Aus dem Experimental and Clinical Research Center
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Using quantitative measures of stepping in place performance to assess motor symptoms of Parkinson's Disease

Quantitative Messung vom Gehen auf der Stelle zur Erhebung von motorischen Symptomen bei Morbus Parkinson

zur Erlangung des akademischen Grades
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Abkürzungsverzeichnis

FOG	Freezing of Gait
HC	Healthy Controls
ICC	Intraclass Correlation Coefficient
LOA	Limit of Agreement
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
OFF	Group of Participants during State where oral medication and DBS were withdrawn
ON	Group of Participants during State where either oral medication or DBS was adjusted to minimize symptom severity
PASS-PD	Name of the Test Protocol
PD	Parkinson's Disease
PwPD	Persons with Parkinson's Disease
RGBD	Red green blue + depth (Name of 3D-color Camera)
SD	Standard Deviation
SEM	Standard Error of Measurement
SIP	Stepping in Place

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Abstract

Abstract (English)

Introduction:

Fluctuating motor symptoms are one of the main challenges in the assessment and evaluation of treatment effects in Parkinson's disease (PD). The stepping in place task was previously proposed as an assessment of postural control and as surrogate for gait tests, two important evaluations of disturbed motor functions in this disorder. Due to its low spatial requirement, this motor task might specifically be suitable for an instrumental assessment even in remote application. Objective of this study was to explore the quantification of motor features associated with Parkinson's Diseases during stepping in place performance.

Methods:

Performance of 40 sec stepping in place (SIP) was recorded with a marker-free motion analysis system using a single RGB-Depth camera system. Data from 25 Persons with PD (PwPD, 7 female, Age: mean 65.3 years ± 9.4 years, MDS-UPDRS III 5-65) in up to two different treatment states (OFF: 13, ON: 20) and data from 83 healthy controls (HC, 52 female, Age: 36.8y ± 13.8y) was available for algorithm development, feature extraction and statistical analysis. Based on knee movements, eight spatiotemporal parameters were extracted including cadence, average knee movement amplitude, average and longest step and stance times, asymmetry and arrhythmicity. Parameters were analysed regarding potential confounding effects, technical accuracy and repeatability in HC, their relation to disease severity (MDS-UPDRS III) and postural instability (pull test score) in PwPD and intra-individual differences in treatment states (OFF vs. ON).

Results:

Six out of eight features showed good accuracy and repeatability in HC subgroup (n=19). Asymmetry and arrhythmicity showed only poor to moderate accuracy (ICC(A,1) > .3; Pearson's r > .5) and repeatability (ICC(1,1) >.4). No linear confounding effects of age, height and weight were found in HC and PwPD. Decreased knee amplitude was associated with higher disease severity (rho = -.503, p-value = .003) and higher postural instability (rho = -.436, p-value = .014). Knee amplitudes showed also increase of 85.4% from OFF to ON in a subgroup in which recordings were available from both treatment states (n=10). Longer stance time measures were associated with higher disease severity (rho = .523, p-value =

.002) and higher postural instability (rho = .468, p-value = .008). 50% of patients with ratings of freezing of gait during MDS-UPDRS III assessment showed freezing during SIP.

Conclusion:

Instrumental assessment of a 40 sec stepping in place performance may be suitable to quantify common motor symptoms, specifically postural instability, in PwPD. Derived parameters described motor symptoms of PD including decreased ranges of motion (hypokinesia), slower motions (bradykinesia) and increased asymmetry as well as arrhythmicity of stepping movements during SIP. Sensitivity to intra-individual changes, indicates potential use of SIP to monitor fluctuation of motor symptoms in PD.

Abstract (German)

Einleitung:

Motorische Fluktuationen sind eine der größten Herausforderungen bei der Beurteilung von Behandlungseffekten bei Morbus Parkinson (PD). Das auf der Stelle Gehen (SIP), wurde ursprünglich als Test zur Haltungskontrolle und als Surrogat für Ganganalyse vorgeschlagen, zwei wichtige Aspekte der gestörten motorischen Funktionen bei Parkinson. Ziel dieser Studie war es, die Quantifizierung von Parkinson-assoziierten motorischen Merkmalen während des Gehens auf der Stelle zu untersuchen.

Methoden:

Ein makerfreies Bewegungsanalysesystem (RGB-Tiefenkamera) wurde verwendet, um die Ausführung vom SIP über 40 Sekunden aufzuzeichnen. Für die Entwicklung der Algorithmen, die Merkmalsextraktion und die statistische Analyse standen Daten von 25 Personen mit Morbus Parkinson (PwPD, 7 weiblich, Alter: 65,3 Jahre ± 9,4 Jahre, MDS-UPDRS III 5-65) in bis zu zwei verschiedenen Therapiezuständen (OFF: 13, ON: 20) und Daten von 83 gesunden Personen (HC, 52 weiblich, Alter: 36,8 Jahre ± 13,8 Jahre) zur Verfügung. Auf Grundlage der Kniebewegungen wurden acht Parameter extrahiert: Kadenz, durchschnittliche Amplitude der Kniebewegung, durchschnittliche und längste Schritt- und Standzeiten, Asymmetrie und Arrhythmie. Die Parameter wurden im Hinblick auf potenzielle Störfaktoren, technische Genauigkeit und Wiederholbarkeit bei HC, Zusammenhang mit dem Schweregrad der Erkrankung (MDS-UPDRS III) und der posturalen Instabilität (Pull-Test-Score) in PwPD sowie auf intraindividuelle Unterschiede bei den Behandlungszuständen (OFF vs. ON) analysiert.

Ergebnisse:

Sechs von acht Merkmalen zeigten eine gute Genauigkeit und Wiederholbarkeit in HC (n=19). Asymmetrie und Arrhythmie zeigten nur geringe bis mäßige Genauigkeit (ICC(A,1) > .3; Pearson's r > .5) und Wiederholbarkeit (ICC(1,1) >.4). Bei HC (n=83) und PwPD (n=33) wurden keine linearen Effekte von Alter, Größe und Gewicht festgestellt. Eine verringerte Knieamplitude war mit höherer Krankheitsschwere (rho=-.503, p-Wert = .003) und höherer posturalen Instabilität (rho=-.436, p-Wert=.014) verbunden. Die Knieamplituden nahmen in einer Untergruppe (n=10), von OFF zu ON um 85,4 % zu. Längere Standzeiten waren mit höherer Krankheitsschwere (rho=.523, p-Wert=.002) und höherer posturalen Instabilität

(rho=.468, p-Wert=.008) verbunden. 50 % der Patienten, die im MDS-UPDRS-III ein Einfrieren des Gangs zeigten, zeigten auch beim SIP ein Einfrieren.

Schlussfolgerung:

Die instrumentelle Analyse vom 40-sekündigen Gehen auf der Stelle kann geeignet sein, häufige motorische Symptome, insbesondere posturale Instabilität, bei PwPD zu quantifizieren. Die abgeleiteten Parameter beschrieben die motorischen Symptome von Morbus Parkinson, einschließlich verringerten Bewegungsumfang (Hypokinese), langsamerer Bewegungen (Bradykinese) und Asymmetrie sowie Arrhythmie der Schrittbewegungen. Die Empfindlichkeit gegenüber intraindividuellen Veränderungen deutet auf einen möglichen Einsatz des SIP zum Monitoring motorischer Symptome von PD hin.

1 Introduction

Since its first description in 1817 by the London physician James Parkinson [1], the awareness of Parkinson's disease (PD) increased and is now seen as "one of the most important disabling illnesses of later life" [2]. With aging societies, its prevalence increases.

1.1 Parkinson's Disease

1.1.1 Introduction to Parkinson's Disease

For Parkinson's Disease, the disease onset is age dependent. The typical time of diagnosis is after the age of 50, where estimates are that 1% of the population who is 70 years and older are affected [2]. Only 10% of PD cases are "juvenile" with symptoms appearing before the age of 21, or "young onset PD" where symptoms are present before the age of 40 [2]. The four cardinal motor signs of PD include tremor at rest, specific stiffness of muscles (rigidity), absence or slowness of movements (akinesia / bradykinesia), and disturbed balance (postural instability). Also common are reduced range of movement (hypokinesia). Excessive, involuntary movements (hyperkinesia / dyskinesia) often occur as side effect of PD medication. Nonmotor symptoms of PD include olfactory deficits, depression, and REM sleep behaviour disorder and may even be present in the preclinical stage of the disease. PD Symptoms are caused by neurodegeneration predominantly of the substantia nigra which results in a decrease of dopamine production, affecting the basal ganglia function and thalamic connectivity [2,3].

The diagnosis of PD is typically made in line with the Movement Disorder Society clinical diagnostic criteria for Parkinson's Disease [2,4] which includes evaluation of diagnostic criteria like the response to dopamine therapy, appearance of motor symptoms and investigation of exclusion criteria. Additional neuroimaging may confirm pre-synaptic dopamine depletion or help to exclude differential diagnoses [2,4].

Symptoms of PD can be alleviated by dopamine replacement by levodopa, reuptake inhibitors or dopamine agonists. The medication regimen is often complex and may result in motor fluctuations throughout the day. During these fluctuations, persons with PD (PwPD) may experience periods where the medication is working properly (ON state) and periods where the medication is wearing-off and the motor symptoms return (OFF state). Delayed-ON or sudden, unpredictable OFF periods can also occur [2]. One of the long-term side effects of levodopa is dyskinesia, where involuntary hyperkinetic movements are temporarily present.

Approaches to overcome these medication fluctuations and levodopa side effects are the use of implantable apomorphine pumps for continuous medication dosing or implantable electrodes for deep brain stimulation [2,3] to stimulate the internal globus pallidus or the subthalamic nucleus [2,3]. Dosing of these therapies must usually be adjusted several times to compensate for the individual patient's experience.

1.1.2 Clinical Testing of PD Symptoms

Since motor symptoms and their intensity are playing a major role in the diagnosis and management of PD, standardized clinical testing is crucial [2]. The most widely used clinical rating scale is the 'Movement Disorder Society Unified Parkinson Disease Rating Scale' (MDS-UPDRS), where part III [5] consists of 14 structured assessments or observations of specific motor symptoms. The derived clinical score ranges from 0 to a maximum of 56 points calculated as a sum of each assessment rating.

The MDS-UPDRS III includes the pull test to identify postural instability [6]. For this test, an operator is standing behind the patient and gives them a firm pull on their shoulders. The number of steps a person needs to stabilize themselves to prevent falling is then rated in a score between 0 to 4, where a rating of 4 indicates that the patient would have fallen.

Nonmotor symptoms of PD are not easily observed and often assessed using questionnaires such as the patient-reported nonmotor symptoms questionnaire (NMSQuest) [7] or the first part of the MDS-UPDRS [5]. In recent years, the importance of the assessment of non-motor symptoms of PD increased [2] with the concept of prodromal disease. Further review of this topic is given elsewhere [2,3,7].

1.2 Gait

1.2.1 Gait behaviour and measurement

The human gait behaviour can be seen as a rhythmic, repetitive, alternating movement of legs providing forward locomotion while maintaining an upright posture [8–10]. This ability is seen as one of the important evolutionary steps of humankind and requires unique anatomy and biomechanics unmatched in other bipedal species [11]. Although earlier theories did consider walking to be an automated process and did not discuss involvement of higher cognitive function [8], recent studies provided evidence of cognitive load even in unchallenging walking conditions [9].

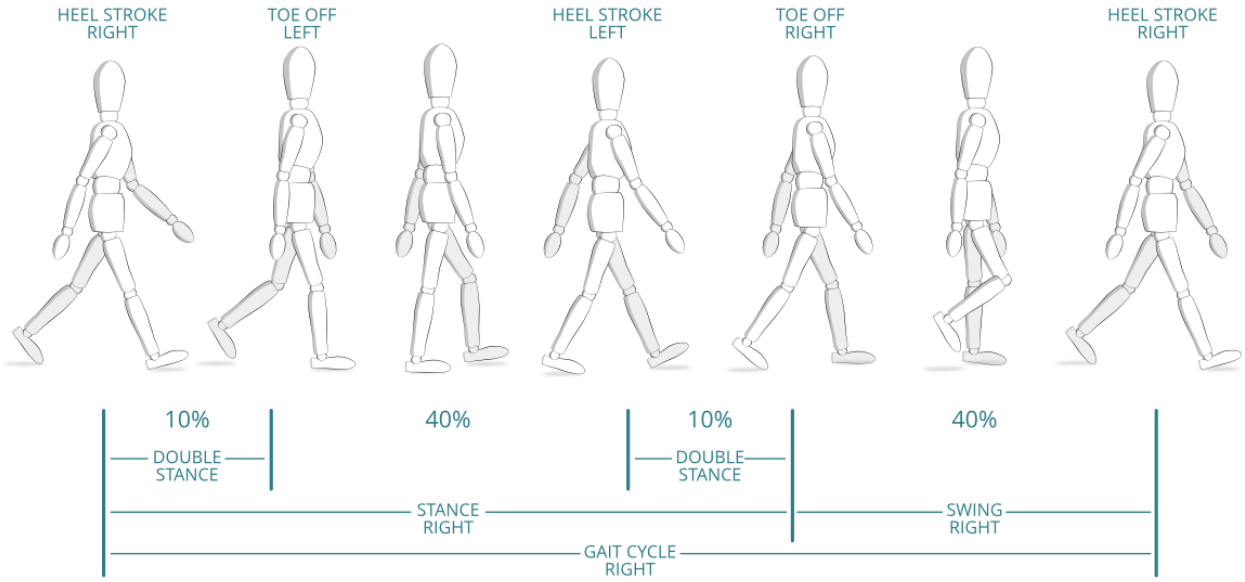

Figure 1 Phases of the human gait cycle for the right body side

When describing gait behaviour, the repetitive movement of each leg is separated into gait cycles [8]. During normal, forward gait of healthy adults, each cycle consists of a proportion of 40% swing phase, where the foot is moving freely and 60% stance phase where the foot has contact to the ground (see Figure 1). Since the right and left gait cycles are asynchronous to each other, only 20% of each gait cycle consists of a double stance phase where both feet have contact to the ground [8]. Within these cycles, distinct gait events can be identified, like the heel stroke which describes the moment of ground contact and indicates the transition from swing to stance phase.

For a quantitative description of gait, a large variety of spatiotemporal, kinematic, and kinetic parameters as well as muscle activity patterns can be derived [9]. Lord et al. [12] proposed five independent clusters of spatiotemporal gait parameters, called gait domains, based on data from healthy, elderly people. These independent domains are Pace, Rhythm, Asymmetry, Variability and Postural Control (see Table 1). When analysing pathological gait behaviour, higher gait variability is associated with lower gait automation, which indicates gait instability and has been associated with a higher risk of falling [9,13].

Table 1 Overview of a selection of commonly used spatiotemporal parameters to describe gait behaviour and their respective gait domain according to [12]

Parameter	Description	Associated Gait Domain [12]
Cadence (steps/min)	The number of steps that are made within one minute of walking.	-
Gait speed (m/s)	The walked distance in a defined timespan.	Pace
Step length (cm)	The anterio-posterior distance between feet during double stance phase.	Pace
Stride length (m)	The distance of the same food at the beginning and end of the gait cycle.	Pace
Step time (s)	The timespan between toe off and heel stroke of the same foot.	Rhythm
Stride time (s)	The timespan required to perform a full gait cycle for one side.	Rhythm
Stance time (ms)	The timespan between heel stroke and toe off from the same foot.	Rhythm
Swing time (ms)	See Step time.	Rhythm
Step time asymmetry (ms)	The difference or ratio between step times from both body sides.	Asymmetry
Gait speed / step velocity variability (m/s or %)	The standard deviation or coefficient of variation of velocity from several strides.	Variability
Step length variability (m or %)	The standard deviation or coefficient of variation from several step lengths.	Variability
Step width (cm)	The medio-lateral distance between feet during double stance phase.	Postural control
Step length asymmetry (cm or %)	The difference or ratio of step lengths from both body sides.	Postural control

In general, gait behaviour is known to be influenced by a variety of confounders. For example, persons with longer legs tend to show larger average step length and higher movement speed [8,14]. It is also important where, when and how gait measurements are made. For example, the inclusion of turns to maximize available walking space increases gait variability even when turns are excluded in post processing [15]. This is likely to be attributed to the difference of steady-state gait, where gait behaviour is stable and speed constant, and gait adjustments by acceleration or deceleration i.e. associated with turning or during start and stop of a gait task. This is especially important for the use of gait parameters as markers for pathologies.

1.2.2 Gait in PD

For PwPD, gait disturbances have a high impact on a person's mobility and their quality of life [16]. A stooped posture and shuffling gait were two of the features initially described by James Parkinson [1] and are some of the most prominent motor signs of the disease. In more detail, disease related changes are reduced step and stride length, decreased arm swing, increased movement asymmetry, increased gait variability, stepping hesitations as well as a typical forward-bent posture [3]. Although these changes in gait behaviour become more prominent in later stages of the disease, gait disturbance is often reported as the first symptom [3].

After 10 years of diagnosis, 70% of patients experience freezing of gait (FOG) [17] which is defined as "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [18]. Freezing of gait is reported to be one of the most disabling symptoms of PD and is associated with decreased quality of life and with high risk of falls [18]. Interestingly, appearance of freezing episodes is known to depend on environmental factors as well as cognitive and emotional states, making it challenging to assess in clinical routine [18].

Gait behaviour and associated motor symptoms are assessed clinically by patient-reported, or operator reported questionnaires (e.g. NFOG-Q [19]). Clinical rating is based on observational assessments (e.g. MDS-UPDRS) while performance-based testing uses a standard task (e.g. Timed Up and Go) to derive parameters such as performance time [3].

For freezing of gait, specific questionnaires such as the "New Freezing of Gait Questionnaire" (NFOG-Q) [19] assess the occurrence and severity of this phenomenon in patients' everyday life. Clinical assessment may use specific gait courses [20] that aim to elicit freezing for standardized rating. The most frequently used courses include standing up from a chair and initiating gait, performing a 360 degree turn as well as walking through a door frame. Performance-based tests may be combined with instrumented measurement technology to derive additional parameters for a quantitative description.

1.2.3 Stepping in Place

The first clinical description of a stepping in place (SIP) task was made by S. Unterberger in 1938 to test for vestibular dysfunction using SIP with closed eyes [21]. The test was later refined by T. Fukuda [22] and is therefore also known as Fukuda Stepping Test in Japan and the United States of America [23]. Typically, stepping in place is instructed in a way

that participants are asked to walk on the spot in a comfortable, self-selected pace [23–30] or by giving a pre-defined stepping pace [31,32]. The trial lengths are not standardized and range from 15sec [33,34] to 120sec [31], where 30sec [25,30,35,36] and 100sec [26,27,37] trials seem to be most common.

Stepping in place is frequently combined with task alterations like performance with closed eyes or blindfolded [21] or with additional cognitive dual-task [28]. Depending on the respective research questions, reported parameters range from cadence [24,26,28], step and stance timing [29], asymmetry and arrhythmicity measures [26,28] to the maximal range of movement in the measurement area [23]. Rarely, muscle activity patterns are reported [31,38].

When comparing to movement during forward gait, stepping in place behaviour is reported to show similar step frequency (cadence) in healthy people [24] with slightly longer stance times (60-70% in SIP, 60% in Gait) [29,38]. Both tasks are also reported to involve higher-level cognitive function to maintain a regular stepping [9,28]. Unfortunately, publications on the comparison of these tasks are sparse and available reports feature only small cohorts with limited parameter selection.

The suitability of SIP as a diagnostic test was explored in a variety of small cohorts including stroke survivors [24], elderly people [39] and people with Parkinson's Disease [26,27,30,37]. Nantel et al. reported that PwPD show a similar cadence to healthy age-matched volunteers while having higher asymmetry and arrhythmicity measures [26] which is consistent with reports on gait behaviour in this disorder [9]. In the same cohort, up to 87% of participants who self-reported frequent freezing of gait, also showed freezing during stepping in place. Later studies confirmed the occurrence of freezing episodes during stepping in place, although reporting lower test sensitivity [30,37].

In summary, stepping in place is proposed as a surrogate for conventional forward gait or as test for dynamic postural control but direct comparison against forward gait and balance tests are still lacking.

1.3 Instrumented Motion Analysis

A large variety of technological approaches exist to quantify human motion including wearable inertial sensors (e.g. accelerometer, gyroscope), force plates or mats, and infrared camera-based systems where either reflective markers are attached to the subject (marker-based) or image analysis is used (marker-free) to track movement in a 3D space [40]. All these

approaches come with their own advantages and limitations and require careful consideration of their applicability for a given context.

1.3.1 Motion Analysis using RGBD Cameras

Although commercial 3D cameras are available since decades, the wide us of these sensors in medical research started in 2010 with the release of the Microsoft Kinect for Xbox 360. Due to its open Software Development Kit and low cost, the sensor and its successors were explored regarding their feasibility in clinical settings by various groups [23, 25, 41–43, 47, 48]. As shown in Figure 2, the sensors have the capability to record RGB video data as well as depth information. Therefore, they are commonly referred to as RGB-D or RGBD cameras.

Currently available RGBD sensor technologies are mainly based on two different approaches [44]: 1) structured light, where the projection of an array of points on an object is compared to a reference structure (see Figure 2 and Figure 3, Kinect v1, left), and 2) time of flight, where the traveling time of an infrared pulse towards an object and back is used to estimate the objects distance (see Figure 2 and Figure 3, Kinect v2, right).

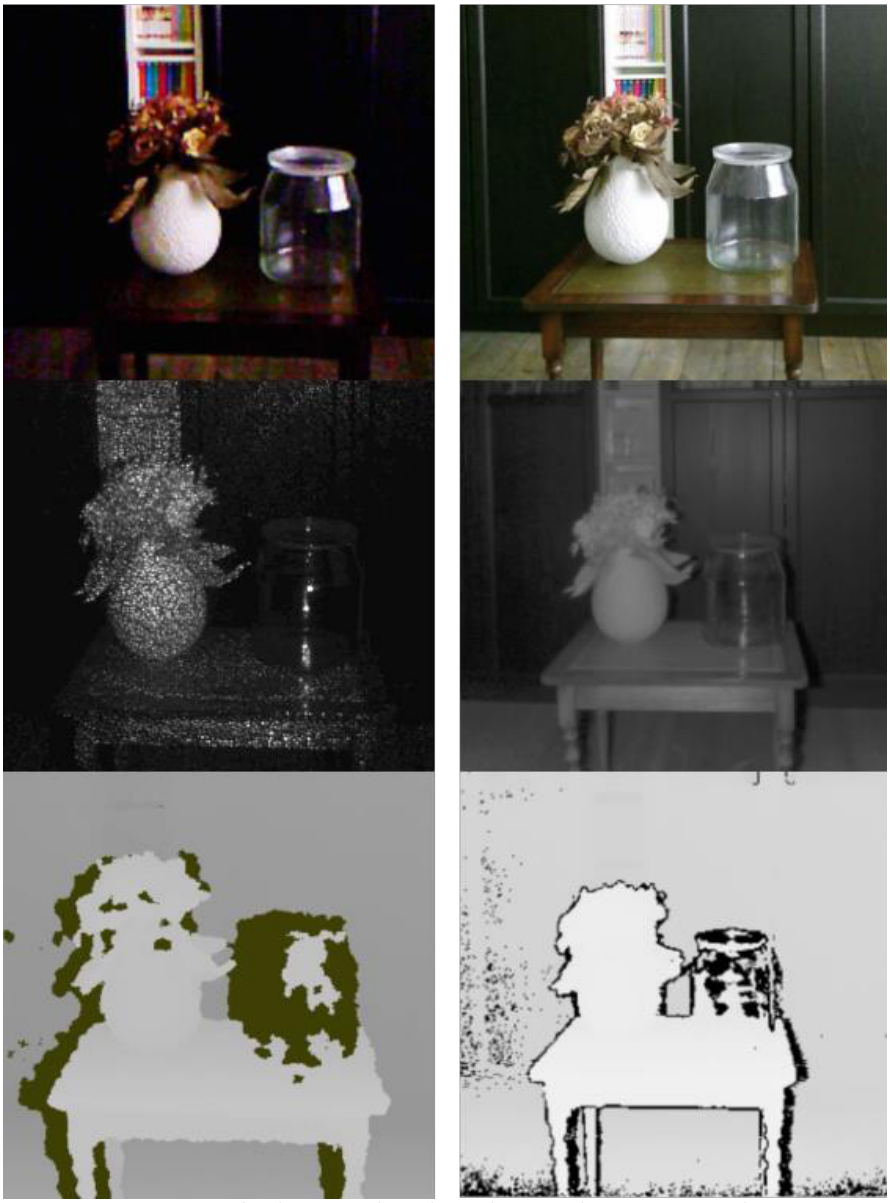

Figure 2 Comparison of the Kinect v1 (left) and v2 (right) in A) RGB, B) infrared and c) depth domains where green-gray/black areas in depth images indicate missing values.

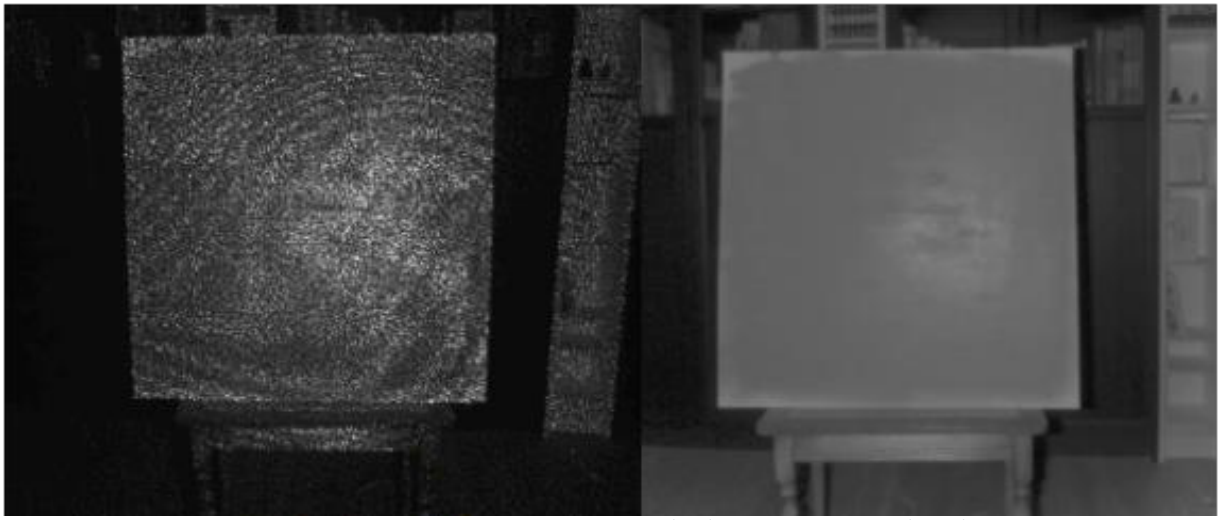

Figure 3 Comparison of emitted infrared light by structured light (left) and time of flight (right) technology

By using RGBD video data, a variety of approaches have been presented to detect human shapes and anatomical landmarks [45]. One of the most commonly used in medical research is the Kinect software development kit, which provides real time person detection and 3D information for sets of up to 25 anatomical landmarks [25,46] (see Figure 4). It is based on randomized decision forests which classify each depth pixel for each frame into different body segments i.e. head, right hand, left ankle. These regions are then used to identify anatomical landmarks. Since no external markers have to be placed on the person to be measured, such approaches are commonly referred to as marker-free motion capture.

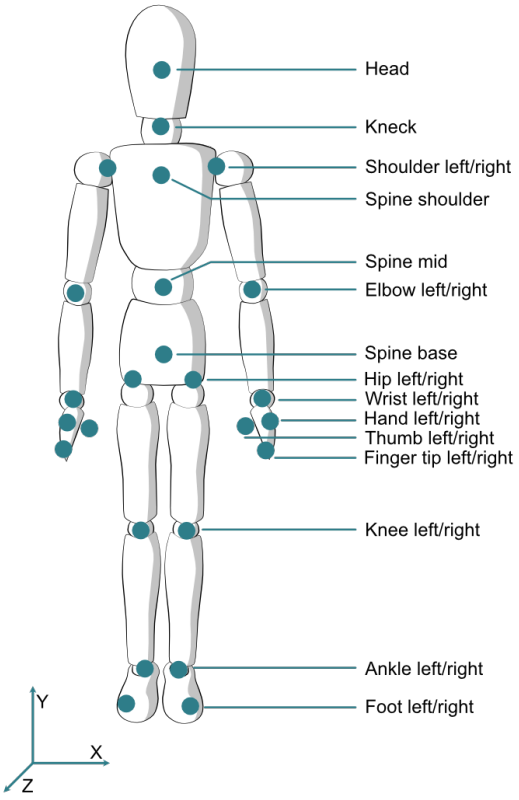

Figure 4 Positions of 25 anatomical landmarks provided by the Microsoft Kinect SDK v2.0

Limitations of these RGBD cameras are their relatively low sampling rate of 30-60Hz, their small recording areas of up to 5m distance and the problem of infrared reflection, absorption and occlusions, where no depth information can be captured (see black Areas in Figure 2 c) left and right). Mapping errors of the anatomical landmarks may appear when the provided depth data is inferred or missing. This happens for example on the edges of the measurement area where the depth resolution of the recorded data is low or when highly

reflective or infrared absorbing material is worn (see missing depth values in Figure 2 c) left and right).

1.3.2 Assessment of Motor Symptoms using RGBD Cameras

The first clinical evaluations of RGBD sensors explored their use for gait analysis [41] and analysis of postural control [25,42]. Spatiotemporal parameters were extracted and compared against marker-based motion capture systems [25,46] or pressure-based gait mats [41]. The spatiotemporal parameters step length and gait speed seem to show highest accuracy and consistent replicability whereas joint angles are overall reported to show low accuracy. Although these findings were focused mainly on an earlier Kinect version 1 (Kinect for Xbox 360), similar findings were reported for Kinect version 2 (Kinect for Xbox One) [43,46]. A general limitation of this technology with respect to gait analysis is the small sensor range which limits recorded walk paths to 3m [41,46] and may explain lower accuracy of extracted stride times [41,47]. Combining several Kinect sensors [48] or gait recordings using treadmills [41] were explored as possible solutions. In sum, the use of RGBD cameras to extract gait parameters was shown to be feasible in a number of pilot studies in persons with Multiple Sclerosis, Parkinson's Disease and Stroke survivors.

Only two studies explored the use of Kinect v2 for stepping in place analysis [23,25]. In the first study, stride times were assessed by using vertical displacement of knee markers, whereas the measurement outcomes of the other studies were limited to the maximum spatial distance which participants showed after 20 sec of stepping.

1.4 Contents of this thesis

This thesis summarizes the work of the publication "Instrumental Assessment of Stepping in Place Captures Clinically Relevant Motor Symptoms of Parkinson's Disease" [49] and provides further information and supplementary materials on data from healthy controls as well as comparisons to short-distance gait recordings of a 3.5m walk.

1.4.1 Scientific question

The main objective of this thesis was to explore motor signs and symptoms associated with Parkinson's Diseases during stepping in place performance. Specifically, the question was:

"Can quantitative measures of stepping in place performance be used to describe motor symptoms of Parkinson's disease?"

To answer this question, SIP performances of a small cohort of patients with Parkinson's Disease were explored in ON and OFF medication states while quantitative outcomes were compared against clinical ratings of disease severity. In addition to the published analysis of stepping in place performance in persons with Parkinson's Disease, data from healthy subjects are presented and potential confounding effects were explored. Further, to explore the clinical feasibility and potential use of SIP, spatiotemporal parameters of stepping in place were related to parameters obtained in a short-distance gait recording. For the motor performance quantification in this thesis, a single RGBD camera (Microsoft Kinect v2) was used.

1.4.2 Content of this document

After this brief introduction into the state of the art and description of the scientific question, an overview of used methods is provided. The methods chapter covers the study designs, datasets, as well as cohort descriptions, and continues with descriptions of the motor task recording and data processing steps for a selected set of spatiotemporal parameters. The section ends with a summary of used statistical methods.

The results section starts with a presentation of the accuracy and repeatability of the parameter set from a HC dataset. Afterwards, the stepping in place performance of a healthy cohort is presented and exploration of potential confounders. Onwards from that, results

from the publication are presented in the context of the main scientific question. Additional unpublished findings are added to interpret the findings from stepping in place against forward gait behaviour. In the last chapter, presented findings are summarized and discussed in the context of existing literature. Finally, limitations and advantages of the work are given, and potential solutions and further works are provided.

2 Methods

2.1 Study population and clinical assessments

While the published study focused on the use of stepping in place in persons with Parkinson's Disease [49], this thesis also included supporting analysis of behaviour in healthy controls. Additionally, measures of short comfortable speed walk were included. These findings were not previously published.

2.1.1 Healthy Cohort

Data from 83 healthy volunteers (52 female, 31 male, age: 36y ± 14y, height: 171cm ± 9cm, weight: 70.5kg ± 13.5kg) was used to provide a reference point for unimpaired, "normal" stepping in place behaviour. The data was pooled from different observational studies which were initiated by the Clinical Neuroimmunology Group, Experimental and Clinical Research Center, and performed in the NeuroCure Clinical Research Center at the Charité Universitätsmedizin Berlin. This database was supplemented with data from a study of young healthy adults performed at the Max-Plank Institute for Human Development. Exclusion criteria for all studies were any self-reported diagnoses, pain or injuries that would limit the movement of the participants. All studies were approved by either the ethics committee of Charité Universitätsmedizin Berlin (EA1/163/12, EA1/339/16, EA1/321/14) or the Human Research Ethics Committee of Max Planck Institute for Human Development, Berlin.

The datasets included sex, age, height and weight as well as recordings of a stepping in place and short-distance gait at comfortable and maximum speed using a RGBD camera (Kinect v2). From these 83 healthy controls, a subgroup of 19 persons (12 female, 7 male, age: 28y ± 4.5y, height: 171cm ± 7cm) performed motor tasks with simultaneous recordings of a marker-based Vicon motion capture system (MX13+, Nexus 2.1; Vicon Motion Systems Ltd., Oxford, UK) and the RGBD system. This subgroup is further called “Vicon cohort” and allows for analysis of technical accuracy and repeatability [46].

2.1.2 PD Cohort

The published data originated from two studies exploring motor function in PwPD as secondary aim. These studies were performed at three different locations at the Charité Universitätsmedizin Berlin involving the departments of Neurology and Experimental Neurology and the NeuroCure clinical Research Center. The ethics committee of Charité Universitätsmedizin Berlin approved both studies (EA1/012/17 and EA1/216/15) and all

participants provided written informed consent prior to study enrolment, agreeing on data usage for secondary research questions and publication of results. Inclusion criteria for data selection from these studies were the clinical diagnosis of Parkinson's Disease and the availability of clinical ratings as well as motor performance recordings of stepping in place and short comfortable speed walk from the same visit. Exclusion criteria were reported movement impairments that were not attributed to PD e.g. due to injuries. Since this work focused on the analysis of the cardinal symptoms of PD, recordings were excluded when dyskinesia was reported in clinical ratings at the time of testing.

The datasets consisted of recordings of motor tasks (PASS-PD) as well as patients' disease severity (MDS-UPDRS part III), including ratings of the pull-test task as indicator for postural instability (item 12) and information on the appearance of freezing of gait episodes during the clinical assessment (item 11). Treatment states at the time of recording were documented as: 1) ON, where either oral medication or DBS was adjusted to minimize symptom severity and 2) OFF, where DBS and oral medication were withdrawn according to the respective study protocol.

In total, data of 33 assessments in 25 PwPD were available for feature extraction and statistical analysis (see Table 2). The Dataset included a subset of 10 PwPD with available recordings from ON and OFF treatment state.

Table 2 Characterization of available datasets from 25 persons with PD, taken from [49]

	ALL	**ON**	**OFF**	**ON-OFF**
N subjects	25	20	13	10
N recordings	33	20	13	2x10
male	18	15	8	6
female	7	5	5	4
Age (years)	65.3 (± 9.4)	65.5 (± 11.05)	66.2 (± 8.0)	65.3 (± 8.7)
Weight (kg)	75.0 (± 13.5)	74.1 (± 13.5)	76.3 (± 12.5)	76.2 (± 13.8)
Height (cm)	168.4 (± 6.8)	167.7 (± 6.1)	170.4 (± 7.8)	168.4 (± 5.3)
Disease Duration (years)	12.8 (± 8.1)	12.1 (± 8.0)	11.6 (± 6.6)	10.1 (± 7.2)
MDS-UPDRS-III	28.3 (± 14.7)	25.3 (± 13.7)	34.9 (± 15.1)	ON: 28.8 (± 13.4) OFF: 37.2 (± 14.5)
N - item 11 (FOG)				ON: 8/2/0/0/0
0 / 1 / 2 / 3 / 4	23 / 4 / 6 / 0 / 0	14 / 3 / 3 / 0 / 0	9 / 1 / 3 / 0 / 0	OFF: 7/3/0/0/0
N - item 12 (Pull test)				ON: 4/3/2/1/0
0 / 1 / 2 / 3 / 4	12 / 10 / 6 / 1 / 1	8 / 4 / 5 / 2 / 0	4 / 6 / 1 / 1 / 1	OFF: 1/6/1/1/1

2.2 Recording of Motor Tasks (PASS-PD)

The PASS-PD protocol is a set of motor tasks developed for the purpose to assess motor signs and symptoms in neurodegenerative diseases using a single RGBD camera. It consists of twelve short motor tests including but not limited to: short comfortable and maximum speed walk [46], stepping in place [49], static balance tasks (standing with open and closed eyes, with closed feet) [50], dynamic balance tasks (standing up and sitting down) as well as tests of upper arm function (Finger Tapping Task, Hand Grip Task and Finger-Nose Test).

For the recording of the stepping in place task, participants were instructed to walk on the spot in comfortable and even pace, as though they would walk normally but should omit forward momentum. The starting positions of both arms were described as relaxed hanging on the side, but no further instructions were given on arm usage during the task.

For the short-distance gait in comfortable speed, participants were instructed to walk in their normal speed "as you would walk as a pedestrian down the street" straight towards the camera and stop directly in front of it after an audio signal was given.

2.3 Technical Setup

A visual perceptive computing system (Motognosis Labs, v2.0, Motognosis GmbH, Berlin, Germany) was developed and used in combination with the Kinect v2 (Kinect for Xbox One, Microsoft, Washington, USA) as RGBD sensor. The camera was placed in 1.4m height on a tripod and was connected to the required power supply and via USB cable to a recording laptop. The system was operated by trained health professionals including physician, doctoral students, and study nurses, according to written operating procedures.

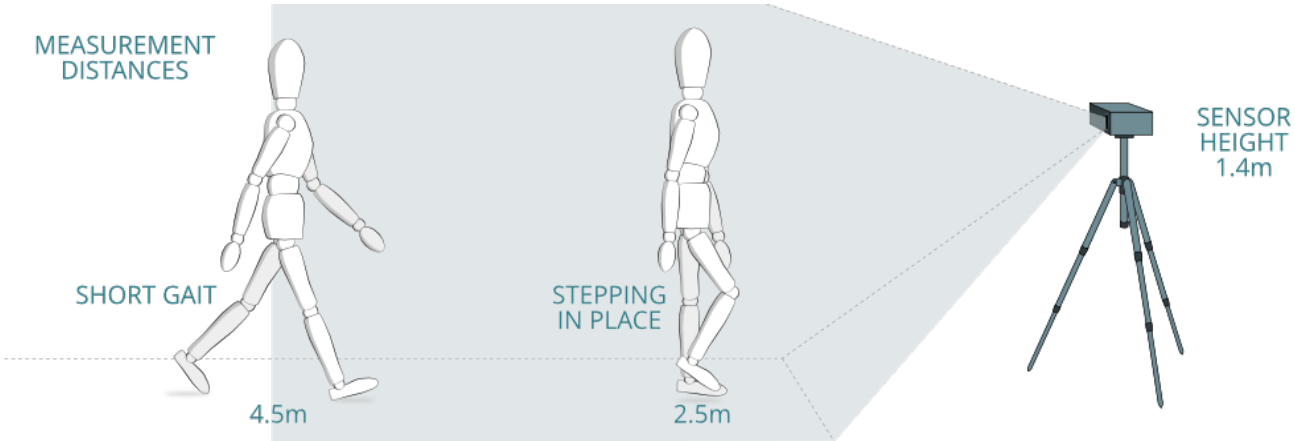

Figure 5 Setup of the Kinect sensor in distance to the performed motor tasks

Gait tasks were recorded with participants starting outside of the camera sensor range at 5m distance and walking straight towards the camera, stopping at roughly 1.5m distance (see Figure 5). For recording of stepping in place tasks, subjects were placed in 2.5m distance towards the camera. The start and stop of each task were indicated to the subject via automated audio signals from the recording software. Gait tasks were repeated three times during one measurement session, whereas stepping in place was not repeated. Only in the Vicon cohort, each task was repeated five times within the same session. Task instructions were given immediately prior to the performance of each task.

2.4 Identification and extraction of parameters

The recording software provided comma-separated-value files (.csv) with metrical, three-dimensional information of each anatomical landmark in roughly 30 frames per second (30Hz). Each frame consisted of an absolute and relative time stamp, the three-dimensional positions of all anatomical landmarks and their estimated reliability score (tracking state) in ordinal scale (0=not tracked, 1=inferred, 2=tracked). The sensor software development kit (Kinect SDK, v02.14) provided landmark location information based on a coordinate system where X is the left-right axis orientation, Y is the up-down axis orientation and Z is the forward-backward axis orientation (see Figure 4).

Algorithms for data import, pre-processing, feature extraction and analysis were developed and implemented in MATLAB (v2018b).

2.4.1 Parameter selection to describe stepping in place performance

As presented in chapter 1.2.3, most publications on stepping in place behaviour used parameters known for gait analysis such as cadence, asymmetry and step or stance times. Therefore, these parameters were included in this work. Other parameters were added in this study to cover the most prominent motor symptoms of PD during gait, hypokinetic and bradykinetic movements as well as freezing of gait. Range of movement was chosen as a potential parameter to describe hypokinesia. The appearances of bradykinesia or freezing of gait episodes would be expected affect step timing. Therefore, information on average and longest stance and step time measures was included.

Due to previously reported noise behaviour in anatomical landmarks of the feet and ankles [46], knee landmark movements were used as main source for step detection. Specifically, the use of knee landmark movements in anterio-posterior direction takes advantage of the notably highest accuracy of the Kinect along the z-axis [46]. Additional

parameters could have been extracted by analysing hand movements or trunk sway during stepping performances. Since these parameters have not been described previously for stepping in place behaviour, this study focused on movements of the legs as well.

In total, a set of eight spatiotemporal parameters was defined where each parameter can either be directly compared to existing literature of stepping in place or to similar measures of gait analysis (see Table 3).

Table 3 Description and units of spatiotemporal parameters derived from recordings of stepping in place behaviour

Parameter Name	Unit	Description
Stepping cadence	Steps/min	Steps per minute
Knee amplitude	cm	Anterio-posterior range of motion of knees
Asymmetry	%	Logarithmic ratio between knee amplitudes of larger side to smaller side
Average step time	s	Average time required for a step during the measurement
Longest step Time	s	Maximal time required for a step during the measurement
Arrhythmicity	%	Ratio between standard deviation and average of the step time
Average stance time	s	Average time between step movements
Longest stance time	s	Maximal time between step movements

2.4.2 Parameter extraction of stepping in place performance

General preprocessing steps were applied including correction of sensor tilt, application of a 10-frame wide moving average filter on all anatomical landmarks in all three dimensions, analysis of mapping errors of the anatomical landmarks (calibration jumps) and analysis of temporal delay between recorded frames (frame gaps). Calibration jumps were detected by calculation of frame-to-frame joint acceleration.

Afterwards, step cycles were detected using knee positions relative to the hip centre landmark. This allows for compensation of subjects' movements within the measurement area. Additional processing steps and filters were applied to stabilize resulting movement signals of the knees as described in the original publication [49]. A manually chosen threshold of 2.5cm for the anterior excursion of the knee landmark was defined to separate stance and step phase. This threshold allowed separation of "real" stepping movement and slight knee bends due to e.g. freezing of gait appearance or noise behaviour of the landmarks when the leg was straight. The average and longest durations of the stepping movements and stance movements were calculated to describe step and stance timing. Under the assumption of correct motor task instruction, the longest stance time could indicate freezing of gait

behaviour and duration. Due to the limited temporal resolution of only 30 Hz, calculation of asymmetry was based on ranges of motion rather than stride time [12].

The procedures of pre-processing and parameter extraction were described in more detail in the original publication [49].

2.4.3 Available Parameters of short comfortable speed walk (SCSW)

The following parameters were used for the description of gait behavior in short-distance comfortable speed walk (SCSW): gait speed, gait cadence, gait step length, gait step duration and gait stride length (Table 4). The individual average of three immediate test repetitions were used for analyses. The technical accuracy of these parameters was shown previously in a cohort of young healthy adults [46] which also forms part of the HC sample in this study.

Table 4 Unit and description of spatiotemporal parameters derived from a short-distance gait test

Parameter Name	Unit	Description
Gait cadence	Steps/min	Steps per minute
Gait speed	m/s	Average distance walked during one second
Gait step length	cm	Anterio-posterior distance between both feet during double stance phase
Gait step duration	s	Time between toe-off and heel stroke of the same foot
Gait stride length	m	Anterio-posterior distance between the toe-off and heel stroke of the same foot

2.1 Statistical Analyses

The significance levels for all tests were set to 5%. Due to the small sample sizes, the application of Bonferroni correction was likely to increase type II error. Therefore, test outcomes were not corrected for multiple testing. All statistics and figures were created using Python 3.5 in combination with the packages statsmodels (v0.12.0), numpy (v1.19.1) and pandas (v0.25.3). The results were additionally confirmed by using SPSS v24.

2.1.1 Stepping in Place performance in healthy adults

Since this healthy cohort is not matched to the clinical cohort of PwPD, the presented parameters are only used for descriptive purposes to present a “normal” movement pattern and to explore potential confounders.

2.1.1.1 Descriptive statistics and confounder analysis

Average measurements as well as standard deviations (SD) were reported for each spatiotemporal parameter. Normality for each parameter was explored by Shapiro-Wilk test as well as by inspection of histograms. For the analysis of potential linear confounding effects of a persons' age, body height and body weight on the presented spatiotemporal parameters, Pearson's correlation coefficients were used. Differences in motor performance between men and women were explored by reporting of average measures and their SD for both subgroups, while an independent t-test for normally distributed parameters and a Mann-Whitney U test for non-normally distributed parameters were used for statistical testing.

2.1.1.2 Technical Accuracy and Repeatability of SIP parameters

Descriptive statistics as mean, and SD were given for spatiotemporal parameters derived from the RGBD camera system (Kinect) and the marker-based gold standard system (Vicon). Additionally, the absolute differences between average measures were given. The Kinect accuracy was expressed as absolute agreement between both systems by intraclass correlation coefficient ICC(A,1) (two-way mixed model) and limits of agreement (LOA). The Pearson's correlation coefficient (r) was used to describe relative agreement (consistency) between systems. The 95% confidence intervals (CI) for ICC and r are provided. The repeatability of derived spatiotemporal measures were expressed as intraclass correlation coefficient ICC(1,1) (one-way random model) and standard error of measurement (SEM) for each system. For better comparison between parameters, the SEM was additionally expressed as proportion of the mean.

2.1.2 Stepping in Place Performance of PwPD

2.1.2.1 Descriptive statistics and confounder analysis

For the pooled dataset (ALL) as well as ON and OFF subgroup, descriptive statics including mean and standard deviations were calculated for each parameter. Due to the small sample size, inspection of histogram plots was used to identify normality. As described above (2.1.1.1), confounder analysis was performed in ON subgroup only using Pearson's correlation coefficients against age, body height and body weight. To analyze the influence of sex on measurement outcomes, an independent t-test for normally distributed parameters and a Mann-Whitney U test for non-normally distributed parameters was performed.

2.1.2.2 Relation to disease severity and postural instability

The MDS-UPDRS part III total score and its item scores are ordinal, whereas spatiotemporal parameters derived from SIP are metric. Therefore, spearman's rho correlations were used to explore their association. Resulting correlation coefficients were interpreted as no relation (rho<0.3), small (rho>= 0.3 rho<0.5), moderate (rho>= 0.5 rho<0.7), large (rho>= 0.5 r<0.7) and very large relations (rho>=0.7). Mathematically significant correlations (p<.05) were plotted as regression plots for further exploration.

2.1.2.3 Comparison of ON and OFF therapeutic states

The subgroup of 10 individuals with recordings available from OFF and ON state was explored using descriptive statistics, including absolute and relative difference between ON and OFF and paired t-test. Additionally, line graphs were used to explore directional consistency in changes between OFF and ON state.

2.1.2.4 Inspection of Freezing of Gait

As the appearance of Freezing of Gait (FOG) during stepping in place was reported earlier [26,27,30], depth videos and knee movement signals were inspected by a trained health professional post hoc to identify episodes of freezing. Appearances of freezing during stepping in place were then related to the report of freezing as part of the MDS-UPDRS part III assessment (item 11 score of >0). Under the assumption, that persons who experience FOG (freezers) are sufficiently detected by the MDS-UPDRS part III score of item 11, these reports are used as ground truth. Thus, the sensitivity and specificity of SIP to induce FOG in known freezers were described.

2.1.3 Relations between Short Gait and Stepping in Place

To identify potential dependencies and relations between stepping behaviour during gait and SIP, Pearson correlation was used. Correlations with significant levels below .05 were additionally plotted as regression plots for further inspections. Confounder analysis and correlations to MDS-UPDRS III were also performed on gait parameters derived from short comfortable speed walk.

3 Results

The presented results on stepping in place performance of PwPD were reported in [49]. Since an updated version of the published algorithm was used here, results may differ slightly. To provide further context of these findings, the technical accuracy and repeatability of the presented parameters, measurements from a healthy cohort and the relation between stepping in place measures and measures from short-distance gait in comfortable speed were presented.

3.1 Stepping in Place Performance of healthy Adults

3.1.1 Descriptive statistics and confounder analysis

Descriptive statistics as mean and SD for the healthy cohort as well as female and male subgroups were given in Table 5. Normal distribution by Shapiro-Wilk test was observed for SIP cadence, knee amplitudes and average step times. Stance time in HC on average covered 31% and step phase made up 69% of the stepping cycle. No significant linear correlation was found for age, height, and weight against presented spatiotemporal parameters. Mann-Whitney U test showed differences between male and female subgroup with shorter average stance time (diff = 0.08 s, p-value = .031) and higher arrhythmicity (diff = 2.77%, p-value = .009) in women.

Table 5 Descriptive statistics and confounder analysis using Pearson correlation in healthy cohort where p-values calculated with independent t-test for normal distributed data ([1]) and Mann-Whitney U test for non-normal distributed data ([U]). Tests with p<.05 are marked bold.

	HC (N=83) mean (SD)	**Age *r* (p-value)**	**Height *r* (p-value)**	**Weight *r* (p-value)**	**Female (N= 52) mean (SD)**	**Male (N= 31) mean (SD)**	**p-value**
Cadence (steps/min)[1]	103.50 (20.3)	.129 (.246)	-.058 (.603)	.093 (.463)	105.78 (17.44)	97.42 (20.98)	.056
Knee Amplitude (cm)[1]	18.40 (5.98)	-.010 (.931)	-.022 (.845)	-.100 (.434)	17.56 (5.91)	19.88 (6.00)	.094
Asymmetry (%)	9.19 (7.87)	.092 (.407)	.075 (.501)	-.019 (.879)	8.31 (7.24)	10.85 (8.84)	.209[U]
Average step time (s)[1]	0.84 (0.12)	-.131 (.239)	.041 (.713)	-.048 (.705)	0.83 (0.12)	0.87 (0.12)	.148
Longest step time (s)	0.97 (0.16)	-.110 (.320)	-.003 (.978)	-.108 (.396)	0.97 (0.16)	0.98 (0.16)	.661[U]
Average stance time (s)	0.37 (0.16)	-.016 (.887)	.111 (.320)	.009 (.947)	0.35 (0.14)	0.43 (0.17)	**.031[U]**
Longest stance time (s)	0.55 (0.19)	-.040 (.719)	.104 (.349)	-.005 (.968)	0.52 (0.18)	0.60 (0.21)	.079[U]
Arrhythmicity (%)	9.31 (5.47)	-.011 (.920)	-.113 (.309)	-.110 (.386)	10.16 (5.81)	7.39 (3.79)	**.009[U]**

3.1.2 Accuracy of SIP parameters in young healthy Adults

Absolute differences between the spatiotemporal parameters derived from the RGBD system and the Vicon system as well as the respective limits of agreement (LOA), Intraclass correlation coefficients for absolute agreement (ICC(A,1)) and Pearson correlation coefficients for relative agreement were presented in Table 6. High absolute and relative agreement between both systems were found (ICC(A,1) > .8; r > .8) with the exception for asymmetry and arrhythmicity measures. A systematic offset of 2.5cm was seen for measurements of knee amplitudes, where the Kinect system provided on average lower measures than the Vicon system. The arrhythmicity parameter showed low absolute (ICC(A,1) = .367) and only moderate relative agreement (r = .509), while Vicon measures showed a higher average arrhythmicity of +2.9%. Measures of asymmetry showed moderate absolute and relative agreements with a bias towards slightly higher asymmetry measures of .5% from the Kinect system.

Table 6 Accuracy of SIP parameters as mean and standard deviations from simultaneous assessment with Kinect and Vicon, and their absolute difference, limit of agreements (LOA), absolute agreement as intra-class correlation coefficient (ICC(A,1)) and Pearson correlation (r) as relative agreement in a subset of 19 young healthy adults.

	Kinect Mean (SD)	**Vicon Mean (SD)**	**Abs. Diff**	**LOA**	**ICC(A,1) (95% CI)**	**Pearson *r* (95% CI)**
Cadence (steps/min)	93.4 (14.5)	94.0 (14.1)	0.61	[-3.5; 4.7]	.989 (.980; .994)	.990 (.982; .994)
Knee Amplitude (cm)	21.1 (5.2)	23.5 (4.2)	2.46	[-1.1; 6.0]	.815 (.050; .942)	.943 (.904; .967)
Asymmetry (%)	6.4 (4.7)	6.0 (6.7)	-0.45	[-10.1; 9.2]	.636 (.446; .771)	.673 (.495; .797)
Average Step Time (s)	0.9 (0.1)	0.9 (0.1)	0.02	[-.03; .06]	.970 (.897; .987)	.979 (.965; .988)
Longest Step Time (s)	1.0 (0.2)	1.1 (0.2)	0.08	[-.08; .24]	.838 (.327; .940)	.932 (.885; .960)
Average Stance Time (s)	0.4 (0.1)	0.4 (0.1)	-0.03	[-.09; .04]	.946 (.774; .979)	.970 (.949; .983)
Longest Stance Time (s)	0.6 (0.2)	0.6 (0.2)	-0.01	[-.15; .14]	.917 (.861; .951)	.919 (.864; .953)
Arrhythmicity (%)	7.0 (3.2)	10.0 (5.5)	2.91	[-6.3; 12.2]	.367 (.077; .592)	.509 (.279; .684)

3.1.3 Repeatability of SIP parameters in young healthy Adults

The repeatability of the presented parameters is expressed as intraclass correlation coefficient for repeated measures (ICC(1,1)) and standard error of measurements (SEM) for each system (see Table 7). Both systems show comparable outcomes for ICC and SEM measures for each kinematic parameter. ICC(1,1) show overall good repeatability (>.8), except for asymmetry and arrhythmicity. For these two parameters, repeatability was moderate (ICC(1,1) <.75) for the Vicon system and poor (ICC(1,1) < .5) for the Kinect system.

Table 7 Repeatability of SIP parameters as intra-class correlation coefficient (ICC(1,1)) and standard error of measurement (SEM) as absolute values and as percentage of system mean in a subset of 19 young healthy adults with five repetitions each.

	Kinect ICC(1,1)	Kinect SEM abs	Kinect SEM [%]	Vicon ICC(1,1)	Vicon SEM abs	Vicon SEM [%]
Cadence (steps/min)	.968 (.933; .987)	2.58	2.77	.957 (.910; .982)	2.93	2.93
Knee Amplitude (cm)	.946 (.887; .978)	1.20	5.71	.941 (.878; .976)	1.03	4.35
Asymmetry (%)	.434 (.148; .704)	3.55	55.1	.662 (.419; .842)	3.90	65.2
Average Step Time (s)	.978 (.954; .991)	0.02	1.91	.960 (.916; .984)	0.02	2.63
Longest Step Time (s)	.938 (.871; .974)	0.04	4.09	.930 (.856; .971)	0.06	5.02
Average Stance Time (s)	.966 (.929; .986)	0.03	5.90	.939 (.874; .975)	0.03	7.74
Longest Stance Time (s)	.844 (.698; .933)	0.07	12.6	.808 (.638; .916)	0.07	12.9
Arrhythmicity (%)	.463 (.179; .723)	2.32	33.0	.777 (.587; .901)	2.59	26.1

3.2 Stepping in Place Performance of PwPD

3.2.1 Descriptive statistics and confounder analysis

The mean and standard deviations of all eight spatiotemporal parameters for the pooled data (ALL), ON and OFF subgroups are given in Table 8. Normality for stepping cadence, knee amplitude and average step time was identified by inspection of histograms. The relative duration between average stance to average step time was 47% to 53% in ON which changed to 52% to 48% in OFF measures.

Table 8 Descriptive statistics for eight spatiotemporal parameters describing stepping in place behaviour for pooled, ON and OFF PwPD data where parameters with normality are marked by [1].

	Descriptive Statistics Mean (SD)		
	ALL (N=33)	ON (N=20)	OFF (N=13)
Stepping cadence (steps/min) [1]	98.44 (28.98)	97.10 (29.64)	100.51 (28.99)
Knee Amplitude (cm) [1]	12.17 (7.34)	13.16 (5.42)	10.64 (9.63)
Asymmetry (%)	18.94 (20.32)	16.31 (14.30)	23.00 (27.34)
Average step time (s) [1]	0.71 (0.21)	0.76 (0.22)	0.64 (0.19)
Longest step time (s)	0.87 (0.24)	0.91 (0.23)	0.80 (0.25)
Average stance time (s)	0.68 (0.71)	0.67 (0.78)	0.70 (0.62)
Longest stance time (s)	1.80 (2.74)	1.85 (3.25)	1.72 (1.80)
Arrhythmicity (%)	11.66 (5.75)	11.13 (6.74)	12.48 (3.86

Confounder analysis showed only small, non-significant correlations between patients' age, height and weight with spatiotemporal parameters during ON (see Table 9).

Table 9 Analysis of potential confounding effects of age, height, weight and sex in PwPD during ON where p-values calculated with independent t-test for normally distributed data ([1]) and Mann-Whitney-U test for non-normally distributed data ([U]). Tests with p<.05 are marked bold.

	ON (N=20)	**Age** *r* **(p-value)**	**Height** *r* **(p-value)**	**Weight** *r* **(p-value)**	**ON female (N=5)**	**ON male (N=15)**	**p-value**
Cadence (steps/min)[1]	97.1 (29.6)	-.205 (.386)	.030 (.926)	-.295 (.352)	98.1 (21.7)	96.8 (32.5)	.935
Knee Amplitude (cm)[1]	13.2 (5.4)	-.413 (.070)	.066 (.838)	-.337 (.284)	11.32 (6.1)	13.8 (5.3)	.394
Asymmetry (%)	16.3 (14.3)	.305 (.191)	.104 (.747)	.316 (.318)	11.0 (10.5)	18.1 (15.3)	.432[U]
Average step time (s)[1]	0.76 (0.22)	-.187 (.429)	-.020 (.951)	-.046 (.888)	0.70 (0.16)	0.78 (0.23)	.485
Longest step time (s)	0.91 (0.23)	-.178 (.452)	-.213 (.507)	-.127 (.695)	0.90 (0.25)	0.92 (0.23)	.930[U]
Average stance time (s)	0.67 (0.78)	.257 (.274)	.118 (.715)	.400 (.198)	0.55 (0.40)	0.71 (0.87)	.432[U]
Longest stance time (s)	1.85 (3.25)	.274 (.243)	.132 (.683)	.368 (.239)	1.43 (2.00)	1.98 (3.63)	.663[U]
Arrhythmicity (%)	11.1 (6.7)	.219 (.353)	-.005 (.987)	.155 (.631)	13.4 (5.8)	10.4 (7.0)	.256[U]

3.2.2 Relation to disease severity and postural instability

Spearman's rank correlation between spatiotemporal parameters with MDS-UPDRS III as well as Pull Test scoring were given in Table 4 of [49]. Smaller knee movement amplitudes were associated with higher disease severity (rho=-.507, p-value=.003) and postural stability (rho=-.436, p-value=.014). Moderate correlations in the opposite direction were found between longest stance time and clinical ratings (MDS-UPDRS III: rho=.523, p-value=.002; pull test: rho=.468, p-value=.008), where longer stance times were associated with higher disease severity and higher postural instability. Small correlations were seen for arrhythmicity and average stance time (|rho| <.5, p-value<.05) which both increased with higher ratings of disease severity. No correlations were found for cadence, asymmetry, average and longest step time. All correlations with p< .05 were given in Figure 6 Regression plots of significant correlations (p<.05) between spatiotemporal parameters and MDS-UPDRS III total score as well as pull test score in pooled PD data (n=33).

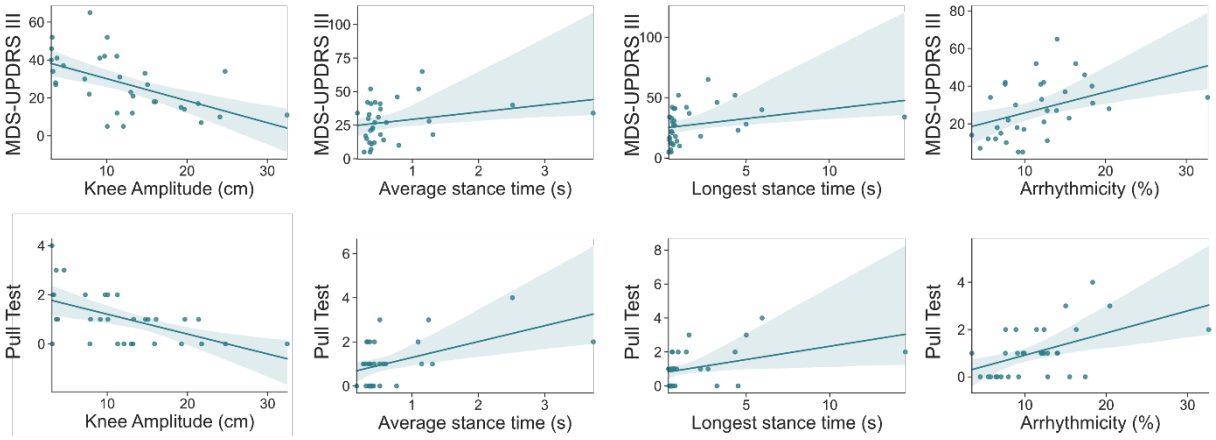

Figure 6 Regression plots of significant correlations (p<.05) between spatiotemporal parameters and MDS-UPDRS III total score as well as pull test score in pooled PD data (n=33).

3.2.3 Comparison of ON and OFF therapeutic states

For the subset of 10 PwPD with data available in both states, descriptive statistics, absolute and relative difference as well as p-values from paired t-tests were given in [49] in Table 5. The MDS-UPDRS III decreased at group level from OFF to ON state by -28.6%, which indicates, a clinically relevant reduction in motor symptoms and disease severity. Likewise, an increase of knee amplitudes of 6.05 cm from OFF to ON was observed at group level, which equals to +85.4% change to OFF measures. Further, changes were seen for asymmetry (-19.6%) and average step time measures (+14.5%), though relative differences were below 20% and therefore might not be clinically relevant.

Although a high relative difference of +94.6% at group level was found for the measured longest stance time between OFF and ON state, this finding is not statistically significant and was caused by one very long freezing of gait episode in one SIP recording during ON. No statistical difference between ON and OFF was found for cadence, arrhythmicity and average stance time.

3.2.4 Inspection of Freezing of Gait (FOG)

During clinical assessments of PwPD (n=33), FOG was reported 10 times (ON: n=6, OFF: n=4) by a rating of MDS-UPDRS III item 11 above or equal to 1. Inspection of depth videos by an independent health professional showed episodes of freezing during 5 stepping in place recordings (ON: n=4, OFF: n=1) which were independently confirmed by inspection of knee movement signals.

Since no false positive detection of freezing occurred when inspecting stepping in place behavior, the test specificity is here at 100%. Freezing during stepping in place was observed

in only 5 out of 10 assessments, in which MDS-UPDRS III item 11 indicated freezing episodes resulting in a sensitivity of 50% to detect FOG in PwPD.

3.3 Relations between Short Gait and Stepping in Place

Measures of gait speed, gait cadence, step length, step duration and stride length from short comfortable speed walk were available for all PwPD (N=25) and all HC (N=83) assessments. Results are provided as group average and standard deviation for PwPD and HC in Table 10.

Table 10 Descriptive statistics of five spatiotemporal parameters describing short comfortable speed walk for pooled, ON and OFF PwPD data as well as data from HC

	Descriptive Statistics Mean (SD)			
	ALL (N = 33)	**ON (N=20)**	**OFF (N=13)**	**HC (N=83)**
Gait cadence (steps/min)	109.81 (13.51)	107.12 (14.39)	114.30 (11.02)	110.76 (11.70)
Gait speed (m/s)	0.92 (0.25)	0.92 (0.25)	0.92 (0.26)	1.11 (0.19)
Gait step length (cm)	55.49 (13.86)	56.06 (14.61)	54.55 (13.08)	66.64 (8.55)
Gait step duration (s)	0.53 (0.08)	0.55 (0.09)	0.50 (0.05)	0.53 (0.06)
Gait stride length (m)	1.12 (.29)	1.13 (.29)	1.09 (0.28)	1.35 (0.16)

From the presented five gait parameters, gait speed, gait step length and gait stride length showed moderate correlations to patient's age ($r < -.5$; p-value $<.05$) only in PwPD (ON), but not in HC (see Table 11). The same parameters showed also moderate correlations to MDS-UPDRS III total score, which points to a possible interaction. Only in HC, small correlations were seen for body height with gait step length, gait stride length and step duration which is supported by existing literature.

Table 11 Analysis of potential confounding effects of age, height, weight, and sex in PwPD during ON and HC for 5 parameters of short comfortable speed walk. Correlations with p<.05 are marked bold.

	Pearson's correlation coefficient r (p-value)						
	Confounder Analysis in ON (N=20)				Confounder Analysis in HC (N=83)		
	Age	Height	Weight	MDS UPDRS III	Age	Height	Weight
Gait cadence (steps/min)	-.217 (.358)	-.512 (.089)	.142 (.660)	-.233 (.324)	.091 (.414)	-.255 (.020)	-.157 (.216)
Gait speed (m/s)	**-.532 (.016)**	-.088 (.786)	-.052 (.872)	**-.548 (.012)**	.043 (.698)	.139 (.209)	.013 (.919)
Gait step length (cm)	**-.508 (.022)**	.136 (.673)	-.067 (.837)	**-.543 (.013)**	-.000 (.999)	**.471 (.000)**	.110 (.386)
Gait step duration (s)	.127 (.595)	.530 (.076)	-.087 (.789)	.171 (.472)	-.107 (.335)	**.293 (.007)**	.159 (.208)
Gait stride length (m)	**-.500 (.025)**	.128 (.691)	-.071 (.826)	**-.539 (.014)**	-.005 (.961)	**.492 (.000)**	.126 (.322)

Correlation analysis between stepping parameters from SIP and those from short comfortable speed walk are presented separately for HC (see Table 12) and PwPD (see Table 13). In HC, only small correlations were seen between gait features and stepping in place asymmetry, arrhythmicity and longest stance times. Scatter plots of these correlations indicated no clear trends (see Figure 7) and no correlations were found for any other pair of parameters.

Table 12 Pearson's correlation coefficients and respective p-values between spatiotemporal parameters of stepping in place and short comfortable speed walk in healthy controls. Correlations with p<.05 are marked bold.

Pearson's correlation coefficient r (p-value) in HC (N=83)					
	Gait cadence (steps/min)	Gait speed (m/s)	Gait step length (cm)	Gait step duration (s)	Gait stride length (m)
Stepping cadence (steps/min)	.073 (.510)	.113 (.308)	.101 (.362)	-.064 (.568)	.094 (.397)
Knee Amplitude (cm)	.202 (.067)	.184 (.096)	.171 (.123)	-.190 (.086)	.165 (.136)
Asymmetry (%)	**-.384 (.000)**	**-.343 (.001)**	-.206 (.061)	**.387 (.000)**	-.201 (.068)
Average step time (s)	-.003 (.982)	-.069 (.535)	-.083 (.453)	.002 (.983)	-.079 (.476)
Longest step time (s)	-.119 (.283)	**-.216 (.049)**	-.181 (.102)	.118 (.289)	-.177 (.110)
Average stance time (s)	-.192 (.082)	-.184 (.097)	-.115 (.300)	.168 (.128)	-.107 (.333)
Longest stance time (s)	**-.365 (.001)**	**-.312 (.004)**	-.169 (.127)	**.352 (.001)**	-.162 (.143)
Arrhythmicity (%)	**-.361 (.001)**	**-.435 (.000)**	**-.305 (.005)**	**.351 (.001)**	**-.305 (.005)**

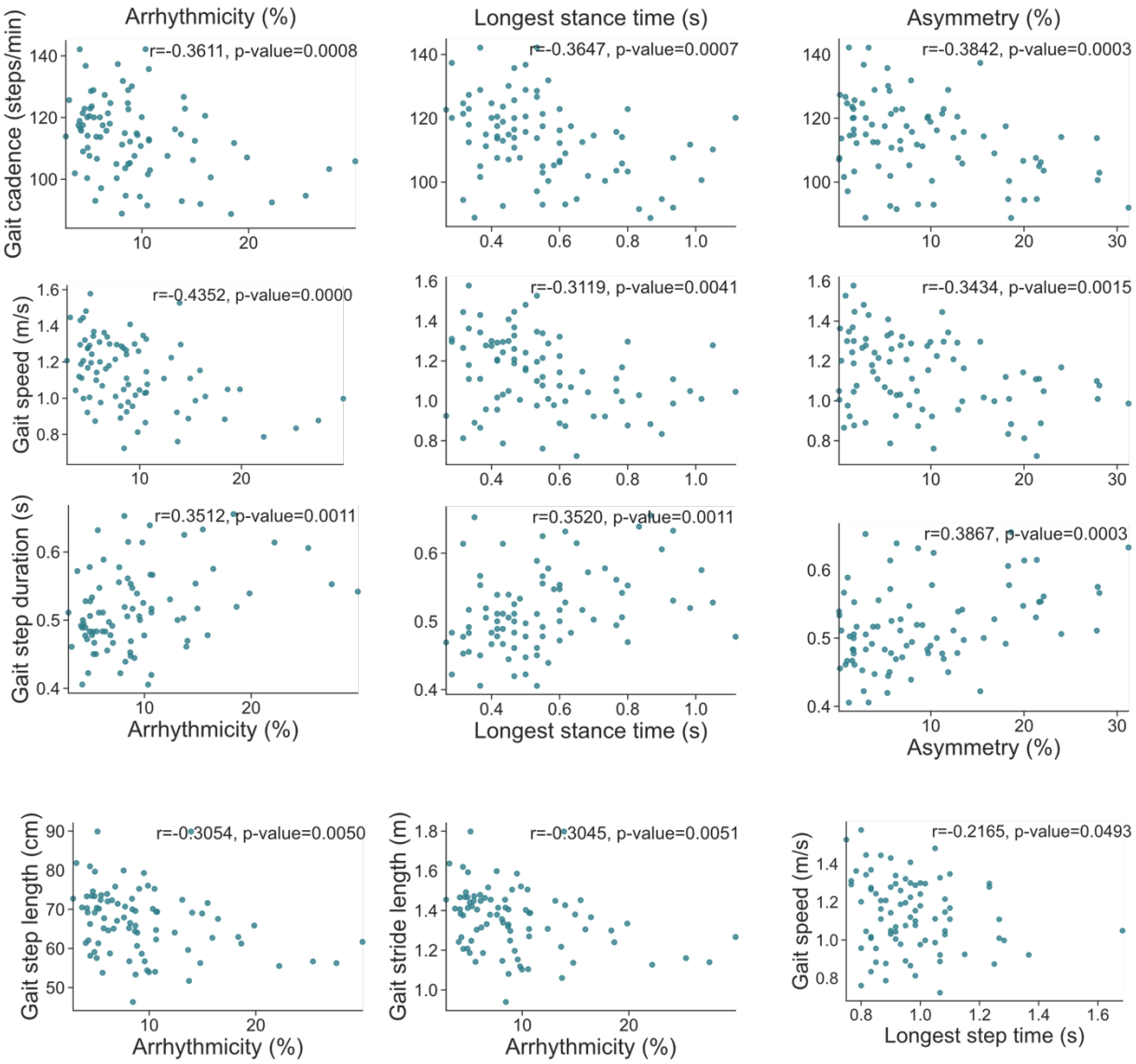

Figure 7 Regression plots significant correlations (p<.05) between spatiotemporal parameters of stepping in place and short comfortable speed walk in healthy controls (n=83).

In contrast to HC, stronger linear relationships between gait and stepping in place measures were found in PwPD (see Table 13). Highest correlations were found for knee amplitude and average step time against gait step length and gait stride length (all r>.5). The same two SIP measures showed also moderate correlations with gait speed (r>.4). Stepping in place arrhythmicity also showed moderate correlations to gait step length and gait stride length (r>0.4) where higher measures of arrhythmicity were associated with shorter step and stride lengths. Scatter plots of all correlations with p-value < .05 are given in Figure 8.

Table 13 Pearson's correlation coefficients and respective p-values between spatiotemporal parameters of stepping in place and short comfortable speed walk in persons with PD. Correlations with p<.05 are marked bold.

Pearson's correlation coefficient r (p-value) in PwPD ON (N=20)					
	Gait cadence (steps/min)	**Gait speed (m/s)**	**Step length (cm)**	**Step duration (s)**	**Stride length (m)**
Stepping cadence (steps/min)	-.003 (.989)	.157 (.509)	.163 (.492)	.082 (.730)	.171 (.472)
Knee Amplitude (cm)	.000 (.999)	**.476 (.034)**	**.549 (.012)**	-.018 (.938)	**.545 (.013)**
Asymmetry (%)	.006 (.978)	-.147 (.538)	-.091 (.703)	.004 (.985)	-.093 (.697)
Average step time (s)	-.004 (.986)	**.458 (.042)**	**.529 (.016)**	-.045 (.852)	**.525 (.017)**
Longest step time (s)	.090 (.707)	.365 (.114)	.385 (.094)	-.155 (.513)	.379 (.100)
Average stance time (s)	.041 (.863)	-.346 (.136)	-.377 (.101)	-.069 (.773)	-.387 (.091)
Longest stance time (s)	.153 (.519)	-.342 (.140)	-.410 (.073)	-.137 (.565)	-.415 (.069)
Arrhythmicity (%)	.173 (.466)	-.368 (.110)	**-.470 (.036)**	-.182 (.444)	**-.473 (.035)**

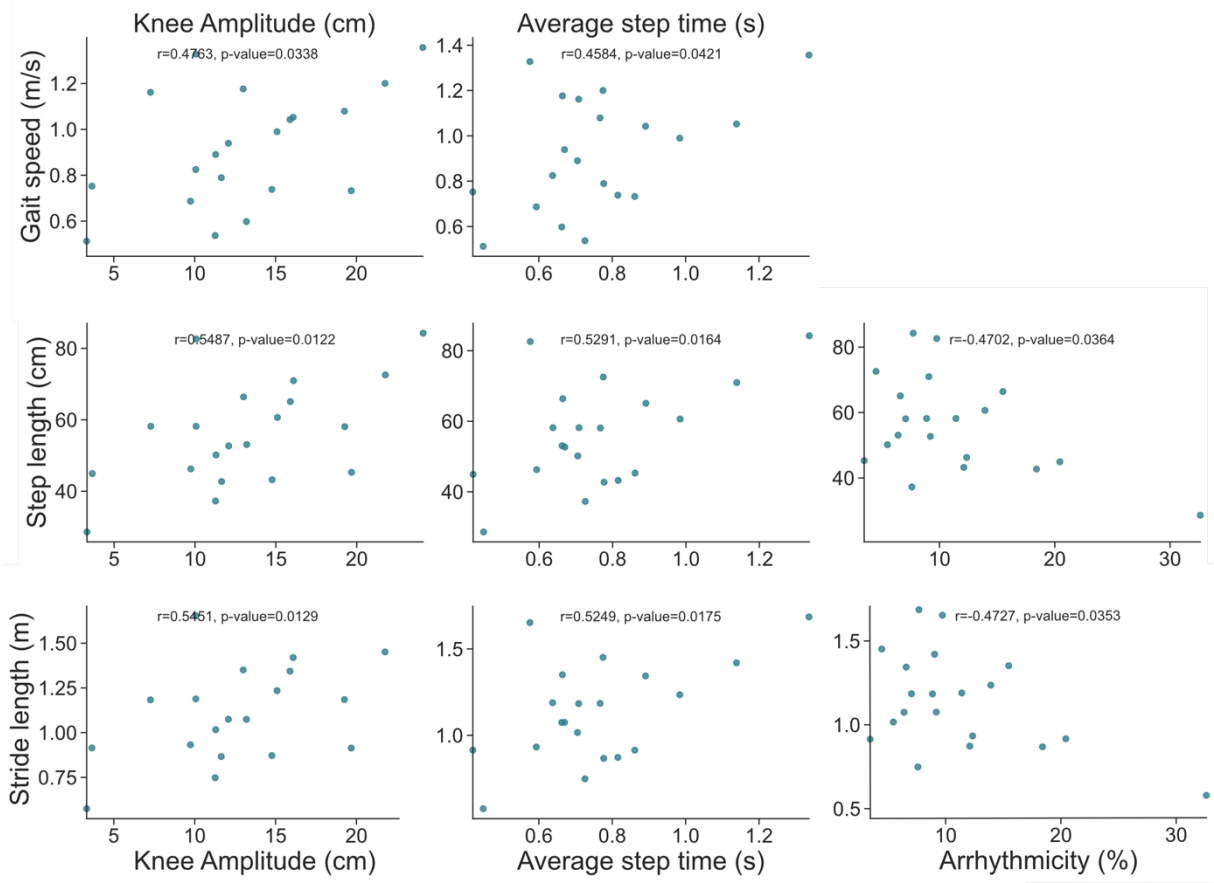

Figure 8 Regression plots for significant correlations (p<.05) between spatiotemporal parameters of stepping in place and short comfortable speed walk in persons with PD.

4 Discussion

The stepping in place task was previously proposed as an assessment of postural control [21] and as a surrogate for gait behavior [24,26–28]. However, existing studies on SIP with PwPD used small sample sizes, lacked normative data, and focused mainly on the exploration of freezing of gait. This study examined motor performances of stepping in place in 25 persons with Parkinson's disease and 83 healthy controls using a single RGBD camera. Eight spatiotemporal parameters were identified and implemented to describe leg movement range and timing. When comparing against performance in healthy subjects, these parameters can be assumed to reflect relevant motor signs and symptoms of Parkinson's disease including bradykinesia, hypokinesia, movement asymmetry and step variability. Specifically, knee amplitude and arrhythmicity of stepping during SIP were moderately correlated to clinical ratings of disease severity and knee amplitude showed sensitivity for change between treatment states. Further, results suggest that performance of this task is related to postural instability in PwPD and may elicit freezing episodes in those who experience freezing of gait.

4.1 Using RGBD Technology to assess SIP

The advantages and limitations of RGBD technology for medical motion analysis were thoroughly explored previously [25,41–43,46], and the technology has been proposed as a low-cost, portable alternative for marker-based motion analysis systems. In this study the accuracy and repeatability of RGBD recordings has been analyzed in 19 young healthy adults and can be considered adequate for six out of eight spatiotemporal parameters derived from SIP. Derived stepping cadence, knee movement amplitude, average and longest stance as well as step time showed good accuracy and repeatability. Despite the high accuracy, a systematic bias may be present against other devices, e.g. -2.5 cm in measurements of knee amplitudes against Vicon system in our study. Measures of asymmetry and arrhythmicity showed only moderate accuracy against Vicon system and lacked repeatability in both systems. This may indicate higher intra-individual variability in these parameters but may in part also be explained by generally narrow ranges of measurements, i.e. low inter-individual variance, for these parameters in healthy cohorts, and generally skewed distributions of these proportional measures. Of note, similarly low repeatability in both systems can exclude a specific disadvantage of RGBD technology in this respect and rather indicate an inherent metric weakness of these parameters.

4.2 Comparison of Results to Literature

The use of knee movements for the analysis of stepping in place performance is not novel (as reported in [25]) but unconventional. Since most of the existing approaches used force plates as measurement devices [26–28,37] they were unable to provide knee range of motion and other spatial information.

Overall, measurements of cadence, asymmetry and arrhythmicity of HC and PwPD were of similar magnitude to previous publications on stepping in place. Reported cadence ranged from 27 to 125 steps/min in PwPD [26,27] and 102 to 118 steps/min in HC [24,25,28]. Measurements of cadence seemed to be influenced by the appearance of freezing of gait where reports are inconsistent since in some publications, freezers have lower cadence than non-freezers [27] but higher cadence in others [26]. The latter might be explained by the appearance of festination, which is an increase of stepping frequency just prior to an episode of freezing.

Arrhythmicity measures are slightly higher than reported in the literature, where average reported measures ranged from 3.2% to 5.0% in PwPD [26,27] and from 2.6% to 6.3% in HC [26,28]. However, Anidi et al. reported exceptionally high values of arrhythmicity in their cohort of freezers ranging from 27.5% to 54.0% [27]. Similarly, reported measures of asymmetry vary, where smaller measures of 6.5% to 10.2% are reported [26,27], while measures for freezers in the Anidi cohort ranged from 16.0% to 27.1%, similar to values reported here. Further investigations might reveal subgroups showing similar movement patterns which would require exclusion of recordings with freezing episodes. Since further subsampling seemed problematic, given the already small sample size, this was not performed during this study. The comparison of average measures for arrhythmicity and asymmetry values is limited since both measures are in general not normally distributed.

The aforementioned studies did not provide information on potential confounding effects of age, height, and weight in PwPD and healthy adults. Therefore, this study was the first to investigate these aspects and found no linear correlation between these measures and the presented spatiotemporal parameters of SIP. Although only slight differences in arrhythmicity were seen between men and women in the HC cohort, further studies should consider matched groups and underlying interactions of sex and body height.

4.3 Association between SIP and PD Motor Symptoms

This study presented spatiotemporal parameters of stepping in place performance with potential for the assessment of PD motor symptoms as suggested by correlation analysis and analysis of intraindividual difference from OFF to ON. When freezing episodes appear during stepping in place, the longest stance time may be used as an indicator for the occurrence of freezing episodes.

In detail, moderate correlations between knee amplitude and longest stance time with MDS-UPDRS total score indicate relations between disease severity and motor performance during SIP. Moderate correlations were also shown with pull test scores, which is a finding of special clinical interest since postural instability in PwPD cannot usually be quantified with conventional posturography. Between OFF to ON treatment states, knee amplitudes showed a consistent increase of 84.5% which can be considered a clinically relevant change as it reflects a clinically relevant (>20%) change in the MDS-UPDRS III total score. Reduced range of motion in OFF compared to ON state, as well as higher knee amplitudes in HC, suggest that this parameter is well-suited to describe hypokinesia in PwPD.

Interestingly, especially knee amplitude measures and measures of longest stance times, as an indicator for freezing of gait, could be linked to clinical ratings of postural instability. It may be reminded that the original intention of the stepping in place task was an assessment of vestibular function [21] which affects postural balance even though later publications raised concerns about its sensitivity and reproducibility [23]. Postural instability in PD, however, rather affects adaptive postural control which involves attentional and cortical functions [28], which – according to our findings – seem also involved in performance of SIP. This study also confirmed previous reports of SIP performance as a trigger of freezing episodes [26,27,30], with reported sensitivities between 37.5% [30] and 87% [26] to correctly detect reported freezers. However, the publication by van Dijsseldonk et al [30] suggested that a more sophisticated and challenging gait parkour might identify more freezers than SIP.

4.4 Comparison of Stepping in Place and short Gait in comfortable Speed

Although SIP was proposed as a surrogate of gait behaviour, this work is the first to briefly explore relations between gait and SIP behavior in HC and PwPD. Lower ranges of motion, i.e. hypokinesia, were expressed by shorter step and stride lengths during gait and smaller ranges of knee movements during SIP resulting in moderate correlations of these parameters in PwPD. Similarly, reduced movement speed was expressed by lower average

step time and gait speed. These correlations were not seen in HC, indicating disease associated motor impairments in both SIP and gait.

The results presented here are consistent with previous reports that, at group level, measured cadence during stepping in place is in a similar range of forward gait for PwPD (SIP: 70.2 – 114.3 steps/min, Gait: 101.7 – 109.1 steps/min [27]) and HC (SIP: 100 steps/min, Gait: 99 steps/min [24]). However, despite assessment within a single session, no correlation was found between cadences from SIP and short-distance gait for PwPD or HC. Possible reasons are narrow distributions of cadence measures within groups, which influences statistical outcomes.

In the literature, comparison of step variability in SIP and gait is inconsistent and seemed to be highly influenced by the appearance of freezing of gait [27] which may also affect the moderate negative correlations of SIP arrhythmicity with gait step length in PwPD. In HC, small to moderate negative correlations of this measure, were seen for all five gait parameters, which could not be confirmed in the scatter plots.

Overall, results do not support tight relations of spatiotemporal parameters derived from stepping in place and those acquired during short gait task at comfortable speed in HC. Since no steady state gait is reached during the short walk [15], relations might be stronger for gait analysis derived from longer gait paths. Another explanation may be the different biomechanics of both tasks with a constraint of locomotion and related trunk movements in SIP which involves voluntary suppression of forward movement compared to normal gait. This may result in a less automated movement behavior and impact on observed parameters. Still, some of the results indicate that assessment of SIP has the potential to assess aspects of gait-like behavior in confined space which would make it useful for applications in clinical routine or remote assessments. Correlations of similar magnitude (rho >0.5) for parameters of both, SIP and short comfortable gait, with clinical ratings of disease severity support the idea that SIP captures relevant aspects of gait disturbance in PwPD. Therefore, further investigations into the relation between stepping in place behavior and forward gait, as well as postural control might be useful to further discuss the use of SIP as a surrogate.

4.5 Limitations and Advantages

The largest limitation of this study was the relatively small cohort of 25 PwPD which limits the power of the presented findings. Considering that the intention of this study was to gain first insights on technical and clinical feasibility of SIP, hence considered a pilot study,

study size is in line with others [24,26,28,30]. To further explore SIP behaviour, the technological approach and to provide reference for non-pathological movements, data of PwPD were pooled and data from 83 HC were added. This allowed for confounder analysis, analysis of accuracy and repeatability of the task and the RGBD camera technology as well as analysis of the relation between SIP and short-distance gait in comfortable speed. Therefore, this study laid the foundation to plan future studies on the clinical validity of SIP to assess cardinal motor symptoms of PD.

Since the data for both cohorts originated from several studies, some variability in assessment instructions, measurement environments and other confounding effects must be assumed. As part of data quality assurance and preprocessing, no systematic bias between study sites and system operators were found, but non-linear or complex influences cannot be ruled out. However, this may not necessarily reduce validity, but rather increase generalizability of results. The use of pooled data from ON and OFF measures to analyze correlations between spatiotemporal parameters with disease severity and postural instability (see Chapter 3.2.2) was chosen to increase the spectrum of MDS-UPDRS III scores but is likely to overestimate the relations due the use of ON and OFF measures from a single individual. Missing differentiation between performances with and without freezing is also likely to increase heterogeneity of results and limits comparison against literature. To provide more resilient outcomes, these aspects should be explored in a larger, clinically heterogeneous cohort preferably with freezers and non-freezers subgroups.

Another limitation of the approach is the accuracy of the RGBD technology and its provided anatomical landmarks. The spatial accuracy of the depth data reported as a resolution of ± 4mm at a distance of 2m [51] can be considered sufficient for the application for our research question. Optimally, this should be the limit of the derived spatiotemporal parameters as well which is challenging given the lower spatial accuracy of the anatomical landmarks [46], especially foot and knee landmarks during stance time. Although high accuracy and repeatability of most of the parameters was found, the limits of agreement are of similar magnitude as the presented group differences, e.g. between ON and OFF treatment states. This limitation especially applies to the asymmetry and arrhythmicity measures, but do not seem specific to this technology or task. While this work was based on already established formulas for these two measures for stepping in place [26], both approaches are likely to provide relatively high results due to their non-linear nature. More recent

approaches from gait research might be more suitable and robust [52] since it is based on continuous movement signals rather than snapshots of single movements.

Besides the mentioned limitations, the RGBD technology is suitable as a low-cost, time-effective, and portable alternative to established marker-based motion analysis systems. Specifically, the presented results suggest that RGBD recordings of stepping in place performances may provide a useful parameter set to describe relevant motor symptoms in PwPD with feasibility for the clinical setting. Such quantifications of motor outcomes are still not fully established in clinical routine, but recommended by e.g. the Movement Disorder Society [53]. Since wearable devices for activity tracking and motor symptom assessment typically cover only one limb or specific motor aspects, motion analysis of the full body as provided by RGBD assessment might be a good complementing approach.

4.6 Further works and outlook

As described previously, the assessment of motor functions in patient's homes are difficult but needed for objective evaluation of motor symptom fluctuation throughout the day. With the possibility to use the RGBD motion capture system conveniently at patients' homes, a software was developed which provides videos for standardized motor task instructions and records the PASS-PD assessment set automatically. This software is currently used in a longitudinal observation of up to 100 PwPD as part of the "Telepark – Telemedizin für Parkinsonpatienten" study at the university clinic Dresden. This study will provide further information on the use of stepping in place measures in a larger clinical cohort, information on longitudinal changes and information on the feasibility of "at home" assessments of standardized motor tasks.

As described above in more detail, there is room for improvement on the feature extraction and preprocessing of recorded RGBD data. Currently, the presented parameters are derived only from lower limb movements during SIP. With the extension of the algorithms to analyze arm, trunk, and head movements, it might be possible to assess arm asymmetry, hand or head tremors, posture as well as unvoluntary movements like dyskinesia.

Furthermore, adaptations of the stepping in place task could be explored such as in- or decrease of measurement duration or dual-tasking paradigms. The research on cognitive load during automated movement tasks increased in recent years and has been proposed as an indicator of cognitive reserve [54]. This suggests potential for the use of the SIP task to

assess symptoms of clinical relevance also in other neurological conditions. There, it might be of interest to use SIP to analyze disease progression or treatment efficacy.

4.7 Conclusion

Analysis of the stepping in place performances of a small cohort of PwPD and a larger non-matched HC cohort showed that spatiotemporal parameters derived from a single RGBD camera seem to represent major motor symptoms of PD. At group level, PwPD showed decreased ranges of motion (hypokinesia), slower motions (bradykinesia), increased asymmetry as well as in some patients episodes of freezing. Measures of knee amplitudes, longest stance times and arrhythmicity were related to clinical ratings of postural instability and disease severity, while not being confounded by person's age, height, and weight. Additionally, knee amplitudes showed a consistent and clinically relevant increase from OFF to ON treatment state in a subgroup of 10 PwPD. Therefore, an instrumental assessment of stepping in place could be considered for the assessment of postural instability and motor symptoms in PwPD and as monitoring tool to quantify motor function fluctuations.

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Eidesstaatliche Versicherung

„Ich, Karen Otte, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:

„Using quantitative measures of stepping in place performance to assess motor symptoms of Parkinson's Disease"
("Quantitative Messungen von Gehen auf der Stelle zur Beurteilung der motorischen Symptome bei Morbus Parkinson")

selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst."

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Datum Unterschrift

Karen Otte hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Otte K, Ellermeyer T, Vater T-S, Voigt M, Kroneberg D, Rasche L, Krüger T, Röhling HM, Kayser B, Mansow-Model S, Klostermann F, Brandt AU, Paul F, Lipp A, Schmitz-Hübsch T. Instrumental Assessment of Stepping in Place Captures Clinically Relevant Motor Symptoms of Parkinson's Disease. Sensors. 2020;20:5465. doi:10.3390/s20195465.

Beitrag im Einzelnen:

Die erfolgte Publikation wurde in Zusammenarbeit mit den genannten Co-Autor*innen am NeuroCure Clinical Research Center sowie an der Abteilung der Neurologie der Charité Universitätsmedizin Berlin durchgeführt. Die verwendete Messsoftware „Motognosis Labs" wurde im Rahmen der Tätigkeit bei der Motognosis GmbH mitentwickelt.

Datenerhebung: Der Datensatz, welcher für diese Publikation und die vorgelegte Arbeit verwendet wurde, ist ein Zusammenschluss der Daten aus verschiedenen Studien. Deshalb Beteiligung an diesen Studien separat dargestellt. Arbeiten und Aufwände für weitere Datenauswertungen und Publikationen, die nicht in diese Arbeit eingeflossen sind, werden nicht aufgeführt.

1) „Vicon"-Studie: Hauptverantwortliche Planung und Durchführung der Studie inkl. Planung des Messaufbaus und der Messbatterie, Anpassung der Messsoftware, Unterstützung bei der Formulierung des Ethikantrages, Probandenrekrutierung, Erhebung der Daten, Nachbereitung und Aufbereitung der VICON Daten, Nachbereitung und Aufbereitung der Kinect Daten sowie Synchronisation und Mapping der VICON und Kinect Daten in Zusammenarbeit mit B Kayser
2) „Valkinect"-Studie: Feedback zur Studienplanung und zum Messprotokoll, Anpassung der Messsoftware, Schulung der Operatoren zur Datenerhebung, Qualitätskontrolle der erhobenen Kinect Daten, Kombination klinischer, demographischer und Kinect Daten
3) „Occulomotorik"-Studie: Feedback zur Studienplanung und zum Messprotokoll, Anpassung der Messsoftware, Schulung der Operatoren zur Datenerhebung, Qualitätskontrolle der erhobenen Kinect Daten, Kombination klinischer, demographischer und Kinect Daten
4) „BWATCH"-Studie: Anpassung der Messsoftware, Schulung der Operatoren zur Datenerhebung, Qualitätskontrolle der erhobenen Kinect Daten, Kombination klinischer, demographischer und Kinect Daten
5) „VIMS"-Studie: Feedback zur Studienplanung und zum Messprotokoll, Anpassung der Messsoftware, Schulung der Operatoren zur Datenerhebung, vereinzelte Datenerhebung, Qualitätskontrolle der erhobenen Kinect Daten, Kombination klinischer, demographischer und Kinect Daten

Identifikation und Entwicklung der Bewegungsparameter: Die Identifikation interessanter Bewegungsparameter erfolgte anhand einer eigenständigen Literaturrecherche und in Rücksprache mit TSH und SMM. Die Implementierung der Parameter erfolgte eigenständig in MATLAB.

Konzeption der Datenauswertung: In Absprache mit TSH erfolgte die Konzeption des Datensatzes wofür zunächst Daten von Personen mit Parkinson eingeschlossen wurden. Die Wahl und Formulierung der primären und sekundären Fragestellungen an die Daten erfolgte ebenfalls in enger Zusammenarbeit mit TSH.

Datenanalyse und -auswertung: Eigenständige Zusammenstellung des Datensatzes und Vereinheitlichung der Datenformate aus den jeweiligen Studien, Qualitätsanalyse des Datensatzes, statistische Auswertung bezüglich der primären und sekundären Fragestellung, sowie nach Rücksprache mit TSH und SMM Erweiterung der Auswertungen, Erstellung verschiedener graphischer Darstellungen zur Interpretation und Exploration der Ergebnisse

Publikation: In Zusammenarbeit mit TSH und TE Literaturrecherche und Erstellung des Manuskriptes. Dafür Verfassung der Einleitung in Zusammenarbeit mit TE, selbstständiges verfassen der Methoden und Ergebnisse sowie der Verfassung der Diskussion mit Feedback von TE. Alle Abbildungen (Fig. 1-5) und Tabellen (Tab. 1-5) wurden selbstständig erstellt. Das Feedback der Co-Autor*innen wurde ebenfalls von mir eingearbeitet. In Absprache mit TSH Einreichung des Manuskriptes sowie Überarbeitung nach Peer-Review.

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Unterschrift des Doktoranden/der Doktorandin

Journal Data Filtered By: Selected Categories: INSTRUMENTS & INSTRUMENTATION
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Rank	Journal name	Total Citations	2020 JIF	Eigenfactor
1	Photoacoustics	1,093	8.484	0.002
2	IEEE TRANSACTIONS ON INDUSTRIAL ELECTRONICS	74,088	8.236	0.099
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6	STRUCTURAL HEALTH MONITORING-AN INTERNATIONAL JOURNAL	4,766	5.929	0.005
7	APPLIED SPECTROSCOPY REVIEWS	2,880	5.917	0.002
8	Biosensors-Basel	2,745	5.519	0.004
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11	IEEE TRANSACTIONS ON INSTRUMENTATION AND MEASUREMENT	18,199	4.016	0.013
12	MEASUREMENT	21,942	3.927	0.024
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14	**SENSORS**	**90,813**	**3.576**	**0.101**
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18	Chemosensors	875	3.398	0.001
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22	PRECISION ENGINEERING-JOURNAL OF THE INTERNATIONAL SOCIETIES FOR PRECISION ENGINEERING AND NANOTECHNOLOGY	6,049	3.156	0.006
23	Micromachines	8,165	2.891	0.012
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29	JOURNAL OF MICROELECTROMECHANICAL SYSTEMS	6,838	2.417	0.004
30	APPLIED SPECTROSCOPY	9,818	2.388	0.004
31	DISPLAYS	1,443	2.167	0.001
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33	JOURNAL OF GUIDANCE CONTROL AND DYNAMICS	10,577	2.048	0.008
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40	TRANSACTIONS OF THE INSTITUTE OF MEASUREMENT AND CONTROL	3,034	1.796	0.003
41	MEASUREMENT & CONTROL	684	1.704	0.001
42	Quantitative InfraRed Thermography Journal	332	1.667	0
43	INSTRUMENTATION SCIENCE & TECHNOLOGY	619	1.584	0
44	Sensor Review	1,088	1.583	0.001
45	Journal of X-Ray Science and Technology	799	1.535	0.001
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47	IEEE INSTRUMENTATION & MEASUREMENT MAGAZINE	840	1.505	0.001
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49	Journal of Astronomical Telescopes Instruments and Systems	860	1.436	0.003

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51	NUCLEAR INSTRUMENTS & METHODS IN PHYSICS RESEARCH SECTION B-BEAM INTERACTIONS WITH MATERIALS AND ATOMS	19,770	1.377	0.01
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58	INSIGHT	1,079	0.878	0.001
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61	Romanian Journal of Information Science and Technology	187	0.643	0
62	INSTRUMENTS AND EXPERIMENTAL TECHNIQUES	1,114	0.573	0.001
63	AUTOMATION AND REMOTE CONTROL	1,895	0.52	0.001
64	tm-Technisches Messen	286	0.49	0

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sensors

MDPI

Article

Instrumental Assessment of Stepping in Place Captures Clinically Relevant Motor Symptoms of Parkinson's Disease

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Abstract: Fluctuations of motor symptoms make clinical assessment in Parkinson's disease a complex task. New technologies aim to quantify motor symptoms, and their remote application holds potential for a closer monitoring of treatment effects. The focus of this study was to explore the potential of a stepping in place task using RGB-Depth (RGBD) camera technology to assess motor symptoms of people with Parkinson's disease. In total, 25 persons performed a 40 s stepping in place task in front of a single RGBD camera (Kinect for Xbox One) in up to two different therapeutic states. Eight kinematic parameters were derived from knee movements to describe features of hypokinesia, asymmetry, and arrhythmicity of stepping. To explore their potential clinical utility, these parameters were analyzed for their Spearman's Rho rank correlation to clinical ratings, and for intraindividual changes between treatment conditions using standard response mean and paired *t*-test. Test performance not only differed between ON and OFF treatment conditions, but showed moderate correlations to clinical ratings, specifically ratings of postural instability (pull test). Furthermore, the test elicited freezing in some subjects. Results suggest that this single standardized motor task is a promising candidate to assess an array of relevant motor symptoms of Parkinson's disease. The simple technical test setup would allow future use by patients themselves.

Keywords: RGBD camera; movement analysis; Parkinson's disease; postural instability

1. Introduction

Parkinson's disease is a progressive neurodegenerative disease with peak of onset in the sixth decade of life. The brain structures and functions affected result in a movement disorder defined by specific motor dysfunctions [1]. Patients with Parkinson's disease (PWPD) may suffer from different combinations of slowing and shortness of movement (bradykinesia), increased muscle tone (rigidity), tremor, and typical postural instability [1]. This results in a hypokinetic gait disturbance, which may also include freezing of gait (FOG), characterized by episodic hesitations of stepping, or inefficient stepping with high frequency (festination), resulting in episodic arrest of locomotor behavior [2–4]. FOG may be triggered by various factors, has been related to increased risk of falling, and is a hallmark of transition into advanced disease stages [2,5].

Today, several treatment options are available to relieve the symptoms of this disorder, and their appropriate dosing depends on close observation of motor signs [6]. Thus, the recognition of these motor signs is not only critical for the diagnosis of Parkinson's disease (PD), but also forms the basis of treatment decisions in PWPD [7]. Several instruments are clinically used for this purpose: a standardized clinical rating scale, such as the 'Movement Disorder Society—Unified Parkinson's disease rating scale (MDS-UPDRS) [7] and the Hoehn and Yahr scale [8], or patient self-reported outcomes [9]. A general limitation when assessing PD motor symptoms in a clinical setting is their fluctuating nature. As a well-known and bothersome complication of long-term medication in PWPD, the presence and severity of symptoms may considerably change in the short-term, e.g., in relation to medication intake, which may span from rather unimpaired, in medication ON state, to immobile, when drug effects wear off (medication OFF). Furthermore, additional motor features, such as dyskinesia, may indicate adverse effects of PD treatment [10]. Single point clinical assessments are not able to capture such fluctuations, and clinical rating scales may have limited sensitivity to quantify small-range changes in motor symptoms.

A manifold of technologies is available for a potentially more sensitive and rater-independent quantification of motor functions [11], which previous reviews explored for their application in PD [12–15]. For the assessment of motor fluctuations in PWPD, two approaches have been proposed: (1) non-standardized assessment, i.e., continuous tracking during everyday activities, which requires wearable sensors [16,17]; and (2) multi-point assessment of relevant motor symptoms in standard motor tasks, which requires technologies that are easily applicable by patients themselves. In this study, we follow the second approach, using 3D full body motion capture by RGB-Depth (RGBD) consumer cameras. The technology has already been applied for movement analysis in the clinical context, e.g., to analyze postural control and gait in different neurological disorders (e.g., PD [18], multiple sclerosis [19], and ataxia [20]), and showed good agreement with marker-based motion analysis standards [21]. The analyses presented here are based on observations from lab-based assessments, but the simple application of this technology would allow future application as patient-based assessment.

The stepping in place task (SIP), where patients are asked to repetitively walk on a spot while suppressing forward locomotion, was used here, based on prior evidence and low requirement of recording space. The task is long known as a clinical test for vestibular dysfunction when performed with eyes closed [22], but may also test components of gait and postural control when performed with eyes open [23]. SIP was used by Nantel et al. [24] to analyze temporal parameters, such as cadence, time symmetry, and arrhythmicity, in PWPD with and without FOG, contrasting their performance to a group of healthy subjects. They were the first to report that SIP triggered a freezing of stepping movements in patients with FOG, which was later confirmed by Dijsseldonk et al. [25]. Based on these findings, an array of relevant PD-specific motor symptoms may potentially be assessed in stepping in place behavior.

Our study is the first to utilize RGBD technology to derive kinematic parameters from SIP, and our spatial analysis of stepping behavior extends previous descriptions of SIP performance in PWPD. The objective was to quantitatively describe PWPDs' performance of an SIP motor assessment using

data from a single RGBD camera. For this purpose, algorithms for kinematic parameter extraction were developed and outcomes were analyzed regarding their potential for clinical use. According to previous experience and published evidence, we expected the test to be feasible for most patients with PD, but might be experienced as challenging for those in higher disease stages. We further expected a relation between test performance and disease severity, which would be expressed in correlations of kinematic parameters to clinical ratings of disease severity, as well as parameter differences between recordings taken in OFF and ON conditions.

2. Materials and Methods

2.1. Subjects and Clinical Testing

In total, data from 25 PWPD were used in this work (see Table 1), originating from two studies performed at an academic medical center (Charité—Universitätsmedizin Berlin, Germany, IRB approval EA1/012/17 and EA1/216/15). The studies explored motor outcomes from an RGBD sensor as a secondary aim while measuring patients in different therapeutic states defined as ON (depending on study defined as either optimized deep brain stimulation (DBS) or optimized symptomatic medication) or OFF (defined as either standardized withdrawal of DBS or medication). Inclusion criteria for the two studies were the clinical diagnosis of PD, according to UK Brain Bank Criteria [26]. Patients with limitations in motor performance unrelated to PD, including major psychiatric or cognitive disturbance, were excluded. For the purpose of this analysis, we additionally excluded recordings with dyskinesia reported at the time of assessment. All participants gave written informed consent for the assessment, analysis, and scientific publication of findings. Study data can be made available only on reasonable request.

Table 1. Description of subgroups, where metrical measures are given as mean and standard deviation and ordinal data as number of reached scores for each value.

	ALL	ON	OFF	ON-OFF
N subjects	25	20	13	10
male	18	15	8	6
female	7	5	5	4
Age (years)	65.3 (±9.4)	65.5 (±11.05)	66.2 (±8.0)	65.3 (±8.7)
Weight (kg)	75.0 (±13.5)	74.1 (±13.5)	76.3 (±12.5)	76.2 (±13.8)
Height (cm)	168.4 (±6.8)	167.7 (±6.1)	170.4 (±7.8)	168.4 (±5.3)
Disease Duration (years)	12.8 (±8.1)	12.1 (±8.0)	11.6 (±6.6)	10.1 (±7.2)
MDS-UPDRS-III	28.3 (±14.7)	25.3 (±13.7)	34.9 (±15.1)	ON: 28.8 (±13.4) OFF: 37.2 (±14.5)
N-item 11 (FOG) 0/1/2/3/4	23/4/6/0/0	14/3/3/0/0	9/1/3/0/0	ON: 8/2/0/0/0 OFF: 7/3/0/0/0
N-item 12 (Pull test) 0/1/2/3/4	12/10/6/1/1	8/4/5/2/0	4/6/1/1/1	ON: 4/3/2/1/0 OFF: 1/6/1/1/1

The dataset comprised 20 assessments in ON and 13 assessments in OFF (including 10 intraindividual data pairs of ON and OFF assessments). The sample size requirements were based on recommendations from [14] for technical feasibility studies, which suggests first trials in up to 10 participants. Each assessment consisted of the performance of the full MDS-UPDRS III, as well as one recording of the stepping in place task. From the MDS-UPDRS III, the total score (range 0–142) and ratings for freezing of gait (item 11, range 0–4) and pull test (item 12, range 0–4) were available for analysis.

2.2. Stepping in Place

The study protocol of both studies included a standardized instruction of SIP to induce performance in self-selected, comfortable pace. To avoid exhaustion after performance, the SIP was limited to 40 s recording length, starting from onset of performance to automated stop of recording. Participants were explicitly told to avoid forward movement, but received no further instructions on leg or arm

movements, nor prior demonstration of the task. A short testing performance of the task was explicitly allowed. If participants moved further than 1 m forward, the task was repeated, while reminding them to remain on spot and avoid moving forward. The tests were performed in common street clothing and usual footwear, excluding heeled shoes. Very loose clothing was asked to be taken off.

2.3. Technical Setup

Instrumental recording of SIP used a marker-free motion capture technology based on a consumer RGBD camera (Microsoft Kinect for Xbox One). The Kinect camera was accessed by the official Microsoft Kinect SDK (Version 14.09) at a framerate of 30 Hz, using software developed for that purpose (Motognosis Labs V1.2, Motognosis GmbH, Berlin, Germany). The camera was placed on a movable trolley at 1.4 m height with a vertical angle of −9° (see Figure 1). Since the area of highest depth resolution is between 1.5 and 3.5 m, participants were placed facing the camera at a 2.5 m distance.

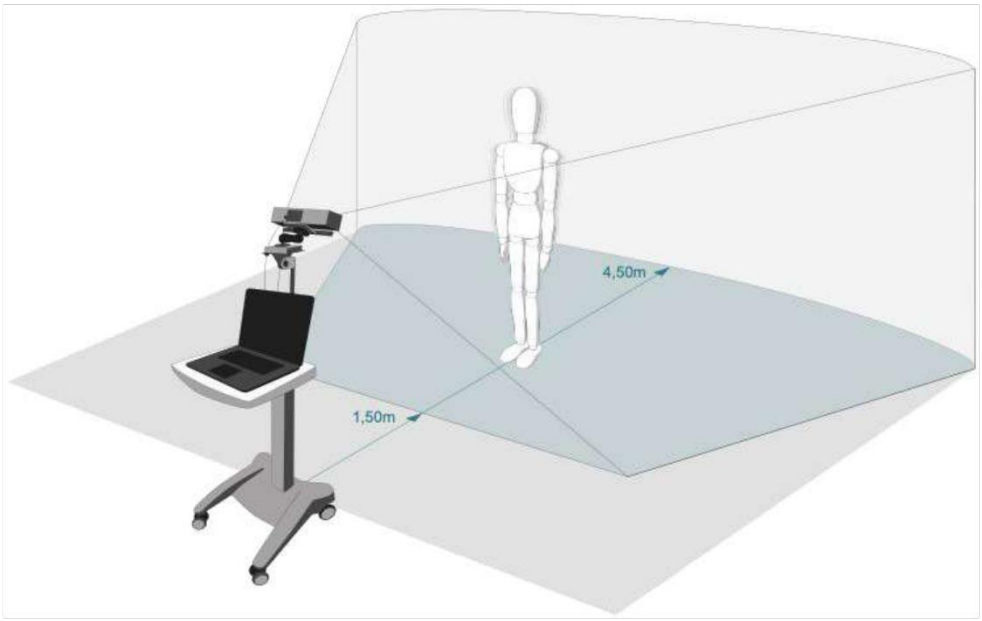

Figure 1. Technical setup of the motion capture system. Kinect camera was attached at 1.4 m height on a movable trolley with a pitch angle of roughly −9° while participants stood at a 2.5 m distance.

The Microsoft Kinect SDK provided depth point clouds of the person in the measurement area, and identified 25 artificial anatomical landmarks (see Figure 2) representing the location of body parts and major joints (e.g., knees, ankles, hands, head), which were recorded and exported as .csv files.

2.4. Data Processing and Calculation of Kinematic Parameters

Since the anatomical landmarks of the feet and ankles tend to show noisy behavior during SIP according to prior technical validation [21], 3D knee movements were used to detect stepping behavior and to derive a parameter set for use in PWPD. Stepping movements were split in stance and step phases, similar to the stance and swing phase of each leg in a gait cycle during normal walking (see Figure 3).

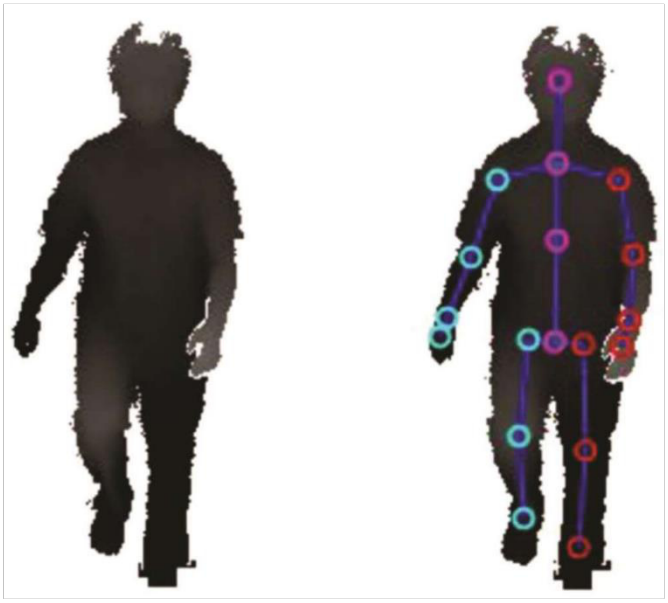

Figure 2. Recorded depth data of a masked participant (**left**) with 25 artificial anatomical landmarks (**right**) provided by the Kinect SDK.

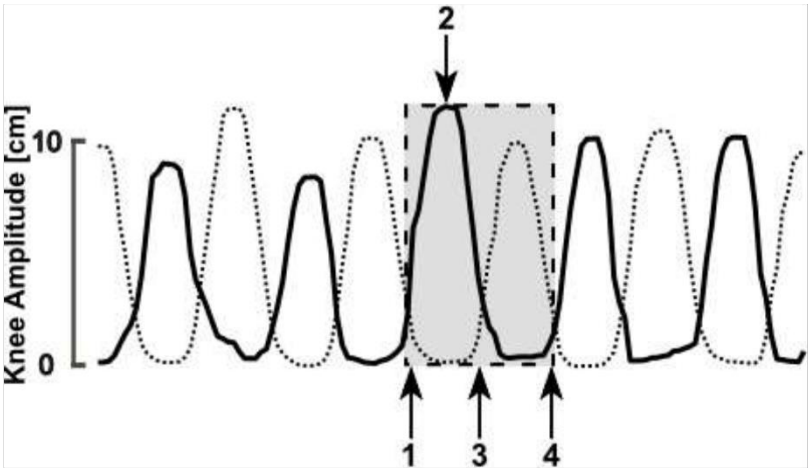

Figure 3. Representation of anterior–posterior movements of the right (thick black line) and left (thin dotted line) knee. The dashed box shows a complete stepping cycle including one step of each side. The following two phases are differentiated: Step phase of the right leg (from point 1 to 3) and stance phase (from point 3 to 4). Point 2 indicates the moment of anterior knee excursion (maximum hip flexion) and is used for the calculation of the knee amplitudes.

Data pre-processing comprised the following steps:

1. To compensate for the subject's position changes in the measurement area, we used the 3D positions of each knee as time series in relative position to the relating hip position. This eliminates possible errors due to the tendency to move towards the sensor.
2. A median filter (window size 5 frames) was applied to smoothen the anterior–posterior knee movement signal and reduce noise.
3. All minima of the filtered signal were detected and interpolated linearly, creating a minima-signal to provide a base level of minor landmark shifts over time caused by changes in the detected 3D user mask.
4. The minima-signal was subtracted from the anterior–posterior knee movement signal to eliminate smaller measurement errors when the knees were straight.

5. A threshold of 2.5 cm for anterior–posterior knee amplitude was defined as suitable to differentiate between step (>2.5 cm) and stance (<2.5 cm) phase. The threshold was identified by visual inspection of recordings.

From the detected step and stance phases, we derived eight kinematic parameters to describe major motor features of PD (Table 2). All parameters, besides cadence and asymmetry, were calculated separately for each body side, and then combined as their mean for further analysis.

Table 2. Description of eight kinematic parameters from VPC recordings of stepping in place (SIP) task performance.

Parameter Name	Unit	Description
Cadence	Steps/min	Steps per minute
Knee Amplitude	cm	Anterior–posterior range of motion of knees
Asymmetry	%	Logarithmic ratio between knee amplitudes of larger side to smaller side
Average Step Time	s	Average time required for a step during the measurement
Longest Step Time	s	Maximal time required for a step during the measurement
Arrhythmicity	%	Ratio between standard deviation and average of the step time
Average Stance Time	s	Average time between step movements
Longest Stance Time	s	Maximal time between step movements

Equations for the calculation of arrhythmicity (step time coefficient of variation) (1) and asymmetry (2) were taken from common definitions, as, for example, provided by Plotnik et al. [27].

$$\text{Arrhythmicity} = 100 * \left| \frac{\text{std}(\text{StepTimes})}{\text{mean}(\text{StepTimes})} \right| \quad (1)$$

$$\text{Asymmetry} = 100 * \left| \left(\frac{\text{mean}(\text{AmplitudesAmplitudes}_{\text{SmallerSide}}}{\text{mean}\left(\text{Amplitudes}_{\text{LargerSide}}\right)} \right) \right| \quad (2)$$

Since asymmetry is expressed as ratio between both sides, persons with small knee amplitudes show higher asymmetry measures for similar absolute amplitude differences.

2.5. Statistical Analysis

Descriptive statistics are given for metric kinematic parameters as mean and standard deviation. To explore confounding effects of age, height, and weight on SIP parameters, Pearson's correlations were performed in the ON subgroup.

Relation to disease severity was explored by correlating pooled recordings with the corresponding MDS-UPDRS III total score and pull test score, using Spearman's rank correlation. Pooled data is here used to provide higher heterogeneity in clinical symptom severity. From the subgroup of 10 patients with paired data from recordings in ON and OFF available, within-group comparisons were calculated between ON and OFF therapeutic states, reported as absolute and relative differences (percentage change from value in OFF condition), along with statistics from paired *t*-tests. Additionally, the standardized response mean (SRM) was provided as ratio of average difference and standard deviation of differences between OFF and ON. Due to the exploratory nature and small cohort size, analyses were not corrected for multiple comparisons, and the significance levels for all tests were set at 1%.

All statistics were calculated using Python 3.5 and the SciPy package version 0.18.1. Diagrams were created with Seaborn (package version 0.7.1) and Matplotlib (package version 2.0.0).

3. Results

3.1. Descriptive Statistics and Analysis of Potential Confounding Effects

The descriptive statistics of all eight derived kinematic parameters are provided for the pooled dataset, as well as the subsets of recordings acquired in ON and OFF (Table 3). In the subset of ON recordings, i.e., in a state of least expression of PD motor symptoms, the correlations between kinematic parameters and age, height, or body weight did not indicate relevant confounding effects by overall non-significant and small correlation coefficients ($|r| < 0.27$ for age, <0.15 for height and <0.36 for weight).

Table 3. Descriptive statistics for SIP parameters on the left for the whole sample and subset of recordings in ON and OFF treatments states, and on the right, estimation of confounding effects of age, height, and weight in the subset of recordings in ON.

	Descriptive Statistics			**Confounder Analysis in ON (n = 20)**		
	Mean (SD)			**Pearson's Correlation Coefficient r (p-Value)**		
	ALL (n = 33)	**ON (n = 20)**	**OFF (n = 13)**	**Age**	**Height**	**Weight**
Cadence (steps/min)	97.6 (27.3)	96.6 (27.1)	99.2 (28.6)	−0.271 (0.247)	0.132 (0.682)	−0.358 (0.253)
Knee Amplitude (cm)	12.5 (7.4)	13.9 (5.5)	10.2 (9.3)	0.228 (0.334)	0.151 (0.640)	0.280 (0.378)
Asymmetry (%)	18.2 (19.9)	15.6 (14.1)	22.1 (26.8)	−0.133 (0.577)	0.066 (0.839)	−0.173 (0.591)
Average Step Time (s)	0.72 (0.21)	0.77 (0.21)	0.64 (0.19)	−0.114 (0.632)	−0.108 (0.739)	−0.215 (0.503)
Longest Step Time (s)	0.88 (0.24)	0.93 (0.23)	0.80 (0.26)	0.209 (0.376)	−0.038 (0.906)	0.259 (0.417)
Arrhythmicity (%)	11.6 (5.58)	11.3 (6.5)	12.2 (4.0)	0.264 (0.261)	0.118 (0.715)	0.350 (0.265)
Average Stance Time (s)	0.65 (0.60)	0.61 (0.60)	0.72 (0.61)	0.258 (0.272)	0.108 (0.739)	0.348 (0.267)
Longest Stance Time (s)	1.69 (2.39)	1.63 (2.75)	1.77 (1.77)	−0.271 (0.247)	0.132 (0.682)	−0.358 (0.253)

3.2. Relation of SIP Parameters to Disease Severity and Postural Instability

In total, two out of the eight parameters—knee amplitude and longest stance time—were correlated with clinical ratings MDS-UPDRS III, and another two (arrhythmicity and average stance time) showed a trend ($p < 0.05$). Specifically, knee amplitude was reduced in subjects with higher clinical ratings (MDS-UPDRS III rho = −0.507, p-value = 0.003), while longest stance time increased (rho = 0.523, p-value = 0.002). The correlations with pull test ratings of postural instability were in the same direction, but reached significance only for longest stance time (Table 4). Trends indicated an increase of arrhythmicity and average stance time with more severe clinical ratings.

Table 4. Spearman's rank correlation of the eight kinematic parameters with clinical ratings acquired at the time of each SIP recording; analyzed from the pooled dataset (n = 33).

	Spear. Corr. MDS-UPDRS III	**Spear. Corr. Pull Test**
	Rho (p-Value)	**Rho (p-Value)**
Cadence (steps/min)	−0.234 (0.189)	−0.328 (0.072)
Knee Amplitude (cm)	**−0.507 (0.003)**	−0.436 (0.014) *
Asymmetry (%)	0.202 (0.260)	0.170 (0.361)
Average Step Time (s)	−0.287 (0.105)	−0.274 (0.136)
Longest Step Time (s)	−0.291 (0.101)	−0.242 (0.191)
Arrhythmicity (%)	0.352 (0.045) *	0.452 (0.011) *
Average Stance Time (s)	0.374 (0.032) *	0.374 (0.038) *
Longest Stance Time (s)	**0.523 (0.002)**	**0.468 (0.008)**

Statistically significant outcomes are set in bold; * indicates trend (p-value < 0.05).

3.3. Comparison between Recordings Taken in ON vs. OFF States

As expected, the clinical rating indicated relevant within-group change in motor symptoms from OFF to ON states (29% decrease in MDS-UPDRS III) in the subset with assessments available from both conditions. Changes in SIP behavior from OFF to ON were reflected in increase of knee amplitude

(85.4%, p-value = 0.002) and average step time (14.5%, p-value = 0.007), a decrease of step asymmetry (−19.6%, p-value = 0.007) with a similar trend for arrhythmicity, while cadence remained unchanged (Table 5). On inspection of corresponding data plots, a consistent change between OFF and ON was only seen for knee amplitude, which closely reflected respective differences in MDS-UPDRS III (Figure 4). The pronounced increase in longest stance time from OFF to ON, though non-significant, was unexpected in direction. This parameter reflects hesitations in stepping that would be expected to become less with effective therapy. However, inspection of data revealed one very long FOG episode (>20 s) during one recording in ON condition with a relevant impact on parameter mean.

Table 5. Changes in SIP parameters and clinical rating from OFF to ON state in the subset with assessments in both conditions available (n = 10).

	Mean (SD) OFF	Mean (SD) ON	Diff Abs.	Diff [%]	SRM	Paired t-Test p-Value
MDS-UPDRS III	**37.2 (14.53)**	**28.8 (13.37)**	**10.64**	**−28.6**	1.69	**<0.001**
Cadence (steps/min)	96.6 (29.0)	96.9 (20.7)	0.36	0.4	−0.02	0.954
Knee Amplitude (cm)	**7.08 (4.0)**	**13.1 (6.2)**	**6.05**	**85.4**	−1.34	**0.002**
Asymmetry (%)	**21.9 (27.6)**	**17.7 (18.3)**	**−4.30**	**−19.6**	0.14	**0.007**
Average Step Time (s)	**0.61 (0.17)**	**0.71 (0.14)**	**0.09**	**14.5**	−1.09	**0.007**
Longest Step Time (s)	0.76 (0.21)	0.81 (0.14)	0.05	7.2	−0.35	0.298
Arrhythmicity (%)	11.9 (3.50)	8.46 (3.93)	−3.49	−29.3	0.84	0.025
Average Stance Time (s)	0.80 (0.67)	0.62 (0.51)	−0.18	−23.0	0.55	0.114
Longest Stance Time (s)	1.88 (1.87)	3.67 (8.04)	1.79	94.6	−0.27	0.423

Statistically significant outcomes are set in bold.

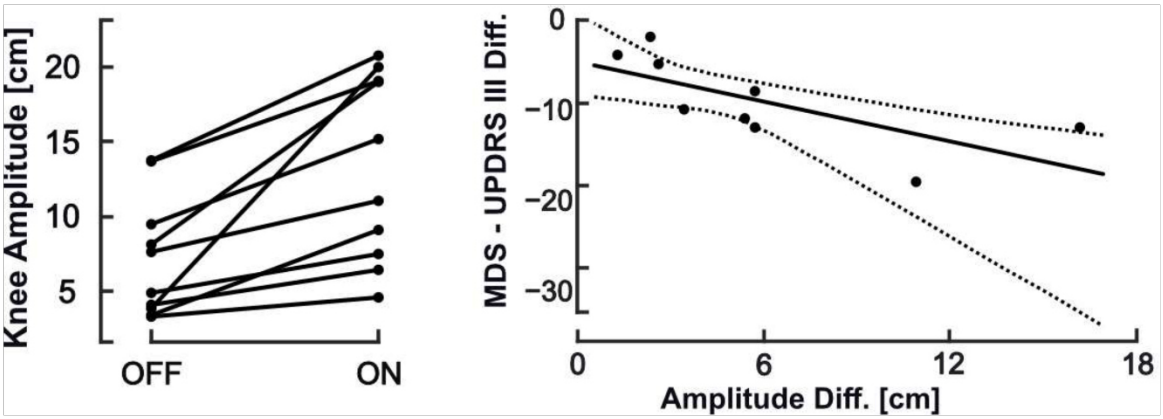

Figure 4. Changes of knee amplitude between treatment states (left) and knee amplitude changes related to disease severity change.

3.4. Implications of FOG and Other Motor Patterns

Freezing of stepping was clinically observed during 7 out of 33 recordings (ON: n = 6; OFF: n = 1). Examples from our sample (Figure 5) illustrate possible effects of FOG behavior on SIP parameters. In contrast to normal stepping behavior with constant rhythm and amplitude (Figure 5 top), hesitations and slower movements would be expected to result in increase of longest and average stance time, step time, and, therefore, lower cadence (Figure 5, line two from top). Related to this movement behavior, arrhythmicity can be found as well, and may show remarkable asymmetry (lines two and three). Festination prior to freezing manifestation may result in decrease of average knee amplitude, step, and stance timing, with remarkable asymmetry (third example). The manifestation of freezing will clearly result in massive increases of longest stance time as the prominent and possibly defining feature (lines three and four), usually in company with reduced knee amplitude and increased arrhythmicity.

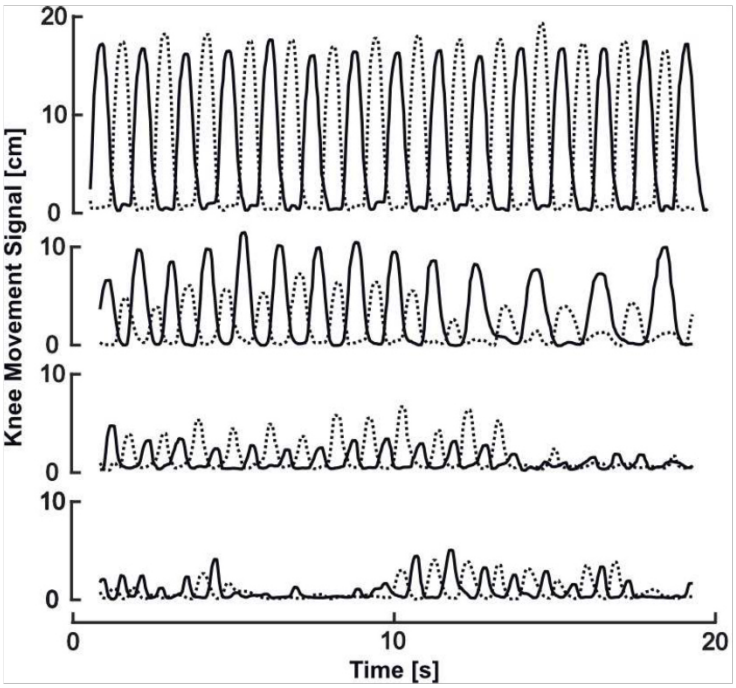

Figure 5. Illustration of freezing of gait (FOG) related changes on SIP behavior from our sample: normal rhythmic stepping behavior of regular and symmetric amplitude (**top**); hesitations of stepping with asymmetrical inconsistent stepping behavior and slowing of movements at the end (**second from top**); progressively ineffective stepping with small movement, asymmetry, and freezing of stepping at the end (**third from top**); ineffective highly irregular low-amplitude stepping and freezing of stepping in first half and at the end (**bottom**).

4. Discussion

Our study explored the instrumental assessment of motor signs in patients with Parkinson's disease using SIP as a standard motor task performed in front of a single RGBD camera. Both technology and task were chosen for their potential application as patient-based assessment in the home setting, although recordings were done in the lab at this stage.

The 3D motion signals of knees were used to derive eight different kinematic parameters for the description of stepping behavior in SIP. This extends previous SIP descriptions [23,24,28] to the spatial domain, including amplitude and spatial symmetry of stepping. Although foot signals from RGBD recordings have been used for step detection in normal gait [29,30], we preferred knee signals, because they showed less noise behavior compared to foot and ankle landmarks in an earlier validation of our system [21]. The kinematic parameters were selected to reflect key motor aspects of PD. Knee amplitude and step time are conceived to describe hypo/bradykinesia, similar to shortening of stepping during gait at self-selected speed, which can be considered the main gait characteristic in PWPD [31,32]. Temporal asymmetry is an important feature, specifically in the early stages of the disease [33,34], and reduced interlimb coordination has also been related to FOG [4,27]. Interestingly, spatial asymmetry of stepping during gait has been related to postural control [35] instead of temporal asymmetry, and might be specifically affected in subtypes of PWPD [36].

Changes in cadence were not consistently seen in previous gait descriptions in PWPD, but an increase of cadence and shorter step times in PWPD may indicate festination of stepping. In contrast, increasing stance times may indicate hesitations, and excessive longest stance times may indicate episodes of ineffective stepping or freezing. Variability of stepping, specifically step and stride timing during gait, forms a separate domain of gait as conceptualized by Lord et al. [32], which has gained increasing interest in the assessment of PWPD [16,37]. We therefore included arrhythmicity of stepping, similar to the coefficient of variance for step or stride time that is used as common descriptor in gait

analysis, which is sensitive to number of steps, as well as the gait paradigm used for recording [38]. Although the similarity of SIP movement to stepping during gait is intriguing, we are aware of only one small study [23] which compared cadence from SIP and gait recordings. Thus, our parameter wording should not imply that we consider specific parameters directly comparable to gait descriptions in PWPD. We therefore also refer to freezing of stepping in our observations, although it obviously shares features with FOG.

Prior to this work, there were only a few publications on the instrumental assessments of SIP. In our study, stepping in place was instructed to evoke self-selected stepping pace without any external cueing. Differences in task instructions as well as sample characteristics may contribute to explain the slightly lower cadence reported here, compared to previous reports (97–99 steps/min in our study vs. 100–112 steps/min from [23,24,28]). Derived spatial asymmetry values presented in this work were notably higher than the reported temporal swing time asymmetry during SIP by Nantel et al. [24], which may indicate limitations in the comparability of spatial and temporal asymmetry measures. Comparability of measurements to age-matched healthy volunteers should be considered for future works, to define normal stepping behavior in this task and corroborate evidence on analogies and differences to stepping behavior during gait. Furthermore, although our results did not suggest dependency on age, body height, or weight, potential confounders need to be analyzed in more appropriate datasets, as well as variability of performance with repeated testing. For use in PWPD, this test series showed excellent applicability of RGBD-instrumented SIP, even in higher disease stages. Still, the need for well-standardized procedures of data acquisition and for quality control of acquired data, specifically in remote application, needs not be neglected to make this a useful aid to clinicians and disease management in PWPD.

With respect to clinical validity, correlation analysis in our cohort indicated that smaller knee amplitude and longer stance times reflect higher disease severity. As knee amplitude can be conceived as the spatial parameter of stepping, this finding corresponds well to reduced step length during gait. While stance time during gait may increase with need to stabilize gait, often in parallel with reduction in gait speed, it has, to our knowledge, not been explored as an indicator of hesitations in stepping, nor has longest stance time been reported as an indicator of FOG episodes. Our observation of excessive longest stance time in individuals who experience freezing of stepping during SIP would support this concept. Future study may define useful thresholds for an automated detection of freezing and related behaviors, as exemplified in Figure 5. Both knee amplitude and longest stance time, but also arrhythmicity, showed substantial correlations to the clinical rating of postural instability from pull test performance. This is remarkable, as postural instability in PWPD is a motor feature of high clinical relevance regarding prognosis, fall risk, and interventions, yet hard to assess clinically. Pull test performance and rating notably suffers low reliability [39]. Therefore, future study should aim to corroborate this finding, which further supports the notion that SIP tests aspects of postural control, in addition to aspects of gait.

From the 33 SIP recordings, seven included freezing episodes, according to operator observation, as well as inspection of knee signals. This supports the notion that the SIP task triggers freezing of stepping [24,25]. The occurrence of FOG is known to depend on environmental cues as well as the type of motor task, where increased task complexity and cognitive demands increase FOG appearance [40,41]. Previous reports indicating cognitive demand of SIP execution [28] could explain the appearance of freezing in this task. However, our study was not designed to further explore the diagnostic accuracy of SIP for FOG detections. This would need a study design that compares matched samples of freezers and non-freezers, defined along established standards and against more detailed clinical ratings of FOG and related phenomena. Other motor tasks, such as 360° turns or walking through doorways, might have a higher probability of triggering FOG [25]. Unfortunately, due to occlusion of body parts during execution, the extraction of reliable kinematic parameters from turn tasks proves difficult when using markerless motion capture technology.

The comparison between ON and OFF recordings from a subgroup of 10 PWPD aimed to explore the sensitivity to effects of intervention. As expected, these were reflected in a decrease in MDS-UPDRS III from OFF to ON, which can be considered as clinically relevant, both with regard to absolute and relative change [42,43]. This overt change in clinical state, however, left cadence unchanged, while knee amplitude and average step time increased and spatial asymmetry decreased (trend for decrease in arrhythmicity). Specifically, the average proportional increase of knee amplitude (85%) was much higher than the relative change observed in clinical ratings (−29%), suggestive of a higher sensitivity to change compared to clinical rating. This can, however, only be confirmed if retest reliability has been determined. Concerning average step time, the appearance of a very long FOG episode (>20 s) in one ON recording might have influenced statistical analysis of this parameter, and explains the massive increase in longest stance time for OFF to ON.

The advantage of markerfree motion capture, in comparison to single or multiple wearable sensors, is the potential analysis of the full body. After consideration of required accuracy levels, signal analysis may extend to other body parts, and could be used to describe arm swing or torso sway dynamics during task performance. From clinical observation, such measures seem interesting candidates for a description of dyskinesia in PWPD. This was not considered in our study, as recordings with dyskinesia were deliberately excluded, but is clearly needed in further validation of this task for clinical application in PWPD.

From this first kinematic analysis, SIP alone may capture a variety of clinically relevant PD motor symptoms within one test, including FOG, although the relation of SIP performance to hand functions and dyskinesia have not yet been investigated. The task could also be modified with respect to duration or by adding cognitive or motor dual task conditions. The literature shows that, in conventional gait tasks, adding further cognitive load via dual tasking increases FOG appearance and alters movement patterns in PWPD [8,44]. Whether this also holds true for SIP, as a non-locomotor stepping task, still needs to be shown.

5. Conclusions

In this sample of 25 PWPD, all patients were able to perform the 40 s stepping in place task in OFF and ON therapeutic state. Freezing episodes were seen during some of the SIP performances in OFF as well as ON, confirming previous reports. From all recordings, a set of kinematic parameters were derived, describing range of movement (knee amplitude), arrhythmicity, and asymmetry, as well as stance timing. As an indicator of clinical validity, some parameters showed relations to clinical ratings of disease severity, specifically postural instability. Measures of knee amplitude showed also consistent changes between OFF and ON states, indicating high responsiveness of this parameter.

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Conflicts of Interest: K.O., S.M.-M., and A.U.B. are shareholders of Motognosis GmbH and named as inventors on patent applications describing perceptive visual computing for tracking of motor dysfunction. H.M.R. and B.K. are employed at Motognosis GmbH. K.O. was involved in the design of the study; in data collection, analyses, and interpretation of data; and in the writing of the manuscript.

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Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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