. J. Thompson, S. E. Baranzini, J. Geurts, B. Hemmer, and O. Ciccarelli, "Multiple sclerosis," *The Lancet*, vol. 391, no. 10130, pp. 1622–1636, 2018.

[59] A. J. Thompson, A. T. Toosy, and O. Ciccarelli, "Pharmacological management of symptoms in multiple sclerosis: Current approaches and future directions," *The Lancet Neurology*, vol. 9, no. 12, pp. 1182–1199, 2010.

[60] L. Comber, R. Galvin, and S. Coote, "Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis," *Gait and Posture*, vol. 51, pp. 25–35, 2017.

[61] M. H. Cameron and S. Lord, "Postural control in multiple sclerosis: Implications for fall prevention," *Current Neurology and Neuroscience Reports*, vol. 10, no. 5, pp. 407–412, 2010.

[62] S. Citaker, A. G. Gunduz, M. B. Guclu, B. Nazliel, C. Irkec, and D. Kaya, "Relationship between foot sensation and standing balance in patients with multiple sclerosis," *Gait and Posture*, vol. 34, no. 2, pp. 275–278, 2011.

[63] M. Absinta, H. Lassmann, and B. D. Trapp, "Mechanisms underlying progression in multiple sclerosis," *Current opinion in neurology*, vol. 33, no. 3, pp. 277–285, 2020.

[64] N. P. F. Pequeno, N. L. d. A. Cabral, D. M. Marchioni, S. C. V. C. Lima, and C. d. O. Lyra, "Quality of life assessment instruments for adults: a systematic review of population-based studies," *Health and Quality of Life Outcomes*, vol. 18, no. 1, pp. 1–13, 2020.

[65] M. Richards, K. Marder, L. Cote, and R. Mayeux, "Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination.," *Mov Disord*, vol. 9, no. 1, pp. 89–91, 1994.

[66] M. Topley and J. G. Richards, "A comparison of currently available optoelectronic motion capture systems," *Journal of Biomechanics*, vol. 106, p. 109820, 2020.

[67] W. Maetzler, J. Domingos, K. Srulijes, J. J. Ferreira, and B. R. Bloem, "Quantitative wearable sensors for objective assessment of Parkinson's disease," *Movement Disorders*, vol. 28, no. 12, pp. 1628–1637, 2013.

[68] M. Iosa, P. Picerno, S. Paolucci, and G. Morone, "Wearable inertial sensors for human movement analysis," *Expert Review of Medical Devices*, vol. 13, no. 7, pp. 641–659, 2016.

[69] S. Del Din, A. Godfrey, C. Mazzà, S. Lord, and L. Rochester, "Free-living monitoring of Parkinson's disease: Lessons from the field," *Movement Disorders*, vol. 31, no. 9, pp. 1293–1313, 2016.

[70] J. Klucken, T. Gladow, J. G. Hilgert, M. Stamminger, ·. Christian Weigand, and B. Eskofier, ""Wearables" in der Behandlung neurologischer Erkrankungen-wo stehen wir heute?," *Der Nervenarzt*, vol. 90, pp. 787–795, 2019.

[71] S. Del Din, A. Godfrey, B. Galna, S. Lord, and L. Rochester, "Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length," *Journal of NeuroEngineering and Rehabilitation*, vol. 13, no. 46, 2016.

[72] Y. Moon, J. Sung, R. An, M. E. Hernandez, and J. J. Sosnoff, "Gait variability in people with neurological disorders: A systematic review and meta-analysis," *Human Movement Science*, vol. 47, pp. 197–208, 2016.

[73] D. A. Marinho, H. P. Neiva, and J. E. Morais, "The use of wearable sensors in human movement analysis in non-swimming aquatic activities: A systematic review," *International Journal of Environmental Research and Public Health*, vol. 16, no. 24, 2019.

[74] L. C. Benson, C. A. Clermont, E. Bošnjak, R. Ferber, E. Bosnjak, and R. Ferber, "The use of wearable devices for walking and running gait analysis outside of the lab: a systematic review," *Gait and Posture*, vol. 63, pp. 124–138, 2018.

[75] H. Dowd, M. A. Zdrodowska, K. H. Radler, T. E. Cersonsky, A. K. Rao, E. D. Huey, S. Cosentino, and E. D. Louis, "Prospective Longitudinal Study of Gait and Balance in a Cohort of Elderly Essential Tremor Patients," *Frontiers in Neurology*, vol. 11, no. November, pp. 1–14, 2020.

[76] J. C. M. Schlachetzki, J. Barth, F. Marxreiter, J. Gossler, Z. Kohl, S. Reinfelder, H. Gassner, K. Aminian, B. M. Eskofier, J. Winkler, and J. Klucken, "Wearable sensors objectively measure gait parameters in Parkinson's disease," *PLoS ONE*, vol. 12, no. 10, pp. 1–18, 2017.

[77] F. Marxreiter, H. Gaßner, O. Borozdina, J. Barth, Z. Kohl, J. C. M. Schlachetzki, C. Thun-Hohenstein, D. Volc, B. M. Eskofier, J. Winkler, and J. Klucken, "Sensor-based gait analysis of individualized improvement during apomorphine titration in Parkinson's disease," *Journal of Neurology*, vol. 265, no. 11, pp. 2656–2665, 2018.

[78] WordSense, "Dictionary."

[79] V. Robles-Garcia, Y. Corral-Bergantinos, N. Espinosa, M. A. Jacome, C. Garcia-Sancho, J. Cudeiro, and P. Arias, "Spatiotemporal Gait Patterns During Overt and Covert Evaluation in Patients With Parkinson s Disease and Healthy Subjects: Is There a Hawthorne Effect?," *Journal of applied biomechanics*, vol. 31, no. 3, pp. 189–194, 2015.

[80] C. Barthel, E. Mallia, B. Debû, B. R. Bloem, and M. U. Ferraye, "The Practicalities of Assessing Freezing of Gait," *Journal of Parkinson's Disease*, vol. 6, no. 4, pp. 667–674, 2016.

[81] P. A. Rocha, G. M. Porfírio, H. B. Ferraz, and V. F. Trevisani, "Effects of external cues on gait parameters of Parkinson's disease patients: A systematic review," *Clinical Neurology and Neurosurgery*, vol. 124, pp. 127–134, 2014.

[82] K. S. Park, C. J. Hass, B. Patel, and C. M. Janelle, "Musical pleasure beneficially alters stride and arm swing amplitude during rhythmically-cued walking in people with Parkinson's disease," *Human Movement Science*, vol. 74, no. November, p. 102718, 2020.

[83] H. Xu, M. E. Hunt, K. Bo Foreman, J. Zhao, and A. Merryweather, "Gait alterations on irregular surface in people with Parkinson's disease," *Clinical Biomechanics*, vol. 57, pp. 93–98, 2018.

[84] L. Allet, S. Armand, R. A. De Bie, Z. Pataky, K. Aminian, F. R. Herrmann, and E. D. De Bruin, "Gait alterations of diabetic patients while walking on different surfaces," *Gait and Posture*, vol. 29, pp. 488–493, 2009.

[85] B. Hejrati, S. Chesebrough, K. Bo Foreman, J. J. Abbott, and A. S. Merryweather, "Comprehensive quantitative investigation of arm swing during walking at various speed and surface slope conditions," *Human Movement Science*, vol. 49, pp. 104–115, 2016.

[86] S. Kimel-Naor, A. Gottlieb, and M. Plotnik, "The effect of uphill and downhill walking on gait parameters: A self-paced treadmill study," *Journal of Biomechanics*, vol. 60, pp. 142–149, 2017.

[87] E. Smith, T. Cusack, C. Cunningham, and C. Blake, "The influence of a cognitive dual task on the gait parameters of healthy older adults: A systematic review and meta-analysis," *Journal of aging and physical activity*, vol. 25, no. 4, pp. 671–686, 2017.

[88] N. Fritz, F. Cheek, and D. Nichols-Larsen, "Motor-cognitive dual-task training in neurologic disorders: a systematic review," *J Neurol Phys Ther*, vol. 39, no. 3, pp. 142–153, 2016.

[89] I. Hillel, E. Gazit, A. Nieuwboer, L. Avanzino, L. Rochester, A. Cereatti, U. D. Croce, M. Olde Rikkert, B. R. Bloem, E. Pelosin, S. Del Din, P. Ginis, N. Giladi, A. Mirelman, and J. M. Hausdorff, "Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gap between gait performance in the lab and during 24/7 monitoring," *European Review of Aging and Physical Activity*, vol. 16, no. 6, 2019.

[90] A. Atrsaei, M. F. Corrà, F. Dadashi, N. Vila-chã, L. Maia, B. Mariani, W. Maetzler, and K. Aminian, "Gait speed in clinical and daily living assessments in Parkinson's disease patients: performance versus capacity," *npj Parkinson's disease*, vol. 7, 2021.

[91] O. Blin, A. M. Ferrandez, J. Pailhous, and G. Serratrice, "Dopa-sensitive and Dopa-resistant gait parameters in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 103, no. 1, pp. 51–54, 1991.

[92] M. S. Bryant, D. H. Rintala, J. G. Hou, E. C. Lai, and E. J. Protas, "Effects of levodopa on forward and backward gait patterns in persons with Parkinson's disease," *NeuroRehabilitation*, vol. 29, no. 3, pp. 247–252, 2011.

[93] E. C. Kal, J. Van Der Kamp, and H. Houdijk, "External attentional focus enhances movement automatization: A comprehensive test of the constrained action hypothesis," *Human Movement Science*, vol. 32, pp. 527–539, 2013.

[94] K. T. Larkin, S. L. Schauss, D. M. Elnicki, and J. L. Goodie, "Detecting white coat and reverse white coat effects in clinic settings using measures of blood pressure habituation in the clinic and patient self-monitoring of blood pressure," *Journal of Human Hypertension*, vol. 21, pp. 516–524, 2007.

[95] E. Paradis and G. Sutkin, "Beyond a good story: from Hawthorne Effect to reactivity in health professions education research," *Medical Education*, vol. 51, pp. 31–39, 2017.

[96] F. A. Barbieri, P. C. R. Dos Santos, E. Lirani-Silva, R. Vitório, L. T. B. Gobbi, and J. H. Van Diëen, "Systematic review of the effects of fatigue on spatiotemporal gait parameters," *Journal of Back and Musculoskeletal Rehabilitation*, vol. 26, no. 2, pp. 125–131, 2013.

[97] A. Phillips and S. McClinton, "Gait deviations associated with plantar heel pain: A systematic review," *Clinical Biomechanics*, vol. 42, pp. 55–64, 2017.

[98] D. Hamacher, F. Herold, P. Wiegel, D. Hamacher, and L. Schega, "Brain activity during walking: A systematic review," *Neuroscience and Biobehavioral Reviews*, vol. 57, pp. 310–327, 2015.

[99] L. C. Benson, C. A. Clermont, R. Watari, T. Exley, and R. Ferber, "Automated accelerometer-based gait event detection during multiple running conditions," *Sensors (Switzerland)*, vol. 19, no. 7, pp. 1–19, 2019.

[100] F. A. Storm, C. J. Buckley, and C. Mazzà, "Gait event detection in laboratory and real life settings: Accuracy of ankle and waist sensor based methods," *Gait and Posture*, vol. 50, pp. 42–46, 2016.

[101] M. I. Tolea and J. E. Galvin, "Relationship between Mobility Dysfunction Staging and Global Cognitive Performance," *Alzheimer Dis Assoc Disord*, vol. 30, no. 3, pp. 230–236, 2016.

[102] A. Bergland, N. Emaus, and B. H. Strand, "Mobility as a predictor of all-cause mortality in older men and women: 11.8 year follow-up in the Tromsøstudy," *BMC Healt Services Research*, vol. 17, no. 22, 2017.

[103] R. Mahmoudi, J. L. Novella, P. Manckoundia, F. Ahssaini, P. O. Lang, F. Blanchard, D. Jolly, and M. Dramé, "Is functional mobility an independent mortality risk factor in subjects with dementia?," *Maturitas*, vol. 103, no. December 2016, pp. 65–70, 2017.

[104] L. M. Wallace, O. Theou, J. Godin, M. K. Andrew, D. A. Bennett, and K. Rockwood, "Investigation of frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's disease: a cross-sectional analysis of data from the Rush Memory and Aging Project," *The Lancet Neurology*, vol. 18, no. 2, pp. 177–184, 2019.

[105] J. M. T. van Uem, J. Marinus, C. Canning, R. van Lummel, R. Dodel, I. Liepelt-Scarfone, D. Berg, M. E. Morris, and W. Maetzler, "Health-Related Quality of Life in patients with Parkinson's disease—A systematic review based on the ICF model," *Neuroscience and Biobehavioral Reviews*, vol. 61, pp. 26–34, feb 2016.

[106] C. G. Goetz, B. C. Tilley, S. R. Shaftman, G. T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M. B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A. E. Lang, A. Lees, S. Leurgans, P. A. LeWitt, D. Nyenhuis, C. W. Olanow, O. Rascol, A. Schrag, J. A. Teresi, J. J. van Hilten, N. LaPelle, P. Agarwal, S. Athar, Y. Bordelan, H. M. Bronte-Stewart, R. Camicioli, K. Chou, W. Cole, A. Dalvi, H. Delgado, A. Diamond, J. P. Dick, J. Duda, R. J. Elble, C. Evans, V. G. Evidente, H. H. Fernandez, S. Fox, J. H. Friedman, R. D. Fross, D. Gallagher, C. G. Goetz, D. Hall, N. Hermanowicz, V. Hinson, S. Horn, H. Hurtig, U. J. Kang, G. Kleiner-Fisman, O. Klepitskaya, K. Kompoliti, E. C. Lai, M. L. Leehey, I. Leroi, K. E. Lyons, T. McClain, S. W. Metzer, J. Miyasaki, J. C. Morgan, M. Nance, J. Nemeth, R. Pahwa, S. A. Parashos, J. S. J. S. Schneider, A. Schrag, K. Sethi, L. M. Shulman, A. Siderowf, M. Silverdale, T. Simuni, M. Stacy, M. B. Stern, R. M. Stewart, K. Sullivan, D. M. Swope, P. M. Wadia, R. W. Walker, R. Walker, W. J. Weiner, J. Wiener, J. Wilkinson, J. M. Wojcieszek, S. Wolfrath, F. Wooten, A. Wu, T. A. Zesiewicz, and R. M. Zweig, "Movement

Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results," *Movement Disorders*, vol. 23, no. 15, pp. 2129–2170, 2008.

[107] J. Kurtzke, "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)," *Neurology*, vol. 33, pp. 1444–1452, 1983.

[108] R. C. Van Lummel, S. Walgaard, M. A. Hobert, W. Maetzler, J. H. Van Dieën, F. Galindo-Garre, and C. B. Terwee, "Intra-Rater, Inter-Rater and Test-Retest Reliability of an Instrumented Timed Up and Go (iTUG) Test in Patients with Parkinson's Disease," *PLoS ONE*, vol. 11, no. 3, 2016.

[109] M. Mancini, C. Curtze, S. Stuart, M. El-Gohary, J. McNames, J. G. Nutt, and F. B. Horak, "The Impact of Freezing of Gait on Balance Perception and Mobility in Community-Living with Parkinson'S Disease," *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, pp. 3040–3043, 2018.

[110] A. J. Espay, J. M. Hausdorff, A. Sanchez-Ferro, J. Klucken, A. Merola, P. Bonato, S. S. Paul, F. B. Horak, J. A. Vizcarra, T. A. Mestre, R. Reilmann, A. Nieuwboer, R. E. Dorsey, L. Rochester, B. R. Bloem, W. Maetzler, and on behalf of the MDS Technology Task Force, "A Roadmap for Implementation of Patient-Centered Digital Outcome Measures in Parkinson's disease Obtained Using Mobile Health Technologies," *Mov Disord*, vol. 34, no. 5, pp. 657–663, 2019.

[111] E. R. Dorsey, A. M. Glidden, M. R. Holloway, G. L. Birbeck, and L. H. Schwamm, "Teleneurology and mobile technologies: the future of neurological care," *Nature Reviews Neurology*, vol. 14, pp. 285–297, apr 2018.

[112] N. J. Holter, "Radioelectrocardiography: A New Technique for Cardiocasular Studies," *Annals New York Academy of Sciences*, vol. 65, pp. 913–923, 1957.

[113] R. Wachter, K. Gröschel, G. Gelbrich, G. F. Hamann, P. Kermer, J. Liman, J. Seegers, K. Wasser, A. Schulte, F. Jürries, A. Messerschmid, N. Behnke, S. Gröschel, T. Uphaus, A. Grings, T. Ibis, S. Klimpe, M. Wagner-Heck, M. Arnold, E. Protsenko, P. U. Heuschmann, D. Conen, and M. Weber-Krüger, "Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFrandomised): an open-label randomised controlled trial," *The Lancet Neurology*, vol. 16, no. 4, pp. 282–290, 2017.

[114] L. Bally, H. Thabit, S. Hartnell, E. Andereggen, Y. Ruan, M. E. Wilinska, C. Stettler, M. M. Wertli, M. L. Evans, A. P. Coll, and R. Hovorka, "Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care," *N Engl J Med*, vol. 379, no. 6, pp. 547–56, 2018.

[115] J. M. T. Van Uem, T. Isaacs, A. Lewin, E. Bresolin, D. Salkovic, A. J. Espay, H. Matthews, and W. Maetzler, "A Viewpoint on Wearable Technology-Enabled Measurement of Wellbeing and Health-Related Quality of Life in Parkinson's Disease," *Journal of Parkinson's Disease*, vol. 6, pp. 279–287, 2016.

[116] V. A. Block, E. Pitsch, P. Tahir, B. A. Cree, D. D. Allen, and J. M. Gelfand, "Remote Physical Activity Monitoring in Neurological Disease: A Systematic Review," *PloS one*, vol. 11, no. 4, p. e0154335, 2016.

[117] J. M. Ryan, J. Fortune, A. Stennett, C. Kilbride, N. Anokye, C. Victor, W. Hendrie, M. Abdul, L. Desouza, G. Lavelle, D. Brewin, L. David, and M. Norris, "Changing physical activity behaviour for people with multiple sclerosis: Protocol of a randomised controlled feasibility trial (iStep-MS)," *BMJ Open*, vol. 7, no. 11, pp. 1–13, 2017.

[118] T. M. Barrett, M. A. Liebert, J. M. Schrock, T. J. Cepon-Robins, A. Mathur, H. Agarwal, P. Kowal, and J. J. Snodgrass, "Physical function and activity among older adults in Jodhpur, India," *Annals of Human Biology*, vol. 43, no. 5, pp. 488–491, 2016.

[119] M. H. Pham, M. Elshehabi, L. Haertner, T. Heger, M. A. Hobert, G. S. Faber, D. Salkovic, J. J. Ferreira, D. Berg, Á. Sanchez-Ferro, J. H. van Dieën, and W. Maetzler, "Algorithm for Turning Detection and Analysis Validated under Home-Like Conditions in Patients with Parkinson's Disease and Older Adults using a 6 Degree-of-Freedom Inertial Measurement Unit at the Lower Back," *Frontiers in Neurology*, vol. 8, no. 135, 2017.

[120] W. Zhang, G. R. H. Regterschot, H. Geraedts, H. Baldus, and W. Zijlstra, "Chair Rise Peak Power in Daily Life Measured With a Pendant Sensor Associates With Mobility, Limitation in Activities, and Frailty in Old People," *IEEE Journal of Biomedical and Health Informatics*, vol. 21, no. 1, pp. 211–217, 2017.

[121] R. Ramsperger, S. Meckler, T. Heger, J. van Uem, S. Hucker, U. Braatz, H. Graessner, D. Berg, Y. Manoli, J. A. Serrano, J. J. Ferreira, M. A. Hobert, W. Maetzler, C. Godinho, A. T. Santos, J. Domingos, D. Abreu, F. Larsen, Ø. Fagerbakke, I. Akeren, H. Wangen, K. S. Maier, O. Scheck, H. Matthews, T. Isaacs, A. Lewin, and E. Bresolin, "Continuous leg dyskinesia assessment in Parkinson's disease -clinical validity and ecological effect," *Parkinsonism and Related Disorders*, vol. 26, pp. 41–46, 2016.

[122] I. Teshuva, I. Hillel, E. Gazit, N. Giladi, A. Mirelman, and J. M. Hausdorff, "Using wearables to assess bradykinesia and rigidity in patients with Parkinson's disease: a focused, narrative review of the literature," *Journal of Neural Transmission*, vol. 126, pp. 699–710, 2017.

[123] A. L. Silva de Lima, L. J. W. Evers, T. Hahn, L. Bataille, J. L. Hamilton, M. A. Little, Y. Okuma, B. R. Bloem, and M. J. Faber, "Freezing of gait and fall detection in Parkinson's disease using wearable sensors: a systematic review," *Journal of Neurology*, vol. 264, no. 8, pp. 1642–1654, 2017.

[124] K. S. Van Schooten, M. Pijnappels, S. M. Rispens, P. J. Elders, P. Lips, A. Daffertshofer, P. J. Beek, and J. H. Van Dieën, "Daily-life gait quality as predictor of falls in older people: A 1-year prospective cohort study," *PLoS ONE*, vol. 11, no. 7, 2016.

[125] A. Weiss, M. Brozgol, M. Dorfman, T. Herman, S. Shema, N. Giladi, and J. M. Hausdorff, "Does the Evaluation of Gait Quality During Daily Life Provide Insight Into Fall Risk? A Novel Approach Using 3-Day Accelerometer Recordings," *Neurorehabilitation and Neural Repair*, vol. 27, no. 8, pp. 742–752, 2013.

[126] T. Iluz, A. Weiss, E. Gazit, A. Tankus, M. Brozgol, M. Dorfman, A. Mirelman, N. Giladi, J. M. Hausdorff, and S. Kritchevsky, "Can a Body-Fixed Sensor Reduce Heisenberg's Uncertainty When It Comes to the Evaluation of Mobility? Effects of Aging and Fall Risk on Transitions in Daily Living," *J Gerontol A Biol Sci Med Sci*, vol. 71, no. 11, pp. 1459–1465, 2016.

[127] M. Punt, S. M. Bruijn, H. Wittink, I. G. Van De Port, and J. H. Van Dieën, "Do clinical assessments, steady-state or daily-life gait characteristics predict falls in ambulatory chronic stroke survivors?," *Journal of Rehabilitation Medicine*, vol. 49, no. 5, pp. 402–409, 2017.

[128] Clinical Trials Transformation Initiative, "CTTI Recommendations: Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials," tech. rep., 2017.

[129] F. Cerreta, "EMA experience on mHealth technology," tech. rep., 2018.

[130] S. M. Rispens, J. H. Van Dieën, K. S. Van Schooten, L. E. Cofré Lizama, A. Daffertshofer, P. J. Beek, and M. Pijnappels, "Fall-related gait characteristics on the treadmill and in daily life," *Journal of NeuroEngineering and Rehabilitation*, vol. 13, no. 12, 2016.

[131] W. Zijlstra, R. W. Bisseling, S. Schlumbohm, and H. Baldus, "A body-fixed-sensor-based analysis of power during sit-to-stand movements," *Gait and Posture*, vol. 31, no. 2, pp. 272–278, 2010.

[132] J. M. Van Ancum, K. S. van Schooten, N. H. Jonkman, B. Huijben, R. C. van Lummel, C. G. Meskers, A. B. Maier, and M. Pijnappels, "Gait speed assessed by a 4-meter walk test is not representative of daily-life gait speed in community-dwelling adults," *Maturitas*, vol. 121, pp. 28–34, 2019.

[133] I. H. Jenkins, M. Jahanshahi, M. Jueptner, R. E. Passingham, and D. J. Brooks, "Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow," *Brain*, vol. 123, pp. 1216–1228, 2000.

[134] K. Wessel, T. Zeffiro, C. Toro, and M. Hallett, "Self-Paced Versus Metronome-Paced Finger Movements," *Journal of Neuroimaging*, vol. 7, no. 3, pp. 145–151, 1997.

[135] C. Hunt, A. Paez, and E. Folmar, "Literature Review the Impact of Attentional Focus on the Treatment of Musculoskeletal and," *The International Journal of Sports Physical Therapy*, vol. 12, no. 6, pp. 901–907, 2017.

[136] M. A. D. Brodie, M. J. M. Coppens, S. R. Lord, N. H. Lovell, Y. J. Gschwind, S. J. Redmond, M. B. Del Rosario, K. Wang, D. L. Sturnieks, M. Persiani, and K. Delbaere, "Wearable pendant device monitoring using new wavelet-based methods shows daily life and laboratory gaits are different," *Medical Biological Engineering Computing*, vol. 54, pp. 663–674, 2016.

[137] R. C. van Lummel, S. Walgaard, M. Pijnappels, P. J. M. Elders, J. Garcia-Aymerich, J. H. van Dieën, and P. J. Beek, "Physical Performance and Physical Activity in Older Adults: Associated but Separate Domains of Physical Function in Old Age," *Plos One*, vol. 10, no. 12, 2015.

[138] P. Tamburini, F. Storm, C. Buckley, M. C. Bisi, R. Stagni, and C. Mazzà, "Moving from laboratory to real life conditions: Influence on the assessment of variability and stability of gait," *Gait and Posture*, vol. 59, pp. 248–252, 2018.

[139] N. Toosizadeh, J. Mohler, H. Lei, S. Parvaneh, S. Sherman, and B. Najafi, "Motor Performance Assessment in Parkinson's Disease: Association between Objective In-Clinic, Objective In-Home, and Subjective/Semi-Objective Measures," *PLoS ONE*, vol. 10, no. 4, 2015.

[140] C. Moufawad El Achkar, C. Lenbole-Hoskovec, A. Paraschiv-Ionescu, K. Major, C. Büla, and K. Aminian, "Classification and characterization of postural transitions using instrumented shoes," *Medical Biological Engineering Computing*, vol. 56, pp. 1403–1412, 2018.

[141] D. Jones, L. Rochester, A. Birleson, V. Hetherington, A. Nieuwboer, A. M. Willems, E. Van Wegen, and G. Kwakkel, "Everyday walking with Parkinson's disease: Understanding personal challenges and strategies," *Disability and Rehabilitation*, vol. 30, no. 16, pp. 1213–1221, 2008.

[142] J. A. Lee, S. M. Williams, D. D. Brown, and K. R. Laurson, "Concurrent validation of the Actigraph gt3x+, Polar Active accelerometer, Omron HJ-720 and Yamax Digiwalker SW-701 pedometer step counts in lab-based and free-living settings," *Journal of Sports Sciences*, vol. 33, no. 10, pp. 991–1000, 2015.

[143] M. H. Pham, E. Warmerdam, M. Elshehabi, C. Schlenstedt, L. M. Bergeest, M. Heller, L. Haertner, J. J. Ferreira, D. Berg, G. Schmidt, C. Hansen, and W. Maetzler, "Validation of a lower back "wearable"-based sit-to-stand and stand-to-sit algorithm for patients with Parkinson's disease and older adults in a home-like environment," *Frontiers in Neurology*, vol. 9, 2018.

[144] F. Storm, K. Nair, A. Clarke, J. Van der Meulen, and C. Mazzà, "Free-living and laboratory gait characteristics in patients with multiple sclerosis," *PLoS ONE*, vol. 13, no. 5, pp. 1–15, 2018.

[145] L. Haertner, M. Elshehabi, L. Zaunbrecher, M. Pham, Maetzler C, J. van Uem, M. Hobert, S. Hucker, S. Nussbaum, B. Berg, I. Liepelt-Scarfone, and W. Maetzler, "Effect of Fear of Falling on Turning Performance in Parkinson's Disease in the Lab and at Home," *Frontiers in Aging Neuroscience*, vol. 10, no. 78, 2018.

[146] A. K. Bourke, A. F. Ihlen, and J. Laegdheim Helbostad, "Development of a gold-standard method for the identification of sedentary, light and moderate physical activities in older adults: Definitions for video annotation," *Journal of Science and Medicine in Sport*, vol. 22, no. 5, pp. 557–561, 2019.

[147] A. K. Bourke, E. A. F. Ihlen, R. Bergquist, P. B. Wik, B. Vereijken, and J. L. Helbostad, "A Physical Activity Reference Data-Set Recorded from Older Adults Using Body-Worn Inertial Sensors and Video Technology — The ADAPT Study Data-Set," *Sensors*, vol. 17, 2017.

[148] S. M. Rispens, K. S. van Schooten, M. Pijnappels, A. Daffertshofer, P. J. Beek, and J. H. van Dieën, "Do Extreme Values of Daily-Life Gait Characteristics Provide More Information About Fall Risk Than Median Values?," *JMIR Research Protocols*, vol. 4, no. 1, 2015.

[149] J. M. Hausdorff, I. Hillel, S. Shustak, S. D. Din, E. M. J. Bekkers, E. Pelosin, F. Nieuwhof, L. Rochester, and A. Mirelman, "Everyday Stepping Quantity and Quality Among Older Adult Fallers With and Without Mild Cognitive Impairment: Initial Evidence for New Motor Markers of Cognitive Deficits?," *J Gerontol A Biol Sci Med Sci*, vol. 73, no. 8, pp. 1078–1082, 2018.

[150] A. Supratak, G. Datta, A. R. Gafson, R. Nicholas, Y. Guo, and P. M. Matthews, "Remote Monitoring in the Home Validates Clinical Gait Measures for Multiple Sclerosis," *Frontiers in Neurology*, vol. 9, no. 561, 2018.

[151] I. Dujmovic, S. Radovanovic, V. Martinovic, J. Dackovic, G. Maric, S. Mesaros, T. Pekmezovic, V. Kostic, and J. Drulovic, "Gait pattern in patients with different multiple sclerosis phenotypes," *Multiple Sclerosis and Related Disorders*, vol. 13, no. January, pp. 13–20, 2017.

[152] S. A. Schloemer, J. A. Thompson, A. Silder, D. G. Thelen, and R. A. Siston, "Age-Related Differences in Gait Kinematics, Kinetics, and Muscle Function: A Principal Component Analysis," *Annals of Biomedical Engineering*, vol. 45, no. 3, pp. 695–710, 2017.

[153] L. V. Slater, A. S. Simpson, S. S. Blemker, J. Hertel, S. A. Saliba, A. L. Weltman, and J. M. Hart, "Biomechanical adaptations during running differ based on type of exercise and fitness level," *Gait and Posture*, vol. 60, pp. 35–40, 2018.

[154] U. Lindemann, W. Zijlstra, K. Aminian, S. F. M. Chastin, E. D. D. Bruin, J. L. Helbostad, and J. B. J. Bussmann, "Recommendations for Standardizing Validation Procedures Assessing Physical Activity of Older Persons by Monitoring Body Postures and Movements," *Sensors*, vol. 14, pp. 1267–1277, 2014.

[155] R. Badawy, F. Hameed, L. Bataille, M. A. Little, K. Cleas, S. Saria, J. M. Cedarbaum, D. Stephenson, J. Neville, W. Maetzler, A. J. Espay, B. R. Bloem, T. Simuni, D. R. Karlin, K. Claes, S. Saria, J. M. Cedarbaum, D. Stephenson, J. Neville, W. Maetzler, A. J. Espay, B. R. Bloem, T. Simuni, and D. R. Karlin, "Metadata Concepts for Advancing the Use of Digital Health Technologies in Clinical Research," *Digital Biomarkers*, vol. 3, no. 3, pp. 116–132, 2019.

[156] J. K. Urbanek, V. Zipunnikov, T. Harris, C. Crainiceanu, J. Harezlak, N. W. Glynn, and S. Kritchevsky, "Validation of Gait Characteristics Extracted From Raw Accelerometry During Walking Against Measures of Physical Function, Mobility, Fatigability, and Fitness," *J Gerontol A Biol Sci Med Sci*, vol. 73, no. 5, pp. 676–681, 2018.

[157] K. S. Van Schooten, M. Pijnappels, S. M. Rispens, P. J. M. Elders, P. Lips, and J. H. Van Dieën, "Ambulatory Fall-Risk Assessment: Amount and Quality of Daily-Life Gait Predict Falls in Older Adults," *MEDICAL SCIENCES*, pp. 608–615, 2015.

[158] J. De Fauw, J. R. Ledsam, B. Romera-Paredes, S. Nikolov, N. Tomasev, S. Blackwell, H. Askham, X. Glorot, B. O'Donoghue, D. Visentin, G. van den Driessche, B. Lakshminarayanan, C. Meyer, F. Mackinder, S. Bouton, K. Ayoub, R. Chopra, D. King, A. Karthikesalingam, C. O. Hughes, R. Raine, J. Hughes, D. A. Sim, C. Egan, A. Tufail, H. Montgomery, D. Hassabis, G. Rees, T. Back, P. T. Khaw, M. Suleyman, J. Cornebise, P. A. Keane, and O. Ronneberger, "Clinically applicable deep learning for diagnosis and referral in retinal disease," *Nature Medicine*, vol. 24, pp. 1342–1350, sep 2018.

[159] A. Zhan, S. Mohan, C. Tarolli, R. B. Schneider, J. L. Adams, S. Sharma, M. J. Elson, K. L. Spear, A. M. Glidden, M. A. Little, A. Terzis, E. Ray Dorsey, and S. Saria, "Using smartphones and machine learning to quantify Parkinson disease severity the mobile Parkinson disease score," *JAMA Neurology*, vol. 75, no. 7, pp. 876–880, 2018.

[160] R. Araújo, B. van de Warrenburg, A. Lang, A. Lees, and B. Bloem, "The Waiting Room: neurological observations made outside the movement disorder specialist's consulting office," *Pract Neurol*, vol. 19, no. 4, pp. 295–301, 2019.

[161] J. Domingos, S. H. J. Keus, J. Dean, N. M. de Vries, J. J. Ferreira, and B. R. Bloem, "The European Physiotherapy Guideline for Parkinson's Disease: Implications for Neurologists.," *Journal of Parkinson's disease*, vol. 8, no. 4, pp. 499–502, 2018.

[162] A. C. Buckley, B. Galna, L. Rochester, and C. Mazz, "Upper body accelerations as a biomarker of gait impairment in the early stages of Parkinson's disease," *Gait and Posture*, vol. 71, pp. 289–295, 2019.

[163] T. Arroyo-Gallego, M. J. Ledesma-Carbayo, I. Butterworth, M. Matarazzo, P. Montero-Escribano, V. Puertas-Martín, M. L. Gray, L. Giancardo, and Á. Sánchez-Ferro, "Detecting Motor Impairment in Early Parkinson's Disease via Natural Typing Interaction With Keyboards: Validation of the neuroQWERTY Approach in an Uncontrolled At-Home Setting," *Journal of Medical Internet Research*, vol. 20, mar 2018.

[164] N. Takayanagi, M. Sudo, Y. Yamashiro, S. Lee, Y. Kobayashi, Y. Niki, and H. Shimada, "Relationship between Daily and In-laboratory Gait speed among Healthy Community-dwelling older Adults," *Sci Rep*, vol. 9, 2019.

[165] M. Goudriaan, I. Jonkers, J. H. van Dieen, and S. M. Bruijn, "Arm swing in human walking: What is their drive?," *Gait and Posture*, vol. 40, no. 2, pp. 321–326, 2014.

[166] P. Meyns, S. M. Bruijn, and J. Duysens, "The how and why of arm swing during human walking," *Gait and Posture*, vol. 38, no. 4, pp. 555–562, 2013.

[167] A. Plate, D. Sedunko, O. Pelykh, C. Schlick, J. R. Ilmberger, and K. Bötzel, "Normative data for arm swing asymmetry: How (a)symmetrical are we?," *Gait and Posture*, vol. 41, pp. 13–18, jan 2015.

[168] M. Punt, S. M. Bruijn, H. Wittink, and J. H. van Dieën, "Effect of arm swing strategy on local dynamic stability of human gait," *Gait and Posture*, vol. 41, no. 2, pp. 504–509, 2015.

[169] G. M. Johansson, G. E. Frykberg, H. Grip, E. W. Broström, and C. K. Häger, "Assessment of arm movements during gait in stroke - The Arm Posture Score," *Gait and Posture*, vol. 40, no. 4, pp. 549–555, 2014.

[170] X. Huang, J. M. Mahoney, M. M. Lewis, Guangwei Du, S. J. Piazza, and J. P. Cusumano, "Both coordination and symmetry of arm swing are reduced in Parkinson's disease," *Gait and Posture*, vol. 35, no. 3, pp. 373–377, 2012.

[171] J. Roggendorf, S. Chen, S. Baudrexel, S. van de Loo, C. Seifried, and R. Hilker, "Arm swing asymmetry in Parkinson's disease measured with ultrasound based motion analysis during treadmill gait," *Gait and Posture*, vol. 35, no. 1, pp. 116–120, 2012.

[172] E. Rovini, C. Maremmani, and F. Cavallo, "How wearable sensors can support parkinson's disease diagnosis and treatment: A systematic review," *Frontiers in Neuroscience*, vol. 11, no. 555, 2017.

[173] N. W. Sterling, J. P. Cusumano, N. Shaham, S. J. Piazza, G. Liu, L. Kong, G. Du, M. M. Lewis, and X. Huang, "Dopaminergic modulation of arm swing during gait among Parkinson's disease patients," *Journal of Parkinson's Disease*, vol. 5, no. 1, pp. 141–150, 2015.

[174] L. Brognara, P. Palumbo, B. Grimm, and L. Palmerini, "Assessing Gait in Parkinson's Disease Using Wearable Motion Sensors: A Systematic Review," *Diseases*, vol. 7, no. 18, 2019.

[175] J. A. Vizcarra, Á. Sánchez-Ferro, W. Maetzler, L. Marsili, L. Zavala, A. E. Lang, P. Martinez-Martin, T. A. Mestre, R. Reilmann, J. M. Hausdorff, E. R. Dorsey, S. S. Paul, J. W. Dexheimer, B. D. Wissel, R. L. Fuller, P. Bonato, A. H. Tan, B. R. Bloem, C. Kopil, M. Daeschler, L. Bataille, G. Kleiner, J. M. Cedarbaum, J. Klucken, A. Merola, C. G. Goetz, G. T. Stebbins, and A. J. Espay, "The Parkinson's disease e-diary: Developing a clinical and research tool for the digital age," *Movement Disorders*, vol. 34, no. 5, pp. 676–681, 2019.

[176] E. Warmerdam, J. M. Hausdorff, A. Atrsaei, Y. Zhou, A. Mirelman, K. Aminian, A. J. Espay, C. Hansen, L. J. W. Evers, A. Keller, C. Lamoth, A. Pilotto, L. Rochester, G. Schmidt, B. R. Bloem, and W. Maetzler, "Long-term unsupervised mobility assessment in movement disorders," *Lancet Neurol*, vol. 19, no. 5, pp. 462–470, 2020.

[177] W. R. G. Gibb and A. J. Lees, "The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease," *J Neurol Neurosurg Psychiatry.*, vol. 51, pp. 745–752, 1988.

[178] R. Moe-Nilssen and J. L. Helbostad, "Estimation of gait cycle characteristics by trunk accelerometry," *Journal of Biomechanics*, vol. 37, no. 1, pp. 121–126, 2004.

[179] T. Killeen, M. Elshehabi, L. Filli, M. A. Hobert, C. Hansen, D. Rieger, K. Brockmann, S. Nussbaum, B. Zörner, M. Bolliger, A. Curt, D. Berg, and W. Maetzler, "Arm swing asymmetry in overground walking," *Scientific Reports*, vol. 8, no. 1, pp. 1–10, 2018.

[180] Ø. Gløersen and P. Federolf, "Predicting missing marker trajectories in human motion data using marker intercorrelations," *PLoS ONE*, vol. 11, no. 3, 2016.

[181] J. M. Bland and D. G. Altman, "Statistical methods for assessing agreement between two methods of clinical measurement," *The Lancet*, vol. 327, no. 8476, pp. 307–310, 1986.

[182] A. Salarian, H. Russmann, F. J. Vingerhoets, C. Dehollain, Y. Blanc, P. R. Burkhard, and K. Aminian, "Gait assessment in Parkinson's disease: Toward an ambulatory system for long-term monitoring," *IEEE Transactions on Biomedical Engineering*, 2004.

[183] H. Nguyen, K. Lebel, S. Bogard, E. Goubault, P. Boissy, and Q. P. N. Clinicians, "Using Inertial Sensors to Automatically Detect and Segment Activities of Daily Living in People with Parkinson's Disease," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 26, no. 1, pp. 197–204, 2017.

[184] B. M. Ospina, J. A. V. Chaparro, J. D. A. Paredes, Y. J. C. Pino, A. Navarro, and J. L. Orozco, "Objective arm swing analysis in early-stage Parkinson's disease using an RGB-D Camera (Kinect ®)," *Journal of Parkinson's Disease*, vol. 8, no. 4, pp. 563–570, 2018.

[185] S. Sveinbjornsdottir, "The clinical symptoms of Parkinson's disease," *Journal of Neurochemistry*, vol. 139, pp. 318–324, 2016.

[186] M. El-Gohary, S. Pearson, J. McNames, M. Mancini, F. Horak, S. Mellone, and L. Chiari, "Continuous monitoring of turning in patients with movement disability," *Sensors*, vol. 14, pp. 356–369, 2014.

[187] M. Kubo, R. C. Wagenaar, E. Saltzman, and K. G. Holt, "Biomechanical mechanism for transitions in phase and frequency of arm and leg swing during walking," *Biological Cybernetics*, vol. 91, no. 2, pp. 91–98, 2004.

[188] R. C. Wagenaar and R. E. Van Emmerik, "Resonant frequencies of arms and legs identify different walking patterns," *Journal of Biomechanics*, vol. 33, no. 7, pp. 853–861, 2000.

[189] N. Chockalingam, F. Chatterley, A. Greenhalgh, and P. Dangerfield, "Postural differences in the shoulder girdle during normal locomotion in treadmill vs. over ground walking.," *Stud Health Technol Inform.*, vol. 123, pp. 404–408, 2006.

[190] B. R. Bloem, D. J. Beckley, G. J. Van Dijk, A. H. Zwinderman, M. P. Remler, and R. A. Roos, "Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease," *Movement Disorders*, vol. 11, no. 5, pp. 509–521, 1996.

[191] M. Hong and G. M. Earhart, "Effects of Medication on Turning Deficits in Individuals with Parkinson's Disease," *J Neurol Phys Ther*, vol. 34, no. 1, pp. 11–16, 2010.

[192] M. McNeely, R. Duncan, and G. Earhart, "Medication improves balance and complex gait performance in Parkinson disease," *Gait and Posture*, vol. 36, no. 1, pp. 144–148, 2012.

[193] M. Ferrarin, M. Rizzone, L. Lopiano, M. Recalcati, and A. Pedotti, "Effects of subthalamic nucleus stimulation and L-dopa in trunk kinematics of patients with Parkinson's disease," *Gait and Posture*, vol. 19, no. 2, pp. 164–171, 2004.

[194] M. Hoskovcova, P. Dusek, T. Sieger, H. Brozova, K. Zarubova, O. Bezdicek, O. Sprdlik, R. Jech, J. Stochl, J. Roth, and E. Ruzicka, "Predicting falls in Parkinson disease: What is the value of instrumented testing in off medication state?," *PLoS ONE*, vol. 10, no. 10, pp. 1–13, 2015.

[195] S. Bowes, P. Clark, A. Leeman, C. O'Neill, C. Weller, P. Nicholson, A. Deshmukh, S. Dobbs, and R. Dobbs, "Determinants of gait in the elderly parkinsonian on maintenance levodopa/carbidopa therapy.," *British Journal of Clinical Pharmacology*, vol. 30, no. 1, pp. 13–24, 1990.

[196] M. S. Bryant, D. H. Rintala, J.-g. Hou, R. L. Collins, and E. J. Protas, "Gait Variability in Parkinson's Disease: Levodopa and Walking Direction," *Acta Neurol Scand*, vol. 134, no. 1, pp. 83–86, 2016.

[197] M. Elshehabi, K. S. Maier, S. E. Hasmann, S. Nussbaum, H. Herbst, T. Heger, D. Berg, M. A. Hobert, and W. Maetzler, "Limited effect of dopaminergic medication on straight walking and turning in early-to-moderate parkinson's disease during single and dual tasking," *Frontiers in Aging Neuroscience*, vol. 8, no. 4, 2016.

[198] M. Dagan, T. Herman, H. Bernad-Elazari, E. Gazit, I. Maidan, N. Giladi, A. Mirelman, B. Manor, and J. M. Hausdorff, "Dopaminergic therapy and prefrontal activation during walking in individuals with Parkinson's disease: does the levodopa overdose hypothesis extend to gait?," *Journal of Neurology*, vol. 268, no. 2, pp. 658–668, 2021.

[199] M. Hackney and G. M. Earhart, "The Effects of a Secondary Task on Forward and Backward Walking in Parkinson Disease," *Physiology and behavior*, vol. 24, no. 1, pp. 97–106, 2017.

[200] L. Alcock, B. Galna, R. Perkins, S. Lord, and L. Rochester, "Step length determines minimum toe clearance in older adults and people with Parkinson's disease," *Journal of Biomechanics*, vol. 71, pp. 30–36, 2018.

[201] E. Warmerdam, R. Romijnders, J. Welzel, C. Hansen, G. Schmidt, and W. Maetzler, "Quantification of arm swing during walking in healthy adults and Parkinson's disease: Wearable sensor-based algorithm development and validation," *Sensors*, vol. 20, no. 20, 2020.

[202] E. I. Baron, M. Miller Koop, M. C. Streicher, A. B. Rosenfeldt, and J. L. Alberts, "Altered kinematics of arm swing in Parkinson's disease patients indicates declines in gait under dual-task conditions," *Parkinsonism and Related Disorders*, vol. 48, pp. 61–67, 2018.

[203] P. Crenna, I. Carpinella, L. Lopiano, A. Marzegan, M. Rabuffetti, M. Rizzone, M. Lanotte, and M. Ferrarin, "Influence of basal ganglia on upper limb locomotor synergies. Evidence from deep brain stimulation and L-DOPA treatment in Parkinson's disease," *Brain*, vol. 131, no. 12, pp. 3410–3420, 2008.

[204] J. Romkes and K. Bracht-Schweizer, "The effects of walking speed on upper body kinematics during gait in healthy subjects," *Gait and Posture*, vol. 54, pp. 304–310, 2017.

[205] X. Fang and Z. Jiang, "Three-dimensional thoracic and pelvic kinematics and arm swing maximum velocity in older adults using inertial sensor system," *PeerJ*, vol. 8, 2020.

[206] V. V. Shah, J. McNames, M. Mancini, P. Carlson-Kuhta, J. G. Nutt, M. El-Gohary, J. A. Lapidus, F. B. Horak, and C. Curtze, "Digital Biomarkers of Mobility in Parkinson's Disease during Daily Living," *Journal of Parkinson's Disease*, vol. 10, no. 3, pp. 1099–1111, 2020.

[207] J. Kearney and J. S. Brittain, "Sensory attenuation in sport and rehabilitation: Perspective from research in parkinson's disease," *Brain Sciences*, vol. 11, no. 5, 2021.

[208] B. R. Bloem, Y. A. Grimbergen, J. G. van Dijk, and M. Munneke, "The "posture second" strategy: A review of wrong priorities in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 248, no. 1-2, pp. 196–204, 2006.

[209] M. A. Hobert, R. Niebler, S. I. Meyer, K. Brockmann, C. Becker, H. Huber, A. Gaenslen, J. Godau, G. W. Eschweiler, D. Berg, and W. Maetzler, "Poor trail making test performance is directly associated with altered dual task prioritization in the elderly - baseline results from the trend study," *PLoS ONE*, vol. 6, no. 11, 2011.

[210] D. E. Vaillancourt, D. Schonfeld, Y. Kwak, N. I. Bohnen, and R. Seidler, "Dopamine overdose hypothesis: Evidence and clinical implications," *Movement Disorders*, vol. 28, no. 14, pp. 1920–1929, 2013.

[211] S. Lord, L. Rochester, V. Hetherington, L. M. Allcock, and D. Burn, "Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's Disease," *Gait and Posture*, vol. 31, no. 2, pp. 169–174, 2010.

[212] M. Plotnik, Y. Dagan, T. Gurevich, N. Giladi, and J. M. Hausdorff, "Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations," *Experimental Brain Research*, vol. 208, no. 2, pp. 169–179, 2011.

[213] P. Zham, D. Kumar, R. Viswanthan, K. Wong, K. J. Nagao, S. P. Arjunan, S. Raghav, and P. Kempster, "Effect of levodopa on handwriting tasks of different complexity in Parkinson's disease: a kinematic study," *Journal of Neurology*, vol. 266, no. 6, pp. 1376–1382, 2019.

[214] C. D. Workman and T. A. Thrasher, "The influence of dopaminergic medication on balance automaticity in Parkinson's disease," *Gait and Posture*, vol. 70, no. November 2018, pp. 98–103, 2019.

[215] E. J. Henderson, S. R. Lord, M. A. Brodie, D. M. Gaunt, A. D. Lawrence, J. C. Close, A. L. Whone, and Y. Ben-Shlomo, "Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial," *The Lancet Neurology*, vol. 15, no. 3, pp. 249–258, 2016.

[216] H. Pontzer, J. H. Holloway, D. A. Raichlen, and D. E. Lieberman, "Control and function of arm swing in human walking and running," *Journal of Experimental Biology*, vol. 212, no. 4, pp. 523–534, 2009.

[217] C. L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, and C. E. Clarke, "Systematic review of levodopa dose equivalency reporting in Parkinson's disease," *Movement Disorders*, vol. 25, no. 15, pp. 2649–2653, 2010.

[218] C. Curtze, A. L. Hof, K. Postema, and B. Otten, "Over rough and smooth: Amputee gait on an irregular surface," *Gait and Posture*, vol. 33, no. 2, pp. 292–296, 2011.

[219] G. T. Stebbins and C. G. Goetz, "Factor structure of the Unified Parkinson's Disease Rating Scale: Motor Examination section," *Movement Disorders*, vol. 13, no. 4, pp. 633–636, 1998.

[220] M. J. Forjaz, A. Ayala, C. M. Testa, P. G. Bain, R. Elble, D. Haubenberger, C. Rodriguez-Blazquez, G. Deuschl, and P. Martinez-Martin, "Proposing a Parkinson's disease–specific tremor scale from the MDS-UPDRS," *Movement Disorders*, vol. 30, no. 8, pp. 1139–1143, 2015.

[221] G. T. Stebbins, C. G. Goetz, D. J. Burn, J. Jankovic, T. K. Khoo, and B. C. Tilley, "How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale," *Movement Disorders*, vol. 28, no. 5, pp. 668–670, 2013.

[222] W. F. Abdo, B. P. C. van de Warrenburg, D. J. Burn, N. P. Quinn, and B. R. Bloem, "The clinical approach to movement disorders," *Nature Reviews Neurology*, vol. 6, no. 1, pp. 29–37, 2010.

[223] M. S. Ameen, L. M. Cheung, T. Hauser, M. A. Hahn, and M. Schabus, "About the accuracy and problems of consumer devices in the assessment of sleep," *Sensors (Switzerland)*, vol. 19, no. 19, 2019.

[224] M. T. Imboden, M. B. Nelson, L. A. Kaminsky, and A. H. Montoye, "Comparison of four Fitbit and Jawbone activity monitors with a research-grade ActiGraph accelerometer for estimating physical activity and energy expenditure," *British journal of sports medicine*, vol. 52, no. 13, pp. 844–850, 2018.

[225] W. Maetzler, J. Klucken, and M. Horne, "A clinical view on the development of technology-based tools in managing Parkinson's disease," *Movement Disorders*, vol. 31, no. 9, pp. 1263–1271, 2016.

[226] M. Ghislieri, L. Gastaldi, S. Pastorelli, S. Tadano, and V. Agostini, "Wearable inertial sensors to assess standing balance: a systematic review," *Sensors (Switzerland)*, vol. 19, no. 19, pp. 1–25, 2019.

[227] J. C. Otto, J. Gierthmühlen, V. Kirchhofer, C. Borzikowsky, and R. Baron, "Validation of the Questionnaire for Symptom Assessment in Pain disorders for Back pain patients (Q-SAP)," *European Journal of Pain (United Kingdom)*, vol. 25, no. 3, pp. 513–528, 2021.

[228] R. A. Deyo, D. C. Cherkin, and M. A. Ciol, "Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases," *J Clin Epidemiol*, vol. 45, no. 6, pp. 613–619, 1992.

[229] Z. S. Nasreddine, N. A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, J. L. Cummings, and H. Chertkow, "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *J Am Geriatr Soc*, vol. 53, no. 4, pp. 695–699, 2005.

[230] Y. S. Feng, T. Kohlmann, M. F. Janssen, and I. Buchholz, "Psychometric properties of the EQ-5D-5L: a systematic review of the literature," *Quality of Life Research*, vol. 30, no. 3, pp. 647–673, 2021.

[231] C. Graf, "Instrumental Activities of Daily Living Scale," *American Journal of Nursing*, vol. 108, no. 4, pp. 52–62, 2008.

[232] I. Haase, A. Schwarz, A. Burger, and B. Kladny, "Der funktionsfragebogen hannover (FFbH) und die subskala "körperliche funktionsfähigkeit" aus dem SF-36 im vergleich," *Rehabilitation*, vol. 40, no. 1, pp. 40–42, 2001.

[233] T. K. Malmstrom, D. K. Miller, E. M. Simonsick, L. Ferrucci, and J. E. Morley, "SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes," *Journal of Cachexia, Sarcopenia and Muscle*, vol. 7, pp. 28–36, 2016.

[234] A. Williamson and B. Hoggart, "Pain: A review of three commonly used pain rating scales," *Journal of Clinical Nursing*, vol. 14, no. 7, pp. 798–804, 2005.

[235] A. Pestronk, J. Florence, T. Levine, M. T. Al-Lozi, G. Lopate, T. Miller, I. Ramneantu, W. Waheed, and M. Stambuk, "Sensory exam with a quantitative tuning fork: Rapid, sensitive and predictive of SNAP amplitude," *Neurology*, vol. 62, no. 3, pp. 461–464, 2004.

[236] K. Herlofson and J. P. Larsen, "Measuring fatigue in patients with Parkinson's disease - the Fatigue Severity Scale.," *European journal of neurology : the official journal of the European Federation of Neurological Societies*, vol. 9, no. 6, pp. 595–600, 2002.

[237] A. Luszczynska, U. Scholz, and R. Schwarzer, "The General Self-Efficacy Scale: Multicultural Validation Studies," *The Journal of Psychology*, vol. 139, no. 5, pp. 439–457, 2005.

[238] M. M. Hoehn and M. D. Yahr, "Parkinsonism : onset, progression, and mortality," *Neurology*, vol. 17, no. 5, pp. 427–442, 1967.

[239] T. Brott, H. P. A. Jr, C. P. Olinger, J. R. Marler, W. G. Barsan, J. Biller, J. Spilker, R. Holleran, R. Eberle, V. Hertzberg, M. Rorick, C. J. Moomaw, and M. Walker, "Measurements of Acute Cerebral Infarction :," *Stroke*, vol. 20, no. 7, pp. 864–871, 1989.

[240] G. Faber, C. Chang, I. Kingma, J. Dennerlein, and J. van Dieën, "Estimating 3D L5/S1 moments and ground reaction forces during trunk bending using a full-body ambulatory inertial motion capture system," *Journal of Biomechanics*, vol. 49, no. 6, pp. 904–912, 2016.

[241] M. P. Mavor, G. B. Ross, A. L. Clouthier, T. Karakolis, and R. B. Graham, "Validation of an IMU suit for military-based tasks," *Sensors (Switzerland)*, vol. 20, no. 15, pp. 1–14, 2020.

[242] X. Robert-Lachaine, H. Mecheri, C. Larue, and A. Plamondon, "Validation of inertial measurement units with an optoelectronic system for whole-body motion analysis," *Medical and Biological Engineering and Computing*, vol. 55, no. 4, pp. 609–619, 2017.

[243] M. Delrobaei, N. Baktash, G. Gilmore, K. McIsaac, and M. Jog, "Using Wearable Technology to Generate Objective Parkinson's Disease Dyskinesia Severity Score: Possibilities for Home Monitoring," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 25, no. 10, pp. 1–1, 2017.

[244] M. Delrobaei, S. Memar, M. Pieterman, T. W. Stratton, K. McIsaac, and M. Jog, "Towards remote monitoring of Parkinson's disease tremor using wearable motion capture systems," *Journal of the Neurological Sciences*, vol. 384, pp. 38–45, 2018.

[245] X. Robert-Lachaine, G. Parent, A. Fuentes, N. Hagemeister, and R. Aissaoui, "Inertial motion capture validation of 3D knee kinematics at various gait speed on the treadmill with a double-pose calibration," *Gait and Posture*, vol. 77, no. July 2019, pp. 132–137, 2020.

[246] U. Gottlieb, T. Balasukumaran, J. Hoffman, and S. Springer, "Agreement of Gait Events Detection during Treadmill Backward Walking by Kinematic Data and Inertial Motion Units," *Sensors*, vol. 20, no. 21, 2020.

[247] A. M. Turcato, M. Godi, M. Giardini, I. Arcolin, A. Nardone, A. Giordano, and M. Schieppati, "Abnormal gait pattern emerges during curved trajectories in high-functioning Parkinsonian patients walking in line at normal speed," *PLoS ONE*, vol. 13, no. 5, 2018.

[248] C. J. Lamoth, F. J. Van Deudekom, J. P. Van Campen, B. A. Appels, O. J. De Vries, and M. Pijnappels, "Gait stability and variability measures show effects of impaired cognition and dual tasking in frail people," *Journal of NeuroEngineering and Rehabilitation*, vol. 8, no. 1, p. 2, 2011.

[249] A. Fasano, C. Schlenstedt, J. Herzog, M. Plotnik, F. E. Rose, J. Volkmann, and G. Deuschl, "Split-belt locomotion in Parkinson's disease links asymmetry, dyscoordination and sequence effect," *Gait and Posture*, vol. 48, pp. 6–12, 2016.

[250] R. Pavasini, J. Guralnik, J. C. Brown, M. di Bari, M. Cesari, F. Landi, B. Vaes, D. Legrand, J. Verghese, C. Wang, S. Stenholm, L. Ferrucci, J. C. Lai, A. A. Bartes, J. Espaulella, M. Ferrer, J. Y. Lim, K. E. Ensrud, P. Cawthon, A. Turusheva, E. Frolova, Y. Rolland, V. Lauwers, A. Corsonello, G. D. Kirk, R. Ferrari, S. Volpato, and G. Campo, "Short Physical Performance Battery and all-cause mortality: Systematic review and meta-analysis," *BMC Medicine*, vol. 14, no. 215, 2016.

[251] A. Christopher, E. Kraft, H. Olenick, R. Kiesling, and A. Doty, "The reliability and validity of the Timed Up and Go as a clinical tool in individuals with and without disabilities across a lifespan: a systematic review: Psychometric

properties of the Timed Up and Go," *Disability and Rehabilitation*, vol. 0, no. 0, pp. 1–15, 2019.

[252] R. W. Bohannon, D. J. Bubela, S. R. Magasi, Y. C. Wang, and R. C. Gershon, "Sit-to-stand test: Performance and determinants across the age-span," *Isokinetics and Exercise Science*, vol. 18, no. 4, pp. 235–240, 2010.

[253] A. Atrsaei, F. Dadashi, C. Hansen, E. Warmerdam, B. Mariani, and W. Maetzler, "Postural transitions detection and characterization in healthy and patient populations using a single waist sensor," *Journal of NeuroEngineering and Rehabilitation*, vol. 17, no. 70, 2020.

[254] R. Morris, S. Stuart, G. McBarron, P. Fino, M. Mancini, and C. Curtze, "Validity of MobilityLab (version 2) for gait assessment in young adults, older adults and Parkinson's disease," *Physiol Meas*, vol. 40, no. 9, 2019.

[255] A. Vienne-Jumeau, F. Quijoux, P. P. Vidal, and D. Ricard, "Wearable inertial sensors provide reliable biomarkers of disease severity in multiple sclerosis: A systematic review and meta-analysis," *Annals of Physical and Rehabilitation Medicine*, vol. 63, no. 2, pp. 138–147, 2020.

[256] K. Uemura, M. Yamada, K. Nagai, and N. Ichihashi, "Older adults at high risk of falling need more time for anticipatory postural adjustment in the precrossing phase of obstacle negotiation," *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, vol. 66 A, no. 8, pp. 904–909, 2011.

[257] F. Pieruccini-Faria, M. Montero-Odasso, and A. Newman, "Obstacle Negotiation, Gait Variability, and Risk of Falling: Results from the "gait and Brain Study"," *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, vol. 74, no. 9, pp. 1422–1428, 2019.

[258] B. A. Da Silva, C. D. Faria, M. P. Santos, and A. Swarowsky, "Assessing timed up and go in Parkinson's disease: Reliability and validity of timed up and go assessment of biomechanical strategies," *Journal of Rehabilitation Medicine*, vol. 49, no. 9, pp. 723–731, 2017.

[259] H. Gaßner, F. Marxreiter, S. Steib, Z. Kohl, J. C. Schlachetzki, W. Adler, B. M. Eskofier, K. Pfeifer, J. Winkler, and J. Klucken, "Gait and cognition in parkinson's disease: Cognitive impairment is inadequately reflected by gait performance during dual task," *Frontiers in Neurology*, vol. 8, no. 550, 2017.

[260] H. Lukas, C. Xu, Y. Yu, and W. Gao, "Emerging telemedicine tools for remote covid-19 diagnosis, monitoring, and management," *ACS Nano*, vol. 14, no. 12, pp. 16180–16193, 2020.

[261] B. R. Bloem, E. R. Dorsey, and M. S. Okun, "The Coronavirus Disease 2019 Crisis as Catalyst for Telemedicine for Chronic Neurological Disorders," *JAMA Neurology*, vol. 77, no. 8, pp. 927–928, 2020.

[262] E. Giannouli, O. Bock, S. Mellone, and W. Zijlstra, "Mobility in old age: Capacity is not performance," *BioMed Research International*, vol. 2016, 2016.

[263] L. Holsbeeke, M. Ketelaar, M. M. Schoemaker, and J. W. Gorter, "Capacity, Capability, and Performance: Different Constructs or Three of a Kind?," *Arch Phys Med Rehabil*, vol. 90, pp. 849–855, 2009.

[264] M. Lesinski, O. Prieske, and U. Granacher, "Effects and dose – response relationships of resistance training on physical performance in youth athletes : a systematic review and meta-analysis," *British journal of sports medicine*, vol. 50, pp. 781–795, 2016.

[265] A. Carvalho, D. Barbirato, N. Araujo, J. Martins, J. Cavalcanti, T. Santos, E. Coutinho, J. Laks, and A. Deslandes, "Comparison of strength training, aerobic training, and additional physical therapy as supplementary treatments for Parkinson's disease: pilot study," *Clinical Interventions in Aging*, vol. 10, pp. 183–191, 2015.

[266] L. B. Bakker, T. Nandi, C. J. Lamoth, and T. Hortobágyi, "Task specificity and neural adaptations after balance learning in young adults," *Human Movement Science*, vol. 78, no. June, 2021.

[267] J. Geritz, S. Maetzold, M. Steffen, A. Pilotto, M. F. Corrà, M. Moscovich, M. C. Rizzetti, B. Borroni, A. Padovani, A. Alpes, C. Bang, I. Barcellos, R. Baron, T. Bartsch, J. S. Becktepe, D. Berg, L. M. Bergeest, P. Bergmann, R. Bouça-machado, M. Drey, S. Farahmandi, J. J. Ferreira, A. Franke, A. Friederich, C. Geisler, and P. Hüllemann, "Motor, cognitive and mobility deficits in 1000 geriatric patients: protocol of a quantitative observational study before and after routine clinical geriatric treatment – The ComOn-Study," *BMC Geriatrics*, vol. 20, no. 45, 2020.

[268] M. M. Rieger, S. Papegaaij, F. Steenbrink, J. H. Van Dieën, and M. Pijnappels, "Perturbation-based gait training to improve daily life gait stability in older adults at risk of falling: Protocol for the REACT randomized controlled trial," *BMC Geriatrics*, vol. 20, no. 1, pp. 1–12, 2020.

[269] C. Auepanwiriyakul, S. Waibel, J. Songa, P. Bentley, and A. A. Faisal, "Accuracy and acceptability of wearable motion tracking smartwatches for inpatient monitoring," *Sensors (Switzerland)*, vol. 20, 2020.

[270] T. Loncar-Turukalo, E. Zdravevski, J. M. da Silva, I. Chouvarda, and V. Trajkovik, "Literature on wearable technology for connected health: Scoping review of research trends, advances, and barriers," *Journal of Medical Internet Research*, vol. 21, no. 8, 2019.

[271] A. Keogh, J. F. Dorn, L. Walsh, F. Calvo, and B. Caulfield, "Comparing the usability and acceptability of wearable sensors among older Irish adults in a real-world context: Observational study," *JMIR mHealth and uHealth*, vol. 8, no. 4, 2020.

[272] R. Ganea, A. Paraschiv-lonescu, and K. Aminian, "Detection and Classification of Postural Transitions in Real-World Conditions," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 20, no. 5, pp. 688–696, 2012.

[273] S. Aich, J. Youn, S. Chakraborty, P. M. Pradhan, J. H. Park, S. Park, and J. Park, "A supervised machine learning approach to detect the On/Off state in Parkinson's disease using wearable based gait signals," *Diagnostics*, vol. 10, no. 6, pp. 1–18, 2020.

[274] P. N. Ramkumar, H. S. Haeberle, D. Ramanathan, W. A. Cantrell, S. M. Navarro, M. A. Mont, M. Bloomfield, and B. M. Patterson, "Remote Patient Monitoring Using Mobile Health for Total Knee Arthroplasty: Validation of a Wearable and Machine Learning–Based Surveillance Platform," *Journal of Arthroplasty*, vol. 34, no. 10, pp. 2253–2259, 2019.

[275] L. Sigcha, N. Costa, I. Pavón, S. Costa, P. Arezes, J. M. López, and G. De Arcas, "Deep learning approaches for detecting freezing of gait in parkinson's disease patients through on-body acceleration sensors," *Sensors (Switzerland)*, vol. 20, no. 7, 2020.

[276] Y. Zhou, R. Z. Ur Rehman, C. Hansen, W. Maetzler, S. D. Din, L. Rochester, T. Hortobágyi, and C. J. Lamoth, "Classification of neurological patients to identify fallers based on spatial-temporal gait characteristics measured by a wearable device," *Sensors (Switzerland)*, vol. 20, no. 15, pp. 1–15, 2020.

[277] D. Trojaniello, A. Cereatti, and U. Della Croce, "Accuracy, sensitivity and robustness of five different methods for the estimation of gait temporal parameters using a single inertial sensor mounted on the lower trunk," *Gait and Posture*, vol. 40, pp. 487–492, 2014.

[278] C. Angthong and A. Veljkovic, "Relationships among subjective patient-reported outcome, quality of life, and objective gait characteristics using wearable foot inertial-sensor assessment in foot–ankle patients," *European Journal of Orthopaedic Surgery and Traumatology*, vol. 29, no. 3, pp. 683–687, 2019.

[279] L. di Biase, S. Summa, J. Tosi, F. Taffoni, M. Marano, A. C. Rizzo, F. Vecchio, D. Formica, V. Di Lazzaro, G. Di Pino, and M. Tombini, "Quantitative analysis of bradykinesia and rigidity in Parkinson's disease," *Frontiers in Neurology*, vol. 9, no. MAR, pp. 1–12, 2018.

[280] W. Maetzler, I. Liepelt, and D. Berg, "Progression of Parkinson's disease in the clinical phase: potential markers," *Lancet Neurol*, vol. 8, no. 12, pp. 1158–1171, 2009.

[281] A. Piau, K. Wild, N. Mattek, and J. Kaye, "Current state of digital biomarker technologies for real-life, home-based monitoring of cognitive function for mild cognitive impairment to mild Alzheimer disease and implications for clinical care: Systematic review," *Journal of Medical Internet Research*, vol. 21, no. 8, pp. 1–14, 2019.

[282] C. Hansen, A. Sanchez-Ferro, and W. Maetzler, "How Mobile Health Technology and Electronic Health Records Will Change Care of Patients with Parkinson's Disease," *Journal of Parkinson's Disease*, vol. 8, pp. 41–45, 2018.

[283] J. M. Fisher, N. Y. Hammerla, L. Rochester, P. Andras, and R. W. Walker, "Body-Worn Sensors in Parkinson's Disease: Evaluating Their Acceptability to Patients," *Telemedicine and e-Health*, vol. 22, no. 1, pp. 63–69, 2016.

[284] J. J. Ferreira, C. Godinho, A. T. Santos, J. Domingos, D. Abreu, R. Lobo, N. Gonçalves, M. Barra, F. Larsen, Ø. Fagerbakke, I. Akeren, H. Wangen, J. A. Serrano, P. Weber, A. Thoms, S. Meckler, S. Sollinger, J. Van Uem, H. Graessner, and W. Maetzler, "Quantitative home-based assessment of Parkinson's symptoms: The SENSE-PARK feasibility and usability study," *BMC Neurology*, vol. 15, no. 89, 2015.

[285] X. Yang, L. Ma, X. Zhao, and A. Kankanhalli, "Factors influencing user's adherence to physical activity applications: A scoping literature review and future directions," *International Journal of Medical Informatics*, vol. 134, 2020.

[286] T. S. Marin, C. Kourbelis, J. Foote, P. Newman, A. Brown, M. Daniel, N. T. Coffee, S. J. Nicholls, A. Ganesan, V. L. Versace, H. Beks, C. A. Haedtke, and R. A. Clark, "Examining adherence to activity monitoring devices to improve physical activity in adults with cardiovascular disease: A systematic review," *European Journal of Preventive Cardiology*, vol. 26, no. 4, pp. 382–397, 2019.

[287] A. Cristina Simonet and A. J. Noyce, "Domotics, Smart Homes, and Parkinson's Disease," *Journal of Parkinson's Disease*, pp. 1–9, 2021.

[288] M. Z. Uddin, W. Khaksar, and J. Torresen, "Ambient sensors for elderly care and independent living: A survey," *Sensors (Switzerland)*, vol. 18, no. 7, pp. 1–31, 2018.

Chapter 10

Appendix

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