Objective Monitoring of Motor Symptom Severity and their Progression in Parkinson's Disease Using a Digital Gait Device

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Abstract

Digital technologies for monitoring motor symptoms of Parkinson's Disease (PD) have underwent a strong evolution during the past years. Although it has been shown for several devices that derived digital gait features can reliably discriminate between healthy controls and people with PD, the specific gait tasks best suited for monitoring motor symptoms and especially their progression, remain unclear. Furthermore, the potential benefit as endpoint in a clinical trial context has not been investigated so far.

In this study we employed a digital gait device manufactured by Portabiles HCT, which has been used by 339 patients within the LuxPark cohort (n = 161, Luxembourg) as well as within routine clinical care visits at the University Medical Center Erlangen (n = 178, Erlangen, Germany). Linear (mixed) models were used to assess the association of task-specific digital gait features with disease progression and motor symptom severity measured by several clinical scores. Furthermore, we employed machine learning to evaluate whether digital gait assessments were prognostic for patient-level motor symptom progression.

Overall, digital gait features derived from Portabiles digital gait device were found to effectively monitor motor symptoms and their longitudinal progression. At the same time the prognostic performance of digital gait features was limited. However, we could show a strong reduction in required sample size, if digital gait features were employed as surrogates for traditional endpoints in a clinical trial context. Thus, Portabiles digital gait device provides an effective way to objectively monitor motor symptoms and their progression in PD. Furthermore, the digital gait device bears strong potential as an alternative and easily assessable endpoint predictor in a clinical trial context.

Introduction

Gait abnormalities in people with Parkinson's Disease (PD) are a major motor symptom, along with tremor, bradykinesia, and rigidity, and have a major impact on patients' mobility and quality of life [1–3]. Signs of impaired gait patterns are reduced gait speed and step length, increased axial rigidity, impaired rhythmicity, and freezing of gait [2, 4]. In the early stages of the disease, slower gait speed, shortened step length, and reduced arm swing during walking are the most common signs of gait abnormalities, while in the later stages, movements become even more slow, gait shuffling and freezing of gait appears and patients are thus prone to falls [4]. With progression into an advanced stage, gait abnormalities, including balance and postural control, become worse [4]. Thus, investigating patient's gait impairment is crucial for evaluating the stage of disease progression. Furthermore, objective monitoring of gait could help defining an optimal schedule of when to treat a patient, whether to adjust the dose or whether to switch from one treatment to another.

In the past, digital technologies for monitoring motor symptoms of PD have evolved from non-portable in-lab devices to wearable sensors and at-home phone applications [5]. While each technology has its advantages, wearable sensors are able to measure gait parameters like stride length, gait speed, or the lateral excursion of each patient quantitatively and potentially also in an outpatient setting, while being portable, light weight, less expensive, and easy to use, for patients, as well as, for clinicians [5]. However,

before any application in clinical care, such technologies must be carefully assessed regarding technical robustness as well as medical diagnostic validity [6]. Importantly, a digital gait sensor can only reliably be used in routine medical care after regulatory approval, requiring proof of its safety. Besides that, trustable digital gait features require clear evidence that these sensor measurements correlate significantly with established clinical outcomes such as MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [7]. Although digital gait features have been explored in several studies in PD research, most studies solely focus on distinguishing PD patients from healthy controls in cross-sectional manner [5, 8–13]. Some studies also classify patients into multiple disease stages [14–17], but studies rarely describe the associations between PD progression and gait directly [4–6]. Furthermore, there is a lack of studies investigating the reproducibility of findings from the same gait device across several PD cohorts. Taken together, it is still unclear to date whether digital gait sensors can reproducibly and objectively monitor motor symptoms and their progression over time and whether in that regard there is a demonstrable benefit to classical clinical scales.

The ERA PerMed funded EU-wide project DIGIPD (Validating DIGItal biomarkers for better personalized treatment of Parkinson's Disease—https://www.digipd.eu) tries to fill a gap by evaluating the potential benefit of digitally assessed PD symptoms compared to established clinical outcomes across several cohorts in Europe. In this study, we focused on a sensor-based digital gait device clipped to the shoe of a patient while walking (https://www.portabiles-hct.de/en/product/). The device is currently registered for regulatory approval at the US Food and Drug Administration (FDA) and a certified class I medical device (MDR) with a CE mark in Europe. We investigated data recorded by the device in two independent longitudinal cohorts (one from Germany, one from Luxembourg) and while performing different gait tasks in the clinic. More specifically, we initially modelled PD progression based on several established outcome measures derived from the MDS-UPDRS by fitting a latent time joint mixed-effect model (LTJMM) [18] to longitudinal data from both studies. This allowed us to estimate each patients' true rate of progression and to align disease trajectories on a common disease timescale, taking into account the fact that patients may have progressed differently at baseline. Following that, linear (mixed) models were used to evaluate the association of digital gait features with estimated progression rates as well as UPDRS derived outcomes. In that regard we also explored, in how far a machine learning model could forecast an individual's disease progression rate solely based on digital gait features. Finally, we investigated on the potential benefit of using a digital gait predicted UPDRS III compared to the original UPDRS III as an endpoint in a clinical trial.

Material and Methods

Cohorts

We analyzed data from two independent PD cohort studies: (1) the Luxembourg Parkinson's Study (LuxPARK, NCT05266872) [19] and (2) from the University Medical Center Erlangen, Germany (Erlangen). LuxPARK is an ongoing observational cohort of patients at all disease stages. Data was collected periodically up to four years of follow-up between 2015 and 2022. Data from Erlangen contained

information from patients at all disease stages collected during multiple irregular clinical routine visits between 2011 and 2022. For both studies, we used multiple clinical scores as outcomes in our analysis. In LuxPARK these scores were MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) I, MDS-UPDRS II, MDS-UPDRS III [7], Tremor dominance (TD) score [20], Postural Instability and Gait Dysfunction (PIGD) score [20], and an axial score. The axial score was calculated by summing MDS-UPDRS III sub-items 1 (speech), 2 (facial expression), 9 (arising from chair), 10 (gait), 11 (freezing of gait), 12 (postural instability), and 13 (posture), which is a customized version of the axial score described in [21] to integrate axial changes in the face and freezing of gait more comprehensively. While LuxPARK employed the MDS-UPDRS, the Erlangen data assessed PD symptoms of patients with the original UPDRS [22]. Differences are described in the MDS-UPDRS publication [7]. For the sake of simplicity, we refer to both, the MDS-UPDRS, as well as the original UPDRS, as UPDRS. The Erlangen data evaluated less clinical scores and thus, only UPDRS III and the axial score (without freezing of gait, as this was not part of the UPDRS, but MDS-UPDRS only) were used as outcomes.

For both datasets, patients were selected, such that each patient had data from at least two visits for each outcome. This resulted in 612 PD patients from the LuxPARK cohort and 264 PD patients from the Erlangen cohort. Characteristics of these patients can be found in **Supplementary Table S1** in detail.

Gait Measurements

Additional to the traditional clinical outcome scores described above, gait measurements using Portabiles digital gait device were available in both, LuxPARK and Erlangen. While in LuxPARK only one digital gait assessment, at a single visit, was performed, multiple digital gait assessments over time were available for the Erlangen patients (2.84 ± 2.37 visits per patient on average, total: 506 gait visits). Digital gait assessments in Erlangen were collected irregularly, similar to the clinical data (difference between first and second digital gait assessment: 503.11 ± 488.98 days, median = 364 days). Digital gait data was available for 343 (LuxPARK) and 802 (Erlangen) patients for multiple exercises such as Time-Up-and-Go (TUG), the Turn, manual TUG (Tray), and cognitive TUG (Count), as well as the 2x10m, and 4x10m walking tasks. A detailed description of the different tasks, including differences between Erlangen and LuxPARK, can be found in the **Supplementary Material**. All analysis regarding digital gait were conducted only on the subset of patients for which both longitudinal clinical features (as described above), as well as, digital gait features were available. In total these were 161 patients from LuxPARK and 178 patients from Erlangen. Characteristics of these patients can be found in Table 1. A detailed description of the used device, the raw signal processing, and the derived features for further analysis along with a visualization of their distribution can be found in the **Supplementary Material** (**Supplementary Table S2, Supplementary Figure S1, Supplementary Figure S2**). A data catalogue visualizing all clinical, as well as, digital gait features of both cohorts can be found here: https://p-data.molekulare-neurologie.uk-erlangen.de/.

Table 1

Demographic and clinical characteristics of patients

Patients characteristics for LuxPARK and Erlangen datasets. Only the subset used for the gait analysis is described here. These are all patients having longitudinal clinical features plus digital gait features. Mean and standard deviations are shown for all characteristics but sex and Hoehn & Yahr stages, where absolute (and relative) values are shown. Values for disease duration, age, and clinical scores are reported at baseline. PIGD, TD, UPDRS I, and UPDRS II are not available in the Erlangen cohort.

	LuxPARK	Erlangen
Number of patients	161	178
Number of visits	5.32 ± 1.53	12.08 ± 9.12
Disease duration, years	4.92 ± 5.29	5.31 ± 4.57
Age, years	64.71 ± 10.08	62.39 ± 10.37
Sex		
Male	117 (73%)	110 (62%)
Female	44 (27%)	68 (38%)
Axial score	5.71 ± 3.79	5.35 ± 3.93
PIGD	0.56 ± 0.58	N/A
TD	0.5 ± 0.41	N/A
UPDRS I	9.28 ± 5.68	N/A
UPDRS II	10.32 ± 6.8	N/A
UPDRS III	29.89 ± 14.2	20.2 ± 11.89
H&Y		
0	1	1
1	19	25
1.5	11	14
2	93	35
2.5	20	18
3	12	35
4	4	11
5	1	2

	LuxPARK	Erlangen
N/A	-	37

Modeling approaches

Latent time joint mixed-effect model

The latent time joint mixed-effect model (LTJMM) was first published by Li et al. [18]. Its rational is to align trajectories of patients on a common latent (i.e. unobserved) disease timescale using a multivariate linear mixed effects model. This model is defined by fixed and random effects describing the deviation of each patient from a “mean” reference trajectory, both, on the time axis, as well as with respect to the actual outcome. The model can thus describe piecewise linear progression of multiple clinical outcomes over time by estimating how far the timescale of each patient is shifted away from the timescale of the reference. In our case the timescale was the reported time since PD diagnosis. The inferred patient-specific time shift can be seen as an estimate how far a particular patient is advanced in the severity of symptoms compared to the other patients in the same cohort. Additionally, the model generates an estimate of the patient-specific slope of disease symptoms, meaning that a large “random” slope indicates a higher speed of symptom progression compared to all other patients in the same cohort. Used outcomes were in our case the UPDRS I-III, TD, PIGD, and axial score, depending on the availability in the two different datasets. Additionally, we adjusted for age at diagnosis, sex and medication status (ON/OFF) as fixed effects. All longitudinal data, irrespective of gait data availability, was used. Mathematical details of the model are described in the **Supplementary Material**.

Validation of LTJMM model

Distributions of Hoehn and Yahr (H&Y) stages were examined to validate the alignment of disease trajectories on a common disease timescale. This was based on the assumption that the shifts of each individuals’ trajectory should follow an order, which roughly agrees with the H&Y stages. Patients with lower H&Y stages, who are at the beginning of the development of the disease, should be shifted further to the left on the common disease time scale than those with a higher HY stage who are more advanced in their disease. Additionally, the accuracy of the LTJMM approach was checked by calculating the correlation between real and predicted outcomes at the last observed visit, similar to [23]. For that, a LTJMM was fitted on all outcomes, but the last measurements of each patient were excluded and predicted back by the LTJMM.

Linear mixed models to evaluate gait parameters

Linear mixed models (LMMs) were used for associating digital gait features with different outcomes at the same visit. Therefore, clinical data at the same day of gait data assessment was matched with gait data. Only data from patients having both longitudinal clinical features, as well as, digital gait features available were used in this analysis. Characteristics of this patient subset is shown in Table 1. Modeled

outcomes are patient-specific a) latent disease time, b) clinical outcome scores, and c) progression rate. Both latent disease time and progression rate are a direct outcome of the LTJMM model described above. When modeling patient-specific latent disease time (interpreted as estimated time since disease onset), age at diagnosis and sex were used as adjustment covariates. In case of modeling clinical outcome scores or the patient-specific progression rate, we employed the latent disease time elapsed at the time of the clinical assessment as adjustment covariate to adjust for temporal differences between observed patient trajectories. Furthermore, we added a patient-specific random intercept in case of the Erlangen data, as digital gait features were available at several time points. Different sets of digital gait features were integrated as features in the model. First, all digital gait features were used jointly (**allGait**), then features were selected according to the individual gait tasks, and lastly, we fitted LMMs for each digital gait feature separately (**singleGait**). All these models were tested against a null model containing only adjustment covariates via a likelihood ratio test. Results were adjusted for multiple testing with the Benjamini & Yekutieli method [24].

Simulation of a randomized controlled study

A randomized controlled trial was simulated over a one-year observation period with either original or gait predicted UPDRS III as study endpoints. The gait predicted UPDRS III was estimated from 4x10m tests' digital gait features using a linear mixed effect model. We assumed visits every 60 (bi-monthly), 30 (monthly) or 7 (weekly) days to assess the sample sizes needed for evaluating the efficacy of a potentially disease-modifying drug. We employed the Erlangen data for this task, as longitudinal digital gait features were required. Simulations were inspired by an ongoing trial [25] and assumed a treatment effect on disease progression of 30%. Control and treatment groups were equally sized without different treatment dosage arms. A power of 80%, and a significance level of 0.01 was set as parameters for the outcome simulation of the disease progression difference between treatment and control group. Power and sample size was calculated using linear mixed-effects model, based on the method from Edland [26], implemented in the R package *longpower* [27].

Predictive ML models for disease progression

Random Forest [28], XGBoost [29] and Lasso [30] were used to predict the LTJMM random slope from digital gait features. In Erlangen cohort, where multiple gait visits were conducted, measurements from first and first plus second gait visit were used for prediction. Multiple feature sets were tested: only sex and age, all digital gait features (**allGait**), and task-specific digital gait feature sets. Implementations of algorithms of scikit-learn [31] and xgboost [29] packages were used. Hyperparameter optimization was performed using a randomized search within an inner 5-fold cross validation procedure. Hyperparameter spaces for the different algorithms can be found in the **Supplementary Table S3**. Performance metrics were evaluated in an outer 5-fold repeated cross validation procedure. Performance of the models including gait features was additionally tested with a Wilcoxon signed-rank sum test comparing its R^2 values to those from a model integrating only sex and age as predictors. The best performing model was selected based on these statistical test results.

Results

Overview

Disease trajectories of both studies, LuxPARK and Erlangen, were first aligned on a common disease timescale via LTJMM (Fig. 1A**)** with the aim to adjust trajectories of each patient according to their disease status and to remove bias introduced by including patients from different stages of Parkinson's disease. After aligning the disease trajectories on that common disease timescale, digital gait features were used as predictors in multiple settings, either for monitoring the disease severity or the disease progression (Fig. 1B**)** and additionally for predicting disease severity and progression (Fig. 1C**)**.

Latent time joint mixed-effect models for alignment of disease trajectories

LTJMM models were fitted to Erlangen and LuxPARK data. Both the original trajectories, as well as, the trajectories on the common disease timescale for each study and outcome are shown in the **Supplementary Figure S3** and **Supplementary Figure S4**. **Supplementary Figure S5** and **Supplementary Table S4** confirms that the model orders patient trajectories correctly according to the H&Y stages. Additionally, on average Pearson correlations of real and predicted clinical outcomes were $\rho = 0.73$ for Erlangen and $\rho = 0.42$ for LuxPARK, indicating a sufficient fit of the LTJMM models.

Monitoring disease stage, motor symptom severity and motor symptom progression through digital gait

Statistical associations of clinical outcomes with features derived from the Portabiles digital gait device were analyzed with linear (mixed) models after aligning observed clinical outcome trajectories on a common disease timescale. We found a significant association of digital gait features with traditional clinical outcome measures in both datasets (LuxPARK: axial score, PIGD, TD and UPDRS III; Erlangen: axial score, UPDRS III) (Table 2 and Table 3). Clear task-specificity can be observed in LuxPark cohort, with the TUG being the most informative task. Here, the axial score was found to be highest correlated with digital gait features. When modeling the axial score with digital gait features, stance time (Count: $p = 0.04$), swing time (Tray: $p = 0.009$), gait speed (Tray: $p = 0.029$), stride length (Tray: $p = 0.015$) and the landing impact (TUG: $p = 0.047$) were found to have significant effect sizes in the models. TUG's landing impact shows also significant effect size when modelling the PIGD score ($p = 0.048$). For the PIGD score as model outcome, we have also found the gait speed ($p = 0.014$) and stride length ($p = 0.010$) significant for the Count task. Similar as in Tray task in LuxPark, we could find the swing time in Erlangen's 4x10m task significant ($p = 0.045$) when modelling the axial score as outcome.

Table 2

Associations of digital gait features with dedicated clinical scores, their slope and latent time in LuxPARK cohort.

Adjusted p-values of likelihood ratio testing the association of multiple digital gait feature sets, either all measured digital gait features or task-specific (Count, Tray, TUG, Turn), with clinical outcomes, adjusted for age at diagnosis and sex. Significant (adjusted $p < 0.05$) tests are marked in bold and weakly significant (adjusted $p < 0.1$) tests in italic. Measured outcomes are the clinical scores (top), their slope (i.e. progression, middle) and latent time (i.e. disease stage, bottom).

Outcome	All Gait	Count	Tray	TUG	Turn
Clinical score					
Axial score	**0.0055**	**0.0006**	**0.0006**	**0.0001**	**0.0175**
PIGD	0.2152	**0.0068**	**0.0068**	**< 0.0001**	*0.0629*
TD	**0.0178**	0.4882	0.4882	1	1
UPDRS I	0.2717	*0.0783*	0.2384	0.2504	*0.0783*
UPDRS II	0.4154	0.1427	0.1427	0.1427	0.3601
UPDRS III	**0.0337**	0.2149	*0.0538*	**0.0476**	0.1058
Slope (progression)					
Axial score	0.2765	0.5264	*0.0534*	*0.0990*	0.4970
PIGD	0.6788	1	1	1	1
TD	0.4895	1	0.1709	0.1709	0.6128
UPDRS I	0.3035	0.8514	*0.0621*	*0.0621*	0.5288
UPDRS II	0.3864	0.9143	0.1260	*0.0686*	0.4988
UPDRS III	0.6779	1	1	1	1
Latent time (disease stage)					
Latent time	**0.001**	**0.0288**	*0.0726*	**0.0005**	**0.0023**

Table 3

Associations of digital gait features with dedicated clinical scores, their slope and latent time in Erlangen data.

*Adjusted p-values of likelihood ratio testing the association of multiple digital gait feature sets, either all measured digital gait features or task-specific (*TUG, 2x10m With Stop, 4x10m Without Stop*) with clinical outcomes, adjusted for age at diagnosis and sex. Significant (adjusted p < 0.05) tests are marked in bold and weakly significant (adjusted p < 0.1) tests in italic. Measured outcomes are the clinical scores (top), their slope (i.e. progression, middle) and latent time (i.e. disease stage, bottom).*

Outcome	All Gait	TUG	2x10m With Stop	4x10m Without Stop
Clinical score				
UPDRS III	0.1574	**0.0361**	**0.0203**	**0.0110**
Axial score	**0.0010**	**0.0068**	**0.0068**	**0.0068**
Slope (progression)				
UPDRS III	1	1	1	1
Axial score	1	1	1	**< 0.0001**
Latent time (disease stage)				
Latent time	**0.0047**	**< 0.0001**	**0.0001**	**< 0.0001**

Furthermore, a significant association with the disease stage, represented via the latent time, could be observed in LuxPARK, as well as in Erlangen (Table 2 and Table 3). While we could find the maximal sensor lift significant in LuxPARK for both the TUG (p = 0.031) and Turn (p = 0.048) task, the stride time in 2x10m (p = 0.001) and TUG (p = 0.045) task was the most informative digital gait feature in Erlangen. Estimates for each of the models can be found in **Supplementary Table S6**. A visualization of those, also showing the significance, can be found in the **Supplementary Information**.

The association with the slope of the axial score (i.e. progression) was clearly significant in the Erlangen data for the 4x10m test and demonstrated a weak significance in LuxPARK for the Tray and TUG test. Further weakly significant associations with digital gait included the slope of the UPDRS I (Tray, TUG tests) and the slope of the UPDRS II (TUG test).

Altogether, significant associations of digital gait features were thus identifiable with traditional clinical motor scores, their slopes as well as disease stage. Results of single digital gait features tests can be found in **Supplementary Table S5**, generally supporting the findings reported in this section.

Machine learning based prediction of motor symptom progression with digital gait

We trained different machine learning algorithms to predict the patient-specific slope (i.e. progression) of motor symptom related clinical outcomes. The strongest results could be observed via the Random

Forest algorithm in a 10-fold cross-validation setup (see **Supplementary Figure S7**) in the Erlangen data. When using only the first gait assessment in the Erlangen data for the prediction of the axial scores' slope, a significant improvement compared to only using age and sex as predictors could be observed, specifically when using data from the 4x10m task (Fig. 2). Integrating also a second assessment of gait improved the prediction even more and specifically when using data from all gait tasks. Additionally, the UPDRS III slope could now be predicted significantly better compared to only using age and sex as covariates. It should be noted that similar findings could not be made in LuxPARK, because digital gait features were only available at a single visit (see **Supplementary Figure S6**). Altogether, our findings reported in this section support those made in the previous section, namely that digital gait is associated with traditional motor symptom scores from the UPDRS and is sensitive to changes in those scores.

Randomized controlled trial simulation shows benefit of digital gait features as endpoint

To further evaluate the potential benefit of digital gait features compared to traditional clinical outcome scores, we simulated a longitudinal clinical trial with different visit frequencies. Notably, digital gait features can be collected more easily and cheaper at higher frequency compared to traditional clinical outcome scores, and data collection could potentially even be performed within a patient's home environment. Estimates of the UPDRS III from digital gait features correlated well with the original data ($\rho = 0.77$, see **Supplementary Figure S8**). According to our statistical sample size calculation, which assumes a treatment effect size of 30%, bi-monthly assessments of the UPDRS III require 690 patients in total to reach 80% statistical power at a significance level of 1%. At this visit frequency the same sample size of 690 patients would be needed for a digital endpoint estimating the UPDRS III from digital gait features via the 4x10m task (Fig. 3). However, already a monthly assessment of this gait predicted clinical endpoint can reduce the number of patients to 550, and a weekly assessment even to 380 patients, showing a potential reduction of almost 44%. We would like to highlight once more that assessments of the traditional UPDRS III at a similar frequency in clinic would be highly challenging.

Discussion

Digital Gait Assessments for Symptom Monitoring and Prognosis

Features derived from the Portabiles digital gait device were significantly associated with disease stage (represented by latent time), disease severity assessed via the Unified Parkinson's Disease Rating Scale (UPDRS), specifically the axial score, and the slope of the axial score. Although, the association between axial abnormalities and digital gait with more severe motor symptoms, as well as with lower step lengths and gait speed, has been described by several authors before [32, 33], correlation analysis with digital gait features was still lacking.

Additionally, most studies analyzing digitally assessed gait features, provide only micro analyses [8, 13, 16, 34, 35], looking at single digital gait features, but no overall analysis of multiple digital gait features. Here, a comprehensive analysis of single, but also multiple combined features – on several levels – is provided. In comparison to other studies, which used only one or even no standardized tasks, here,

multiple tasks had to be performed by patients and task specificity was examined, providing a systematic and unique overview about most useful tasks for digital gait analysis. Although, combining all digital gait features turned out to be useful, there were notable task-specific differences between gait tasks. Interestingly, we found the traditional 'Time Up And Go' (TUG) task consistently effective for monitoring the motor symptom severity in both studies. Additionally, it was the only task that could monitor the UPDRS III in the LuxPARK cohort. Digital gait features derived from Tray and Count tasks could also be associated with PIGD score, indicating that these dual tasks, combining motor and cognitive exercises, are efficient in monitoring disease severity in terms of postural instability. In the past, dual tasks also have been seen to trigger Freezing of Gait [36–38]. Thus, investigating the ability to monitor cognitive impairments should be subject for further research.

As expected, a clearly significant association of digital gait features with UPDRS derived motor symptom progression could only be established in the Erlangen dataset, where gait measurements have been taken over a longer period of time. However, this association could only be established for the 4x10m task. This highlights the importance of longer distance walks to identify changes of motor symptoms within an individual patient over several visits. Despite this, prediction of the UPDRS III from digital gait data only is a feasible task, as such estimates correlate well with the original data (ρ = 0.88), although not integrating any information about symptoms other than gait (e.g. hypomimia, dysarthria, or tremor). Potentially, the severity of these other symptoms is correlated to digital gait, or they are relatively stable in terms of disease progression such that their contribution to the UPDRS III progression is low. Right now, the reasons are unclear and further research might help to investigate on this relationship between digital gait and other PD symptoms.

Although other studies have shown relationships between digital gait features and multiple disease stages, none of them quantify disease progression, but only classifying patients into disease stage groups [16, 34, 35, 39]. Often the analysis focuses only on control vs. PD classification [5, 8, 13, 40, 41]. In contrast, our analysis focused on the association of digitally assessed gait features with motor symptoms and their progression. However, machine learning based prediction of the patient-level slope of UPDRS derived motor symptoms, demonstrated only a limited accuracy. When combining data from two subsequent clinical visits the coefficient of determination (R^2) for predicting the slope of the axial score reached 0.45 and for the UPDRS III approximately 0.35. Hence, digital gait features alone have only limited prognostic value despite their ability to objectively monitor motor symptoms and their progression.

Overall, the approach presented here demonstrates the feasibility of monitoring motor symptoms through digital gait assessment and its task specificity for individual symptoms across multiple independent studies.

Potential Value for Clinical Trials

Significant association between the patient-specific slope of the axial score and digital gait features, was found. We thus performed a randomized control trial simulation, with a predicted UPDRS III outcome

using the Portabiles digital gait device derived features from the 4x10m test. Interestingly, a digital gait predicted outcome (i.e. a digitized version of the UPDRS III), although not integrating any information about other symptoms than gait, as mentioned above, requires the same number of patients to show the efficacy of a treatment as the standard UPDRS III, if gait features are collected at the same frequency. However, a large reduction of the number of needed patients could be shown when assessing the “digital” UPDRS III via the Portabiles digital gait device in a weekly manner.

This shows the potential for using gait sensors and associated data in clinical studies, where measurements with a digital device could be taken remotely at a much higher frequency than in a traditional in-hospital setting. This may decrease the burden for patients’ quality of life and increase their willingness to contribute to a clinical study as they are not required to visit the clinic for each assessment. Additionally, data in general can be recorded via the 4x10m task much easier and faster than performing a complete UPDRS exam.

Only limited studies have already investigated the benefit of using digital gait device data for clinical trials. While sensor-based digital gait analysis has shown its potential to overcome limitations of UPDRS based gait assessment in a phase II trial recently [42], most studies only refer to a subjective potential endpoint in studies, but do not test the validity of this hypothesis. Here, for the first time, an objective comparison of both outcomes, original and gait predicted UPDRS III, quantifies the potential of using sensor-based digital gait data as secondary endpoint in trials. Although the potential of the sensor-based digital gait data could clearly be seen, it does not capture quality of life aspects during a trial, which is a limitation for phase III studies and still needs to be addressed by other instruments.

Conclusion

Overall, we have demonstrated the ability to objectively monitor the severity and progression of motor symptoms using the Portabiles HCT digital gait device. Additionally, we investigated the potential benefit of using digital gait as an outcome measure in a clinical trial context. Our work thus adds to the increasing body of literature demonstrating the benefit of digital solutions in the PD field. A distinction point is our focused digital gait device, the analysis of symptom progression and the exploration of the benefit for clinical studies.

We would like to emphasize that the use of any medical device, including the tested Portabiles digital gait device, outside pure research settings in routine medical care requires approval by a regulatory agency, and in that regard Portabiles has recently launched a request to the FDA in the USA. Besides that, it is already certified as a class I medical device (MDR) with a CE mark in Europe.

Declarations

Competing Interests

Ralph Steidl is the CEO of Portabiles HCT. Jean-Christophe Corvol has served in advisory boards for Alzprotect, Bayer, Biogen, Denali, Ferrer, Idorsia, iRegene, Prevail Therapeutic, Servier, Theranexus, UCB; and received grants from Sanofi and the Michael J Fox Foundation outside of this work. Holger Fröhlich has received grants from UCB and AbbVie outside this work.Tamara Raschka, Jackrite To, Tom Hähnel, Stefano Sapienza, Alzhraa Ibrahim, Enrico Glaab, Heiko Gaßner, Jürgen Winkler, and Jochen Klucken declare no competing interests.

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Author Contribution

R.S., J.W., J.C., J.K., and H.F. designed the study. S.S., A.I., E.G., R.S., J.W., E.G., H.G., J.C., J.K., and H.F. contributed to the acquisition of data. T.R., J.T., and T.H. analyzed and interpreted the data. T.R. wrote the initial draft of the paper. H.F. substantively revised it. All authors discussed the results and contributed to revising the paper. All authors approved the final version of the manuscript.

Data Availability

As this study is a retrospective analysis, availability of the clinical data depends on the individual study groups (LuxPARK: rejko.krueger@uni.lu; Erlangen: Alzhraa.Ibrahim@uk-erlangen.de).

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Figures

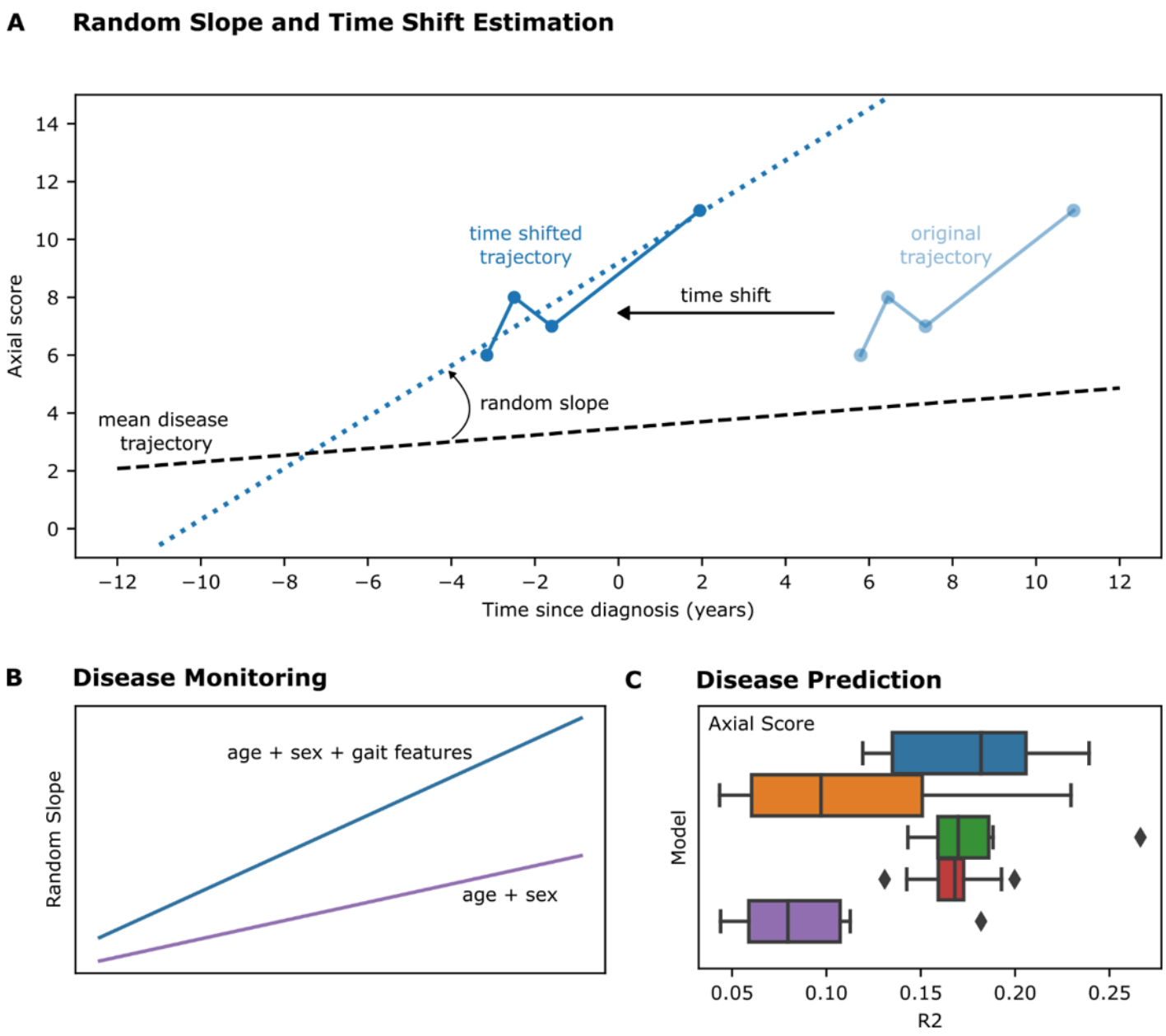

Figure 1

Workflow overview of digital gait analysis.

Depicted is the whole workflow done in this study. A – Random Slope and Time Shift Estimation: First, disease trajectories are shifted on a common disease timescale via a latent time joint mixed-effect model (LTJMM). Here, the time shift, showing the divergence from a 'mean' PD patient, and random slopes, a random effect measuring the progression of each patient compared to the mean patient, are calculated. B – Disease Monitoring: In a next step, the variance of the random slopes is modeled with a linear (mixed) model using either only age and sex (purple) as adjustment covariates or age, sex, and digital gait features (blue). Here, multiple different sets of digital gait parameters are tested: all, task-specific, and single. Models are compared via likelihood ratio tests assessing the statistical significance of digital gait features. C – Disease Prediction: Lastly, scores are predicted via a machine learning algorithm (Random Forest) with multiple digital gait feature sets (blue: all digital gait features plus age

and sex, orange: TUG task plus age and sex, green: 2x10m task plus age and sex, red: 4x10m task plus age and sex, and purple: only Age and Sex).

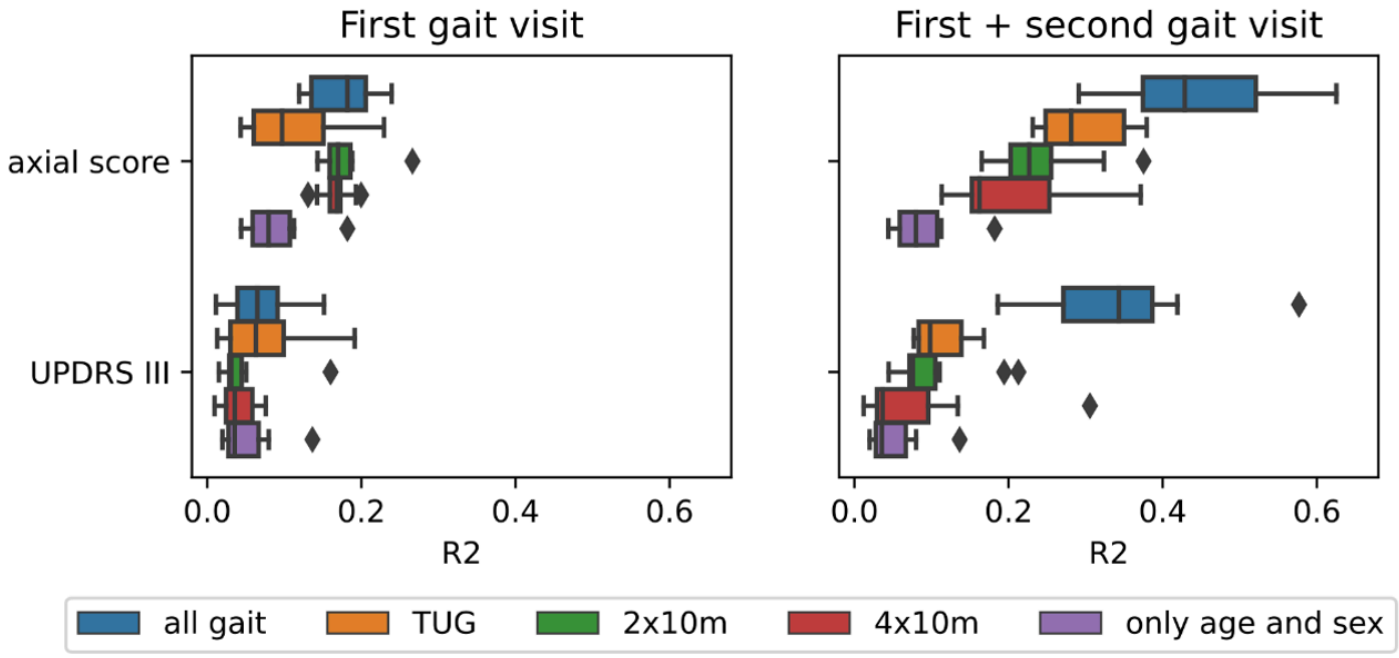

Figure 2

Prediction of patient-specific slopes of traditional clinical outcomes from digital gait features
Boxplots show the squared coefficient of determination (R^2) of multiple repeats of cross-validating a Random Forest machine learning model. The model predicts the (random) slope of the axial and UPDRS III score of each patient trained on data from first gait assessment only (left) or from first plus second gait assessment (left). Different colours indicate the used feature set: all digital gait features plus age and sex (blue), TUG task plus age and sex (orange), 2x10m task plus age and sex (green), 4x10m task plus age and sex (red), and only Age and Sex (purple).

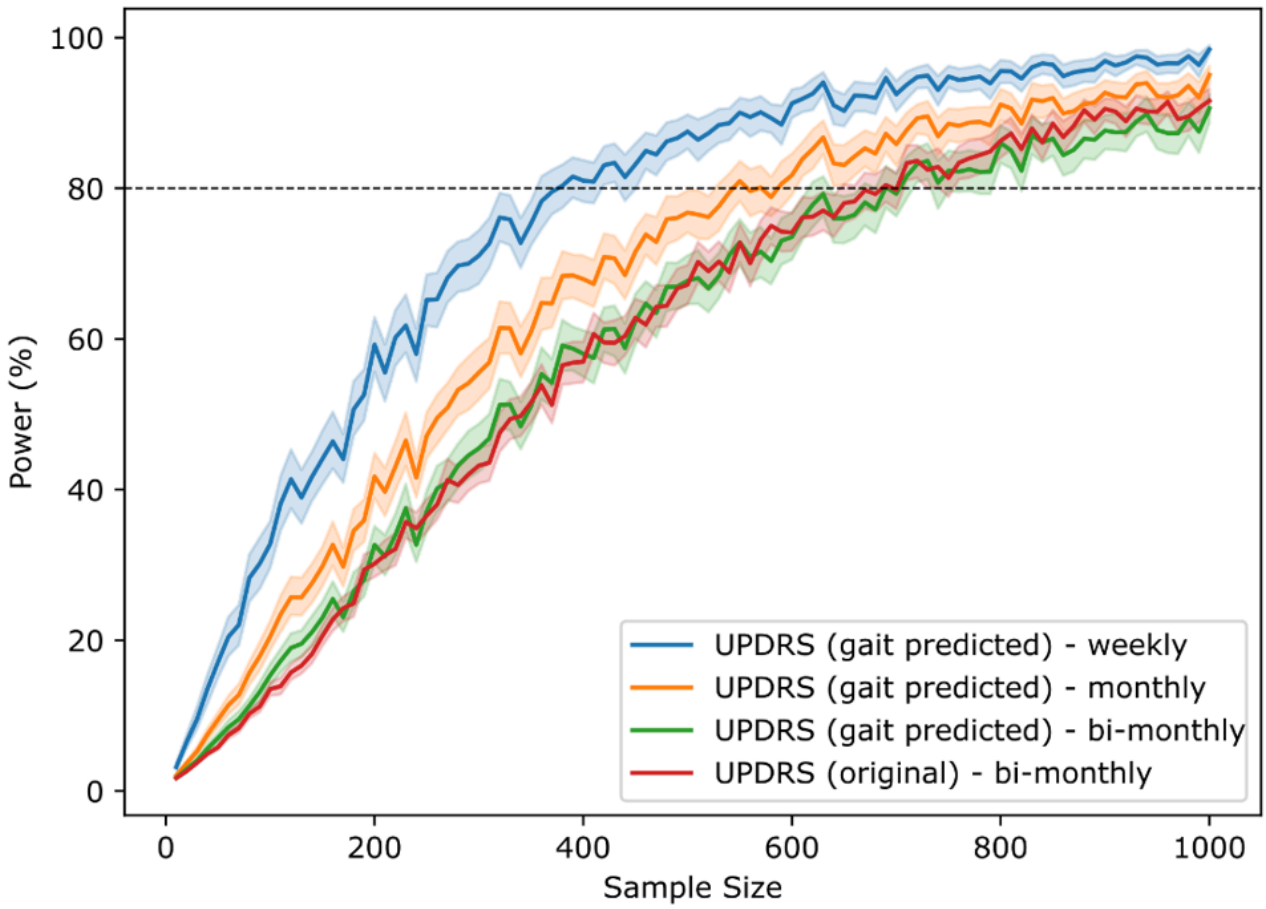

Figure 3

Simulation of randomized clinical trial with multiple visit frequencies
Curves describe the power a clinical study can reach with a specific sample size while expecting a treatment effect of 30% during a one year observation period and a significance level of α=0.01. Dashed line indicates 80% power. Different randomized clinical studies with either original or gait predicted UPDRS III as outcome were simulated with multiple visit frequencies. For gait predicted UPDRS III weekly (blue), monthly (orange), and bi-monthly (green) visits were simulated, while only bi-monthly visits were simulated for original UPDRS III as outcome (red).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GaitManuscriptSupplement.pdf
- SupplementaryTableS5singleFeatureResults.xlsx
- SupplementaryTableS6modelCoefficients.xlsx