NEW ADVANCED WIRELESS TECHNOLOGIES FOR OBJECTIVE MONITORING OF MOTOR SYMPTOMS IN PARKINSON'S DISEASE

EDITED BY: Antonio Suppa, Fernanda Irrera and Joan Cabestany
PUBLISHED IN: Frontiers in Neurology

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88945-486-0
DOI 10.3389/978-2-88945-486-0

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NEW ADVANCED WIRELESS TECHNOLOGIES FOR OBJECTIVE MONITORING OF MOTOR SYMPTOMS IN PARKINSON'S DISEASE

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Red tulips, the worldwide symbol of Parkinson's disease.

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Over the last decade, a growing number of researchers have used advanced wireless technologies including wearable sensors for objective evaluation of specific motor symptoms in patients with Parkinson's disease (PD). In the near future, sensing technologies will likely provide relevant advances in the clinical management of patients with PD, contributing to early diagnosis, disease progression monitoring and therapeutic approach. In this regard, this eBook hosts new original studies focused on the objective monitoring of motor symptoms and therapeutic perspectives of wireless technologies in patients with PD.

Citation: Suppa, A., Irrera, F., Cabestany, J., eds. (2018). New Advanced Wireless Technologies for Objective Monitoring of Motor Symptoms in Parkinson's Disease. Lausanne: Frontiers Media. doi: 10.3389/978-2-88945-486-0

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frontiers in Neurology

EDITORIAL
published: 04 April 2018
doi: 10.3389/fneur.2018.00216

Editorial: New Advanced Wireless Technologies for Objective Monitoring of Motor Symptoms in Parkinson's Disease

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Keywords: inertial measurement unit, wearable sensors, wireless technology, Parkinson's disease, freezing of gait

Editorial on the Research Topic

New Advanced Wireless Technologies for Objective Monitoring of Motor Symptoms in Parkinson's Disease

Nowadays, a growing number of researchers are using advanced wearable technologies with inertial measurement units (IMUs) to improve the evaluation of motor symptoms in patients with Parkinson's Disease (PD). In this context, wearable sensors are promising technologies possibly helpful for the overall clinical management of PD. The present Research Topic entitled "New Advanced Wireless Technologies for Objective Monitoring of Motor Symptoms in Parkinson's Disease" explores advances and perspectives of new wearable devices applied to patients with PD to support clinical assessment with objective methods. The 11 manuscripts included in this research topic deal with the evaluation of a wide range of motor symptoms in patients with PD, including the classical cardinal signs, such as bradykinesia, rigidity, tremor, and postural instability, and disabling gait disorders like freezing of gait (FOG) that significantly increase the risk of falls in patients with PD, resulting in a negative impact on quality of life. Accordingly, di Biase et al. examined the best sensor location on patients' bodies to quantify bradykinesia and rigidity, discriminate patients with PD and healthy subjects and finally distinguish specific motor state (On and Off state of therapy) in PD. Similarly, Spasojević et al. proposed a wireless armband device acquiring electromyography (EMG) and IMU data for quantitative assessment of the arm/hand movements and bradykinesia in PD. The differential diagnosis among various parkinsonian syndromes would also benefit from the objective analysis of motor symptoms through wearable technologies as demonstrated by Bonora et al. These authors used wearable IMU to assess balance in patients with PD and other types of parkinsonian syndromes, as well as in healthy subjects, discriminating specific abnormalities of anticipatory postural adjustments among the three groups. The use of wireless wearable devices also enables long-term monitoring of patients with PD even in a domestic environment, thus overcoming the well-known clinical difficulty of studying motor fluctuations in PD. In this regard, Rodríguez-Molinero et al. proposed a new algorithm that efficiently detects motor fluctuations in patients with PD by using a single inertial sensor located on patient's waist during gait. Additionally, Pham et al. validated in PD patients

Abbreviations: APAs, anticipatory postural adjustments; DBS, deep brain stimulation; EMG, electromyography; FOG, freezing of gait; IMUs, inertial measurement units; LID, L-DOPA-induced dyskinesia; PD, Parkinson's Disease.

OPEN ACCESS

Edited and Reviewed by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *05 February 2018*
Accepted: *20 March 2018*
Published: *04 April 2018*

Citation:
Irrera F, Cabestany J and Suppa A (2018) Editorial: New Advanced Wireless Technologies for Objective Monitoring of Motor Symptoms in Parkinson's Disease. Front. Neurol. 9:216. doi: 10.3389/fneur.2018.00216

and older adults a new step detection algorithm applied to an IMU worn on the lower back, comparing measures with those caught by means of a standardized optoelectronic system. Long-term and objective monitoring of patients' motor symptoms is a crucial aspect especially for paroxysmal motor disorders, such as L-DOPA-induced dyskinesias and FOG, that are difficult to recognize during standard clinical evaluation of PD patients in the outpatient clinic. For this purpose, Suppa et al. examined an unobtrusive sensory system with an innovative algorithm to automatically detect FOG during gait with high sensitivity and specificity to analyze kinematic gait parameters in relation to the specific motor state (On and Off state of therapy). Accordingly, Palmerini et al. used three wearable inertial sensors to predict FOG through the recognition of specific kinematic gait abnormalities preceding the disorder. Predicting FOG would allow to prevent it by providing external cues that commonly improve gait in patients with PD. In this regard, Ginis et al. monitored cadence of patients with PD through a wearable IMU-based system, investigating the most effective auditory feedback able to support gait and the least heavy one for self-perceived fatigue. Janssen et al. tested the effectiveness of smart glasses delivering 3D augmented reality visual cues to reduce FOG and improve gait parameters measured by IMU, in comparison to conventional 3D transverse bars on the floor and auditory cueing *via* a metronome. Wearable technologies are potentially relevant even in the therapeutic approach in patients with PD by objectively assessing the effect of drugs administration and thus ameliorating the therapeutic strategies for symptomatic improvement in patients with PD. Ruonala et al. used a wearable EMG recording system and two triaxial accelerometers to measure objectively the changes of motor symptoms during L-DOPA challenge test and thus help the selection of patients with PD that could benefit from deep brain stimulation treatment. Finally, overall perspectives of the current technological evolution for objective monitoring of motor symptoms in patients with PD and practical examples of wearable devices application are exhaustively summarized in the perspective article of Matias et al. In conclusion, the achievements of the present research topic allow us to confidently affirm that in the near future, new wireless wearable technologies will likely provide relevant contribution to the early diagnosis and disease progression monitoring of PD, and to design new tailored pharmacological and non-pharmacological therapeutic approaches, thus improving further the clinical management of patients with PD.

AUTHOR CONTRIBUTIONS

FI and JC: conception, design, and critical revision of the editorial. AS: conception, design, drafting, and critical revision of the editorial.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 06 March 2018
doi: 10.3389/fneur.2018.00121

Quantitative Analysis of Bradykinesia and Rigidity in Parkinson's Disease

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Background: In the last decades, several studies showed that wearable sensors, used for assessing Parkinson's disease (PD) motor symptoms and recording their fluctuations, could provide a quantitative and reliable tool for patient's motor performance monitoring.

Objective: The aim of this study is to make a step forward the capability of quantitatively describing PD motor symptoms. The specific aims are: identify the most sensible place where to locate sensors to monitor PD bradykinesia and rigidity, and identify objective indexes able to discriminate PD OFF/ON motor status, and PD patients from healthy subjects (HSs).

Methods: Fourteen PD patients (H&Y stage 1–2.5), and 13 age-matched HSs, were enrolled. Five magneto-inertial wearable sensors, placed on index finger, thumb, metacarpus, wrist, and arm, were used as motion tracking systems. Sensors were placed on the most affected arm of PD patients, and on dominant hand of HS. Three UPDRS part III tasks were evaluated: rigidity (task 22), finger tapping (task 23), and prono-supination movements of the hands (task 25). A movement disorders expert rated the three tasks according to the UPDRS part III scoring system. In order to describe each task, different kinematic indexes from sensors were extracted and analyzed.

Results: Four kinematic indexes were extracted: fatigability; total time; total power; smoothness. The last three well-described PD OFF/ON motor status, during finger-tapping task, with an index finger sensor. During prono-supination task, wrist sensor was able to differentiate PD OFF/ON motor condition. Smoothness index, used as a rigidity descriptor, provided a good discrimination of the PD OFF/ON motor status. Total power index, showed the best accuracy for PD vs healthy discrimination, with any sensor location among index finger, thumb, metacarpus, and wrist.

Conclusion: The present study shows that, in order to better describe the kinematic features of Parkinsonian movements, wearable sensors should be placed on a distal location on upper limb, on index finger or wrist. The proposed indexes demonstrated a good correlation with clinical scores, thus providing a quantitative tool for research purposes in future studies in this field.

Keywords: parkinson's disease, wearable sensors, quantitative analysis, kinematic analysis, parkinson's disease diagnosis

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *08 May 2017*
Accepted: *19 February 2018*
Published: *06 March 2018*

Citation:
di Biase L, Summa S, Tosi J, Taffoni F, Marano M, Cascio Rizzo A, Vecchio F, Formica D, Di Lazzaro V, Di Pino G and Tombini M (2018) Quantitative Analysis of Bradykinesia and Rigidity in Parkinson's Disease. Front. Neurol. 9:121. doi: 10.3389/fneur.2018.00121

INTRODUCTION

Parkinsons' disease (PD) diagnosis, staging, and clinical grading, to date, rely on clinical evaluation. Motor symptoms, such as bradykinesia, resting tremor, and rigidity, are hallmarks for the assessment and evaluation of the disease. With the disease progression, daily patients motor status starts to fluctuate between ON and OFF, i.e., to a status when the motor symptoms are adequately controlled by therapy, to a status when motor impairments are more evident. In order to control these motor symptoms changes, with a personalized and fine-tuned therapy, a precise clinical rating is needed, thus requiring periodic clinical visits.

Moreover, clinical diaries can help to evaluate the global motor performance; however, they are affected by poor objectiveness (1), and low compliance. The most objective and standardized clinical evaluation available, is based on semiquantitative scoring system, by means of clinical rating scales like UPDRS (2) or the more recent MDS-UPDRS (3). To date, using current diagnostic criteria (4), even for a neurologist expert of movement disorders, the error rate in the diagnostic accuracy can be estimated around 20% (5). The most relevant problems related to PD clinical evaluation are that: it is a time-consuming activity; it is not objective; to make it reliable a movement disorders expert is needed; it is not remotely administrable. All these issues lead to high direct and indirect cost for the health system and for the patients.

In the last years, the spread of low cost and non-invasive technologies for motion analysis, such as magneto-inertial wearable devices, brings to new methods for the assessment of pathologies characterized by motor dysfunction. Modern technologies like wearable sensors can provide a not invasive, accurate, rapid, remote, low cost, operator independent, objective, and scalable system. The idea to monitor pathological motion deficits using wearable sensors dates back to 1950s (6), and its application for PD patients started in 1990s (7). Although their clinical use is not so common yet, wearable motion sensors are largely used with the purpose of measuring movement and physiological signals. However, further work is needed to validate these systems and bring them to the everyday clinical practice. The cardinal motor symptoms of PD patients are bradykinesia, resting tremor, and rigidity (4). Bradykinesia is considered the most important and representative of the motor symptoms, and is defined as slowness in the initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions (4). Following the definition of bradykinesia, the fatigability of speed and amplitude, is a core feature; however, this is not a simple feature to catch with clinical evaluation, but it can be detected through an instrumented quantitative evaluation. The most studied cardinal symptom, by means of sensors, is the tremor, and in the last years there are several studies that have explored the characteristics of PD tremor (8, 9) in order to allow differential diagnosis with other tremor syndromes (10), or simply to monitor fluctuations of this symptom. Finally, rigidity is the most challenging motor symptom, to measure in an objective way, and only few studies have explored the accuracy of instrumental evaluation of rigidity with different devices (9).

To ensure proper monitoring of PD motor symptoms, a wearable system must be able to discriminate healthy subjects (HSs) from PD patients as well as to differentiate the ON from the OFF motor status in PD patients. In literature, among studies focused on the use of wearable sensors in PD, there is a lot of variability about the body distribution of sensors and about the specific indexes used to sense cardinal motor symptoms.

The aim of this study is to make a step forward the capability of quantitatively describing PD motor symptoms. In particular, the aims of the present study are: identify the most sensible place where to locate sensors to monitor PD bradykinesia and rigidity, and identify objective indexes able to discriminate PD patients from HS, and able to differentiate in PD patients ON from OFF motor status.

MATERIALS AND METHODS

Subjects

Fourteen PD patients (**Table 1**) (8 male, age: 67 ± 6 years) were enrolled in the study to evaluate bradykinesia and rigidity. Inclusion criteria for PD patient group were: a possible-probable diagnosis of PD according to UK PD Brain Bank criteria (4) and an Hoehn and Yahr (11) stage between 1 and 2.5. Exclusion criteria for PD patient was Hoehn and Yahr stage higher than 2.5; and for both PD and HSs group, another exclusion criteria was limitation of the physiological joints range of motion caused by other pathologies.

Thirteen age-matched HSs composed the control group (seven males, age: 69 ± 19 years).

The research was carried out in accordance with the Declaration of Helsinki. All patients and control subjects gave informed consent and the study was approved by local research ethics committee.

For PD group patients, kinematic analysis was performed for the most affected arm. For the HS group, the kinematic analysis was performed on dominant arm, identified with the Oldfield test (12).

Parkinsons' disease subjects were analyzed twice: after 12 h withdrawal of any medications (OFF motor condition) and after 1 h from administration of 150% of patient's l-dopa morning dose (ON motor condition).

Motor Tasks

Subjects were sitting in a chair and were asked to perform three motor tasks from the UPDRS part III. Rigidity (UPDRS task 22) was tested, without an activation maneuver, on slow passive movement of elbow joints, with the patient in a relaxed position. During this task, the examiner, holding against gravity the arm, moved the forearm for 10 times for each side. Bradykinesia was evaluated performing two task: finger tapping (UPDRS task 23) and prono-supination movement of the hands (UPDRS task 25). During the finger-tapping task, subjects were asked to tap the index finger on the thumb 15 times as quickly and as big as possible; each side was evaluated separately. During the prono-supination task, subjects were asked to extend the arm out in front of them with the palms

TABLE 1 | Parkinsons' disease patients characteristics.

ID	Disease duration (years)	Gender	Dominant hand	Most affected side	LEDD (mg)	UPDRS part III score (OFF condition)
S1	10	M	Right	Right	750	45
S2	5	M	Right	Left	750	29
S3	9	F	Right	Left	950	29
S4	7	F	Right	Right	660	36
S5	21	F	Right	Left	660	29
S6	10	M	Right	Right	925	65
S7	4	F	Right	Left	550	23
S8	NA	M	Left	Left	NA	49
S9	7	M	Right	Right	700	20
S10	2	F	Right	Right	300	25
S11	7	F	Right	Left	1,150	29
S12	6	M	Right	Left	600	25
S13	10	M	Right	Left	700	27
S14	7	M	Right	Right	670	43

M, male; F, female; LEDD, levodopa equivalent daily dose; NA, not available; S1-14, subject number.

down; then to turn the palm up and down alternately 15 times as fast and as fully as possible.

A movement disorders expert rated the three tasks according to the UPDRS part III scoring system.

Data Acquisition

In order to identify the most informative parameters to describe PD motor symptoms, motor tasks were recorded using five magneto-inertial units (M-IMU, device OPAL, APDM, Inc., Portland, OR, USA) and a camera GoPro Hero4 (GoPro, San Mateo, CA, USA). The data acquisition software MotionStudio (APDM Inc., Portland, OR, USA) allowed the camera to be synchronized with the sensors. The experiments were performed positioning sensors on the following anatomical landmark: second phalanx of the index finger (with the sensor *X*-axis in line with the same bone), distal phalanx of thumb (with the sensor *X*-axis in line with the same bone), metacarpus (fixed at medium point of third metacarpal bone, on the dorsal metacarpus, with the sensor *X*-axis in line with the third metacarpal bone), wrist (fixed at the medium point between radius and ulna bones, on the most distal dorsal part of radius and ulna bones, with the sensor *X*-axis in line with the radius bone), and arm (fixed at medium point between the greater tubercle of the humerus and its lateral epicondyle, with the sensor *X*-axis in line with the homerus) (**Figure 1**).

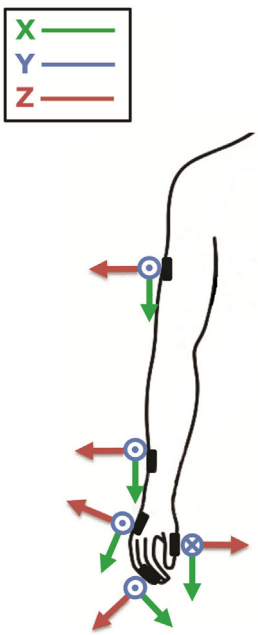

FIGURE 1 | The figure shows where sensors were placed; second phalanx of the index finger, thumb, metacarpus, wrist, and arm; and their orientation around the three axes (*x*, *y*, *z*). Modified from Ref. (13).

Data Analysis

According to the literature (14, 15), raw data were first high-pass filtered with a cut-off frequency of 1 Hz, to remove the effect of gross changes in the orientation of body segments. Moreover, the frequency component of interest for estimating each symptom can be isolated; specifically for tremor a bandpass filter with bandwidth 4–8 Hz was used, while for bradykinesia data were band pass between 1–4 Hz.

In the task used to assess bradykinesia severity, we defined a movement cycle as the set of submovements needed to complete the task for one repetition. For instance, a finger-tapping cycle consists of starting with the hand opened, closing, and then opening the fingers to the initial position for one time. We estimated the movement time as the beginning and end of cycles, identified from the speed profile with a threshold of 10% of the peak value of each cycle. In addition, we calculated the total time needed to complete the full task (Eq. 1) as:

$$t_{\mathrm{TOT}} = t_b - t_a \tag{1}$$

Total time: it is difference between the end time (t_b) of the last cycle and the begin of the first cycle (t_a).

From gyroscope signals in the time domain, we estimated the peak-to-peak values of angular velocity for all three axes. In order to capture the progressive reduction in speed amplitude, we perform a first-order regression between these peak-to-peak values

and the progressive number of cycles. We defined the fatigability index as the slope of the fitted linear equation (Eq. 2):

$$y=mx+q \quad (2)$$

Fatigability index: it is the slope (m) of the linear equation fitted with the peak-to-peak values of angular velocities extracted from the gyroscope signals.

Of note, for the fatigability index we consider for each task only the gyroscope axis most relevant for that specific task.

As regards the frequency domain, we extracted the total power (the integral of the power spectrum) from the power spectrum density (PSD) of angular velocity as suggested by Kim et al. (16). In fact, one of the results of Fourier analysis is the Parseval's theorem, which states that the area under the energy spectral density curve is equal to the area under the square of the magnitude of the signal, i.e., the total energy. A similar result holds for power. The total power is expected to represent the overall intensity of movement.

We also introduced a smoothness parameter as a bradykinesia descriptor. According to previous studies (17, 18), we measured smoothness using the spectral arch length (SAL) of movement speed profile as an appropriate index of movement fluidity (**Figure 2**). We decided to look at this type of smoothness measure because Balasubramanian et al. (17) showed that the SAL can account for the change in the number of submovements and the inter-submovement interval, which are movement features influenced by bradykinesia. As explained by the authors (17, 18), to compute smoothness it was not necessary to filter data because of the inherent low-pass filtering action performed. Specifically, we compute the SAL within the frequency range 0–4 Hz of the speed profile in each movement cycle and in each single movement.

Spectral arch length estimates smoothness by calculating the arc length of the magnitude of the Fourier Spectrum of a given speed profile $v(t)$, within a frequency range $(0 - \omega_c)$ (Eq. 3). Definition of SAL as introduced by Ref. (17, 18):

$$\mathrm{SAL} \triangleq -\int_0^{\omega_c}\left[\left(\frac{1}{\omega_c}\right)^2+\left(\frac{\mathrm{d}\hat{V}(\omega)}{\mathrm{d}\omega}\right)^2\right]^{\frac{1}{2}} d\omega; \quad \hat{V}(\omega)=\frac{V(\omega)}{V(0)}, \quad (3)$$

where $V(\omega)$ is the magnitude of the Fourier spectrum of $v(t)$, $\hat{V}(\omega)$ is the spectrum magnitude normalized with respect to the magnitude at zero frequency $V(0)$, and ω_c is adaptively selected based on the following equation:

$$\omega_c \triangleq \min\left\{\omega_c^{\max}, \min\left\{\omega, \hat{V}(r)<\bar{V}\,\forall r>\omega\right\}\right\} \quad (4)$$

Definition of the frequency value ω_c for the calculus of the SAL in Eq. 3.

Equation 4 defines ω_c as the minimum value between: (i) an upper bound limit for this parameter $\omega_c^{\max}$, which has been set in our analysis to 4 Hz; (ii) the value of frequency above which the normalized spectrum magnitude is always lower than a given threshold $\bar{V}$, set in our analysis to 10%.

The definition of the SAL modified with the adaptive parameter ω_c is referred in literature as the SPARC index (18).

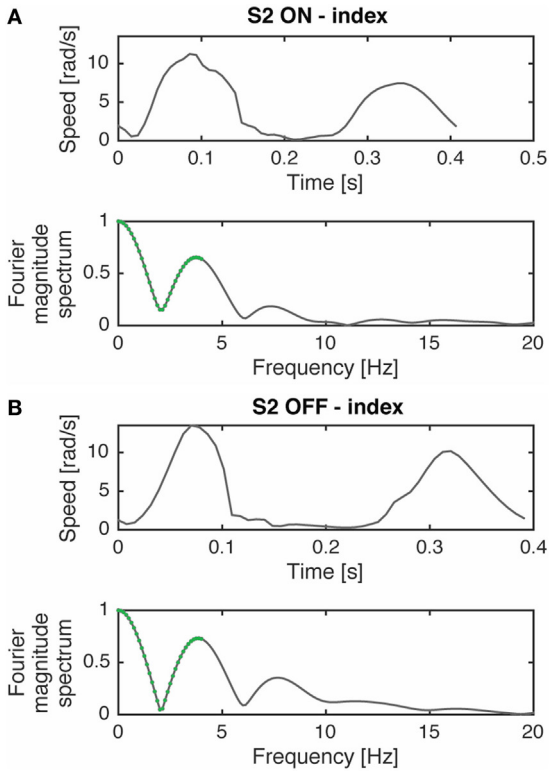

FIGURE 2 | Movement speed profile, during a prono-supination task, of a typical subject (S2) in ON **(A)** and OFF **(B)** phases and their respective Fourier magnitude spectrum. The segments used for computing spectral arch length are highlighted in green. The complexity of the Fourier magnitude spectrum changes with the submovement characteristics variations (i.e., inter-submovement interval) of the movement speed profile, as already shown by Ref. (17). Modified from Ref. (13).

Finally, we investigated the relationship between this index and the elbow joint rigidity and we tested the smoothness index as rigidity descriptor. In PD, the classic cogwheel rigidity causes a fragmentation and decomposition of the passive movement, leading to less smooth than normal passive movements. We estimated the beginning and the end of movement looking at the speed profile with a threshold of 10%. Then we computed the averaged SAL of movement speed profile for each movement and looked at differences between OFF and ON motor statuses. Specifically, we computed the SAL within the frequency range 0–20 Hz of the speed profile in each movement cycle.

Statistical Analysis

First, we looked for normality of distributions with the Shapiro–Wilk test, because of the number of participants in each group (19).

As mentioned previously, we are investigating those indexes able to differentiate the OFF motor status from the ON one in PD patients; moreover, we want to identify the most sensible place where to locate sensors. Therefore, for each indicator we conducted two-way repeated measures ANOVA with state

(ON vs OFF) and sensor locations—5 levels in bradykinesia tasks (arm, index, metacarpus, thumb, and wrist) and two levels in rigidity task (left wrist and right wrist)—as within-subject factor. We additionally assessed the most sensible place where to locate sensors while discriminating the state factor. That is, the multiple comparisons of the interactive effect state × sensor location.

For OFF vs HS discrimination, data were analyzed using a mixed-design ANOVA with a within-subjects factor sensor location and a between-subject factor the group (OFF or Healthy). For ON vs HS discrimination, we ran a mixed-design ANOVA with a within-subjects factor sensor location and a between-subject factor the group (ON or Healthy). We additionally assessed the most sensible place where to locate sensors while discriminating the group factor. That is, the multiple comparisons of the interactive effect group × sensor location.

Sensor location in bradykinesia task (arm, index, metacarpus, thumb, and wrist).

In order to identify the most sensible place where to locate sensors, to monitor PD bradykinesia and rigidity, while excluding false-positive results under multiple testing, we applied Bonferroni correction and *p*-values were compared against α/(number of comparison) instead of $\alpha = 0.05$.

For total time index, we used a paired-sample *t*-test, to test its capability to differentiate the ON/OFF motor status. Similarly, we used an independent sample *t*-test to see if total time index was capable to discriminate HS from the OFF or from the ON condition.

We also looked at the correlation of each indicator in the OFF and the ON condition, with the UPDRS part III scale. Correlation was reported as *R*-squared values.

For data analysis was used Matlab (Mathworks, Natick MA, USA).

TABLE 2 | Bradykinesia task clinical rating.

Subjects	UPDRS part III score			
	Task 23, finger tapping		Task 25, arm prono-supination	
	OFF	ON	OFF	ON
S1	3	3	2	2
S2	2	1	1	1
S3	1	0	1	0
S4	2	1	2	1
S5	1	1	1	1
S6	3	2	4	4
S7	1	0	1	0
S8	3	2	2	2
S9	2	1	1	1
S10	1	1	1	1
S11	2	1	1	0
S12	2	1	2	1
S13	1	1	1	1
S14	3	2	1	1

TABLE 3 | Rigidity task clinical rating.

Subjects	UPDRS part III score, Task 22			
	Right arm rigidity		Left arm rigidity	
	OFF	ON	OFF	ON
S1	2	2	2	2
S2	2	1	2	1
S3	2	2	2	2
S4	2	1	1	1
S5	2	1	2	2
S6	2	2	2	2
S7	1	0	1	1
S8	2	2	3	2
S9	0	0	0	0
S10	2	1	2	1
S11	1	1	2	1
S12	1	1	2	2
S13	1	1	2	1
S14	2	2	1	1

RESULTS

Clinical Rating

The results of clinical rating with UPDRS part III scale, for each task are shown in **Tables 2** and **3**, respectively, for bradykinesia and rigidity task.

Kinematic Index

Parkinsons' disease patients S13 and S14 were excluded from the kinematic analysis due to artifacts into accelerometric signal.

Movement Time

First of all, we looked at the total time needed to complete the finger-tapping and the arm prono-supination tasks. In the OFF condition, PD subjects needed more time to complete the task than during the ON condition. Considering the arm prono-supination task, statistical analysis showed that the total time is able to discriminate the OFF vs ON motor condition ($p = 0.01$) and also to differentiate the HS group from PD patients in OFF and ON conditions (OFF $p = 0.001$; ON $p = 0.04$) (**Figure 3B**). For the finger-tapping task, the total time is able to discriminate the OFF vs ON motor condition ($p = 0.001$) and also to differentiate the HS group from PD patients in OFF condition ($p = 0.02$) (**Figure 3A**). Good correlations were found in the finger-tapping task, between total time and UPDRS item 23 score, for both motor conditions (OFF $R^2 = 0.34$; ON $R^2 = 0.74$). No correlation was found between total time and UPDRS item 25 score in arm prono-supination task.

Peak-to-Peak Velocity and Fatigability

To catch the whole kinematic information related to the task performed is important to consider where to place the sensor and which orientation axis use for analysis. For finger-tapping task, the *y*-axis was chosen for the analysis, instead for the prono-supination task the *x*-axis was the most informative (**Figure 4**). Therefore, we looked at the fatigability on these two axes depending on the task (**Tables 4** and **5**).

The fatigability index assessed in the finger-tapping and arm prono-supination tasks are shown, respectively, in **Figures 5** and **6**.

As mentioned before, the fatigability represents the progressive reduction in speed of the movement, see **Figure 4**.

Analyzing the finger-tapping task, the ANOVA analysis showed no significant main effect of the state in none among the three state comparison, ON/OFF state, OFF/HS, and ON/HS on fatigability index (**Figure 5**).

Analyzing the arm prono-supination task, there was a significant main effect of ON/OFF state [$F(1) = 9.899$; $p = 0.009$] and of sensor location [$F(4) = 8.548$; $p < 0.001$] on fatigability index. There was a significant interaction between ON/OFF state and sensor location on fatigability index [$F(4) = 3.957$; $p = 0.008$].

The *post hoc* test, showed the following sensors significances, thumb $p = 0.003$; wrist $p = 0.006$.

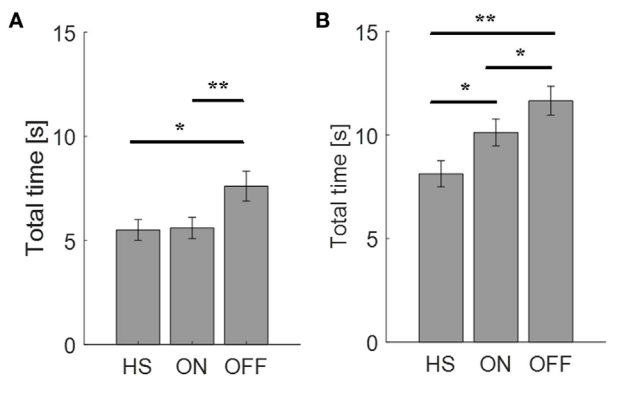

FIGURE 3 | Total time needed (seconds) to complete the finger-tapping **(A)** and the arm prono-supination tasks **(B)**. Values are averaged for each group. Bars denote the SE. *$p < 0.05$ (*t*-test); **$p < 0.01$ (*t*-test).

There was no significant effect of OFF/healthy state on fatigability index, there was a significant main effect of sensor location on this index [$F(4; 92) = 3.556$; $p = 0.01$] and there was no interaction between OFF/healthy state and sensor location on this index.

In addition, there was a significant main effect of ON/healthy state [$F(1; 23) = 5.76$; $p = 0.025$] and of sensor location [$F(4; 92) = 6.509$; $p < 0.001$] on this index. There was no interaction between ON/healthy state and sensor location on fatigability index. *Post hoc* analysis showed no statistically significant differences among sensors.

We found a good correlation between the UPDRS item 23 score and fatigability measured in the finger-tapping task but only in the OFF condition for the index finger ($R^2 = 0.49$). No correlation was found between the fatigability and UPDRS item 25 score in arm prono-supination task.

Total Power

Power spectral density in PD subject in ON phase increases in amplitude compared with the one in OFF phase (**Figure 7**).

For the finger-tapping task (**Table 4**), there was a significant main effect of ON/OFF state [$F(1) = 14.047$; $p = 0.003$] and of sensor location [$F(4) = 47.709$; $p < 0.001$] on total power index, with a significant interaction between ON/OFF state, and sensor location on this index [$F(4) = 16.786$; $p < 0.001$] (**Table 4**). *Post hoc* analysis showed the following sensors location significances, index finger $p = 0.001$ (**Figure 8**).

ANOVA analysis showed a significant main effect of OFF/healthy state [$F(1; 23) = 16.247$; $p < 0.001$] and of sensor location [$F(4; 92) = 82.576$; $p < 0.001$] on total power index, with a significant interaction between OFF/healthy state and sensor

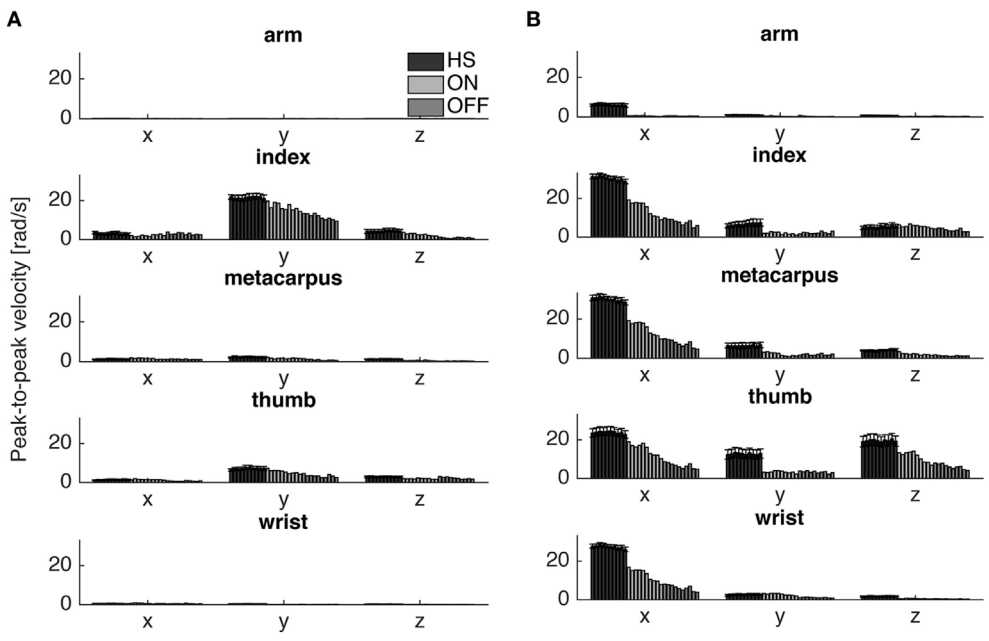

FIGURE 4 | Peak-to-peak velocity of all cycles of a typical Parkinson's disease subject (S6) in comparison with the averaged values of healthy subject (HS) group, for the finger-tapping **(A)** and the arm prono-supination tasks **(B)** for each gyroscope channel. Values HS group values are averaged and bars denote the SE.

location on this index [$F(4) = 15.946$; $p < 0.001$]. *Post hoc* analysis showed the following sensors location significances, index finger $p < 0.001$ (**Figure 8**).

TABLE 4 | Finger-tapping task kinematic results.

	Kinematic index		
	Fatigability	**Total power**	**Fatigability**
State (PD ON vs PD OFF)		**	**
Sensor location		**	**
State (ON/OFF) × sensor location interaction		**	
State (PD OFF vs HS)		**	**
Sensor location		**	**
State (OFF/HS) × sensor location interaction		**	
State (PD ON vs HS)			
Sensor location		**	**
State (ON/HS) ×sensor location interaction		*	

*$p < 0.05$ (ANOVA); **$p < 0.01$ (ANOVA).
PD ON, Parkinson's disease patients in ON motor status; PD OFF, Parkinson's disease patients in OFF motor status; HSs, healthy subjects.

TABLE 5 | Prono-supination task kinematic results.

	Kinematic index		
	Fatigability	**Total power**	**Smoothness**
State (PD ON vs PD OFF)	**	**	**
Sensor location	**	**	**
State (ON/OFF) × sensor location interaction	**	**	
State (PD OFF vs HS)		**	**
Sensor location	**	**	**
State (OFF/HS) × sensor location interaction		**	
State (PD ON vs HS)	*	**	**
Sensor location	**	**	**
State (ON/HS) × sensor location interaction		**	

*$p < 0.05$ (ANOVA); **$p < 0.01$ (ANOVA).
PD ON, Parkinson's disease patients in ON motor status; PD OFF, Parkinson's disease patients in OFF motor status; HSs, healthy subjects.

There was no significant effect of ON/healthy state on total power index, during the finger-tapping task.

In this task, the correlation between total power and the UPDRS item 23 score in OFF motor condition is good for the index finger ($R^2 = 0.57$) and the thumb ($R^2 = 0.47$).

If we use the arm prono-supination to assess bradykinesia (**Figure 9**), it is possible to discriminate OFF vs ON motor status, OFF vs HS, and ON vs HS group (**Table 5**).

There was a significant main effect of ON/OFF state [$F(1) = 16.087$; $p = 0.002$] and of sensor location [$F(4) = 33.45$; $p < 0.001$] on total power index, with a significant interaction between ON/OFF state and sensor location on this index [$F(4) = 7.684$; $p < 0.001$]. *Post hoc* analysis showed the following sensors location significances, index $p = 0.003$; thumb $p = 0.001$; wrist $p = 0.005$ (**Figure 9**).

ANOVA analysis showed a significant main effect of OFF/healthy state [$F(1; 23) = 34.776$; $p < 0.001$] and of sensor location [$F(4; 92) = 84.44$; $p < 0.001$] on this index, with a significant interaction between OFF/healthy state and sensor location on this index [$F(4) = 22.31$; $p < 0.001$]. *Post hoc* analysis showed the following sensors location significances, index, wrist, and metacarpus $p < 0.0001$; thumb $p = 0.0003$, and arm $p = 0.0002$ (**Figure 9**).

ANOVA analysis showed a significant main effect of ON/healthy state [$F(1; 23) = 23.892$; $p < 0.001$] and of sensor location [$F(4; 92) = 93.198$; $p < 0.001$] on this index, with a significant interaction between ON/healthy state and sensor location on total power index [$F(4) = 13.583$; $p < 0.001$]. *Post hoc* analysis showed the following sensors location significances, index, wrist, and metacarpus $p < 0.0001$; thumb $p = 0.001$; arm $p = 0.0004$ (**Figure 9**).

The total power well correlates with the UPDRS item 25 score assigned. The sensor located on the index finger and thumb showed correlation in both OFF and ON motor condition (index OFF $R^2 = 0.35$; ON $R^2 = 0.34$; thumb OFF $R^2 = 0.35$; ON $R^2 = 0.35$), while for the wrist and metacarpus there was a correlation only in OFF motor status (wrist OFF $R^2 = 0.36$; metacarpus OFF $R^2 = 0.38$).

Smoothness

Since smooth and well-coordinated movements are typical features of a healthy and well-developed human motor behavior, we

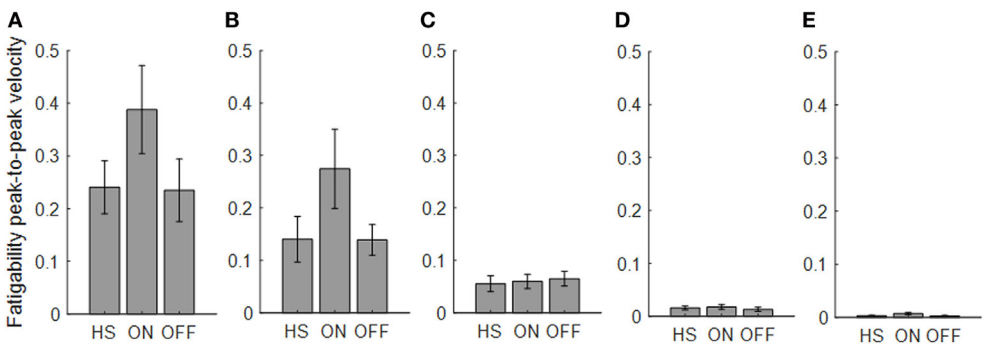

FIGURE 5 | Fatigability index computed from the finger-tapping task. Each panel shows the averaged values for each group OFF, ON, and healthy subject (HS) for index finger **(A)**, thumb **(B)**, metacarpus **(C)**, wrist **(D)**, and arm **(E)**. Bars denote the SE.

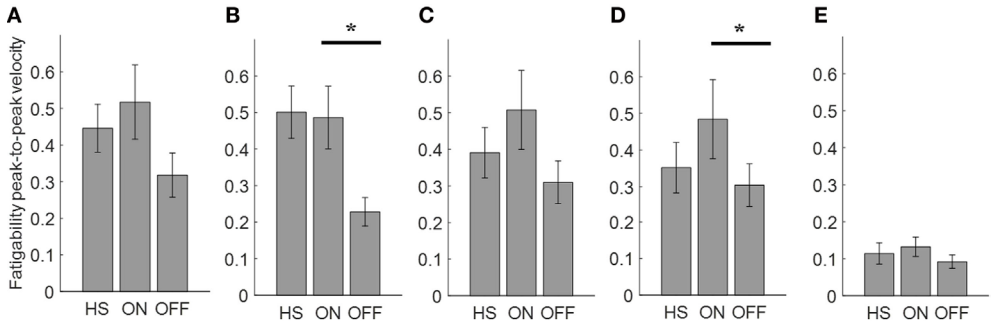

FIGURE 6 | Fatigability index computed from the arm prono-supination task. Each panel shows the averaged values for each group OFF, ON, and healthy subject (HS) for index finger **(A)**, thumb **(B)**, metacarpus **(C)**, wrist **(D)**, and arm **(E)**. Bars denote the SE. Bonferroni correction *$p < 0.01$.

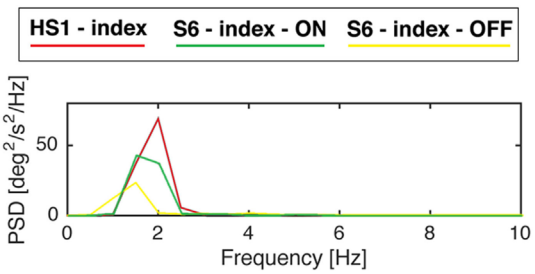

FIGURE 7 | Power spectral density of gyroscope signal of subjects S6 from the Parkinson's disease group and S1 from the healthy subject (HS) group while performing finger-tapping task. Modified from Ref. (13).

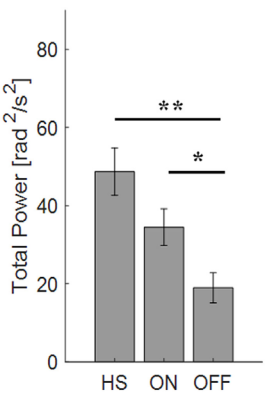

FIGURE 8 | Total power index computed from the finger-tapping task, with sensor on index finger. Values are averaged for each group OFF, ON, and healthy subject (HS). Bars denote the SE. Bonferroni correction *$p < 0.01$; **$p < 0.001$.

expect that the intake of the medication should be assessed by smoothness values near to zero.

For the finger-tapping task (**Table 4**), ANOVA analysis showed a significant main effect of ON/OFF state [$F(1) = 16.984$; $p = 0.002$] and of sensor location [$F(4) = 157.654$; $p < 0.001$] on smoothness index, without an interaction between ON/OFF state and sensor location on this index [$F(4) = 2.33$; $p = 0.071$]. *Post hoc* analysis showed the following sensors location significances, index finger $p = 0.003$; thumb $p = 0.004$; metacarpus $p = 0.005$; arm $p = 0.0001$ (**Figure 10**).

ANOVA analysis, showed a significant main effect of OFF/healthy state [$F(1; 23) = 11.427$; $p = 0.003$] and of sensor location [$F(4; 92) = 138.011$; $p < 0.001$] on smoothness index, without an interaction between OFF/healthy state and sensor location on this index [$F(4) = 1.58$; $p = 0.186$]. *Post hoc* analysis showed the following sensors location significances, index $p = 0.003$; metacarpus $p = 0.006$; wrist $p = 0.008$; arm $p = 0.002$ (**Figure 10**).

There was no significant effect of ON/healthy state on smoothness index.

For arm prono-supination task (**Table 5**), ANOVA analysis showed a significant main effect of ON/OFF state [$F(1) = 5.025$; $p = 0.047$] and of sensor location [$F(4) = 8.409$; $p < 0.001$] on smoothness index, without an interaction between ON/OFF state and sensor location on this index [$F(4) = 0.607$; $p = 0.659$]. *Post hoc* analysis showed no statistically significant differences among sensors (**Figure 10**).

ANOVA analysis showed a significant main effect of OFF/healthy state [$F(1; 23) = 12.089$; $p = 0.002$] and of sensor location [$F(4; 92) = 7.315$; $p < 0.001$] on this index, without an interaction between OFF/healthy state and sensor location on smoothness index [$F(4) = 0.514$; $p = 0.726$]. *Post hoc* analysis showed the following sensors location significances, index, and metacarpus $p = 0.005$; wrist $p = 0.001$, thumb $p = 0.008$, and arm $p = 0.002$ (**Figure 10**).

ANOVA analysis showed a significant main effect of ON/healthy state [$F(1; 23) = 8.271$; $p = 0.009$] and of sensor location [$F(4; 92) = 15.072$; $p < 0.001$] on this index, without an interaction between ON/healthy state and sensor location on smoothness index [$F(4) = 1.354$; $p = 0.256$]. *Post hoc* analysis showed the following sensors location significances, arm $p = 0.005$ (**Figure 10**).

No correlation was found with the arm prono-supination task, between the UPDRS item 25 score and the smoothness index, but there was a good correlation, between UPDRS item 23 score in ON motor condition and the smoothness index for sensors placed on wrist ($R^2 = 0.36$), thumb ($R^2 = 0.47$), metacerpus ($R^2 = 0.49$), and arm ($R^2 = 0.43$) during the finger-tapping task.

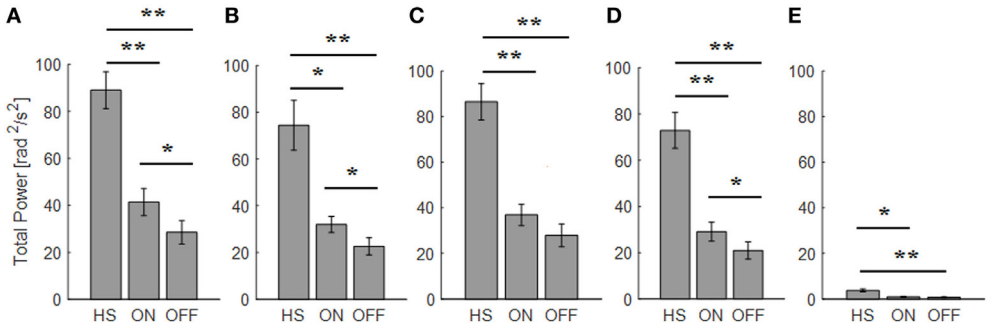

FIGURE 9 | Total power index computed from the arm prono-supination task. Each panel shows the averaged values for each group OFF, ON, and healthy subject (HS) for index finger **(A)**, thumb **(B)**, metacarpus **(C)**, wrist **(D)**, and arm **(E)**. Bars denote the SE. Bonferroni correction $^{*}p < 0.01$; $^{**}p < 0.001$.

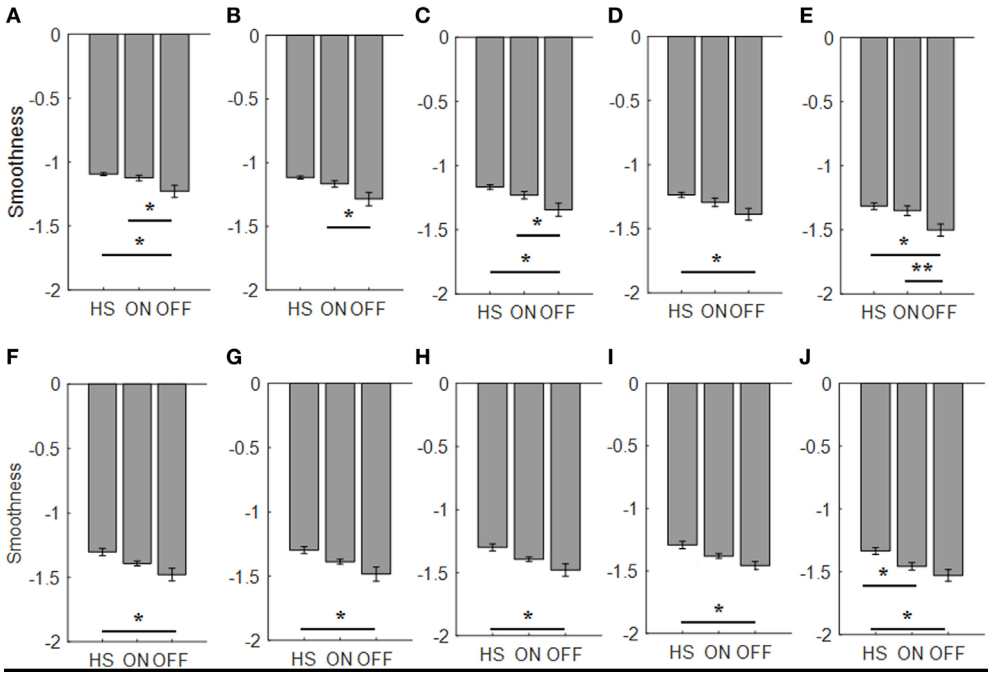

FIGURE 10 | Smoothness index. Each panel shows the averaged values for each group OFF, ON, and healthy subject (HS) for index finger [**(A)**: finger tapping; **(F)**: arm prono-supination], thumb [**(B)**: finger tapping; **(G)**: arm prono-supination], metacarpus [**(C)**: finger tapping; **(H)**: arm prono-supination], wrist [**(D)**: finger tapping; **(I)**: arm prono-supination], arm [**(E)**: finger tapping; **(J)**: arm prono-supination]. Bars denote the SE. *Bonferroni correction $^{*}p < 0.01$; $^{**}p < 0.001$.

Taking into account, the relationship between elbow rigidity and the smoothness index, results showed no discrimination ability between PD OFF condition and ON condition, or PD and HSs (**Figure 11**). In addition, no correlation between UPDRS item 22 score and smoothness index was found for rigidity.

DISCUSSION

In the last years, a huge number of studies were published about the quantitative analysis of movement in PD (9, 14–16, 20). The variety of indicators extracted by accelerometer, gyroscope, compass, and other sensors signal in the literature is high. Nevertheless, several questions are still open, since we have not yet reached the stage of a consensus about: which kind of sensor is more suitable for evaluating PD patients, and if it is better to have a single index for each Parkinsonian symptom, or a global index of impairment; where is the best place on the body to wear these sensors, the level of invasiveness acceptable by the patient for at home long-term recording. A recent review (9), focused on published research papers on wearable technologies for PD in the last 10 years, showed that among the 848 analyzed studies only the 6% presents a reliable quantitative assessment system ready for clinical use in the next future. However, a huge number of studies present proof of concepts that could become useful for clinical use in the next years.

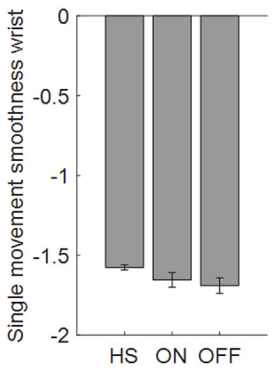

FIGURE 11 | Smoothness index computed from the wrist in the rigidity task. Values are averaged for each group. Bars denote the SE.

An example of an experimental portable device is an instrumented glove used to quantify motor symptoms during deep-brain stimulation surgery (14); authors used only one six-axis IMU placed on the middle finger for tremors and bradykinesia assessment. In this study, five UPDRS motor tasks addressing the upper arm were analyzed (rest tremor, postural tremor, finger-to-nose, repeated hand movements, and rigidity). Experimental results showed that their system is reliable for tremor amplitude determination and movement angles measurement only. Such a similar device was also proposed by Di Pino et al. (21).

A network of uniaxial accelerometers—four located on the upper limbs and four on the lower limbs was proposed by Patel et al. (15). Data were acquired during the execution of UPDRS motor tasks including finger-to-nose, finger tapping, repeated hand movements, heel tapping, sitting, and alternating hand movements. The results of the study, indicated that it is possible to reliably estimate clinical scores on the basis of four features such as root mean square value of accelerometers, data range value of accelerometers, dominant frequency, and the ratio of energy of the dominant frequency component to the total energy. Although differences were observed, several motor tasks performed equally well. This suggests that the proposed parameters capture aspects of the movement patterns that are not specific for a given motor task. This further suggests that the proposed analyses could be extended to activities of daily living.

Heldman et al. (20) used two six-axis motion sensors located on the index finger and thumb, and analyzed only the gyroscope signals. The authors tested PD patients in the OFF and ON motor condition while performing bradykinesia tasks (e.g., finger tapping, hand grasping, and pronation supination). The authors showed a correlation among UPDRS scores and kinematic measures: speed of movements was correlated with log of root mean square of the angular velocity; amplitude of movements was correlated with the root mean square of the excursion angle; and movement rhythm was correlated the coefficient of variation. Their results suggest that motion sensors can objectively measure speed, amplitude, and rhythm and that they are highly correlated with clinician scores.

The state of the art of quantitative assessment tools for PD clearly shows that interactive motor tasks recorded using wearable magneto-inertial devices, allowed to deeply analyze the kinematic and dynamic characteristics of goal-directed movements of upper limb, and to extract quantitative and useful indices for the motor symptoms evaluation.

With the present study, we have searched answer to open questions, which slow the progression to clinical application of the available technologies.

The first question was, where is the best place where to locate sensors. By using a redundant number of upper arm sensors (index finger, thumb, metacarpus, wrist, and arm), our results showed that a distal location of sensors on upper arm (i.e., on index finger) is more sensible to catch the kinematic features of Parkinsonian movements. The following questions were, which index can better differentiate PD patients OFF from ON motor condition and patients in these two conditions from HSs. Our results introduced new indexes that well describe the clinical motor symptoms, and are able to differentiate PD ON/OFF condition and PD vs HSs.

For the first time, we have provided a complete kinematic description of the classic definition of bradykinesia (4) through different quantitative kinematic indexes: the "slowness of voluntary movement" was well described by the total time needed (seconds) to complete a task (the finger-tapping or the arm prono-supination task), and the "progressive reduction in speed and amplitude of repetitive actions," was well described by a new kinematic index, defined fatigability index. These two kinematic indexes are able to discriminate the ON from the OFF motor condition in PD patient. Moreover, in order to describe bradykinesia, the prono-supination task seems to be the most informative, since with this simple task we can discriminate PD ON vs OFF motor condition (with any sensor location among thumb or wrist), and in addition we can discriminate PD patients in any of these two conditions from HSs. The intrinsic features of prono-supination task, which involves an highest number of muscles, leads to a more versatile task, able to describe the variability of Parkinsonian movement, with sensors placed in different location on upper arm. Conversely, the features of finger-tapping task, lock its utility to the sensor location on the index finger, in this case the results showed a good discrimination ability to distinguish the PD ON vs OFF motor condition.

Overcoming the classic bradykinesia definition, we have described the kinematic of Parkinsonian movement with further two indexes. In order to describe the overall "intensity" of movement, we have extracted the total power that is the power spectrum of the frequency of movement during finger-tapping and prono-supination task. Also for this kinematic index the prono-supination task showed to be more informative compared with other condition, since the total power index can discriminate PD ON vs OFF motor condition and PD patients in any of these conditions from HSs with any sensor location among index finger, thumb, or wrist. Even, the most proximal sensor (arm) is useful to discriminate HS from PD in OFF condition during the prono-supination task. For finger-tapping task, with a sensor placed on the index finger, the total power can discriminate PD ON vs OFF motor condition, and the later from HSs. Therefore, the results show that using prono-supination task, with sensors placed on index finger, thumb, or wrist, total power index is able to perform a complete PD ON/OFF and PD/HS discrimination. The good performance of this index could be explained from its

neurophysiological interpretation. In PD, repetitive movement, are supposed to be arhythmic, other than slow, and characterized from a progressive reduction in speed and amplitude. Therefore, the total power index is a perfect index to catch the arhythmicity and the variability of a movement, since an arhythmic movement will be characterized from a more broad and flat PSD graph compared with a rhythmic movement.

The last index that we proposed for the kinematic analysis, the smoothness index, could be interpreted as a bridge parameter, able to describe features that belong to both bradykinesia and rigidity. This kinematic index describes the fluidity of movements, so that it can catch the features of both the bradykinesia, related to the variation of movements rhythm, caused by interruptions or hesitations during task, as well as the cogwheel rigidity, which fragment and decompose passive movement around the joint. For bradykinesia, the smoothness index during prono-supination task is able to discriminate PD in OFF motor condition form HSs, with any sensor location among index finger, thumb, metacarpus, wrist and arm, and PD in ON motor condition form HSs with sensor placed on arm. During finger-tapping task, the smoothness index is able to discriminate PD in OFF from ON motor condition, with any sensor location except the wrist, and PD in OFF from HSs, with any sensor location except the thumb.

Total power was the only index which showed a good correlation with the related UPDRS score, for both task finger-tapping and arm prono-supination, in the last both condition OFF/ON motor status. These versatile features suggest to explore this index, in future studies, as a candidate to monitor PD motor symptoms. Total time, total power, and smoothness showed a good correlation with the UPDRS score for finger-tapping task, therefore the use of these indexes is suggested only for this task.

CONCLUSION

The first aim of the present study was identify the most sensible place where to locate sensors to monitor PD motor symptoms. Our results suggest that a distal location of wearable sensors, on index finger or wrist, should be preferred in these kinds of studies in order to better describe the kinematic features of Parkinsonian movements.

In order to differentiate PD OFF from ON motor condition, the best solution seems to be placing a magneto-inertial sensor on index finger during finger-tapping task, so obtaining data from which to extract the kinematic indexes proposed (total time, total power, or smoothness). In addition, this sensor location guarantees a good correlation between the clinical score as expressed by UPDRS scale and the kinematic measure (total time, total power).

In order to differentiate PD patients from HSs, the total power index, computed from data acquired by a sensor placed in any location among index finger, thumb, metacarpus, wrist, and arm during prono-supination task has shown the best accuracy. However, also total time, during the same task, with any sensor location could be a valid alternative to differentiate PD patients from HSs.

In conclusion, combing all results, our study shows that considering all variables (sensors location; motor task performed; kinematic index analyzed), the most versatile, and complete solution, that could answer to both questions (PD OFF vs ON differentiation and PD vs HS differentiation), with highest accuracy, is to place one sensor on index finger, thumb, or wrist, perform a prono-supination task and use the total power as kinematic index. However, keeping in mind the small sample size of the present study, the proposed indexes, are good candidates to be explored in further confirmation studies with larger population.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Good Clinical Practice with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees of IRCCS San Raffaele Pisana and Campus Bio-Medico University of Rome.

AUTHOR CONTRIBUTIONS

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique; LB: 1A, 1B, 1C, 2C, 3A, 3B. SS: 1B, 1C, 2A, 2B, 2C, 3A, 3B. JT: 1B, 1C, 2C, 3B. FT: 1A, 1B, 2C, 3B. MM: 1B, 1C, 2C, 3B. AR: 1C, 2C, 3B. FV: 1A, 1B, 2C, 3B. DF: 1A, 1B, 2A, 2C, 3B. VL: 1B, 2C, 3B. GP: 1A, 1B, 2C, 3B. MT: 1A, 1B, 2C, 3B.

FUNDING

This study was partially supported by the Italian Ministry of Health within the Research program "Ricerca Finalizzata - Giovani Ricercatori" (PDmeter project, no. GR-2011-02352674).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with one of the authors (VL) and states that the process nevertheless met the standards of a fair and objective review.

frontiers in Neurology

ORIGINAL RESEARCH
published: 11 August 2017
doi: 10.3389/fneur.2017.00388

Quantitative Assessment of the Arm/Hand Movements in Parkinson's Disease Using a Wireless Armband Device

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OPEN ACCESS

Edited by:
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Reviewed by:
Susan Elizabeth Esposito, Life University, United States
Ilaria Carpinella, Fondazione Don Carlo Gnocchi Onlus (IRCCS), Italy
Laura Avanzino, Università di Genova, Italy

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *29 April 2017*
Accepted: *21 July 2017*
Published: *11 August 2017*

Citation:
Spasojević S, Ilić TV, Stojković I, Potkonjak V, Rodić A and Santos-Victor J (2017) Quantitative Assessment of the Arm/Hand Movements in Parkinson's Disease Using a Wireless Armband Device. Front. Neurol. 8:388. doi: 10.3389/fneur.2017.00388

We present an approach for quantitative assessment of the arm/hand movements in patients with Parkinson's disease (PD), from sensor data acquired with a wearable, wireless armband device (Myo sensor). We propose new *Movement Performance Indicators* that can be adopted by practitioners for the quantitative evaluation of motor performance and support their clinical evaluations. In addition, specific *Movement Performance Indicators* can indicate the presence of the bradykinesia symptom. The study includes seventeen PD patients and sixteen age-matched controls. A set of representative arm/hand movements is defined under the supervision of movement disorder specialist. In order to assist the evaluations, and for progress monitoring purposes, as well as for assessing the amount of bradykinesia in PD, a total set of 84 *Movement Performance Indicators* are computed from the sensor readings. Subsequently, we investigate whether wireless armband device, with the use of the proposed *Movement Performance Indicators* can be utilized: (1) for objective and precise quantitative evaluation of the arm/hand movements of Parkinson's patients, (2) for assessment of the bradykinesia motor symptom, and (3) as an adequate low-cost alternative for the sensor glove. We conducted extensive analysis of proposed *Movement Performance Indicators* and results are indicating following clinically relevant characteristics: (i) adequate reliability as measured by ICC; (ii) high accuracy in discrimination between the patients and controls, and between the disease stages (support to disease diagnosis and progress monitoring, respectively); (iii) substantial difference in comparison between the left-hand and the right-hand movements across controls and patients, as well as between disease stage groups; (iv) statistically significant correlation with clinical scales (tapping test and UPDRS-III Motor Score); and (v) quantitative evaluation of bradykinesia symptom. Results suggest that the proposed approach has a potential to be adopted by physicians, to afford them with quantitative, objective and precise methods and data during clinical evaluations and support the assessment of bradykinesia.

Keywords: Parkinson's disease, wireless sensors, arm/hand movements, bradykinesia, movement performance indicators

1. INTRODUCTION

Contemporary approach to evaluation of the patient's condition in Parkinson's disease (PD), as well as assessment of the rehabilitation effectiveness, is based on the clinical assessment tools and evaluation scales, such as Hoehn and Yahr (HY) (1) and Unified Parkinson's Disease Rating Scale (UPDRS) (2). However, although beneficial and commonly used, those scales are descriptive (qualitative), primarily intended to be carried out by a trained neurologist, and are prone to subjective rating and imprecise interpretation of patient's performance.

Recent developments in the field of affordable sensing technologies have a potential to improve and support traditional evaluation techniques, aiming at defining quantitative movement indicators to assist practitioners and clinicians. Various types of wearable sensors have been proposed in the literature for the measurement and assessment of the arm/hand movements: accelerometers (3, 4), gyroscopes (5, 6), magnetic sensors (7, 8), force sensors (9, 10), and inertial sensors (11). However, these sensor systems only modestly contribute to the arm/hand movement assessment. Specifically, the use of one or two isolated sensors in motion acquisition restricts the movement quantification, due to the limited amount of the collected data.

More informative sensors are the ones that measure muscle activity, and the standard approach for obtaining the muscle activity information is the placement of the surface Electromyography (EMG) electrodes on the skin, which detect the electrical potential generated by muscles. The main drawback of the standard EMG electrodes is the wired connection with a device for EMG signal representation. Consequently, muscle activity tests are available only in the hospital environment. The analysis of the muscle activity is reported in some recent studies concerning PD (12–14). The authors in Ref. (12, 13) particularly observe the muscles' behavior during deep brain stimulation. They report that Parkinson's disease symptoms change the EMG signal properties and suggest that EMG analysis is able to detect differences between the deep brain stimulation settings. The authors in Ref. (14) use the EMG data, along with the readings from the accelerometer, to successfully differentiate essential tremor from Parkinson's disease. However, all these studies collect the EMG data using surface electrodes relying on the wired system.

The authors have suggested many different features to characterize the EMG signals in the time domain (13–21) and frequency domain (15, 16, 19, 21). The two most common approaches for the EMG signal analysis are the wavelet transform (14, 21) and the window approach (15, 19). In our study, we have adopted the window approach and the features suggested in the literature that emphasize the amplitude characteristics of the EMG signal. Such choice has been convenient for our case as it will be explained in detail in the Results section.

In our previous studies (22, 23), we have used a vision-based sensor (Kinect device) to quantify full-body movements (gait and large-range upper body movements) and a sensor glove (CyberGlove II device) to quantify hand movements of Parkinson's patients. We proposed novel scores called Movement Performance Indicators that were extracted directly from the sensor data and quantify the symmetry, velocity, and acceleration of the movement of different body/hand parts. Our approach for the hand movement characterization, based on the sensor glove data, has demonstrated significant results and ability to support the diagnosis and monitoring evaluations in PD (23). Still, due to the high cost, it does not fit into our concept of a low-cost rehabilitation system for movement analysis. Another limitation arises from the right-hand design of the sensor glove device. This implies that only right-hand movements can be tested; and hence, only right side affected patients are taken into account. Consequently, left–right side analysis cannot be conducted as an important indicator of the disease progression.

In this study, we focus on quantification of the arm/hand movements from measurements acquired with a wireless wearable armband device—the Myo sensor,[1] in order to investigate whether the armband sensor can assess fine movements and be used as a suitable alternative to the sensor glove. This device is placed on the forearm and outputs Electromyography (EMG) data from eight channels. EMG data provide insight into the muscle activity information. Impaired muscle activity and restriction of motor functions are common characteristics of PD. The armband device contains also three-axis accelerometer and three-axis gyroscope, which output acceleration and angular velocity information (Inertial Measurement Unit (IMU) data), respectively.

The accelerometer and gyroscope have been widely tested in studies related to PD and showed significant potential toward quantification of PD symptoms (14, 24–26). The authors in Ref. (24) use accelerometers, while the authors in Ref. (26) use both, accelerometers and gyroscopes, to observe the gait characteristics in PD patients. They state that freezing of the gait episodes can be detected using sensor data, along with the feedback about gait performance. The study (25) focuses on the quantification of bradykinesia from finger-tapping movement using two gyroscopes placed on the fingers. Although the results of bradykinesia quantification using gyroscope data are promising, the analysis is limited to one movement and two sensors. The overall conclusion is that signals from accelerometer and gyroscope demonstrate meaningful patterns in the patient's movements and reveal the presence/intensity of the disease motor symptoms. Like in the case of EMG signals, we concentrate on the signal features from accelerometer and gyroscope that take into account the signal amplitude characteristics.

The wireless armband device has been launched very recently and only a few conceptual studies report some preliminary results concerning its inclusion into medical protocols (27–29). However, to the best of our knowledge, it has not been previously used in any study regarding the quantification of the arm/hand movements in PD assessment.

Our study overcomes the scope of conceptual studies published so far, by introducing the comprehensive processing modules and interpretation of the sensor measurements from armband device. We propose new scores for the arm/hand movement characterization denoted as Movement Performance Indicators (hereinafter, MPIs). The MPIs are intended to support diagnosis

[1] https://www.myo.com/.

and monitoring evaluations, as well as the assessment of the motor symptoms, with a special emphasis on bradykinesia. The MPIs we propose are built upon both domain-specific knowledge (provided by movement disorder specialist), as well as data analysis. They are primarily designed in accordance with clinically relevant aspects and tested toward official clinical tests and scales. We thus propose an affordable, reliable, and portable sensor system along with an approach for movement quantification, with the potential to be used as a support for the conventional motor performance evaluations and the possibility of home rehabilitation.

In this article, we present extensive experiments and analysis conducted to address the following aspects: (1) quantitative evaluation of the arm/hand movements of Parkinson's patients, (2) objective assessment of bradykinesia motor symptom, and (3) investigation whether the armband sensor can be an adequate low-cost alternative for the sensor glove, due to its high cost. Aspects addressed in (1) and (2) are worth to be investigated in the treatment of Parkinson's disease, but their direct assessment is not possible considering the limited resources and standard techniques used by doctors.

2. MATERIALS AND METHODS

2.1. Participants

Seventeen Parkinson's disease patients (age = 63.5 ± 8.3,[2] disease duration = 4.7 ± 2.5, HY[3] disease stage = 2.59 ± 0.93, UPDRS-III[4] = 31.82 ± 15.43 during ON-period) have been tested in this study. Patients are examined during their first ON-period in the morning. For ten patients, the right hand is affected by the disease, while seven patients have the left hand affected. A control group is formed by sixteen age-matched volunteers without any history of neurological or movement disorder. All subjects have been examined under the same conditions and instructed by a neurologist and therapists. This study was approved by the local ethics committee according to the Declaration of Helsinki. After the experimental procedures were explained, all subjects signed written informed consent forms.

2.2. Experimental Protocol

The experimental protocol, designed by the movement disorder specialists (**Table 1**; **Figure 1**), includes six exercises performed with the left and right hand: four arm/hand movements and two tapping test movements, well-established experimental paradigm designed for bradykinesia assessment (30). The tested movements are chosen to closely reflect the patient's activities of daily living that engage forearm muscles. The movements have been performed with the left and right hand, respectively, and acquired using the armband sensor. The subjects were instructed to perform the movements as fast as possible.

[2]Statistics are shown as *mean* ± *SD*.

[3]Parkinson's disease stadium according to Hoehn & Yahr clinical scale (1).

[4]Evaluation of the motor performance according to the Unified Parkinson's Disease Rating Scale, section III—motor scores (2).

TABLE 1 | Acquired movements according to the experimental protocol and their acronyms used in the article.

	Movements acquired according to the experimental protocol	Acronyms used in the article
1.	**R**otation of the **H**and with **E**lbow **E**xtended	RH-EE
2.	**R**otation of the **H**and with **E**lbow **F**lexed at 90°	RH-EF
3.	Object **G**rasping, **P**ick and **P**lace in the case of **E**asy **L**oad	GPP-EL
4.	Object **G**rasping, **P**ick and **P**lace in the case of **H**eavy **L**oad	GPP-HL
5.	The **P**roximal **T**apping **T**ask	TT-P
6.	The **D**istal **T**apping **T**ask	TT-D

The medical procedure adopted in PD analysis includes a set of movements/exercises, in order to allow doctors to make a qualitative evaluation of the disease stage and progress. The first two exercises emulate the bulb screwing/unscrewing in two variations: *Rotation of the Hand with Elbow Extended* (**RH-EE**, **Figure 1A**) and *with Elbow Flexed* at 90° (**RH-EF**, **Figure 1B**). Those movements were acquired during the period of 10 s. The following two exercises relate to the object *Grasping, Pick and Place in the case of Easy Load* (**GPP-EL**, **Figure 1C**) and *Heavy Load* (**GPP-HL**, **Figure 1D**). Those movements were repeated five times. The last two exercises represent the tapping test. The test consists of the proximal and distal tapping tasks using a specially designed board as the one proposed in Ref. (30). *The Proximal Tapping Task* refers to the alternate pressing of two large buttons located 20 cm apart with the palm of the hand, during the 30 s interval (**TT-P**, **Figure 1E**). *The Distal Tapping Task* is related to the alternate pressing of two closely located buttons (3 cm apart) with the index finger while the wrist is fixed on the table during 30 s (**TT-D**, **Figure 1F**). The acquired data consist of: (i) EMG data from 8 channels (sensor data rate 200 Hz) and (ii) three-axes IMU data—acceleration and angular velocity (sensor data rate 50 Hz).

The armband sensor consists of eight EMG channels labeled as shown in **Figure 2A**. During the experiments, the sensor was placed in the same position for every subject (**Figure 2B**, right hand). It can be seen that for the right-hand channels 3, 4, and 5 cover the upper forearm (extensors muscles), channels 7, 8, and 1 are placed on the lower forearm (flexors muscles), channel 2 covers the external forearm muscles, while the channel 6 is placed on the internal forearm muscles. As for the left hand, extensors and flexors are covered with the same groups of channels, while the channels 2 and 6 are replaced between internal (channel 2) and external (channel 6) forearm muscles.

2.3. Data Processing

In this section, we explain the design of the seven basic measurements, based on which MPIs are grounded. The choice of the basic measurements is based on the properties of the sensor signals in the time domain (signal amplitude). The readings from the EMG electrodes, as well as outputs from an accelerometer and gyroscope, are used for movement characterization.

Before the basic measurements calculation, the signals are preprocessed to remove the measurement noise and for performing temporal segmentation. In our experiments, all signals were filtered with regular Butterworth low pass filter. Cutoff frequencies

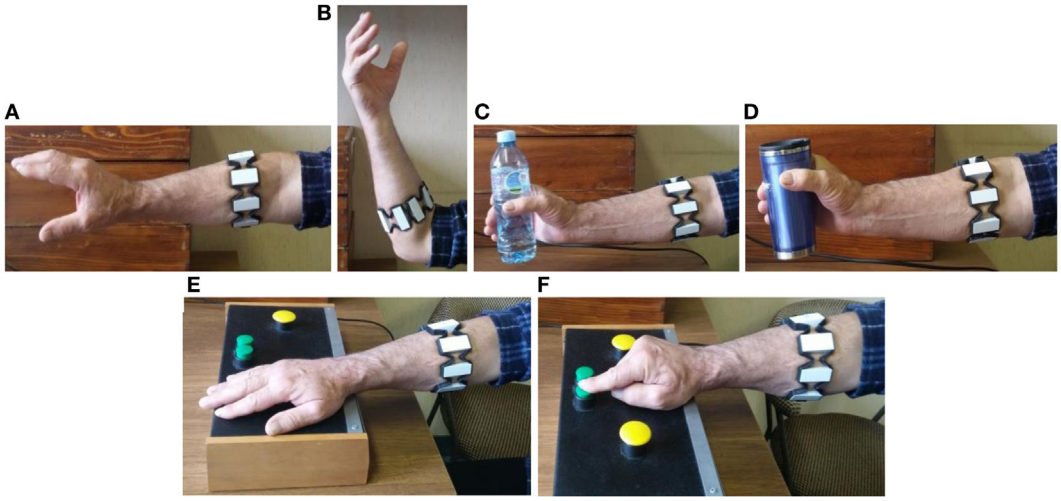

FIGURE 1 | Movements acquired according to the experimental protocol: RH-EE **(A)**, RH-EF **(B)**, GPP-EL **(C)**, GPP-HL **(D)**, TT-P **(E)**, and TT-D **(F)**.

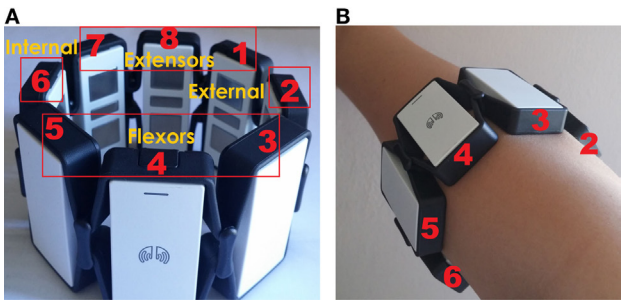

FIGURE 2 | Labeled channels of the armband sensor **(A)** and armband sensor placement on the right hand during experiments **(B)**.

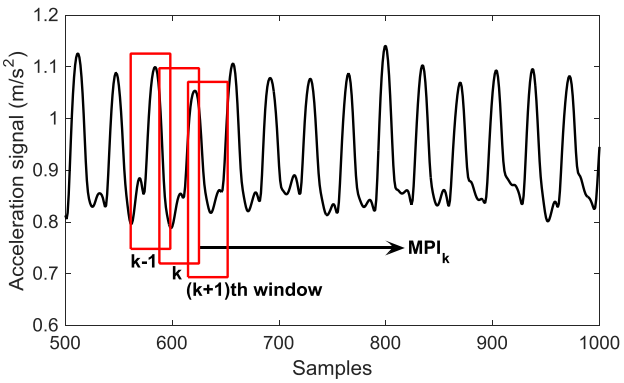

FIGURE 3 | Window approach for basic measurements extraction illustrated for the case of the acceleration signal.

and order of the filter were chosen in accordance with the signal sampling rate and the frequency characteristic of the meaningful signal content. EMG signals are filtered using 4th order filter with cutoff frequency of 20 Hz. As for the accelerometer and gyroscopes signals, the cutoff frequency is set to 5 Hz and filter order to 3. The segmentation procedure is required in order to remove the non-informative signal parts at the beginning and at the end of the signals. For this purpose, the threshold based on the signal energy in the time domain has been adopted (0.4 times the maximum signal energy).

Since the EMG signals are highly non-stationary, the most common approach for the processing of the EMG signals is the window approach (15, 19). This method implies the temporal segmentation of the signal into sliding windows and calculating the particular value of basic measurements for each separate window (**Figure 3**). The same technique has been applied to the signals obtained from the accelerometer and gyroscope. The main benefit of the window analysis is to characterize the temporal evolution of basic measurements during the movement.

Different lengths of the window and overlapping segment are tested and the results were not sensitive to those choices of the length. We set the window length to 200 ms for EMG signals and 800 ms for signals from accelerometer and gyroscope. The length of the overlapping segment usually amounts 25–50% of the window length as suggested in Ref. (15, 19). We choose the length of the overlapping segment as 25% of the window size, hence 50 ms for EMG signals and 200 ms for signals from accelerometer and gyroscope.

2.3.1. Quantification of the EMG Signals

Various measurements have been proposed in the literature for characterization of the EMG signal (15–19). Our choice of suitable basic measurements from EMG signal relies on the signal amplitude properties; hence, we tested amplitude-based measurements that are most often used in the literature. Thus, we have quantified obtained EMG signals using the Mean Absolute Value (**Emg-mav**) (1), Variance (**Emg-var**) (2), and Waveform

Change (**Emg-wc**) (3). In equations (1)–(3), W_n represents the window length, expressed in signal samples.

$$Emg_{MAV} = \frac{1}{W_n}\sum_{t=1}^{W_n} |EMG(t)| \quad (1)$$

$$Emg_{VAR} = \frac{1}{W_n}\sum_{t=1}^{W_n} EMG(t)^2 \quad (2)$$

$$Emg_{WC} = \sum_{t=1}^{W_n-1} |EMG(t+1) - EMG(t)| \quad (3)$$

2.3.2. Quantification of the Signals from an Accelerometer and Gyroscope

The accelerometer (ACC) and gyroscope (GYRO) signals are quantified using the same time-window approach as for EMG signals. The choice of basic measurements is different, in accordance with the signal characteristics and the properties of its transformations (such as signal derivative). The accelerometer and gyroscope signals are not processed in their original form. Instead, the basic measurements are extracted from their time-derivatives since the signal derivative enlarges the differences between controls and patients. Extracted basic measurements are *Simple Square Integral* (**SSI**) and *Range* (**RAN**), given by equations (4) and (5), respectively, where $\dot{x}(t)$ represents the accelerometer or gyroscope signal derivative.

$$(Acc/Gyro)_{SSI} = \sum_{t=1}^{W_n} \dot{x}(t)^2 \quad (4)$$

$$(Acc/Gyro)_{RAN} = max(\dot{x}(t)) - min(\dot{x}(t)), \quad t \in \{1, W_n\} \quad (5)$$

The above specified basic measurements are directly related to the signal amplitude—larger amplitude indicates larger value of basic measurements defined by equations (4) and (5).

2.4. Data Analysis

The MPIs are designed to emphasize the largest differences between patients and controls. We investigate whether the EMG data from particular channels are more discriminative than others. The comparative statistical analysis between patients and controls across six collected movements and eight EMG channels has been conducted using Wilcoxon rank sum test. In addition, we consider the difference of the group mean values as an indicator of the difference between groups of interest.

The same statistical test is conducted for accelerometer and gyroscope sensor data. They have three axes and depending on the particular movement, the data from one axis are more relevant than the data from the remaining two. Consequently, for each movement, corresponding axis of interest is adopted based on the statistical analysis using Wilcoxon rank sum test and comparison between group mean values.

2.4.1. Reliability Analysis

In order to test the reliability of the extracted MPIs, the split-half method for reliability analysis (31) has been applied. The split-half method divides the conducted tests into two parts and correlates the scores on one-half of the test with scores on the other half of the test. Thus, the split-half method estimates the reliability based on the repetitions inside the same trial. Reliability of the extracted MPIs is assessed using *Intraclass Correlation Coefficient* (**ICC**) (31). ICC has a value inside range [0–1], whereby the values closer to 1 indicate higher reliability.

2.4.2. Dimensionality Reduction

Finding lower dimensional representations which still preserve the most relevant information contained in the original data is key for many machine learning and data mining applications. It results in reduced data needs, reduced computational cost for algorithms, and often even increases the predictive performance of the learned models. Therefore, we have used two popular approaches for dimensionality reduction and feature selection, LDA (32) and LASSO regression (33), to find most relevant MPIs. LDA is a dimensionality reduction approach which finds the most discriminative principal components (linear combination of features), but can also rank the features by their importance. LASSO regression performs feature selection by assigning zero weights to less relevant features, giving them zero influence on the targeted outcome. Theoretically, the LASSO regression is more adequate to non-Gaussian type of data than LDA, but in practice they have similar predictive performance. Both algorithms have the same computational complexity, cubic in the number of features ($O(k^3)$) and linear in the number of examples ($O(k^{3*}n)$), where k is the number of features and n is the number of examples.

2.4.3. Classification

We want to investigate how designed MPIs can be used to differentiate between the groups of interest. We analyze two distinct classification problems in order to support the diagnosis (patients against controls) and progress monitoring (disease stages). The diagnosis task is posed as discriminating the PD patients from the healthy controls, based on the measured values of MPIs, which is a well-known binary classification problem. We define the monitoring task as discerning among the three severity stages in PD patients, which is the multiclass classification problem. Multi-class disease stage classification problem we reduced to three simple binary classification problems, one for each stage, in a common "one vs all" manner (34).

To obtain the desired classifiers for diagnostic and monitoring purposes, we employed six common classification approaches: Logistic Regression, Decision Trees, Support Vector Machines (with RBF kernel), K-nearest neighbors (with number of nearest neighbors $k = 10$), Naive Bayes, and Neural Networks (multilayer perceptron with two hidden layers containing four nodes each).

2.4.4. Comparison between Right and Left Side

To investigate which MPIs illustrate the differences in the performance of the left and right hand at patients and similar performance of the both hands in controls, statistical comparison has been performed. The choice of statistical tests depends on the data distribution. We performed the Kolmogorov-Smirnov test to assess the normal distribution hypothesis. The test rejected the normal distribution hypothesis with a 0.05 significance level. Consequently, two-sided Wilcoxon rank sum test is applied between the MPI values obtained with the left and right hand. There are forty-two MPIs in total for each hand—seven different

MPIs for six movements. Three groups of interest have been considered (patients with the right side affected, patients with the left side affected and controls). For the disease stage analysis, both groups of the left and right side affected patients are additionally divided into the first three stage groups according to the Hoehn and Yahr scale (HY) (1).

The corresponding MPI is considered as relevant for the left–right side analysis between patients and controls if it satisfies the following conditions: (i) patients group: (a) if the difference between the MPI values for the left and right hand is statistically significant ($p < 0.05$) and (b) the left-hand MPI values are larger than the right-hand MPI values (for the right side affected patients) and the opposite for left-side affected patients and (ii) controls: if the difference between the MPI values for the left and right hand is not statistically significant ($p > 0.05$).

The same statistical tests were conducted for the left–right side analysis between disease stages. Statistical investigation is based on the following conditions: (i) the difference between the MPI values of the left and right hand is statistically significant ($p < 0.05$); (ii) the left-hand MPI values are larger than the right-hand MPI values (for the right side affected patients) and the opposite for left-side affected patients; and (iii) MPI values decrease with more severe disease stage, while their differences between the left and the right hand increase.

2.4.5. Correlation Analysis

The correlation analysis is carried out between the proposed MPIs and tapping test (30) and UPDRS-III clinical scale (2). The tapping-test outcomes and UPDRS-III values are obtained as a result of a neurologist's evaluation. The tapping test consists of two tapping tasks—proximal and distal tapping task explained in the Section 2.2. In the case of UPDRS-III, we take into account the general UPDRS-III score (items 18–31 of UPDRS scale (2)) and UPDRS-III subscore related to the examination of the bradykinesia in the hand movements (items 23–25 of the UPDRS scale (2)).

Correlations were calculated using Spearman correlation coefficient ρ (higher values of ρ indicate better correlation), along with the p-value. If the correlation coefficient ρ is in the range [0.5–1] and p-value less than 0.05, the corresponding MPI is correlated with the tapping test (positive correlation). On the other side, the correlation coefficient ρ between −1 and −0.5 and p-value less than 0.05, indicate the correlation of the particular MPI with UPDRS-III scale (negative correlation).

3. RESULTS

3.1. Preliminary Comparison between PD and Controls

Figure 4 illustrates the mean absolute value and the standard deviation graph of Emg-mav basic measurement (1) calculated for patients and controls across eight EMG channels for RH-EE movement. The results underline the largest mean value differences between controls and patients on the channel 2 in the case of the right-hand movements and channel 6 for the left-hand movements.

Figure 2 shows that those electrodes cover the same group of external forearm muscles in the case of both hands. In addition, channels 3 and 4 (right-hand movements) and channels 4 and 5 (left-hand movements) highlight the large differences, as well (external and upper flexor muscles). The data from all channels demonstrated statistically significant difference between patients and controls ($p < 0.01$). However, in the following analysis, we take into account channels that emphasize the largest difference between group mean values and consequently, the extraction of the basic measurements has been performed only for the signals from channel 2 for the right-hand movements and from channel 6 for the left-hand movements. The same results are confirmed for remaining EMG basic measurements (2 and 3) and all other collected movements.

Figure 5 illustrates the mean absolute value and the standard deviation graph of Acc-ran and Gyro-ran basic measurement (5) calculated for patients and controls across three axes for RH-EE movement. The results underline the largest mean

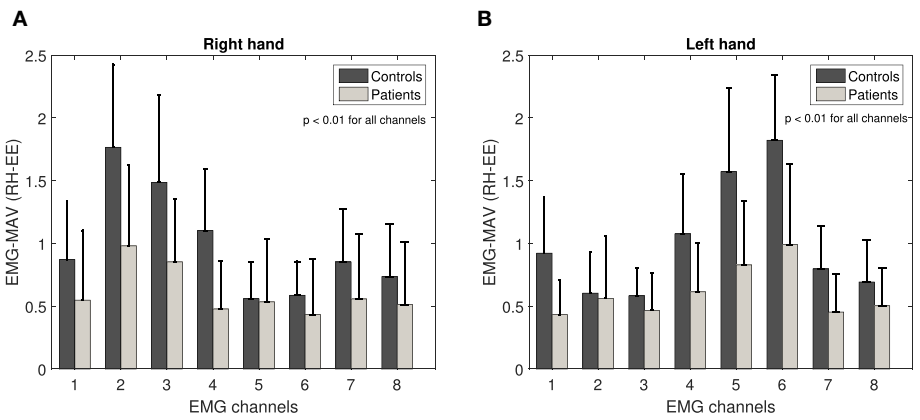

FIGURE 4 | Emg-mav basic measurement across eight EMG channels for RH-EE movement: right hand **(A)** and left hand **(B)**. Channels 2 (right hand) and 6 (left hand) underline the largest mean value difference between controls and patients.

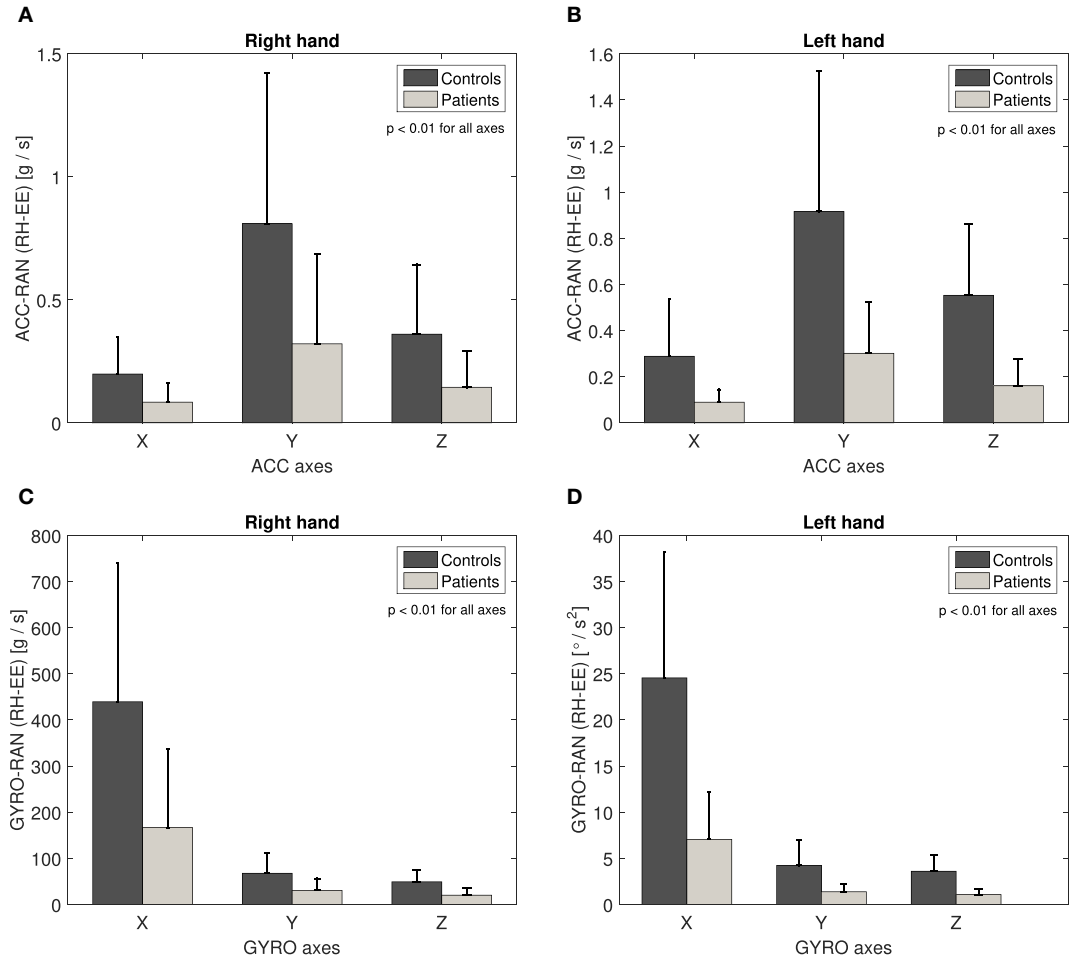

FIGURE 5 | Acc-ran basic measurement across three axes for RH-EE movement: right hand **(A)** and left hand **(B)**. *Y*-axis underline the largest mean value difference between controls and patients. Gyro-ran basic measurement across three axes for RH-EE movement: right hand **(C)** and left hand **(D)**. *X*-axis underline the largest mean value difference between controls and patients.

value differences between controls and patients on the *Y*-axis for Acc-ran and on the *X*-axis for Gyro-ran in the case of both, right- and left-hand movements. The same analysis is performed for the other ACC and GYRO basic measurement (4) and all other collected movements. In contrast to EMG channels, the axis of interest for ACC and GYRO basic measurements is different across movements, but for the particular movement, the axis of interest is the same for right and left-hand movements. The data from all axes demonstrated the statistically significant difference between patients and controls ($p < 0.01$). However, in the following analysis, for each movement, we take into account the axis that emphasizes the largest difference between group mean values.

In total, we have extracted seven basic measurements (**Table 2**) for each movement. We characterize twelve movements—six different movements (**Table 1** and **Figure 1**) were performed by both left and right hand. Consequently, based on the seven basic measurements calculated for each movement, we obtained a total set of 84 Movement Performance Indicators (MPIs) for all movements (seven basic measurements times twelve movements). The design of these MPIs was grounded on the information provided by neurologists and therapists with the goal of delivering quantitative information about subject's performance. In the following sections, we will reveal which MPIs are the most relevant and informative, from the viewpoint of the particular clinical aspects.

TABLE 2 | Calculated basic measurements.

	Calculated basic measurements	Acronyms used in the article
1.	**M**ean **A**bsolute **V**alue from **EMG** signal	Emg-mav
2.	**Var**iance from **EMG** signal	Emg-var
3.	**W**aveform **C**hange from **EMG** signal	Emg-wc
4.	**S**imple **S**quare **I**ntegral from **Acc**elerometer signal derivative	Acc-ssi
5.	**Ran**ge from **Acc**elerometer signal derivative	Acc-ran
6.	**S**imple **S**quare **I**ntegral from **Gyro**scope signal derivative	Gyro-ssi
7.	**Ran**ge from **Gyro**scope signal derivative	Gyro-ran

3.2. Reliability

The results of the reliability analysis indicate high reliability for all 84 MPIs, with ICC values in range [0.84–0.99], **Figure 6**.

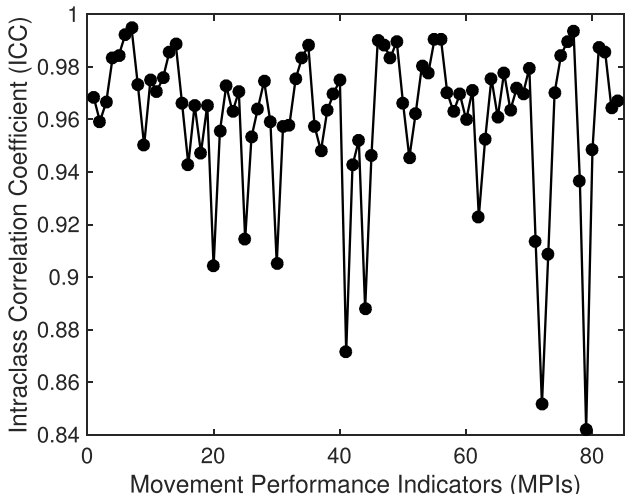

FIGURE 6 | Intraclass Correlation Coefficient (ICC) across Movement Performance Indicators (MPIs).

3.3. Quantitative Assessment of Bradykinesia Symptom

In this section, we investigate whether our proposed MPIs can reveal the presence of bradykinesia symptom in patients. Two main properties of bradykinesia symptom are (1) slowness of the movements and (2) the progressive decrease in amplitude of sequential movements (so-called "sequence effect"). **Figure 7** illustrates the bradykinesia pattern, relying on the designed MPIs. The difference in movement speed between patients and controls is demonstrated for GPP-HL movement since this movement was repeated five consecutive times during the experiment. **Figure 7A** shows the temporal evolution of the EMG-mav over window segments, for patients and controls, during the GPP-HL movement. The patients have demonstrated slower movements—they needed more time to perform five consecutive movements than controls.

In order to investigate the presence of "sequence effect" in the context of our proposed basic measurements, we analyze their evolution during the movement performance. We focus on the TT-P and TT-D movements since those movements are recorded in the period of 30 s, which enables enough sensor data for sequence effect analysis. **Figure 7C** demonstrates the temporal evolution of Emg-mav basic measurement during TT-P movement for right-hand affected patient (third disease

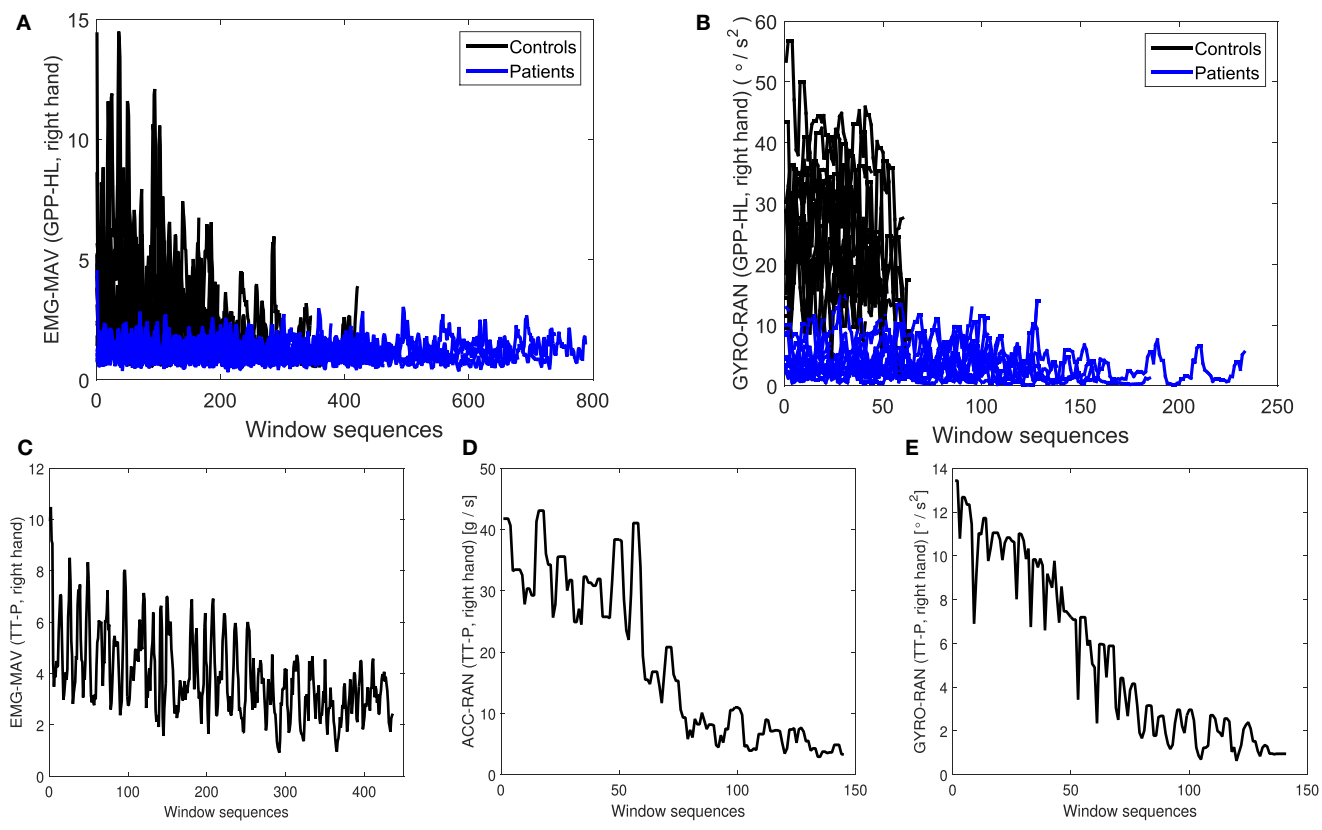

FIGURE 7 | Illustration of bradykinesia symptom: temporal evolution of **(A)** EMG-mav and **(B)** GYRO-ran during GPP-HL movement. Patients performed slower movements than controls. Temporal evolution of **(C)** EMG-mav, **(D)** ACC-ran, and **(E)** GYRO-ran during TT-P movement for patient data. The values of basic measurements sequentially drop over time (bradykinesia "sequence effect"). * *Y*-axes are labeled in the form: basic measurement(s) (performed movement, hand).

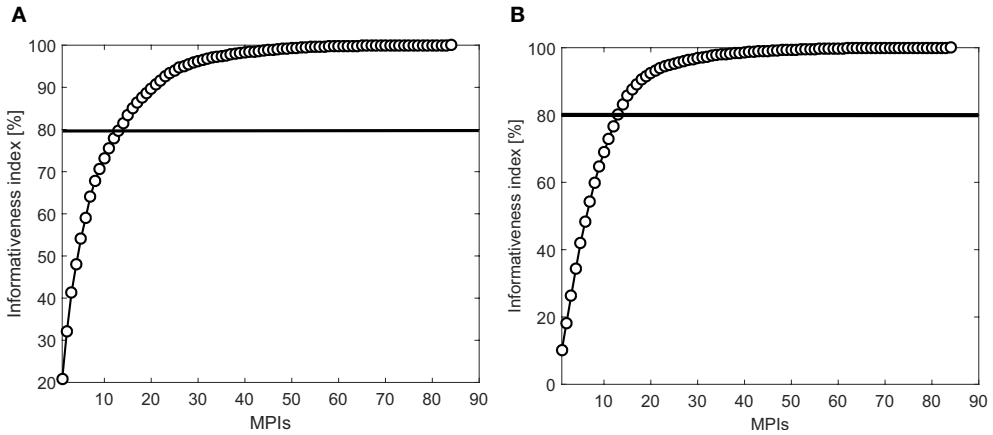

FIGURE 8 | LDA Informativeness index: **(A)** patients–controls and **(B)** disease stages.

stage according to Hoehn and Yahr (HY) (1)). The decrease of Emg-mav basic measurement over time is slow, but constant (**Figure 7C**). Such outcome suggests the presence of bradykinesia symptom.

The bradykinesia symptom is visible from the time evolution of ACC and GYRO basic measurements, as well. **Figure 7B** illustrates the temporal evolution of the Gyro-ran over window segments, for patients and controls, during the GPP-HL movement. The result is the same as in the case of EMG data—slower movements at patients are confirmed based on the evolution of Gyro-ran basic measurement over time. Bradykinesia "sequence effect" is confirmed based on the ACC and GYRO basic measurements, as well. However, the decreasing pattern is different from EMG data. ACC-ran values are significantly larger in the first-half period compared to the second-half period (**Figure 7D**). Finally, GYRO-ran basic measurement (**Figure 7E**) shows the constant and significant drop in values over time.

3.4. Dimensionality Reduction and MPIs Selection

We applied Linear Discriminant Analysis (LDA) (32) to determine the most relevant MPIs for the decision-making process based on the clinical group parameter, between patients and controls (diagnosis support) and between disease stages (monitoring support). The implementation of the LDA method is based on the procedure described in detail in our previous research (23). Information index plots (**Figures 8A,B**) show the importance of the MPIs for classification tasks from the ones most important toward less important MPIs. The LDA method results that, for keeping 80% of information from the original data set, it is sufficient to select first 13 out of 84 MPIs for both conditions: patients/controls (**Figure 8A**) and disease stages (**Figure 8B**). The selected MPIs are listed in **Table 3**. Information index plots also demonstrate that some MPIs have the negligible impact on the classification tasks. After the first 50 MPIs, adding more MPIs will not bring significant information.

TABLE 3 | The most relevant MPIs obtained by LDA approach and LASSO regression[a] (bolded MPIs are the ones selected by both approaches).

	Patients/controls		Disease stage (HY)	
#	LDA	LASSO	LDA	LASSO
1.	Gyro-ssi TT-D-R	**Gyro-ssi TT-D-L**	**Emg-mav GPP-HL-R**	**Gyro-ssi TT-D-L**
2.	**Gyro-ssi TT-D-L**	**Emg-mav GPP-EL-L**	Emg-mav TT-P-R	**Emg-mav RH-EF-R**
3.	**Emg-mav GPP-EL-L**	**Emg-mav TT-D-R**	**Gyro-ssi TT-D-L**	**Gyro-ran TT-D-L**
4.	**Emg-mav GPP-HL-R**	**Emg-mav GPP-HL-R**	**Emg-mav RH-EF-R**	**Emg-mav GPP-HL-R**
5.	**Emg-mav TT-P-R**	**Gyro-ssi GPP-EL-L**	**Gyro-ran TT-D-L**	**Emg-mav GPP-EL-R**
6.	**Gyro-ssi GPP-EL-L**	Gyro-ran GPP-HL-L	**Emg-mav GPP-EL-R**	**Emg-mav TT-D-R**
7.	**Gyro-ran TT-D-L**	**Gyro-ssi GPP-HL-R**	**Emg-mav TT-D-R**	Emg-mav RH-EE-R
8.	Gyro-ssi GPP-HL-L	**Gyro-ran GPP-EL-L**	**Emg-mav RH-EE-L**	Gyro-ran GPP-HL-R
9.	**Gyro-ran GPP-EL-L**	**Gyro-ran TT-D-L**	Emg-mav GPP-HL-L	Gyro-ran TT-D-R
10.	Gyro-ran TT-D-R	**Emg-mav TT-P-R**	Gyro-ssi GPP-HL-L	Emg-mav TT-P-L
11.	Emg-mav GPP-HL-L	Emg-mav RH-EF-L	Emg-mav RH-EF-L	**Emg-mav RH-EE-L**
12.	**Emg-mav TT-D-R**	Gyro-ssi RH-EF-D	Gyro-ran GPP-HL-L	Gyro-ran TT-P-L
13.	**Gyro-ssi GPP-HL-R**	Gyro-ssi TT-P-D	Gyro-ssi TT-D-R	Emg-mav TT-D-L

[a]*MPIs are listed in the format MPI movement-hand (R-right or L-left).*

In order to verify the results obtained by LDA, we have used the LASSO regression analysis (33), which performs both feature selection and regularization, in order to enhance the classification accuracy. Using the LASSO regression, the response variable (corresponding class of the interest—patients/controls or disease stage) is modeled as a linear combination of the MPIs (model parameters). The model parameters with strongest dependence of the response variable will have higher coefficients, while the

TABLE 4 | Performance of six classification approaches in diagnostic and monitoring tasks for two sets of MPIs.

Classifier	Original (Full) set (84 MPIs)				Selected subset (13 MPIs—LDA)			
	PD vs C	Disease stages			PD vs C	Disease stages		
		I vs. II and III	II vs. I and III	III vs. I and II		I vs. II and III	II vs. I and III	III vs. I and II
Logistic regression	1 (0)	1 (0)	1 (0)	1 (0)	0.9967 (0.0034)	0.9942 (0.0088)	0.8969 (0.0569)	0.9961 (0.0074)
Decision trees	0.9905 (0.0114)	0.9670 (0.0286)	0.9499 (0.0582)	0.9649 (0.0441)	0.9823 (0.0091)	0.9542 (0.0504)	0.8840 (0.1074)	0.9308 (0.0344)
Support vector machines	1 (0)	1 (0)	1 (0)	0.9993 (0.0022)	0.9967 (0.0039)	0.9927 (0.0072)	0.8759 (0.0835)	0.9972 (0.0028)
K-nearest neighbors	1 (0)	0.9999 (0.0002)	1 (0)	1 (0)	0.9981 (0.0039)	0.9983 (0.0031)	0.9899 (0.0140)	0.9956 (0.0077)
Naive Bayes	0.9948 (0.0037)	0.9908 (0.0078)	0.9757 (0.0269)	0.9743 (0.0202)	0.9878 (0.0056)	0.9903 (0.0060)	0.9158 (0.0371)	0.9798 (0.0170)
Neural networks	1 (0)	1 (0)	0.9997 (0.0009)	0.9978 (0.0070)	0.9923 (0.0141)	0.9910 (0.0162)	0.9769 (0.0336)	0.9971 (0.0034)

All approaches are very successful on the given tasks, although K-Nearest Neighbor and Neural Networks appear to be the best performers.

coefficients corresponding to the less important parameters will weight toward zero. In such way, we select the most important model parameters (corresponding MPIs) according to the classification task of interest. Results of both techniques, LDA and LASSO, giving the 13 most relevant MPIs (out of 84 MPIs in total), and for the classification criterion between groups of interest, are listed in **Table 3**.

Table 3 shows that the 13 most relevant MPIs (out of 84 MPIs) are Gyro-ssi, Gyro-ran and Emg-mav extracted mostly from the movements of object grasping, pick and place (GPP-EL and GPP-HL) and tapping test movements (TT-P and TT-D). The list of the most relevant MPIs is not the same in case of LDA and LASSO regression, but the majority of representative MPIs are selected by both methods (marked as bold text in **Table 3**). Such result can be a consequence of the adjustment of regularization parameter $\lambda \in [0.01–0.5]$ during Lasso regression. This parameter determines the strength of the penalty. As λ increases, more coefficients of the model are reduced to zero, hence more parameters (MPIs) are excluded from the model.

3.5. Classification: Diagnosis and Monitoring Evaluations

Classifiers were built for four tasks: (i) PD patients vs controls (PD vs C); (ii) stage I vs stages II and III PD; (iii) stage II vs stages I and III PD; and (iv) stage III vs stages I and II PD, and by using two sets of MPIs: (a) original (full) set of 84 MPIs and (b) set of 13 MPIs selected by LDA in **Table 3**. As a criterion of the classification success, the area under the ROC curve (AUC) is calculated (35). ROC curve represents the graph of the true positive rate (TPR) against the false positive rate (FPR). AUC is the calculated surface area under the ROC curve. AUC values that indicate high-performance classifiers are in the range [0.80–1]. The performance of each classifier is assessed in a (10-fold) cross-validation procedure, and the results are provided in **Table 4** in form of a *mean (standard deviation)* calculated from 10-folds.

Table 4 shows that the AUC values for all employed classification approaches are very high (near or equal to the perfect score of 1), suggesting that reliable decisions can be made by using the proposed MPIs. The most difficult task appears to be discerning the stage II patients from stages I and III PD, based on the selected subset of 13 features. However, K-Nearest Neighbor and Neural Network classifiers seem to achieve quite consistent high performance under all tested conditions. Also, using only the 13 features instead of all 84 results in just a slight reduction in performance, providing another evidence in favor of informativeness of the selected MPIs.

TABLE 5 | Relevant MPIs for the left–right side analysis across clinical groups of interest[a].

Patients/controls	Disease stages (HY)
2 EMG MPIs RH-EE	EMG-VAR RH-EF
2 EMG MPIs RH-EF	ACC MPIs RH-EF
ACC MPIs RH-EF	ACC MPIs GPP-EL
GYRO MPIs RH-EF	GYRO MPIs GPP-EL
EMG MPIs GPP-EL	ACC-RAN MPI GPP-HL
EMG MPIs GPP-HL	GYRO MPIs GPP-HL
	ACC-SSI TT-P

[a]*MPIs are listed in the format MPI movement.*

3.6. Left-Right Side Analysis

Results of the statistical analysis suggest that 14 MPIs out of 84 MPIs in total are relevant for the left-right side analysis between patients and controls (**Table 5**). Such result indicates that EMG MPIs for grasping, pick and place movements are the most relevant for the left–right side analysis, as well as MPIs extracted from the rotation of the hand movement while the elbow is flexed.

Figure 9A illustrates the mean and standard deviation graph for controls and right-side affected patients for Acc-ssi MPI (RH-EF movement). It can be seen the mean MPI values are almost the same in the case of controls, while in patients, the mean MPI value for the left hand movement is larger than for the right hand movement. Such outcome is expected, since the right side is affected by PD and consequently, has lower performance.

The results of the statistical analysis suggest that 11 MPIs out of 84 MPIs in total are relevant for the left-right side analysis between disease stages (**Table 5**). It turns out that the ACC and GYRO MPIs for RH-EF, GPP-EL, and GPP-HL are the most common MPIs to evaluate the difference in performance between left and right hand across the disease stages.

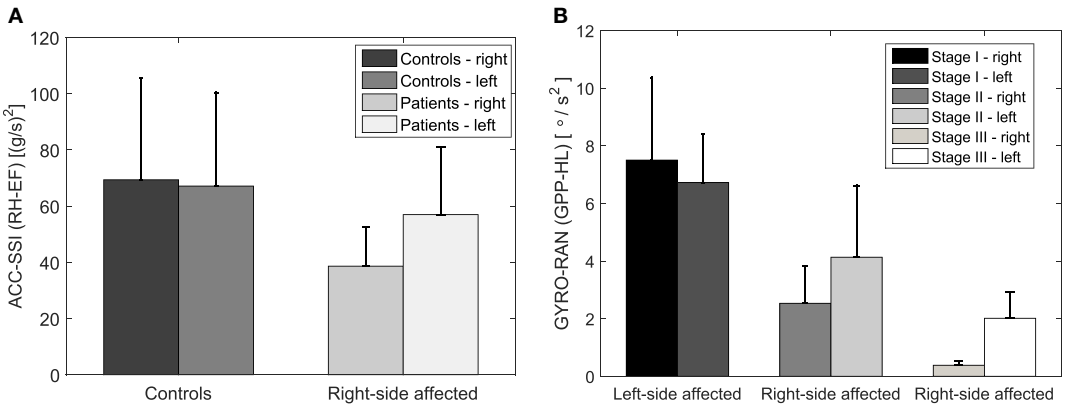

FIGURE 9 | Acc-ssi MPI (RH-EF movement) for controls and right side affected patients **(A)** and Gyro-ran (GPP-HL movement) for different disease stages **(B)**. The mean MPI values for the left and right hand are similar in controls opposite to the patients **(A)**. The mean MPI values decrease from the first to the third stage and their difference between the left- and the right-hand increases **(B)**.

Figure 9B illustrates the mean and standard deviation graph across disease stages for Gyro-ran MPI (GPP-HL movement). It can be seen that the mean MPI values decrease from the first to the third stage and their difference between the left- and the right-hand increases. Such result suggests that differences in the performance of the left and right hand become larger with the disease progression. It can be seen that in the case of the left-side affected group (first stage) the MPI values are greater for the right hand. The situation is opposite for the right-side affected group of the second and third disease stage. In both cases, MPI values are greater for the hand less affected by the disease, which is an expected outcome.

3.7. Correlations with Clinical Scales

In this section, we want to investigate whether the proposed MPIs are correlated with clinical test and scales. This is particularly important for the possible inclusion of the proposed MPIs into medical protocols. All MPIs that satisfy correlation conditions (explained in the Section 2.4.5) for the tapping test and UPDRS-III scale are listed in **Table 6**.

Scatter plots in **Figure 10** illustrate a few examples of the correlation between MPIs and clinical parameters, where the line represents the regression curve. It can be seen that the selected MPIs have a positive correlation with the tapping test (**Figures 10A,B**), more concretely with the number of taps in two cases of the tapping test (procedure of the tapping test is explained in the Section 2.2). This is expected since the patients who have higher values of MPIs potentially can achieve a larger number of taps within defined time interval (30 s). On the other side, our MPIs have a negative correlation with the UPDRS-III general score (**Figure 10C**) and subscore for bradykinesya (**Figure 10D**), since the lower values of our MPIs and higher values on UPDRS-III scale indicate a more severe state of the patient, i.e., more advanced disease stage.

Results of the correlation analysis regarding the tapping test (**Table 6**) have shown that the most correlated MPIs for both tapping tasks are the ones extracted from the tapping test movements (TT-P and TT-D). Such result is expected, since the same movements are tested during clinical protocol and our sensor measurements. Those MPIs refer to all ACC and GYRO MPIs of both, left- and right-hand movements. In addition to the tapping test movements, ACC and GYRO MPIs from the right-hand RH-EE and GPP-EL movements, as well as from the left hand

TABLE 6 | List of MPIs[a] correlated with tapping test[b] ($\rho > 0.5$, $p < 0.05$) and UPDRS-III scale[c] ($\rho < -0.5$, $p < 0.05$).

Tapping test		UPDRS-III scale	
Proximal taping task	**Distal taping task**	**UPDRS-III general**	**UPDRS-III subscore**
EMG MPIs RH-EE L	ACC MPIs RH-EE R	**EMG MPIs RH-EE R L**	**EMG MPIs RH-EE R L**
ACC MPIs RH-EE R	GYRO MPIs GPP-EL R	ACC-RAN RH-EE R	**GYRO MPIs RH-EE R L**
EMG MPIs RH-EF L	**ACC MPIs TT-P R L**	**GYRO MPIs RH-EE R L**	**EMG MPIs RH-EF R L**
ACC MPIs RH-EF R L	**GYRO MPIs TT-P R L**	**EMG MPIs RH-EF R L**	**ACC MPIs RH-EF L**
GYRO MPIs RH-EF L	**ACC MPIs TT-D L**	**ACC MPIs RH-EF L**	**GYRO MPIs RH-EF L**
GYRO MPIs GPP-EL R	**GYRO MPIs TT-D L**	**GYRO MPIs RH-EF L**	**2 EMG MPIs GPP-HL R**
ACC-RAN GPP-HL R		**2 EMG MPIs GPP-HL R**	**GYRO MPIs GPP-HL R**
EMG MPIs TT-P L		ACC-RAN GPP-HL R	**EMG MPIs TT-P L**
ACC MPIs TT-P R L		**GYRO MPIs GPP-HL R**	**ACC MPIs TT-P R L**
GYRO MPIs TT-P R L		**EMG MPIs TT-P L**	**GYRO MPIs TT-P R L**
ACC MPIs TT-D R L		**ACC MPIs TT-P R L**	ACC-RAN TT-D L
GYRO MPIs TT-D R L		**GYRO MPIs TT-P L**	GYRO-RAN TT-D L
		GYRO MPIs TT-D L	

[a]*MPIs are listed in the format MPI(s) movement hand (R-right or/and L-left).*
[b]*MPIs extracted from the tapping test movements (TT-P and TT-D) are correlated with both tapping tasks (bold text).*
[c]*MPIs correlated with both UPDRS-III scores are marked as bold text.*

RH-EF movement have high values of Spearman correlation coefficient ρ. MPIs extracted from EMG signals are mostly poorly correlated with tapping test ($\rho < 0.5, p > 0.05$), except EMG MPIs in the case of the left-hand RH-EE, RH-EF, and TT-P movements (**Table 6**).

Results of the correlation analysis regarding the UPDRS-III scale for the general score and bradykinesia subscore highlight mostly the same MPIs in both cases (**Table 6**). The most correlated MPIs are the ones extracted from the rotation of the hand movements (RH-EE and RH-EF), **Table 6**. In addition to the rotation of the hand movements, the MPIs from right hand GPP-HL and TT-P movements, as well as MPIs from the left TT-P and TT-D movements have high (absolute) values of Spearman correlation coefficient ρ. Since higher values of ρ indicate better correlation,

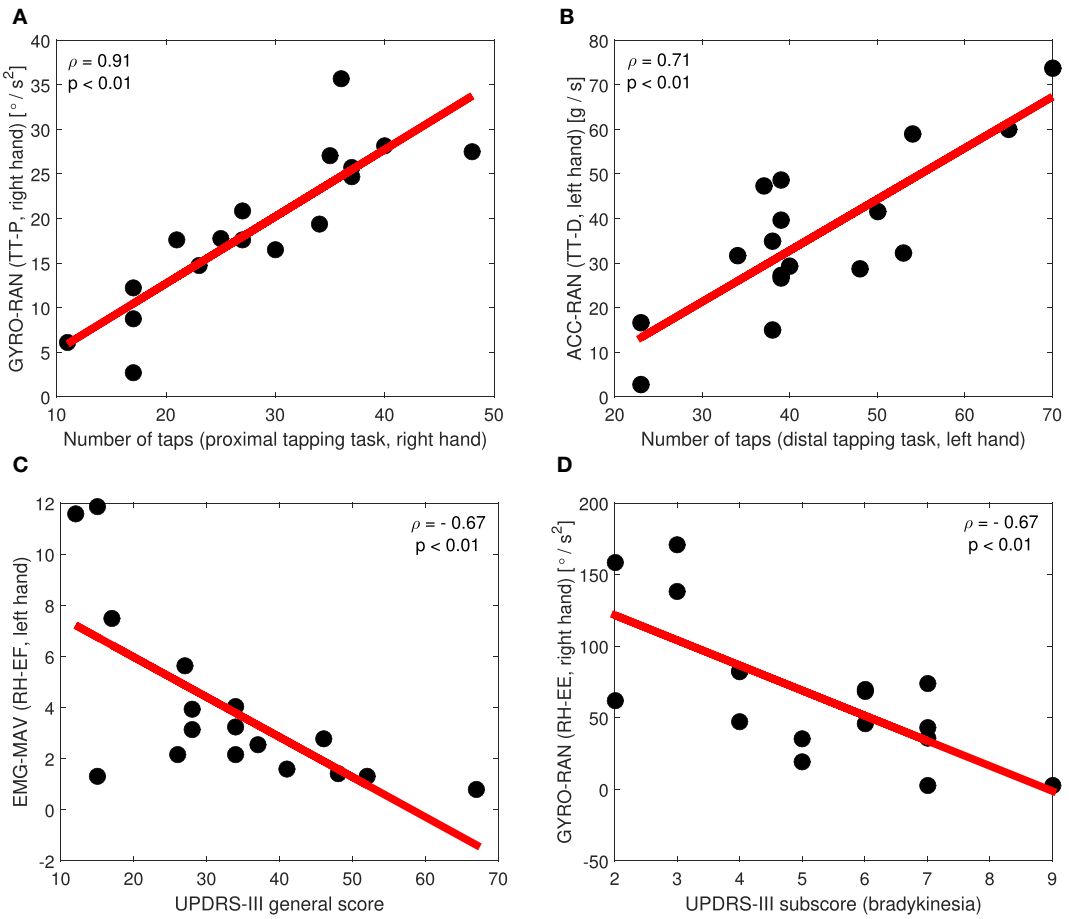

FIGURE 10 | Scatter plots of the correlation between particular MPIs and tapping test **(A,B)**, UPDRS-III general score **(C)**, and UPDRS-III bradykinesia subscore **(D)**.

TABLE 7 | Importance of the MPIs and tested movements across criterions of clinical interest.

	Criterion	MPIs							Movement (left and right hand)					
		EMG			ACC		GYRO		RH		GPP		TT	
		mav	var	wc	ssi	ran	ssi	ran	EE	EF	EL	HL	P	D
1.	Reliability	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.	Classification patients-controls LDA	✓					✓	✓			✓	✓	✓	✓
3.	Classification patients-controls LASSO	✓					✓	✓		✓	✓	✓	✓	✓
4.	Classification disease stages LDA	✓					✓	✓	✓	✓	✓	✓	✓	✓
5.	Classification disease stages LASSO	✓					✓	✓	✓	✓	✓	✓	✓	✓
6.	Left-right side analysis patients-controls	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
7.	Left-right side analysis disease stages		✓		✓	✓	✓	✓		✓	✓	✓	✓	
8.	Correlation—tapping test				✓	✓	✓	✓	✓	✓	✓		✓	✓
9.	Correlation—UPDRS-III	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	

those MPIs are very good in terms of correlation with UPDRS-III scale.

3.8. Summary

Table 7 summarizes the importance of the MPIs and tested movements across nine criterions of clinical interest. Gyro-ssi and Gyro-ran MPIs are relevant according to all criterions. Particular EMG MPIs are important for the classification aspect and left–right side analysis (both conditions—patients vs. controls and disease stages), while the ACC MPIs are of interest for the left–right side analysis and correlation with clinical scales. Among tested movements, object grasping, pick, and place (both variations—easy and heavy load) turn out to be the most relevant for listed clinical aspects. Reliability analysis has demonstrated the high reliability for all proposed MPIs across all movements (**Table 7**).

4. DISCUSSION AND CONCLUSION

In recent studies, the use of an armband device has been considered for medical and rehabilitation applications, especially for physiotherapy healthcare (27) and recovery after the stroke (28). The authors in Ref. (27) use MYO Diagnostics application for medical diagnosis and to understand how comfortable subjects feel while performing the movements using the armband device. The study (28) proposes a low-cost rehabilitation system for recovery after the stroke, which consists of an armband device and a data glove. The authors present just the concept of a rehabilitation system based on the virtual environment and gaming to enhance the patient's motivation. Both studies (27, 28) lack the signal processing, feature extraction analysis, and decision-making procedure behind the interface.

In Ref. (29) the authors propose a multi-sensory gesture-based occupational therapy system, which consists of a Kinect v2, a Leap motion sensor and a Myo armband device. The system is intended to support the everyday activities in the home environment and to encourage the patients to practice and obtain the feedback about their movement performance during usual daily routines. Again, as in Ref. (27, 28) only the concept of the system is presented, along with the general implementation details.

Lack of the sensor signal analysis and processing toward the extraction of the meaningful signal features, as well as the development of the clinically-oriented approaches based on the sensor movement data, are the main drawbacks of the related studies. We have used a wireless armband sensor to acquire arm/hand movements defined by the PD protocol. We propose a set of 84 Movement Performance Indicators (MPIs) to characterize acquired movements. We conducted a thorough analysis of the properties of these MPIs, to identify their importance in terms of relevant clinical aspects (**Table 7**): (i) reliability; (ii) classification between patients and controls and between disease stages (support to diagnosis and monitoring, respectively); (iii) left–right side analysis between controls and patients, as well as between disease stage groups; and (iv) correlation with clinical scales (tapping test and UPDRS-III). The overall conclusion is that Gyro-ssi and Gyro-ran MPIs are relevant according to all clinically relevant criterions. Particular EMG MPIs are important for the classification aspect and left–right side analysis, while the ACC MPIs are of interest for the left–right side analysis and correlation with clinical scales.

This study complements our previous research (23) with an approach for quantitative movement analysis, based on the arm/hand movement data acquired with an EMG sensor. Our results show that the proposed approach has the potential to be adopted by therapists, to enhance objectivity and precision, during the diagnosis/monitoring evaluations and bradykinesia assessment. At the same time, it opens the possibility of the low-cost assessment tool for patients with the mild to moderate PD stages (I–III according to the modified HY clinical scale).

The armband electromyographic sensor is worn on the forearm and collects the data from the four groups of muscles—flexors, extensors, internal, and external forearm muscles (Section 2.2, **Figure 2**). One very important conclusion is that external forearm muscles of both hands in PD patients have demonstrated the lowest performance of all forearm muscles in the sense of the muscle activity compared with a control group. This result suggests that external forearm muscles are the most affected by the Parkinson's disease. Such result is derived from our sensor data but requires additional clinical testing and confirmation.

In the Parkinson's disease, one side of the body is more affected than the other. Furthermore, the first symptoms of the disease are observed on a particular body side. Along with the disease progress, both sides become affected, but the side on which PD symptoms were first detected, is always affected more. The quantitative assessment of the difference between left and right side of the body would be significant information for the neurologists, since they cannot evaluate it directly or using subjective clinical scales. Consequently, we investigated the differences in the movement performance with left and right hand, relying on the proposed MPIs. Our finding is that those differences are negligible in control subjects, while they can become quite large for Parkinson's patients, depending on the disease stage.

Collected sensor data in the context of designed MPIs have revealed the bradykinesia patterns in patient movement data. The slowness of the movement and sequential drop of the amplitude over time (so-called "sequence effect") are visible from the MPIs temporal evolution. Such results indicate the potential of our proposed MPIs to be used by therapists for quantitative assessment of bradykinesia.

Finally, we conclude that sensor data collected from the wireless armband device successfully addressed the same set of relevant aspects in PD like the sensor glove data in our previous research (23). Even more, in this study, we have performed the left–right side analysis, which is not feasible with the sensor glove data, due to its right-hand design. Consequently, our results suggest that the wireless armband sensor can be a possible alternative for high-cost data glove that we used in our previous research. However, the experimental setup, tested movements and extracted Movement Performance Indicators (MPIs) are different in accordance with sensor choice. The advantage of the sensor glove data over the armband device is the quantification of the fine finger movements.

One limitation of the study is the collection of the sensor measurements during the ON-stage only. It would be worth to investigate the movement data characteristics during OFF-stage. The number of subjects and tested movements could be extended in the future. Finally, MPIs proposed in this study are the result of the signal processing in the time domain. Additional MPIs could be extracted from the frequency domain of the sensor signals.

In the future work, we will focus on another important aspect of Parkinson's disease—balance and stability. We are considering using a low-cost device with sensors of pressure for balance quantification. Furthermore, we plan to test our system on patients recovering from the stroke.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Declaration of Helsinki and the Ethics Committee of the Medical Faculty of Military Medical Academy, University of Defence (Belgrade, Serbia) approved the present study. After the experimental procedures were explained, all subjects signed written informed consent forms.

AUTHOR CONTRIBUTIONS

SS, TI, and JS-V designed the study; SS and TI collected the data; SS processed the data; SS and IS analyzed the data; SS wrote the manuscript; and TI, IS, VP, AR, and JS-V revised the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank all volunteers who were willing to participate in this study.

FUNDING

This work is partially funded by the Ministry of Education, Science and Technology Development of the Republic of Serbia under the contracts TR-35003, III-44008, III-44004, #ON175012 and by the Ministry of Defense of the Republic of Serbia MFVMA/7/16-18. This work was partially funded by the EU Project POETICON++ and the Portuguese FCT Project [UID/EEA/50009/2013]. The work is complementary supported by the Alexander von Humboldt project "Emotionally Intelligent Robots—EIrobots," Contract no. 3.4-IP-DEU/112623.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 July 2017
doi: 10.3389/fneur.2017.00361

Investigation of Anticipatory Postural Adjustments during One-Leg Stance Using Inertial Sensors: Evidence from Subjects with Parkinsonism

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The One-Leg Stance (OLS) test is a widely adopted tool for the clinical assessment of balance in the elderly and in subjects with neurological disorders. It was previously showed that the ability to control anticipatory postural adjustments (APAs) prior to lifting one leg is significantly impaired by idiopathic Parkinson's disease (iPD). However, it is not known how APAs are affected by other types of parkinsonism, such as frontal gait disorders (FGD). In this study, an instrumented OLS test based on wearable inertial sensors is proposed to investigate both the initial anticipatory phase and the subsequent unipedal balance. The sensitivity and the validity of the test have been evaluated. Twenty-five subjects with iPD presenting freezing of gait (FOG), 33 with iPD without FOG, 13 with FGD, and 32 healthy elderly controls were recruited. All subjects wore three inertial sensors positioned on the posterior trunk (L4–L5), and on the left and right frontal face of the tibias. Participants were asked to lift a foot and stand on a single leg as long as possible with eyes open, as proposed by the mini-BESTest. Temporal parameters and trunk acceleration were extracted from sensors and compared among groups. The results showed that, regarding the anticipatory phase, the peak of mediolateral trunk acceleration was significantly reduced compared to healthy controls ($p < 0.05$) in subjects with iPD with and without FOG, but not in FGD group ($p = 0.151$). Regarding the balance phase duration, a significant shortening was found in the three parkinsonian groups compared to controls ($p < 0.001$). Moreover, balance was significantly longer ($p < 0.001$) in iPD subjects without FOG compared to subjects with FGD and iPD subjects presenting FOG. Strong correlations between balance duration extracted by sensors and clinical mini-BESTest scores were found ($\rho > 0.74$), demonstrating the method's validity. Our findings support the validity of the proposed method for assessing the OLS test and its sensitivity in distinguishing among the tested groups. The instrumented test discriminated between healthy controls and people with parkinsonism and among the three groups with parkinsonism. The objective characterization of the initial anticipatory phase represents an interesting improvement compared to most clinical OLS tests.

Keywords: Parkinson's disease, frontal gait disorders, anticipatory postural adjustments, wearable sensors, balance control, unipedal balance, single-leg stance

OPEN ACCESS

Edited by:
Antonio Suppa, Sapienza Università di Roma, Italy

Reviewed by:
Massimiliano Pau, Università degli studi di Cagliari, Italy
Pedro J. Garcia-Ruiz, Hospital Universitario Fundación Jiménez Díaz, Spain

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *30 April 2017*
Accepted: *07 July 2017*
Published: *25 July 2017*

Citation:
Bonora G, Mancini M, Carpinella I, Chiari L, Ferrarin M, Nutt JG and Horak FB (2017) Investigation of Anticipatory Postural Adjustments during One-Leg Stance Using Inertial Sensors: Evidence from Subjects with Parkinsonism. Front. Neurol. 8:361. doi: 10.3389/fneur.2017.00361

INTRODUCTION

Ability to control anticipatory postural adjustments (APAs) prior to lifting one leg while standing in unsupported equilibrium represents a complex motor task that is significantly impaired by idiopathic Parkinson's disease (iPD) (1, 2). Two types of parkinsonism, such as iPD and frontal gait disorders (FGD, also called lower body parkinsonism or vascular parkinsonism), result in similar tendencies to freeze with gait initiation, to walk with short, shuffling steps, and to fall frequently (3–7). However, it is not known how FGD affects APAs. The effects of different types of parkinsonism on APAs may differ because people with iPD stand and walk with a narrow base of support whereas people with FGD stand and walk with wider than normal base of support (8, 9). APAs prior to voluntary movement are known to improve with improvements in bradykinesia from levodopa replacement therapy in patients with iPD (2). In contrast, levodopa seldom improves lower body bradykinesia in FGD so the postural deficits in these two types of parkinsonism likely have different underlying mechanisms (9, 10).

Anticipatory postural adjustments may also differ in iPD with freezing of gait (FOG) compared with iPD without FOG. Freezing, associated with the impression that the feet are "glued to the floor" can be associated with multiple, large APAs (11, 12). In fact, it has been hypothesized that FOG is due to lack of inhibition of repetitive APAs prior to a step, resulting in "trembling of the knees" (12). FOG eventually affects 80% of people with iPD and is associated with reduced white matter tracks in the right-sided, inhibitory circuitry between the supplementary motor cortex and the subthalamic nucleus of the basal ganglia (6). APAs prior to single-leg stance have not been compared between iPD with and without FOG.

Balance control while standing on a single leg is necessary to accomplish several activities of daily living (e.g., walking, obstacle crossing, and stair climbing) that are required to preserve personal autonomy and a satisfying quality of life (13, 14). Also, the ability to maintain unipedal balance for less than 10 s has been associated with increased fall risk (15–18). The ability to stand on a single limb is therefore an important feature to be assessed in older people and people with parkinsonism. In particular, the One-Leg Stance (OLS) test is a fast and simple tool already adopted for the clinical assessment of balance in the elderly (19, 20) and in subjects with neurological disorders, such as iPD (13, 15–18). Due to its simplicity, the test is also included as an item in more comprehensive clinical scales, such as the Berg Balance Scale (21, 22), the Ataxia Test Battery (23), and the Balance Evaluation System test, both in its complete (BESTest) (24) and short (mini-BESTest) (25) versions. Currently, the only measured outcome in the OLS test is the time the single stance position is held, commonly measured by a stopwatch. However, a previous study of postural steadiness in the OLS test in healthy young and elderly adults (14) underlined the importance of evaluating the anticipatory weight shift toward the stance leg that is a critical balance requirement in daily activities. The OLS task can be divided into two phases: (1) an initial dynamic balance phase, consisting of the postural action of moving the center of mass (CoM) over the forthcoming stance leg, and (2) a following static balance phase in which one leg is lifted while one foot postural orientation is maintained.

Recently, the availability of cost-effective, easy-to-manage, wearable, inertial sensors allows the assessment of motor disorders outside a typical movement analysis laboratory. This wearable technology allows clinicians to easily perform an instrumental evaluation of motor deficits during routine exams. For example, wearable inertial measurement units (IMUs) have been demonstrated to be effective for the assessment of weak APAs that precede step initiation (26–30) and step climbing (28) in iPD. Algorithms to quantify dynamic APAs and static balance associated with OLS are needed.

The aim of this study is to develop and test an instrumented version of the OLS test with wearable inertial sensors that provides objective information of both the dynamic and static phases of the task. The instrumented OLS test was assessed in subjects with iPD, FGD, and elderly healthy adults to characterize: (1) the sensitivity of the method to distinguish differences among groups and (2) the validity of the proposed instrumental indexes for evaluating balance deficits in subjects with different types of parkinsonism.

MATERIALS AND METHODS

Participants

Seventy-one subjects with parkinsonism and a control group of 32 healthy elderly adults (HC) were recruited through the Parkinson's Center of Oregon at Oregon Health & Science University (OHSU) and VA Portland Health Care System (VAPORHCS). All participants provided informed consent approved by the OHSU or VAPORHCS Institutional Review Boards.

Subjects with parkinsonism were divided into three groups: (a) 25 subjects with idiopathic PD presenting FOG (iPD-FOG), (b) 33 iPD without FOG (iPD-noFOG), and (c) 13 subjects with FGD. Subjects with FGD were included if gait and balance difficulties were the initial symptom of their movement disorder. Clinical features necessary for inclusion were slow short steps, unsteadiness, and difficulty lifting the feet off the floor (shuffling). In addition, wide-based gait, FOG, postural instability, or minor features of parkinsonism (rigidity and tremor) were present in some subjects (optional but supportive for inclusion). For inclusion, clinical characteristics were preferred to radiographic white matter lesion burden. An internationally recognized expert in movement disorders (John G. Nutt) reviewed all the participants with FGD through videos and medical records to confirm inclusion in the FGD group.

Exclusion criteria for subjects with FGD were as follows: idiopathic PD and Parkinson plus syndromes such as progressive supranuclear palsy, multiple system atrophy, corticobasal syndrome, or cerebellar ataxia, Lewy body dementia, and normal pressure hydrocephalus post-shunting. MRI excluded large strokes, masses, cerebellar, and brainstem atrophy or ventricular dilation not related to cortical atrophy (31). Individuals with large, space-occupying lesions on previous imaging or significant pyramidal weakness on exam were also excluded. Other

exclusionary criteria were as follows: severe tremor, peripheral neuropathy with proprioceptive deficits, severe peripheral vascular disease, uncorrected vision or vestibular problems, joint disease significantly limiting gait, and inability to tolerate an MRI due to claustrophobia or other medical contraindications.

Subjects were also excluded if they presented: neurological disorders other than iPD or FGD, vestibular disorders, peripheral neuropathy with proprioceptive deficits, musculoskeletal impairments that could affect gait, and inability to stand and walk unassisted. Participants with iPD and FGD were tested in their practical OFF-medication state, after at least 12 h washout from antiparkinson medications.

Subjects with iPD and FGD were clinically rated by a trained examiner on the MDS Motor Section of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) (32) immediately before the experimental sessions.

Demographic and clinical characteristics of the groups are reported in **Table 1**.

Experimental Protocol

Participants performed the OLS test as part of the mini-BESTest (Item 3). Subjects stood barefoot in an upright posture with feet shoulder-width apart. Their hands were maintained on their hips for the entire duration of the test. In accordance with the general guidelines for the OLS test, participants received the instruction: "Look straight ahead. Keep your hands on your hips. Lift your leg off of the ground behind you without touching or resting your raised leg upon your other standing leg. Stay standing on one leg as long as you can." The task was performed twice per limb but subjects were not warned in advance which leg to lift so they would not anticipate a weight shift prior to data collection. At the beginning of each repetition, the examiner gave a vocal instruction specifying which leg had to be lifted. Each trial ended after maintaining unipedal balance for 30 s (15) or when the lifted foot touched the ground again.

For concurrent, clinical validity, test duration was also measured with a stopwatch from the movement initiation to the final foot contact. The correspondent clinical task score was assigned, in accordance with the mini-BESTest guidelines, as follows: (0) unable; (1) moderate: $T < 20$ s; (2) normal: $T \geq 20$ s.

All the remaining 13 items of the mini-BESTest were also performed by subjects and assessed with clinical scores.

Three IMUs (Opals, APDM Inc., Portland, OR, USA), positioned on the posterior trunk at the level of L4–L5, and on the left and right frontal face of the tibias, measured 3D acceleration and 3D angular velocity of the corresponding body segments. The location of the sensors and the orientation of their sensing axes are shown in **Figure 1**. IMUs were placed directly on the skin

TABLE 1 | Demographic and clinical characteristics of healthy controls (HC), idiopathic Parkinson's disease without freezing of gait (iPD-noFOG), idiopathic Parkinson's disease with freezing of gait (iPD-FOG), and frontal gait disorders (FGD) groups.

Group	*N*	Gender (M/F)	Age (years)	Hoehn and Yahr stage (0–5)	UPDRS-III motor section (0–100)
HC	32	15/17	69.4 (7.1)	–	–
iPD-noFOG	33	23/10	67.5 (7.7)	2.1 (0.3)	33.2 (10.7)
iPD-FOG	25	21/4	67.0 (6.5)	2.5 (0.8)	48.2 (14.0)
FGD	13	9/4	73.3 (6.5)	3.2 (0.9)	31.9 (15.9)

Values are mean (SD) or number.

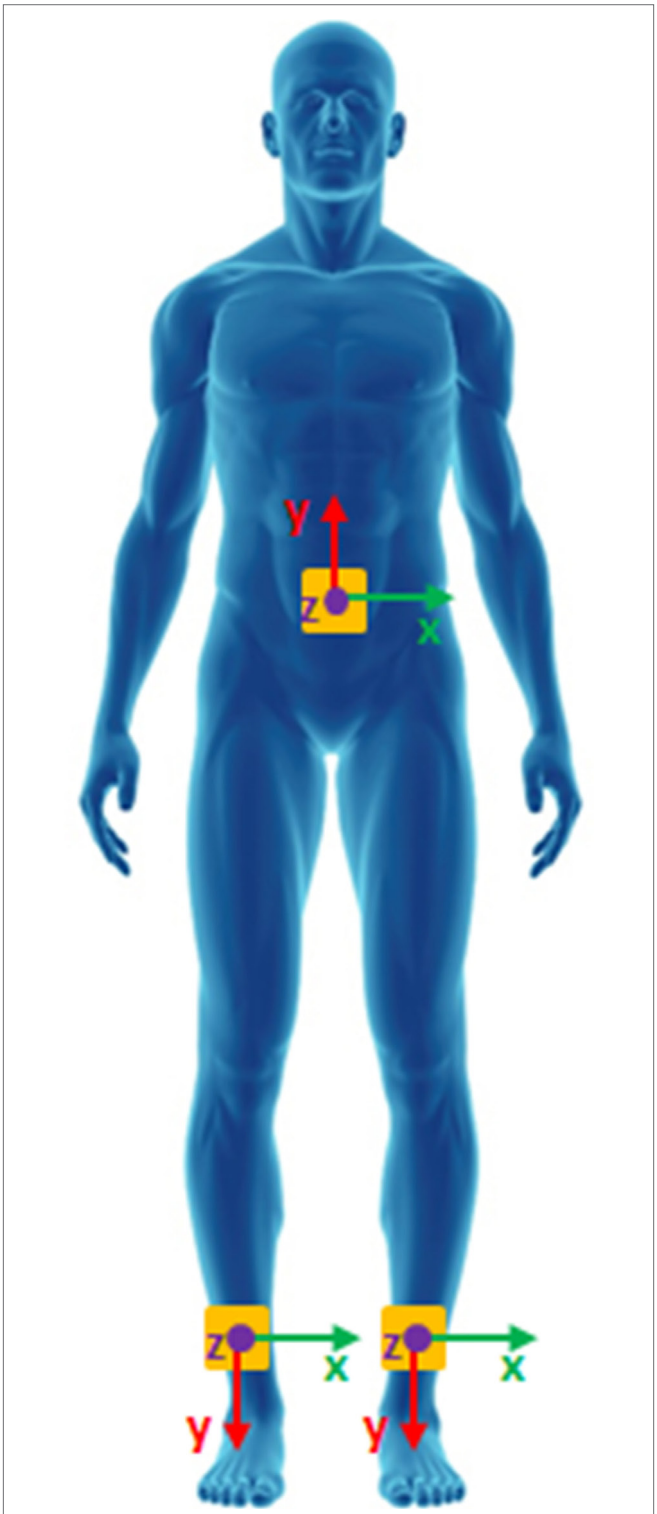

FIGURE 1 | Wearable sensors placement.

and fixed with self-adhering elastic (Coban) bandages. Data were recorded at a sampling frequency of 128 Hz and later downsampled at a frequency of 50 Hz in accordance with previous studies (26, 28–30).

Data Processing

The acceleration signals recorded from the trunk sensor were transformed to a horizontal–vertical coordinate system (33) and filtered using a fourth-order, zero-phase, low-pass Butterworth filter with a cutoff frequency of 3.5 Hz, as previously proposed in several studies (26, 28–30). The same low-pass filter was adopted for the angular velocities recorded by the sensors on the shanks.

For each repetition, the lifted leg was detected automatically on the basis of the highest absolute maximum of the shank angular velocity around the mediolateral (ML) axis (ω_{ML}). The initial raising movement of the leg was detected in correspondence of the first instant (T_{lift}) in which ω_{ML} exceeded a threshold set as 40% of its maximum absolute value, as shown in **Figure 2A**. The adopted threshold is significantly higher than the value proposed in a previous work on APAs prior to gait initiation and stair climbing (28) to guarantee that the APA phase already ended before T_{lift}. Thus, starting from the recognized instant T_{lift}, two different analyses were performed: (1) the assessment of the APAs preceding the leg rising, thus preceding T_{lift}, and (2) the evaluation of balance during the unipedal stance that follows T_{lift}.

The former dynamic phase was assessed through the analysis of the trunk ML acceleration, as shown in **Figure 2B**. The instant corresponding to the maximum absolute peak of the trunk ML acceleration preceding T_{lift} was detected (T_{peak}) and the signal amplitude (ML-peak) was adopted as a descriptive parameter of the APAs (26, 27, 29). Specifically, the ML-peak acceleration was considered representative of the CoM anticipatory spatial behavior because of the demonstrated good correlation with the center of pressure (CoP) displacement measured through a force platform during step initiation (26–29) and stair climbing (28).

The APA onset (T_{onset}) was then identified as the first instant, starting from the beginning of the recorded signal, in which the trunk ML acceleration exceeded a threshold set as 5% of the extracted ML-peak value.

Considering the balance phase that follows T_{lift}, ω_{ML} was used to detect the initial and final instants of unipedal balance, as reported in **Figure 3**. The static balance condition while standing on a single limb was reached at the end of the leg lifting, thus at the first instant following the initial rise in which ω_{ML} became negative for the first time (T_{start}), and ended at the beginning of the

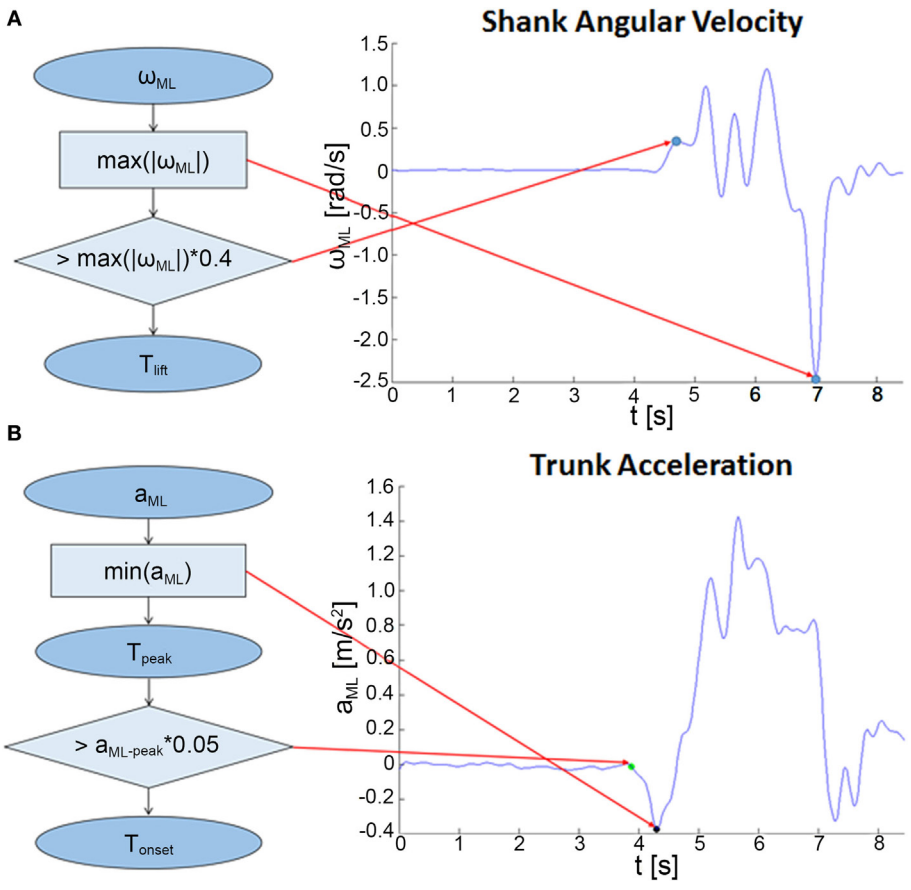

FIGURE 2 | Algorithms for the analysis of the dynamic phase. **(A)** Flowchart describing the procedure for the detection of the beginning of the rising movement of the lifted limb (T_{lift}). **(B)** Procedure for the identification of the anticipatory postural adjustment onset (T_{onset}) and the mediolateral (ML)-peak acceleration (T_{peak}).

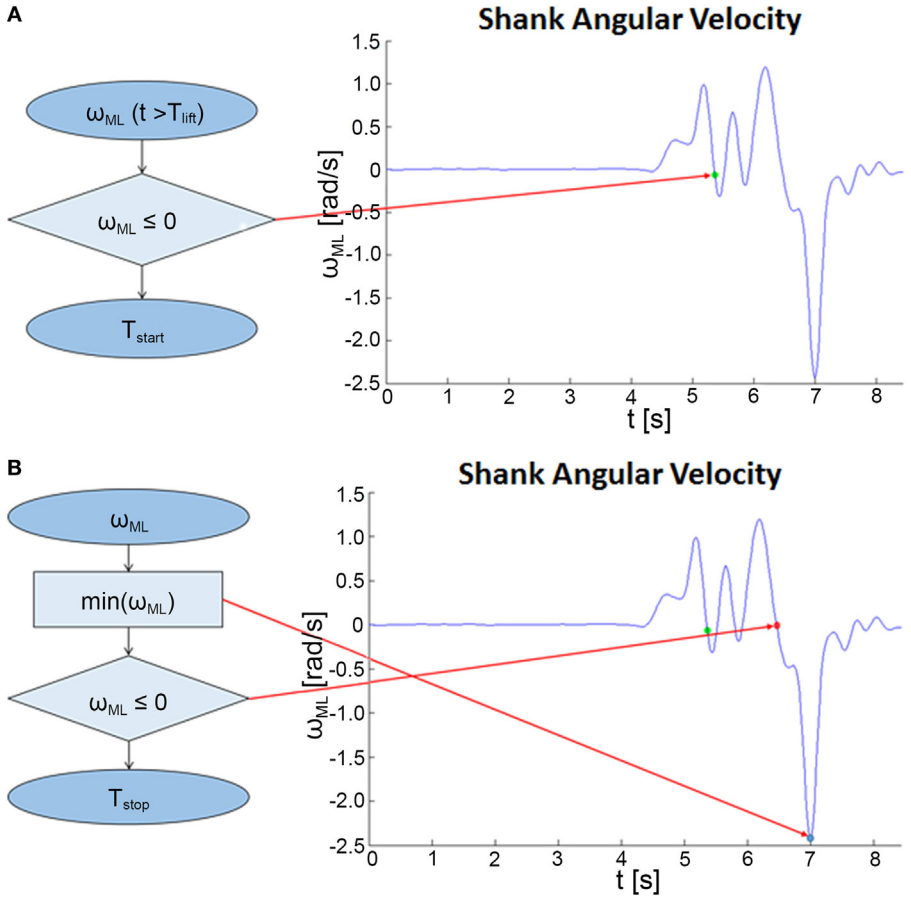

FIGURE 3 | Algorithms for the analysis of the static balance phase. **(A)** Flowchart describing the procedure for the detection of the beginning of the unipedal balance (T_{start}). **(B)** Procedure for the identification of the end of the unipedal balance (T_{stop}).

final descending movement (detected by the minimum of ω_{ML}), hence at the instant in which the shank ω_{ML} became negative for the last time (T_{stop}).

Following the guidelines for the clinical administration of the OLS test as part of the BESTest (24) and mini-BESTest (25), only the longer trial per leg was considered. In case of equal durations, the selection was performed considering the ML-peak amplitude. Thus, the one presenting the highest amplitude was adopted for subsequent analysis.

The evaluation of body sway during the unipedal balance phase was performed through the analysis of the trunk acceleration. Specifically, the root-mean-square (RMS) values of both the antero-posterior (AP) and ML acceleration were calculated. To take into account the different duration of the balance phase for each subject, RMS values were normalized to the balance duration measured by the sensors (nRMS).

After the detection algorithm was applied, the following temporal parameters were extracted (**Figure 4**):

- Time-to-peak: from T_{onset} to T_{peak};
- Peak-to-balance: from T_{peak} to T_{start};
- Balance duration: from T_{start} to T_{stop}.

Statistical Analysis

In accordance with the general guidelines for the OLS test, measures obtained from the most affected side were considered to assess the method sensitivity in discriminating between groups. In addition, the statistical analyses were repeated on the least affected side.

Comparison among the four groups of participants (i.e., HC, iPD-FOG, iPD-noFOG, and FGD) was performed on the parameters extracted through wearable sensors, as well as on the manually measured test durations, and the clinical scores.

Parametric statistical tests were used for the analysis of data extracted through wearable sensors or stopwatch. Data normality and homogeneity of variances were tested with Kolmogorov–Smirnov test and Levene's test, respectively. In case of variables that did not meet the above mentioned assumptions, the statistical analysis was performed on data transformed with Box–Cox transformation (34).

To reduce the effect of age which showed an almost significant difference between FGD subjects and the two groups of iPD participants ($p = 0.07$ and 0.06, respectively), between-group comparisons were assessed by analysis of covariance (ANCOVA) with one between-group factor (group: HC, iPD-FOG, iPD-noFOG,

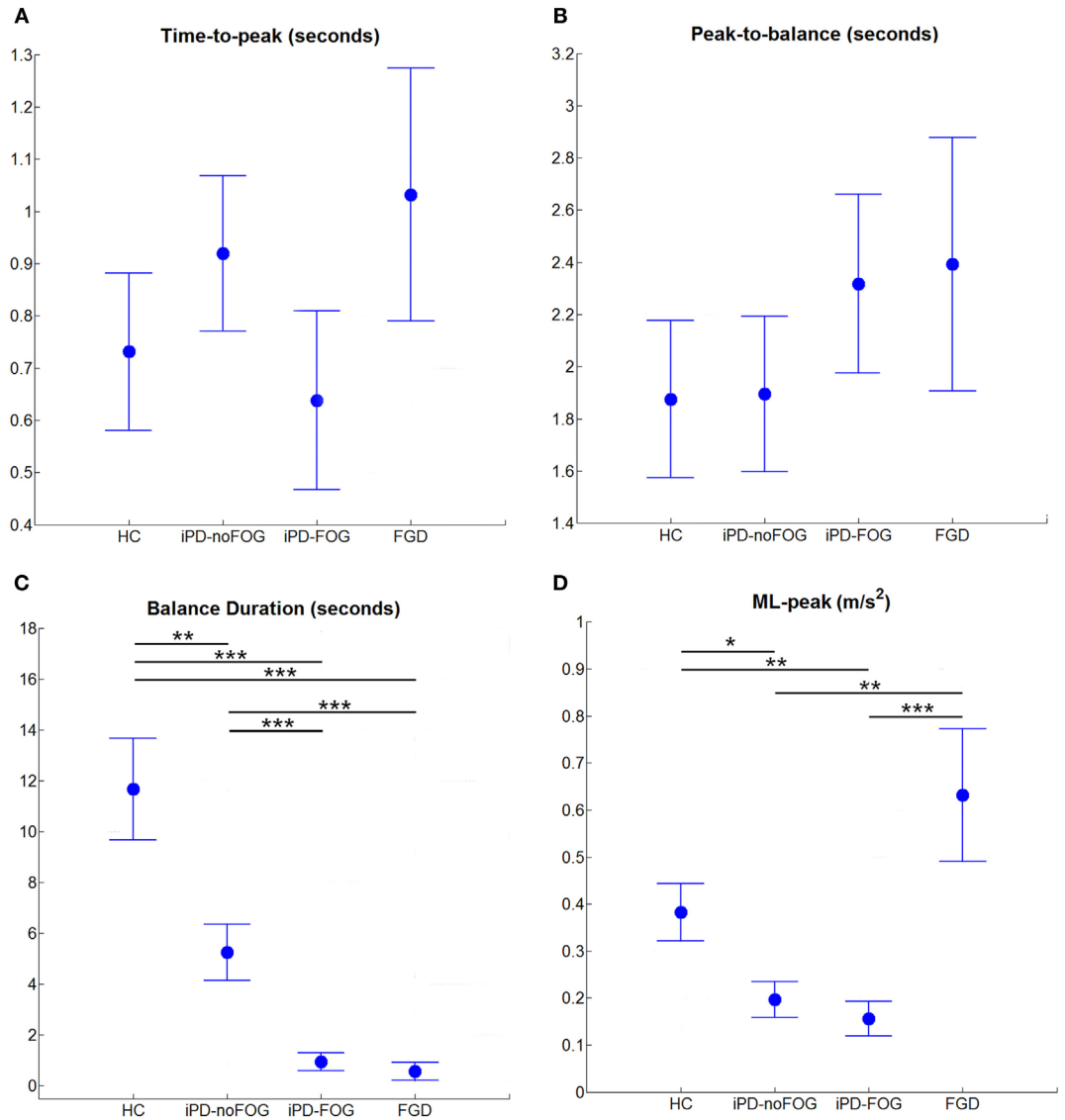

FIGURE 4 | Instrumental parameters extracted from wearable sensors during One-Leg Stance on the most affected side for healthy controls (HC), idiopathic Parkinson's disease without freezing of gait (iPD-noFOG), idiopathic Parkinson's disease with freezing of gait (iPD-FOG), and frontal gait disorders (FGD) groups. **(A)** Time-to-peak, **(B)** peak-to-balance, **(C)** balance duration, **(D)** peak of mediolateral trunk acceleration [mediolateral (ML)-peak]. Circles and whiskers represent, respectively, mean and SE adjusted for age through analysis of covariance procedure. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (Bonferroni–Holm *post hoc* comparison).

and FGD) and the factor "age" as covariate. In case of significant difference ($p < 0.05$), separate *post hoc* comparisons were performed using Bonferroni–Holm procedure.

The clinical scores of the OLS test as proposed in the mini-BESTest, the Anticipatory Subscore, and the total mini-BESTest score were analyzed through non-parametric methods due to their discrete nature. Thus, differences among groups were assessed using the Kruskal–Wallis Rank Sum Test and Bonferroni–Holm *post hoc* procedure. The same procedure was adopted to investigate differences in the MDS-UPDRS Part 3—Motor Subscore among subjects with iPD-noFOG, iPD-FOG, and FGD.

Considering the discrete nature of the mini-BESTest clinical score, the Spearman's rank correlation coefficient (ρ) was used to investigate the associations between the balance duration measured through wearable sensors and the clinical score. Pearson's correlation coefficient (r) was used to investigate the associations between the parameters extracted by wearable sensors and the test duration measured through a stopwatch. In both cases, the strength of all correlations was interpreted as follows: trivial ($r < 0.1$), small ($0.1 < r < 0.3$), moderate ($0.3 < r < 0.4$), strong ($0.5 < r < 0.7$), very strong ($0.7 < r < 0.9$), and perfect ($r = 1.0$) (35). Bland–Altman analysis was also carried out to investigate the relationship between balance duration measured through wearable sensors and the stopwatch (36).

The level of significance was set at 0.05 for all the conducted analyses. All the analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

All the participants completed the test. However, considering the execution of the test on the most affected side, 13 subjects with parkinsonism (1 iPD-noFOG, 8 iPD-FOG, and 4 FGD) were not able to lift their leg, while considering the least affected side only 3 persons (1 iPD-noFOG, 1 iPD-FOG, and 1 FGD) could not get the foot off the ground. Due to the impossibility to maintain unipedal balance, subjects who did not get their foot off the ground were excluded from the assessment of the body sway during the balance phase by lower trunk acceleration data.

Clinical Scores of OLS Differentiate Parkinsonism from Healthy Controls

Results are reported in **Table 2**. Specifically, statistically significant differences among groups were found for the OLS task of the mini-BESTest, the Anticipatory Postural Subscore, and the mini-BESTest total score ($p < 0.001$). Differences in the OLS task score were also found between healthy controls (mean ± SD: 1.6 ± 0.6) and iPD-noFOG (1.2 ± 0.6, $p = 0.01$), iPD-FOG (0.9 ± 0.6, $p < 0.001$), and FGD (0.5 ± 0.6, $p < 0.01$). Furthermore, FGD presented significant lower score when compared to iPD-noFOG ($p = 0.002$) and iPD-FOG ($p = 0.04$), but no differences were found between iPD groups ($p = 0.15$). Analyses of the Anticipatory Subscore showed differences between all the groups, but not between iPD-FOG and FGD subjects (iPD-FOG: 3.2 ± 1.4, FGD: 2.6 ± 1.3, $p = 0.25$). In particular, HC (5.0 ± 1.2) had higher score than iPD-noFOG (4.3 ± 1.3, $p = 0.03$), iPD-FOG, and FGD ($p < 0.001$). Similarly, iPD-noFOG reported higher score than iPD-FOG ($p = 0.01$) and FGD ($p < 0.001$). Finally, the mini-BESTest total score demonstrated the highest sensitivity by discriminating all the four considered groups of participants ($p < 0.02$ for all the comparisons).

TABLE 2 | Comparison of the clinical measures among healthy controls (HC), idiopathic Parkinson's disease without freezing of gait (iPD-noFOG), idiopathic Parkinson's disease with freezing of gait (iPD-FOG), and frontal gait disorders (FGD).

	HC	iPD-noFOG	iPD-FOG	FGD	*p*-Value
Mini-BESTest One-Leg Stance Task score (0–2)	1.6 ± 0.6	1.2 ± 0.6	0.9 ± 0.6	0.5 ± 0.6	<0.001
Mini-BESTest Anticipatory Subscore (0–6)	5.0 ± 1.2	4.3 ± 1.3	3.2 ± 1.4	2.6 ± 1.3	<0.001
Mini-BESTest Total Score (0–28)	24.2 ± 2.4	21.3 ± 4.0	16.6 ± 5.7	11.9 ± 5.3	<0.001

Values are mean ± SD. Higher scores indicate better performance. Reported p-values refer to Kruskal–Wallis Rank Sum Test.

Specific Characteristics of the Instrumented OLS Differentiate between Parkinsonism and Healthy Controls

Results related to the most affected side are reported in **Figure 4**. Regarding the anticipatory phase, the peak of ML trunk acceleration (ML-peak) revealed a statistically significant difference among groups [$F(3, 98) = 7.94$, $p < 0.001$]. As shown in **Figure 4D**, the ML-peak was significantly lower in the two iPD groups (iPD-noFOG: $p = 0.027$; iPD-FOG: $p = 0.007$) compared to healthy controls, and surprisingly compared to FGD (iPD-noFOG: $p = 0.002$; iPD-FOG: $p < 0.001$). Also surprisingly, the ML-peak was similar in subjects with FGD compared to healthy controls ($p = 0.151$). Considering the body sway during the unipedal balance phase (**Table 3**), differences among groups in normalized root-mean-square acceleration (nRMS) were found in both the AP [AP-nRMS, $F(3, 85) = 4.83$, $p = 0.004$] and ML [ML-nRMS, $F(3, 85) = 7.49$, $p < 0.001$] directions. *Post hoc* analysis showed that healthy controls were characterized by significant lower nRMS values, thus lower body sway, in both the AP (iPD-noFOG: $p = 0.040$; iPD-FOG: $p = 0.036$; FGD: $p = 0.018$) and ML (iPD-noFOG: $p = 0.002$; iPD-FOG: $p = 0.004$; FGD: $p = 0.005$) directions. No difference among the three groups of subjects with parkinsonism was found.

Regarding temporal aspects, a statistically significant difference among groups emerged only for balance duration [$F(3, 98) = 24.07$, $p < 0.001$], while no significant differences were found for the time-to-peak [$F(3, 98) = 0.89$, $p = 0.448$] and peak-to-balance [$F(3, 98) = 0.58$, $p = 0.628$] (**Figures 4A,B**). Further *post hoc* analysis (**Figure 4C**) showed that healthy control subjects were able to maintain balance longer than subjects with iPD-noFOG ($p = 0.007$), iPD-FOG ($p < 0.001$), and FGD ($p < 0.001$). Furthermore, iPD-noFOG subjects stayed in unipedal stance longer than iPD-FOG ($p < 0.001$) and FGD ($p < 0.001$), while no difference was found between iPD-FOG and FGD ($p = 0.489$). These results were confirmed by ANCOVA analysis conducted on the test duration measured through stopwatch [$F(3, 98) = 21.54$, $p < 0.001$]. Healthy elderly controls presented longer, thus better, time (mean ± SE: 14.6 ± 1.5 s) than iPD-noFOG (7.7 ± 1.1 s, $p < 0.001$), iPD-FOG (3.8 ± 0.9 s, $p < 0.001$), and FGD (1.8 ± 0.8 s, $p < 0.001$). Furthermore, iPD-noFOG subjects presented better performances than iPD-FOG ($p = 0.013$) and FGD ($p < 0.001$),

TABLE 3 | Normalized root mean square of the lower trunk acceleration during unipedal balance on the most and least affected sides for healthy controls (HC), idiopathic Parkinson's disease without freezing of gait (iPD-noFOG), idiopathic Parkinson's disease with freezing of gait (iPD-FOG), and frontal gait disorders (FGD) groups.

		HC	iPD-noFOG	iPD-FOG	FGD	*p*-Value
Most affected	Antero-posterior (AP)-nRMS (m/s^3)	0.027 ± 0.007	0.071 ± 0.018	0.085 ± 0.030	0.141 ± 0.071	0.004*
	Mediolateral (ML)-nRMS (m/s^3)	0.045 ± 0.010	0.152 ± 0.036	0.172 ± 0.055	0.253 ± 0.116	<0.001*
Least affected	AP-nRMS (m/s^3)	0.012 ± 0.002	0.017 ± 0.004	0.023 ± 0.006	0.029 ± 0.011	0.067
	ML-nRMS (m/s^3)	0.026 ± 0.005	0.035 ± 0.007	0.054 ± 0.014	0.076 ± 0.029able 5	<0.028*

*Values are mean ± SE adjusted for age through analysis of covariance procedure. Significant differences (p-value < 0.05) are marked with *.*

while no difference was found between iPD-FOG and FGD ($p = 0.117$).

Data from the least affected side are summarized in **Tables 3** and **4**. Regarding the anticipatory phase, no differences were found among groups for the peak of ML trunk acceleration [$F(3, 98) = 1.82$, $p = 0.148$], in contrast with the analysis of the most affected side (**Table 4**). Analysis of the normalized body sway during unipedal balance (**Table 3**) showed a significant difference among groups only in the ML direction [$F(3, 95) = 3.16$, $p = 0.028$]. However, after *post hoc* analysis, only a tendency toward significance was found between HC and FGD groups ($p = 0.066$).

Results related to the temporal aspects (**Table 4**) confirmed those obtained from the most affected side, showing a significant difference among groups for balance duration [$F(3, 98) = 14.74$, $p < 0.001$], which was significantly prolonged in control subjects compared to iPD with and without FOG ($p = 0.019$ and $p < 0.001$, respectively) and subjects with FGD ($p < 0.001$) and in iPD-noFOG compared to iPD-FOG ($p = 0.004$) and FGD ($p = 0.020$). No differences among groups were found for the other temporal parameters [time-to-peak: $F(3, 98) = 0.05$, $p = 0.986$; peak-to-balance: $F(3, 98) = 1.02$, $p = 0.389$], in accordance with the results from the most affected side. The statistical analysis performed on the test duration measured with a stopwatch confirmed differences among groups [$F(3, 98) = 13.26$, $p < 0.001$]. *Post hoc* analysis highlighted that healthy controls presented longer unipedal standing (21.8 ± 1.5 s) than iPD-noFOG (15.3 ± 1.5 s, $p = 0.010$), iPD-FOG (10.7 ± 1.7, $p < 0.001$), and FGD (6.9 ± 2.3, $p < 0.001$). iPD-noFOG showed longer time than FGD ($p = 0.011$), but no differences were found between iPD-FOG and iPD-noFOG ($p = 0.08$) and between iPD-FOG and FGD ($p = 0.193$).

Correlation between Clinical and Instrumented Features of the OLS Test

Figures 5 and **6** summarize the results of the correlation analysis between clinical and instrumental parameters related to the most affected side.

The balance duration measured by wearable sensors presented a strong correlation with the mini-BESTest OLS task score ($\rho = 0.82$, $p < 0.001$), the mini-BESTest Anticipatory Subscore ($\rho = 0.74$, $p < 0.001$) and the mini-BESTest total score ($\rho = 0.76$, $p < 0.001$) (see **Figure 5**), while no significant correlation was found between balance duration and the MDS-UPDRS-III Motor Subscore ($\rho = -0.15$, $p = 0.219$). In contrast, ML-peak acceleration presented only a moderate correlation with the MDS-UPDRS-III Motor Subscore ($\rho = -0.33$, $p = 0.012$), and no significant correlation was found with the other clinical measures. As shown in **Figure 6** (left panel), a very strong correlation ($r = 0.93$, $p < 0.001$) emerged between the task duration measured with a stopwatch and the balance duration computed from wearable sensors. Besides, Bland–Altman analysis (**Figure 6**, right panel) showed no obvious relation between the difference and the mean value of the balance duration measured by wearable sensors and test duration measured by stopwatch. Moreover, the mean value of the difference in duration between the two measures ($\overline{\Delta t} = 1.6$s) can be ascribed to the difference in the measured intervals. Indeed, the instrumental measure of the unipedal balance phase excludes the initial rise and final fall of the leg, while these

TABLE 4 | Instrumental parameters extracted from wearable sensors during One-Leg Stance on the least affected side for healthy controls (HC), idiopathic Parkinson's disease without freezing of gait (iPD-noFOG), idiopathic Parkinson's disease with freezing of gait (iPD-FOG), and frontal gait disorders (FGD) groups.

	HC	iPD-noFOG	iPD-FOG	FGD
Balance duration (s)	19.81 ± 1.90	13.37 ± 1.54	6.56 ± 1.24	6.40 ± 1.74
Time-to-peak (s)	0.39 ± 0.08	0.42 ± 0.09	0.39 ± 0.10	0.44 ± 0.15
Peak-to-balance (s)	1.31 ± 0.16	1.22 ± 0.15	1.39 ± 0.19	0.92 ± 0.19
ML-peak (m/s²)	0.34 ± 0.05	0.25 ± 0.04	0.21 ± 0.04	0.33 ± 0.07

Values are mean ± SE adjusted for age through analysis of covariance procedure.

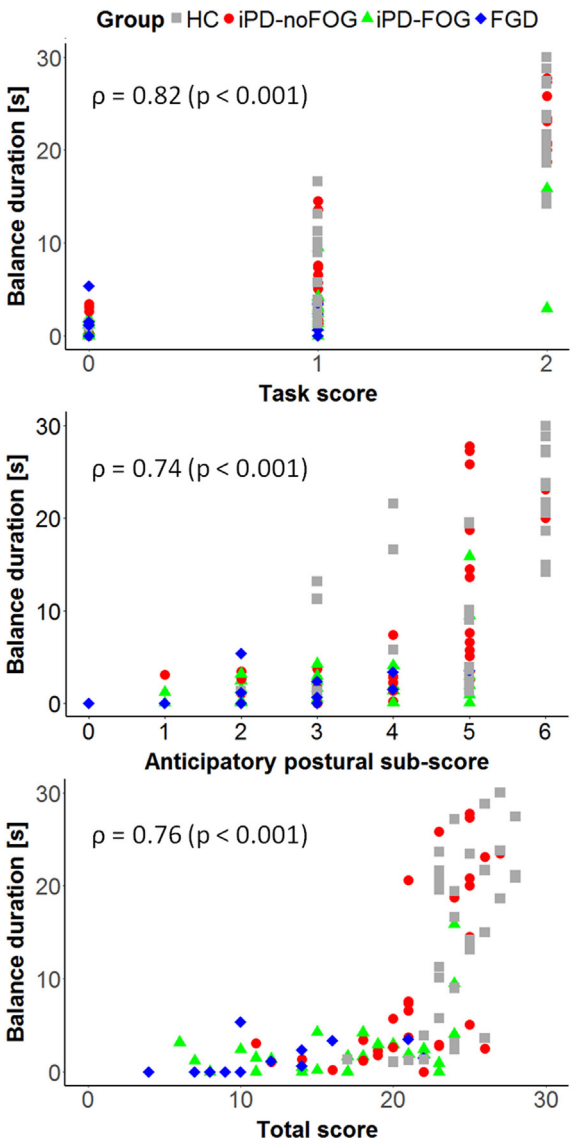

FIGURE 5 | Correlation between the balance duration on the most affected leg measured through the wearable sensors and the mini-BESTest task score (top), Anticipatory Subscore (center), and total score (bottom). Spearman's rank correlation coefficient (ρ) and the correspondent *p*-values are reported.

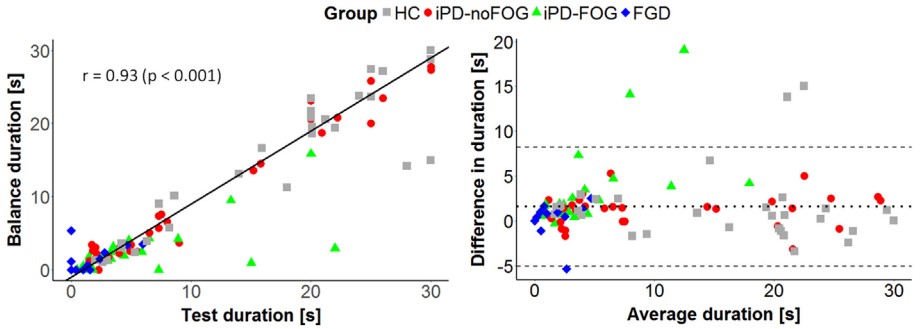

FIGURE 6 | Comparison between balance duration measured through wearable sensors and task duration measured by stopwatch during the execution of the One-Leg Stance test on the most affected side. On the left, linear correlation between the two variables. Pearson's correlation coefficient (*r*) and the correspondent *p*-value are reported. On the right, Bland–Altman plot. The central dotted lines represent the mean difference between the two measures, while the upper and lower lines represent the limits of agreement.

transient movements are considered in the measure performed with stopwatch. Taking into account that the two methods do not evaluate the same exact intervals, the collected results suggest an equal agreement between the proposed and the traditional methods through the entire range of measurements.

The above results were confirmed by data related to the least affected side, which also showed a very strong correlation between the balance duration measured by wearable sensors and the mini-BESTest task score ($\rho = 0.71$, $p < 0.001$), the Anticipatory Subscore ($\rho = 0.69$, $p < 0.001$), and the total score ($\rho = 0.76$, $p < 0.001$). Moreover, the lack of significant correlation between the ML-peak acceleration and the clinical mini-BESTest scores was found also for the least affected side. In addition, no correlation with the MDS-UPDRS-III Motor Subscore was found neither for the balance duration nor for the ML-peak acceleration.

DISCUSSION

This study developed and tested algorithms for an instrumented version of the OLS test based on wearable inertial sensors with healthy people, subjects with idiopathic PD, with and without FOG, and subjects with FGD. Our findings support the validity of the proposed method for assessing the OLS test and its sensitivity in distinguishing among the tested groups. Specifically, the objective characterization of dynamic ML acceleration of the trunk during the APAs that precede the unipedal static balance phase represents an improvement of the discriminatory ability of the OLS test compared to most clinical tests of OLS. The instrumented OLS test discriminated between healthy older people and people with parkinsonism and was sensitive to all the groups with parkinsonism. Only the complete mini-BESTest presented similar sensitivity to distinguish performance among group balance performance.

To the best of our knowledge, this is the first study in which wearable sensors were used for assessing both the initial dynamic (i.e., APAs and leg lifting) and the subsequent static balance phases of the OLS task. The importance of the evaluation of the two phases has been already reported in laboratory studies (14) as necessary for the correct comprehension of the weight-shifting mechanisms, but the use of IMUs for the objective observation of the phases was never investigated. Previously, the assessment of the dynamic and static phases of the task was performed with a force plate (14), that is, generally confined to motion analysis laboratories. Two previous studies developed a wearable sensor-based version of the OLS test for assessing balance deficits and risk of falling. In one study, the test was instrumented by using sensorized insoles for the estimation of CoP parameters (37), while in a second study a trunk-worn smartphone was used to estimate trunk displacements during task execution without considering the APA phase and balance phase separately (38). In addition, the present work is the first effort to adopt an instrumented version of the OLS test to discriminate subjects with idiopathic PD, with and without FOG, and FGD.

Four temporal (time-to-peak, time-to-balance, peak-to-balance, and balance duration) and three accelerometric (ML-peak acceleration and the normalized RMS of the lower trunk acceleration in the AP and ML directions) features were automatically extracted. The acceleration of the lower trunk has already shown to be appropriate for describing the behavior of the CoM during APAs preceding intentional movements in healthy elderly and young adults and subjects with iPD (26–29). In all those studies, the ML component of the acceleration had a good correlation with the CoP displacement measured through a force platform, while the acceleration in the AP direction had weaker correlations (26, 29) or no correlation at all (28). Therefore, on the basis of these results, only the ML-peak acceleration was adopted in our study as a spatial parameter to characterize APAs. The RMS acceleration of the lower trunk in the AP and ML directions was adopted to assess the postural sway while standing on a single leg. Indeed, this parameter has been already addressed as a valid and reliable measure to characterize postural control in PD (39). In this study, to take into account the ability in maintaining unipedal balance of subjects with different clinical conditions, the extracted measures were normalized to the corresponding balance duration, automatically extracted by the sensors. Finally, the four temporal features were intended to characterize the different subcomponents of the dynamic phase and the static balance phase. In particular, Mancini et al. (26) reported that

the time-to-peak trunk acceleration correlated with both the amplitude of the CoM acceleration and the CoP displacement in APAs preceding gait initiation.

A significant difference in ML-peak acceleration was found between healthy elderly and iPD subjects, with and without FOG. This result agrees with the literature, as people with iPD also show hypometric APAs in other motor tasks, such as gait initiation (26–30) and stair climbing (28). The reduced initial shift of the CoM prior to step initiation has been associated with start hesitation and akinetic FOG (12, 40). Thus, it has been suggested that the typical alteration in postural control during the initial dynamic phase may determine an insufficient recruitment and an under-scaled muscle force (13) that can result in balance difficulties in the subsequent static phase (13, 14, 19).

Subjects with iPD and FOG showed a reduced ability to maintain balance on a single leg, resulting in a significant shorter balance duration compared to subjects with iPD without FOG. This result might either reflect the higher level of motor impairment in this cohort of iPD presenting with FOG, as confirmed by a significantly worse, MDS-UPDRS Part 3—Motor Subscore, or be the result of differentially impaired control of balance in subjects experiencing freezing (41). No other differences were found between iPD-FOG and iPD-noFOG in the other objective measures.

Subjects with FGD showed ML-peak acceleration significantly higher than subjects with iPD and comparable with healthy controls. This very interesting result of normal APA size seems to be in contrast with the FGD subjects' short one-legged balance duration as well as their worst, mini-BESTest total score, worst Anticipatory Subscore and worst OLS subscore. However, FGD subject may not correctly scale the consequent weight shift to maintain the CoM projection inside the base of support, thus resulting in short lifting attempt, immediately followed by ground foot contact. These results are similar to those reported in a previous study on gait initiation by Elble et al. (42). In that case, subjects with lower body parkinsonism (FGD) showed initial postural shifts on a force plate qualitatively similar to those of comparable-aged, healthy controls, with no significant differences in the amplitude of the ML CoP displacement. However, due to a significant reduction in the moment of force measured by a force plate in the AP direction, people with FGD had abnormal postural shifts followed frequently by one or more aborted attempts at lifting the foot. Since patients with FGD do not benefit from dopamine replacement therapy, it is likely their parkinsonian balance and gait problems, and inability to stand on one foot, stem from deficits in different neural circuits than those with iPD (9).

Significant differences were found in duration of the one foot balance phase between healthy elderly subjects and the groups with parkinsonism, as well as between the iPD with FOG versus the non-FOG and FGD group, respectively. However, no significant differences were found between iPD-FOG and FGD group performance. Reduced one foot balance times are generally associated with poor balance capabilities and higher fall risk (15–18, 43), so the differences in balance duration between groups seem to correctly reflect different levels of balance abnormality, confirmed by the clinical mini-BESTest assessments. In particular, the lack of a significant difference between iPD-FOG and FGD subjects in the mini-BESTest's Anticipatory Subscore suggests that those subjects presented similar anticipatory balance deficits, even though FGD also had worse balance in other domains than the iPD-FOG group, as showed by the mini-BESTest's total score. No other differences in temporal parameters were found among groups, in line with previous studies demonstrating that time-to-peak did not discriminate between healthy older adults and subjects with iPD during gait initiation (26, 29).

The higher values of the nRMS showed by subjects with parkinsonism while standing on their most affected side compared to healthy controls correctly reflect the poor control of posture typical of iPD (44) and the spectrum of locomotor impairment comprising postural instability that are associated with frontal lobe pathology (42).

The very strong correlation found between the balance duration extracted through wearable sensors and the test duration measured by a stopwatch, and the strong correlation with the mini-BESTest one foot standing task score, Anticipatory subscore and total score support the validity of our parameters for assessing the OLS test. This fact is enforced by Bland–Altman analysis that shows no obvious relationship between the difference and the mean value of the balance duration measured by wearable sensors and test duration measured by stopwatch. By contrast, no significant correlation was found between balance duration and disease severity, as measured by the MDS-UPDRS-III Motor Subscore. This result could be ascribed to the fact that MDS-UPDRS-III scale contains not only subscores specific to balance stability and gait, typically impaired in subjects with both iPD and FGD, but also components related to tremor, rigidity and arm bradykinesia, which are typical of iPD but that are not usually present in people with FGD (6).

The proposed, instrumented method of assessing one foot standing demonstrated a higher sensitivity compared to the generally adopted stopwatch approach. In fact, the analysis of both the initial dynamic phase (by ML-peak acceleration) and of the subsequent static balance phase (by balance duration) allowed us to correctly differentiate between healthy elderly and subjects with parkinsonism, and to discriminate among groups with different types of parkinsonisms and disease stages. Notably, the ability to characterize the initial APAs prior to leg lift represents a novel, clinically valuable evaluation of unipedal balance.

In accordance with the general guidelines for the OLS test as presented in the mini-BESTest, the analysis was performed considering the best performance from the most affected side. Further investigation conducted by repeating the data analysis on the least affected side confirmed lower duration of the balance phase for subjects with iPD or FGD compared to healthy controls and for subjects with iPD-FOG and FGD compared to iPD-noFOG. However, no significant differences were found among groups in the anticipatory phase. This result suggests the possibility that the ability to generate the anticipatory adjustments needed for the OLS test may be preserved in people with parkinsonism. Considering that APAs are known to be asymmetric in healthy subjects (45–47) and even more in subjects with iPD (48), this result supports the practice of performing the test on the most affected side to exacerbate differences in balance control.

Some limitations are present in this study. The first limitation is represented by the small number of subjects with FGD involved in the study. The limited size of this cohort and the lack of previous studies on the APAs in FGD suggest caution in data interpretation. Second, the adoption of ML-peak acceleration as a discriminatory parameter of APAs is based on previous studies already published, that showed a good correlation between the acceleration signals measured by an inertial sensor placed on the lower trunk and the CoP displacement in quiet standing and prior to step initiation, however no similar assessment has been conducted yet for FGD subjects. These considerations suggest that further studies are needed to validate the proposed method on a wider cohort of subjects with FGD. Moreover, a comparison between data from inertial sensors and a force plate (considered as gold standard) should be performed to allow an improvement of the algorithms for the detection of heel-off and toe-off instants, permitting a further assessment of the imbalance and unloading phases, separately (28, 30).

Even though caution is needed, based on previous studies where similar algorithms were used, it is opinion of the authors that the proposed method appears to be robust enough for subjects with parkinsonism. The adoption of cost-effective, wearable sensors allowed us to enhance the sensitivity of the OLS test, without introducing any further complexity. This represents a potentially useful instrument for the fast assessment of balance deficits in clinical settings.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethics Committee of the Oregon Health & Science University and of the VA Portland Healthcare System with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Oregon Health & Science University and of the VA Portland Healthcare System.

AUTHOR CONTRIBUTIONS

FH and MM designed the work. MM and GB performed data acquisition. GB implemented algorithms for data processing and drafted the manuscript. GB and IC analyzed data. FH, LC, MF, and JN contributed to the interpretation of the data. FH, MM, IC, LC, MF, and JN participated in the critical revision process. All the authors approved the manuscript.

ACKNOWLEDGMENTS

The authors thank Natassja Pal, Heather Schlueter, Michael Fleming, Graham Harker, and Peter Martin for scheduling and helping with data collection; Patricia Carlson-Kuhta for project management. A preliminary analysis of the data reported in this work was presented in condensed form at the XVII SIAMOC Conference (49).

FUNDING

This publication was made possible with support from NIH 2R01 AG006457 (Horak), VA Merit I01 RX001075 (Horak), NIH Career Development Award K99 HD078492 01A1 (Mancini), and R00 HD078492 (Mancini) and funding from the Italian Ministry of Health (Ricerca Corrente and Ricerca Finalizzata GR-2009-1604984).

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Conflict of Interest Statement: FH had a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology. This potential institutional and individual conflict has been reviewed and managed by OHSU and the Portland VA.

frontiers in Neurology

ORIGINAL RESEARCH
published: 01 September 2017
doi: 10.3389/fneur.2017.00431

Analysis of Correlation between an Accelerometer-Based Algorithm for Detecting Parkinsonian Gait and UPDRS Subscales

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OPEN ACCESS

Edited by:
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Erwin Montgomery,
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Erwin Van Wegen,
VU University Medical Center, Netherlands

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *28 January 2017*
Accepted: *08 August 2017*
Published: *01 September 2017*

Citation:
Rodríguez-Molinero A, Samà A, Pérez-López C, Rodríguez-Martín D, Alcaine S, Mestre B, Quispe P, Giuliani B, Vainstein G, Browne P, Sweeney D, Quinlan LR, Moreno Arostegui JM, Bayes À, Lewy H, Costa A, Annicchiarico R, Counihan T, Laighin GÒ and Cabestany J (2017) Analysis of Correlation between an Accelerometer-Based Algorithm for Detecting Parkinsonian Gait and UPDRS Subscales. Front. Neurol. 8:431. doi:10.3389/fneur.2017.00431

Background: Our group earlier developed a small monitoring device, which uses accelerometer measurements to accurately detect motor fluctuations in patients with Parkinson's (On and Off state) based on an algorithm that characterizes gait through the frequency content of strides. To further validate the algorithm, we studied the correlation of its outputs with the motor section of the Unified Parkinson's Disease Rating Scale part-III (UPDRS-III).

Method: Seventy-five patients suffering from Parkinson's disease were asked to walk both in the Off and the On state while wearing the inertial sensor on the waist. Additionally, all patients were administered the motor section of the UPDRS in both motor phases. Tests were conducted at the patient's home. Convergence between the algorithm and the scale was evaluated by using the Spearman's correlation coefficient.

Results: Correlation with the UPDRS-III was moderate (rho −0.56; $p < 0.001$). Correlation between the algorithm outputs and the gait item in the UPDRS-III was good (rho −0.73; $p < 0.001$). The factorial analysis of the UPDRS-III has repeatedly shown that several of its items can be clustered under the so-called Factor 1: "axial function, balance, and gait." The correlation between the algorithm outputs and this factor of the UPDRS-III was −0.67 ($p < 0.01$).

Conclusion: The correlation achieved by the algorithm with the UPDRS-III scale suggests that this algorithm might be a useful tool for monitoring patients with Parkinson's disease and motor fluctuations.

Keywords: Parkinson's disease, objective monitoring, accelerometers, gait, UPDRS

INTRODUCTION

Although no assessment methods can substitute the clinical judgment, subjective and objective measures in PD complement each other, each method having strengths and weaknesses (1). Objective data from inertial sensors are interesting new way of assessment, with some strengths such as their comparability among physicians, their independence of the observer training, and the fact that their results can be understandable even by the patients (2, 3).

Inertial sensors are of great interest in the case of patients with *motor fluctuations*. These patients experience fluctuations between a state called On, where symptoms are satisfactorily controlled with medication, and a state called Off, where symptoms reappear and patients experience difficulties in motor function (4, 5). As the disease progresses, these motor fluctuations become increasingly frequent and difficult to control with medication, so objective and detailed information about their intensity and chronology could be an invaluable aid for the fine-tuning of the medication.

Accelerometers can detect different motor symptoms and fluctuations in patients with Parkinson's disease (6–9). Our group earlier developed an algorithm capable of detecting the motor state in patients with motor fluctuations (On and Off) based on accelerometry data from a single inertial sensor located on the patient's waist. As published before, the algorithm detects whether the patient is walking in Off with specificity and sensitivity of 96 and 94%, respectively, under real conditions of use. To that end, the algorithm first detects gait, then identifies strides and extracts a frequency characteristic of them, which has been shown to be related to the motor state (10). This frequency characteristic consists in the power spectra between 0 and 10 Hz.

Although the motor status has traditionally been classified dichotomously in On and Off states, motor symptoms are a continuum between these two states, and are more precisely scored by numerical scales such as the Unified Parkinson's Rating Scale part III (UPDRS-III). As the output of the previously developed algorithm is a continuous numerical variable, in this study, we aim to investigate its possible correlation with the UPDRS, to further validate the algorithm.

MATERIALS AND METHODS

This prospective study was conducted on a sample of 75 patients suffering from idiopathic Parkinson's disease, according to the criteria of the UK Brain Bank (11), in moderate stage (Hoehn and Yahr scale >2) with motor fluctuations. Patients older than 80 years and those with implanted electronic devices, dementia, or gait-impairing health problems other than Parkinson's disease, were excluded from the study. Patients unable to recognize their own On–Off motor states, were also excluded. Participants were selected by convenience sampling among those attending the neurology clinics in any of the participating hospitals: Centro Médico Teknon (Spain), Fondazione Santa Lucia (Italy), Maccabi Healthcare Services (Israel) School of Medicine, NUI Galway (Ireland). We estimated a minimum of 62 patients included to find a significant correlation coefficient of 0.4, considering a <0.05 α error and <0.1 β error. For sample size calculation, the following formula was used (12):

$$N = [(Z_\alpha + Z_\beta)/\mathrm{C}] \cdot 2 + 3 \quad (1)$$

where N is the minimum sample size, the standard normal deviate for $\alpha = 0.05$ is $Z_\alpha = 1.960$, the standard normal deviate for $\beta = 0.1$ is $Z_\beta = 1.282$, and $C = 0.5 \times \ln[(1+r)/(1-r)] = 0.424$ being r the expected correlation coefficient (0.4).

The study was conducted at the patients' home and neighborhood. The researchers visited the patients within the time period they typically were in the Off phase (occasionally facilitated by reducing or skipping the previous dopaminergic medication dose). Once the Off state was confirmed by the patient and the researchers, the inertial sensor was placed on the patient's waist and he/she was asked to walk for some minutes (inside and outside home). More concretely, patients were asked to (I) show their home; if this took less than 2 min, the patient was asked to repeat it; and (II) walk without assistance 10 m. The researchers waited until the patient entered the On phase and repeated the test with sensor. All patients were also administered the UPDRS-III both in Off and On phase. The sensor readings were not available to the researchers at the moment of data collection, and the researchers involved in data collection did not participate in data analysis. We did not consider necessary to blind the UPDRS assessors to the motor's phase since UPDRS in clinical practice is usually administered by professionals who are aware of the motor phase of the patient at the time of evaluation. The local Ethical Committees approved the research protocol in each study site. All participants signed an informed consent form before their inclusion in the study.

The sensor consisted of a 9 × 2 device, which was worn by patients at the waist through a neoprene belt. This sensor includes a triaxial accelerometer (13). Its measurements were treated by a signal processing algorithm that analyses patient's gait. The algorithm firstly detects gait by using a machine learning technique (Support Vector Machines), which was trained through labeled signals from 10 PD patients of a previous study (14). Second, the algorithm segments the signals into strides by recognizing specific characteristics on the acceleration measurements. Each individual stride is then characterized through a single frequency feature consisting of the power spectra between 0 and 10 Hz. This feature provides a scalar value whose range is usually 3–6 for patients in Off, and 7–10 for patients in On. In a previous study (10), patients in On state provided higher values of this feature than patients in Off state; hence, this frequency feature is expected to be negatively correlated with UPDRS scores. The algorithm analyses walking bouts with 10 or more strides. Patients during the data collection may walk several times; thus, for each patient and motor state, features obtained in the walking bouts done during a data collection were separately averaged, and the resulting value from each patient and motor state was compared to UPDRS.

For data analysis, bivariate correlations (Spearman) were conducted between the numerical results of the algorithm and the UPDRS-III. More concretely, we obtained the correlation

between the algorithm outputs and the total UPDRS-III and, furthermore, between the algorithm outputs and the UPDRS-III items. Every patient was included twice in the same analysis: the first time while he/she was in the Off phase and the second time while in the On phase. For the sake of clarity, we would like to note that each correlation value was obtained by using a single input variable (scalar algorithm results) and a single output variable (UPDRS values, as previously described).

RESULTS

A total of 75 patients fulfilled the required criteria and their data were complete. The clinical and sociodemographic characteristics of the sample are shown in **Table 1**.

The correlation between UPDRS-III and algorithm outputs was −0.56 ($p < 0.001$). The correlation with the gait item of UPDRS-III was −0.73 ($p < 0.001$). **Figures 1** and **2** show scatter plots of the algorithm output against UPDRS-III total score and against the gait item of the scale. The correlation of the rest of items in the motor section of UPDRS with the algorithm outputs is shown in **Table 2**. The factorial analysis of the UPDRS-III had previously shown that the following items are clustered in one factor: speech, facial expression, arising from a chair, gait, postural stability, posture, and body bradykinesia [Factor 1: "axial function, balance, and gait" (15)]. The correlation between the algorithm output and Factor I was −0.67 ($p < 0.01$).

DISCUSSION

According to the most widely used interpretation of the correlation coefficient, the algorithm outputs are moderately correlated with the UPDRS-III (16). Some items of the UPDRS-III, related to axial function, are well correlated with the algorithm results: gait, arising from chair, global bradykinesia, and posture. Such

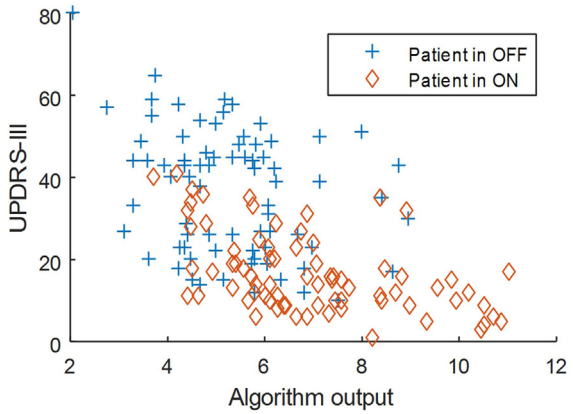

FIGURE 1 | Scatter plot of the algorithm output against UPDRS-III total score.

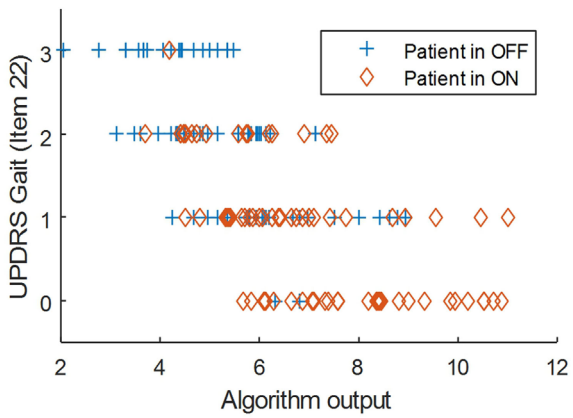

FIGURE 2 | Scatter plot of the algorithm output against UPDRS Gait (item 22).

TABLE 1 | Characteristics of the participants.

	Mean	SD
Age	68.6	7.4
Years of disease progression	11.6	1.5
	n	**%**
Women	27	36
Men	48	64
Married	61	81.3
Single/widower	14	18.7
Dyskinesia		
No	28	37.3
Yes	47	62.7
	Median	**IQR**
Unified Parkinson's Disease Rating Scale Part-III*		
Off	40	25
On	15	13
Mini-mental	29	3
H&Y	3	0.5
FOG-Q	13.5	7.5

*$p < 0.001$.

TABLE 2 | Spearman's correlation coefficient between the Unified Parkinson's Disease Rating Scale-motor items and the data from algorithm.

Item #	Description	Rho	*p*
22	Gait	−0.729	**<0.001**
20	Arising from chair	−0.627	**<0.001**
24	Body bradykinesia and hypokinesia	−0.548	**<0.001**
21	Posture	−0.536	**<0.001**
2	Facial expression	−0.469	**<0.001**
1	Speech	−0.464	**<0.001**
10 + 11	Lower extremities rigidity	−0.453	**<0.001**
8 + 9	Upper extremities rigidity (both)	−0.435	**<0.001**
23	Postural stability	−0.419	**<0.001**
18 + 19	Legs agility (both)	−0.340	**<0.001**
7	Axial rigidity	−0.332	**<0.001**
16 + 17	Alternating movements of hands (both)	−0.322	**<0.001**
12 + 13	Finger taps (both)	−0.314	**<0.001**
14 + 15	Hand grips (both)	−0.297	**<0.001**
3	Tremor lower extremities	−0.253	**0.002**
5	Tremor upper extremities	−0.182	**0.026**
4	Tremor face, lips, chin	−0.129	0.116
6	Action tremor of hands	−0.008	0.924

Bold type: significant results.

items are part of the so-called Factor 1 of the UPDRS, which also includes facial expression and postural stability. Therefore, the correlation with the complete Factor 1 of the UPDRS-III is also good. On the other hand, a low correlation is found for items related to tremor and hand grips with values between −0.3 and 0. These low correlations were expected given that the algorithm analyses gait based on acceleration measurements obtained from the waist.

In a similar work, Weiss et al. (17) tested an accelerometer, placed in the lower back, on 22 Parkinson patients while walking. Their sample of patients was about the same age and sex distribution than ours, although in average had less severe disease: H&Y = 2.5; UPDRS motor in Off = 23.6 ± 9.4; and 4.8 (SD3.8) years of disease progression. The test included a 1-min straight walk in On and Off state and a 500-m walk around the hospital at their self-selected speed. This latter test was only performed in On state. They did not find correlations between the acceleration measures and the UPDRS motor or the Hoehn and Yahr scale; however, they found a lower correlation (Pearson's = 0.5) between the average stride time and a subset of gait related items of the UPDRS (UPDRS-Gait5): falling, freezing of gait, walking, postural stability, and gait. The lack of significant correlation may be due to using the locomotor band of 0.5–3 Hz, which is suitable for acceleration measurements sensed from the lower limbs but does not match the locomotor band from waist measurements (usually quite above 3 Hz, until 10 Hz).

Zwartjes et al. (18) used four accelerometers and gyroscopes in feet, thigh, chest, and arms, to assess bradykinesia in six Parkinson patients. Their methodology is based on analyzing the signals from the four sensors to extract gait parameters, such as step length and step velocity, and other temporal features such as duration of a standing position and some hand movements. They found good correlations between parameters related to step length and step velocity with the item of body-bradykinesia of the UPDRS-III (rho = 0.7); however, they did not investigate global correlations with the UPDRS-III. These results suggest that step length is well correlated with bradykinesia UPDRS; however, the limited number of patients of their study limits the generalization of the results. For this experiment, they used patients with DBS, who were measured under three conditions: "On" (stimulator at the optimal settings), "Intermediate" (stimulator at a stimulation amplitude of 80% of the optimal setting), and "Off" (stimulator Off). Interestingly, the score derived from their algorithms did not differ significantly between the "Off," "Intermediate," and "On" states; this makes a difference with our algorithm, whose outcomes identifies the On and Off phases with high validity, as published before (10).

Griffiths et al. (19), using the wrist-worn Parkinson's Kinetigraph (Global Kinetics Corporation) in 34 patients with Parkinson's, established the correlation of a *bradykinesia score* with UPDRS-III (Pearson: 0.64); the bradykinesia score was defined as the mean spectral power surrounding the maximum acceleration within a 2-min epoch. For this correlation, a single measure of the UPDRS in On was compared with the average *bradykinesia score* obtained from 10 days of measurement (no data are provided on the severity of the patients' disease). It does not appear that the UPDRS would have been administered in Off at any time and they do not provide data on patients' Off time during the 10 days, so it is not clear how much their algorithm correlates with the scale when the patient moves worse. Also, they did not report correlations with specific items or subscales of the UPDRS-III to compare with.

Although other studies with acceleration measurements exist, it is difficult to compare the results, as they did not use correlations with the UPDRS, or they focused on other very specific tasks of the scale, such as tremor or dyskinesia items, which are unrelated to our algorithm.

Classical methods to assess Parkinson's symptoms include questionnaires that are administered in the office, which collect information reported by the patient, and measurement instruments based on physical exams, such as the UPDRS. The former are affected by memory bias and the latter only record the motor state at the time of exploration (advanced Parkinson's is a fluctuating pathology; therefore, the symptoms present at the consultation time, may not represent well the whole clinical picture). As a consequence, the classic instrument often used as gold standard is the diary of motor fluctuations, which has to be filled by patients for several days. The problem is that these diaries also have their limitations, as some patients do not recognize their symptoms and patients' adherence to the method is poor, since recording symptoms' timeline is a hard task, difficult to complete beyond few days (20). On the other hand, sensors are not subject to memory bias or awareness of symptoms and do not require human intervention so they could be used in the long term if needed. However, sensors-based systems could have usability problems that have to be carefully addressed, and adherence of patient to such systems has to be demonstrated yet.

We agree with those who argue that the correlation of the new objective instruments (sensors), with the classic clinical scales, does not have to be perfect (1). The classical instruments are more qualitative, and are influenced by multiple variables; thus, a high correlation between them and pure quantitative measurements, such as the accelerometer signal, is not expected. In addition, it is the limitations of the classical instruments that prompt researchers to search for new methods of assessment; therefore, the perfect correlation of new methods with the old ones would only indicate that the former are no better than the later. It is to be demonstrated in future studies whether the measurements of the new sensors lead or not to a better clinical control, compared to the traditional methods, although it is likely that, at least in the case of patients who do not recognize their motor fluctuations correctly, sensors would improve the time mapping of the motor phase. Furthermore, we think that the sensors would describe the motor phase better than the diaries, in those moments in which the patients are not clearly in Off or On, but in an intermediate state or switching the phase.

Our algorithm is limited by the fact that it is an algorithm that analyses the patient's gait, which means that it does not provide data on motor status if the patient does not walk. The authors believe that this limitation is not very important in clinical practice, since patients with Parkinson's who walk, do so multiple times a day, producing enough data to map symptoms

related with axial function (21, 22). In any case, the information of our sensor could be supplemented with additional sensors (for example, in the extremities), in the event that a more exhaustive monitoring of the motor state were required. In addition to this, a further correlation analysis on a more extensive population of PD patients may help to ensure the reliability of the measurements taken from the strides.

The studied algorithm has previously proven to accurately detect the Parkinson's motor phase (On or Off) (10). Our present results encourage the interpretation that the measurements of the algorithm correspond to the patient's axial function, especially the influence of bradykinesia on the gait. The observation that the algorithm may monotonically decrease with the UPDRS-III scale suggests that the values offered by the algorithm have a diagnostic value and are more discriminative than the mere dichotomous On/Off classification. Therefore, this kind of algorithm might be an excellent tool for monitoring patients with Parkinson's disease and motor fluctuations related to patient's axial function.

ETHICS STATEMENT

The local Ethical Committees approved the research protocol in each study site. All participants signed an informed consent form before their inclusion in the study.

AUTHOR CONTRIBUTIONS

AR-M conceived the study, designed the study and drafted the first version of the manuscript AS, CP-L, DR-M, and MMA contributed to the study design, and performed algorithmic work and statistical analysis. They contributed to and approved the final version of the manuscript. SA, BM, PQ, BG, GV, PB, DS and LRQ performed the field work and approved the final version of the manuscript. AB, HL, AC, RA, TC, and GOL contributed to the study design and data collection in their respective study site. They contributed to and approved the final version of the manuscript. JC contributed to the study conception, coordinated the project in the different study sites and approved the final version of the manuscript.

FUNDING

This work has been performed in the framework of the FP7 project REMPARK ICT-287677, which is funded by the European Commission. The authors would like to acknowledge the contributions of their colleagues from REMPARK Consortium (http://www.rempark.eu). The study was partially supported by the Monitoring the Mobility of Parkinson's Patients for Therapeutic Purposes Project (PI12/03028), funded by the Instituto de Salud Carlos III–Ministerio de Economía y Competitividad and the European Regional Development Fund.

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Conflict of Interest Statement: AR-M, AS, CP-L, JA, and JC are shareholders of Sense4Care, which is a spin-off company, which may commercialize the results of this research device in future. These authors declare that the possible commercialization of the product is a research outcome, not being the design, the analysis, the interpretation of the results, or the conclusions being affected by commercial interests. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

METHODS
published: 04 September 2017
doi: 10.3389/fneur.2017.00457

Validation of a Step Detection Algorithm during Straight Walking and Turning in Patients with Parkinson's Disease and Older Adults Using an Inertial Measurement Unit at the Lower Back

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OPEN ACCESS

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 17 May 2017
Accepted: 17 August 2017
Published: 04 September 2017

Citation:
Pham MH, Elshehabi M, Haertner L, Del Din S, Srulijes K, Heger T, Synofzik M, Hobert MA, Faber GS, Hansen C, Salkovic D, Ferreira JJ, Berg D, Sanchez-Ferro Á, van Dieën JH, Becker C, Rochester L, Schmidt G and Maetzler W (2017) Validation of a Step Detection Algorithm during Straight Walking and Turning in Patients with Parkinson's Disease and Older Adults Using an Inertial Measurement Unit at the Lower Back. Front. Neurol. 8:457. doi: 10.3389/fneur.2017.00457

Introduction: Inertial measurement units (IMUs) positioned on various body locations allow detailed gait analysis even under unconstrained conditions. From a medical perspective, the assessment of vulnerable populations is of particular relevance, especially in the daily-life environment. Gait analysis algorithms need thorough validation, as many chronic diseases show specific and even unique gait patterns. The aim of this study was therefore to validate an acceleration-based step detection algorithm for patients with Parkinson's disease (PD) and older adults in both a lab-based and home-like environment.

Methods: In this prospective observational study, data were captured from a single 6-degrees of freedom IMU (APDM) (3DOF accelerometer and 3DOF gyroscope) worn on the lower back. Detection of heel strike (HS) and toe off (TO) on a treadmill was validated against an optoelectronic system (Vicon) (11 PD patients and 12 older adults). A second independent validation study in the home-like environment was performed against video observation (20 PD patients and 12 older adults) and included step counting during turning and non-turning, defined with a previously published algorithm.

Results: A continuous wavelet transform (cwt)-based algorithm was developed for step detection with very high agreement with the optoelectronic system. HS detection in

PD patients/older adults, respectively, reached 99/99% accuracy. Similar results were obtained for TO (99/100%). In HS detection, Bland–Altman plots showed a mean difference of 0.002 s [95% confidence interval (CI) −0.09 to 0.10] between the algorithm and the optoelectronic system. The Bland–Altman plot for TO detection showed mean differences of 0.00 s (95% CI −0.12 to 0.12). In the home-like assessment, the algorithm for detection of occurrence of steps during turning reached 90% (PD patients)/90% (older adults) sensitivity, 83/88% specificity, and 88/89% accuracy. The detection of steps during non-turning phases reached 91/91% sensitivity, 90/90% specificity, and 91/91% accuracy.

Conclusion: This cwt-based algorithm for step detection measured at the lower back is in high agreement with the optoelectronic system in both PD patients and older adults. This approach and algorithm thus could provide a valuable tool for future research on home-based gait analysis in these vulnerable cohorts.

Keywords: accelerometer, gait analysis, home-like activities, older adults, Parkinson's disease, turning

INTRODUCTION

Gait deficits are common in older adults (1) and Parkinson's disease (PD) patients, even in early disease stages (2, 3). They are associated with an increased risk of falling and reduced quality of life (4, 5). Temporal step parameters are crucial in describing the quality of gait, e.g., to calculate the risk of future falls and response to treatment. Examples are variability of stride time and kinematics (6, 7), gait speed (8), and symmetry (9). Heel strike (HS) and toe off (TO) (10, 11) are critical events during a gait cycle because they define the beginning and the end of every stance and swing phase, respectively (12) and enable the calculation of all of the above parameters.

Several methods have been successfully utilized to extract time-related gait parameters, including optical systems (13, 14), instrumented walkways (12, 15), and treadmills (16). However, such equipment is expensive, restricted to specialized laboratories, and can thus not be applied in large populations and in home environments. This is a relevant drawback, as the home environment may be the most appropriate setting to capture and study gait related issues that are relevant to the patient's daily functioning (17, 18), rather than constrained lab settings.

Wearable sensors, such as inertial measurement units (IMUs), are relatively cheap, light-weight, easy to use, and therefore a promising alternative approach for data collection in the home environment (19, 20). They are particularly useful for gait analysis, as shown in a relatively large number of studies, e.g., in healthy adults (21, 22) older adults (23), and patients with PD (24). However, for the use of such devices under medical conditions, a thorough validation of detection algorithms is necessary and must be performed in every single population presenting specific gait impairments (17). Furthermore, movement detection algorithms should be able to differentiate between gait episodes, such as straight walking and turning. Parameters like the number of steps during turning might be robust indicators of gait impairment in PD (25, 26). This differentiation could help detecting context-dependent gait deficits, as shown to occur in older adults with poor cognitive flexibility (27).

The algorithm development for IMUs is under constant improvement. Various step detection algorithms have been proposed, but their validation is limited to laboratory settings, and an extrapolation of the results to home-like environments is often lacking. Measurements in the laboratory are very controlled and do not necessarily correspond to real-world applications. Therefore, assessments in home-like environments are of crucial importance and a challenge when detecting gait impairments based on laboratory algorithms. Based on the lack of home-like validated algorithms, this paper presents a detection algorithm for HS and TO for home-like environments. The algorithm is first validated against an optoelectronic system during treadmill walking, in PD patients and older adults and second validated in an unconstrained environment using video footage. To the best of our knowledge, this is the first step detection algorithm using data obtained from an IMU at the lower back with very good accuracy, demonstrated across these divergent conditions in two different vulnerable populations and during different movement episodes.

METHODS

Study Participants and Settings

Lab-Based Assessment

We performed the lab-based sub-study at the Robert Bosch Hospital, Stuttgart, Germany. It was approved by the ethics committee of the Medical Faculty at the University of Tübingen (protocol number 602/2012BO1). All participants provided written informed consent before they were included in the study. Patients were recruited from the outpatient clinic of the Neurology department at the University Hospital of Tübingen, Germany and were diagnosed by movement disorder specialists (Karin Srulijes and Walter Maetzler). Controls were recruited with the support of the office of Sport and Exercise and the Bosch BKK health insurance (Stuttgart, Germany). Exclusion criteria for both groups were inability to walk without walking aids for at least 20 m and the existence of additional neurological disorders. The analyses presented here are part of a larger study that focused on gait and

eye movement interaction (28). The training group for the development of the algorithm consisted of three PD patients and two older adults who were randomly chosen from the dataset. The remaining participants (11 PD patients and 12 older adults) of the treadmill assessment were assigned to the test group. **Table 1** provides demographic and clinical data of the two groups.

TABLE 1 | Demographic and clinical data of the training and test groups.

	PD patients	Older adults
LAB ASSESSMENT		
Training cohort 1		
N (females)	3 (2)	2 (1)
Age (years)	72.3 (4.7)	71.0 (2.8)
MDS-UPDRS III (0–132)	26 (15)	2 (2)
H&Y (0–5)	2 (1)	0 (0)
LED (mg)	640 (353)	0 (0)
Test cohort 1		
N (females)	11 (5)	12 (4)
Age (years)	74.7 (7.2)	70.8 (3.0)
MDS-UPDRS III (0–132)	39 (9)	1 (2)
H&Y (0–5)	3 (1)	0 (0)
LED (mg)	540 (298)	0 (0)
HOME-LIKE ASSESSMENT		
Training cohort 2		
N (females)	4 (2)	2 (1)
Age (years)	69.3 (3.6)	63.0 (17.0)
MDS-UPDRS III (0–132)	20 (8)	1 (0)
H&Y (0–5)	2 (1)	0 (0)
LED (mg)	683 (735)	0 (0)
Test cohort 2		
N (females)	21 (11)	12 (6)
Age (years)	66.4 (9.0)	58.4 (8.9)
MDS-UPDRS III (0–132)	32 (12)	2 (4)
H&Y (0–5)	3 (1)	0 (0)
LED (mg)	841 (604)	0 (0)

Data are shown as mean ± SD, except gender.
H&Y, Hoehn and Yahr; LED, Levodopa equivalent dose; PD, Parkinson's disease; MDS-UPDRS III, motor part of the revised Unified PD Rating scale.

All participants were equipped with 15 reflective markers [head (front, top, and back), trunk (jugulum, seventh cervical vertebra, and fifth lumbar vertebra), right/left arms, and right/left heel and toe; the "gold standard system"]. A six-camera Vicon T10 system (Vicon© Motion Systems Ltd., UK) (28) collected gait information from the reflective markers. The participants were also equipped with the Dynaport® Hybrid, sample rate 100 samples/s, 3DOF accelerometer (range ±2 g), and 3DOF gyroscope (range ±100°/s) (McRoberts BV, Netherlands) at the lower back (the "experimental system").

During the 120s assessment, all participants walked on a treadmill (h/p/cosmos venus, h/p/cosmos sports medical GmbH, Germany) at their preferred speed. PD patients were tested ON medication. Manual markers set with the Dynaport® Hybrid system at the beginning and the end of each 120s test period allowed *post hoc* synchronization of the gold standard and the experimental system. The comparison regarding the detection of step events from both systems was evaluated by one independent clinical observer (Morad Elshehabi). **Figure 1** illustrates the experimental setting that was used in the lab assessment to provide a reliable HS and TO event detection. Treadmill walking guarantees regular straight walking, and the accuracy of the developed algorithm can be evaluated before being applied to more complex movements.

Home-Like Assessment

We performed the home-like sub-study at the University of Tübingen, Germany. This sub-study was approved by the ethics committee of the Medical Faculty at the University of Tübingen (protocol number 399/2012BO2). The study population consisted of a training group of 4 PD patients and 2 older adults, and a test group of 20 PD patients and 12 older adults. Four PD

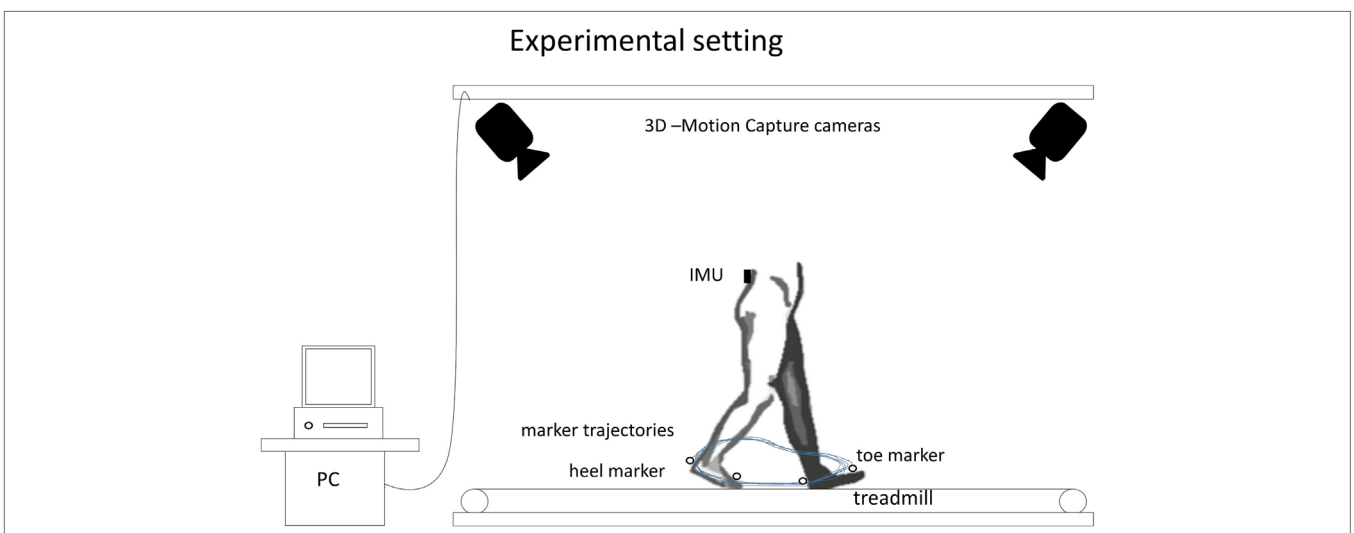

FIGURE 1 | Experimental setting of the lab assessment showing the inertial measurement unit (IMU) position on the lower back, and the heel and toe markers to identify heel strike and toe off using the optoelectronic motion capture system.

patients with challenging symptom constellations (e.g., tremor and dyskinesia) were chosen by Walter Maetzler, to increase specificity of the algorithm. Two older adults were randomly chosen from the database. The remaining participants of the home-like assessment were assigned to the test group. Patients were recruited from the inpatient and outpatient clinics of the Neurology department, University Hospital of Tübingen, and were diagnosed by a movement disorder specialist (Walter Maetzler). Exclusion criteria were deep brain stimulation, Hoehn and Yahr score >3 and Mini Mental State Examination score <24. **Table 1** provides demographic and clinical parameters of the groups.

All participants were equipped with the OPAL system, sample rate 128 samples/s, 3DOF accelerometer (range ±16 g) and 3DOF gyroscope (range ±2,000°/s) (APDM, Inc., Portland, OR, USA). Data obtained from the IMU at the lower back were used for this analysis.

During the 180min (for PD patients) and 90min (for older adults) assessment, all participants were asked to perform daily-life activities such as moving around the labs and corridors, walking backwards, climbing stairs, performing transfers (sit-to-stand and stand-to-sit movements), making coffee, brushing teeth, and ironing clothes without any further restriction. During the whole process, one of the authors (Tanja Heger) followed the participant with a hand-held camera (Sony, resolution 1,920 × 1,080 pixels, frame rate 50 samples/s). Videos were evaluated by two clinical observers (Linda Haertner and Morad Elshehabi), to identify gait bouts, to label turning, and to count the number of steps per bout (29). We discarded those periods in which the feet of the participant were out of sight of the camera (7% of the total time of assessment).

Algorithm Development and Structure (Training Groups)

The algorithm was based on the continuous wavelet transform (cwt) approach. This was justified by previous studies that have shown very good results when extracting HS and TO events in healthy adults and PD patients under constrained condition (12, 30). From the lab-based assessment, HS and TO events were extracted from the anterior–posterior (AP) acceleration of the IMU and compared to the spatial signal of the heel and the toe markers of the Vicon system. From the unconstrained home-like assessment, we extracted only HS information, as the gold standard used in this study does not allow differentiating between HS and TO. **Figure 2** provides the general structure of the algorithm.

Extraction of HS and TO from the Vicon System

HS and TO were extracted from the active Vicon markers from the left heel, right heel, left toe, and right toe. Details are provided in the legend of **Figure 3**. The bottom of the (left/right) heel marker curves, reflecting HS, and the top of the (left/right) toe marker curves, reflecting TO, were detected with the *findpeaks* Matlab function (Matlab R2015b).

Extraction of HS and TO from IMU

The algorithm for HS and TO detection from IMU data is illustrated in **Figure 3** (12). The AP acceleration was preprocessed by linear de-trending and low-pass filtering at 10 Hz with a second-order Butterworth filter. The preprocessed signal was integrated (with *cumtrapz*) and differentiated by cwt (with the *cwt Matlab* function), using an estimated wavelet scale and Gaussian first-order (*gaus1*) wavelet.

The algorithm for wavelet scale estimation was based on the method by Abry (31). The most dominant frequency from the spectrum of the AP acceleration signal was selected and converted to the scale:

$$a = \frac{F_c}{F_a \cdot \Delta},$$

where a is the scale, F_c is the center frequency (Hz) of the wavelet, F_a is the most dominant frequency (Hz) (pseudo-frequency corresponding to the scale), and Δ is the sampling period (s).

Figure 3 illustrates results of HS and TO detection based on the Vicon and the IMU system. The local minima of the differentiated signal (first-order differentiated signal) were the detected HS points (with the *findpeaks* function). The first-order differentiated signal was differentiated again by similarly using cwt with estimated scale and Gaussian second-order (*gaus2*) wavelet, yielding a second-order differentiated signal. The local maxima of the latter signal were defined as TO (*findpeaks* function). The condition for the local extremes to be considered as HS/TO was

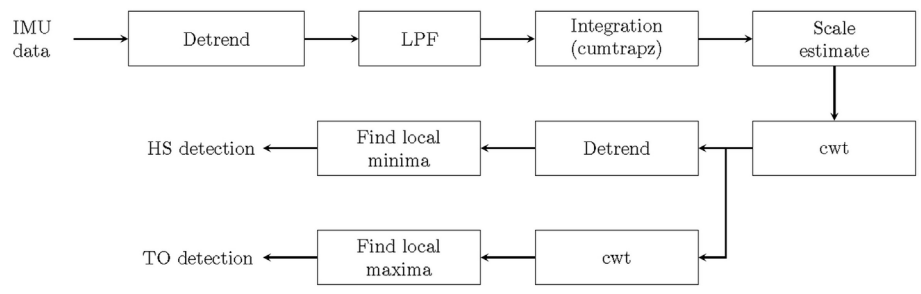

FIGURE 2 | Heel strike (HS) and toe off (TO) detection using continuous wavelet transform (cwt) algorithm. IMU, inertial measurement unit; LPF, low-pass filter.

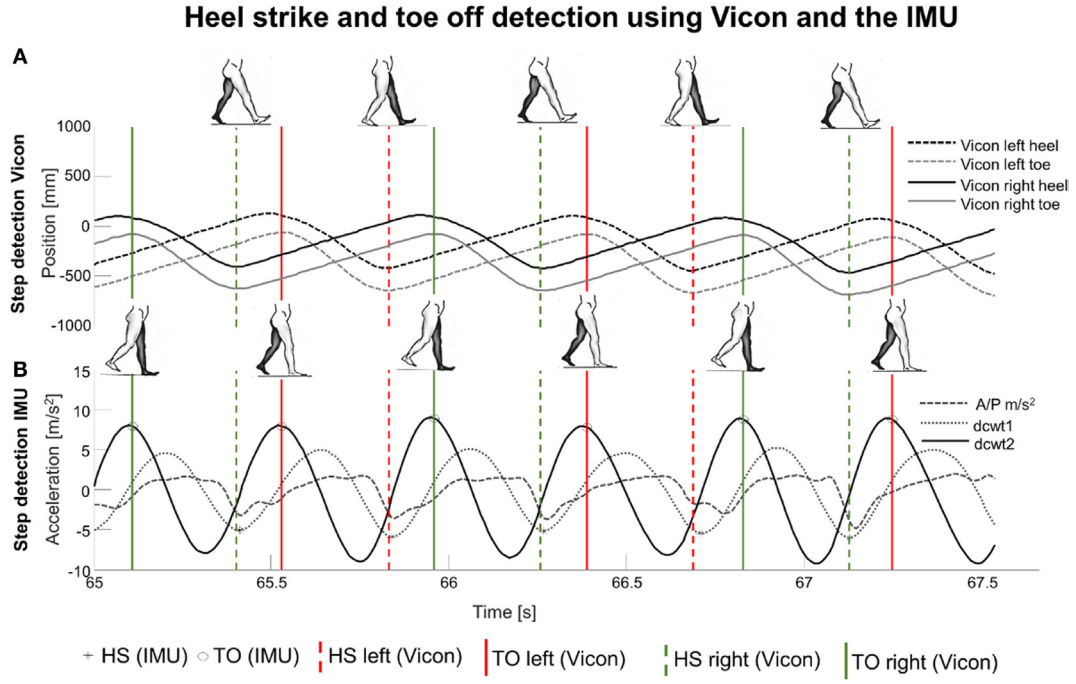

FIGURE 3 | **(A)** Heel strike (HS) and toe off (TO) were detected from the anterior–posterior (AP) coordinates of the heel and toe markers (gold standard). **(B)** Event detection from both feet, from AP acceleration (dashed line), its first-order differential continuous wavelet transform (dcwt) (dotted line, dcwt1) and its second-order dcwt (solid line, dcwt2). Black stars indicate HS, and black circles indicate TO. Dashed and solid vertical lines enable the comparison of the two methods to detect HS and TO, showing an overall good correspondence between them.

as follows: magnitude >40% of the mean of all peaks detected by the *findpeaks* function.

Adaptation of the cwt to the Steps in the Home-Like Assessment

The IMU dataset for home-like assessment was split into two datasets, to evaluate step occurrence (1) during turning periods and (2) during non-turning periods. For the definition of turning periods, an algorithm recently published by our group was used (29). In brief, a change of the yaw angle (i.e., around the vertical axis) with a magnitude >90° and a duration between 0.5 and 10 s was defined as a turn.

As the shape of the integrated AP acceleration of usual steps differed slightly between the lab-based study and the home-like assessment (**Figure 3**), we adapted the wavelets in the home-like assessment as follows: We used a *gaus2* wavelet for step detection during turning periods and a Daubechies second-order (*db2*) wavelet for step detection during non-turning periods. Forty percent of the mean of all peaks detected by the *findpeaks* function served again as the threshold for step definition.

Statistical Analysis

Analyses were performed with JMP 11.1.1 software. Mean and standard deviation (SD) were used to present demographic and clinical data of the groups.

For comparison of HS and TO detection, contingency tables were designed and χ^2 tests conducted to test the relationship between methods and groups. Following the χ^2 tests, the likelihood ratio (LR) was calculated to measure the association between the two methods.

As the dataset does not allow extracting "true negative steps," we present total numbers of steps detected by the methods and accuracy values. True positive HS and TO from IMU were defined as <0.3 s difference relative to the respective Vicon event. Bland–Altman plots were created to evaluate the difference between the HS/TO events from the IMU and the HS/TO events from the gold standard.

For the analysis of the home-like assessment, intraclass correlation (ICC) was used to test the agreement of the step detection between the clinical observers. The ICC shows how likely a step was detected by the first clinical observer and also detected by the second clinical observer. We then calculated Cohen's kappa, true positive, true negative, false positive, and false negative steps during turning and non-turning episodes (including straight walking, shuffling and walking backward episodes), respectively, from the IMU dataset based on the contingency tables. Cohen's kappa yields the level of agreement between the steps detected by the algorithm and the steps detected by the clinical observers. In this dataset, we defined true negative steps as being below the step detection threshold (≤40%) introduced in the Section "Algorithm Development and Structure (Training Groups)."

RESULTS

Validation

In the lab assessment, for the whole group (which is presented here because no relevant differences occurred between the investigated groups; data available on request), the total number of HS/TO detected by Vicon was 2,730/2,739; by the IMU it was 2,729/2,732. Based on the 0.3s threshold, 9 HS/5 TO were considered false positives, and 10/12 false negatives. Accordingly, accuracies for HS/TO detection were 99/99% for all participants, 99/99% for PD patients, and 99/100% for older adults. LR calculated from χ^2 was 0.8 and 0.83 for HS and TO, respectively. Bland–Altman plots showed a mean difference between IMU and Vicon of 0.00 s (95% CI, −0.09 to 0.10) for HS detection, and of 0.00 s (95% CI, −0.12 to 0.12 s) for TO detection (**Figure 4**).

In the home-like assessment, the ICC for step detection between clinical observers was 96%. During turning episodes, the total number of steps detected by clinical observers was 4,831;

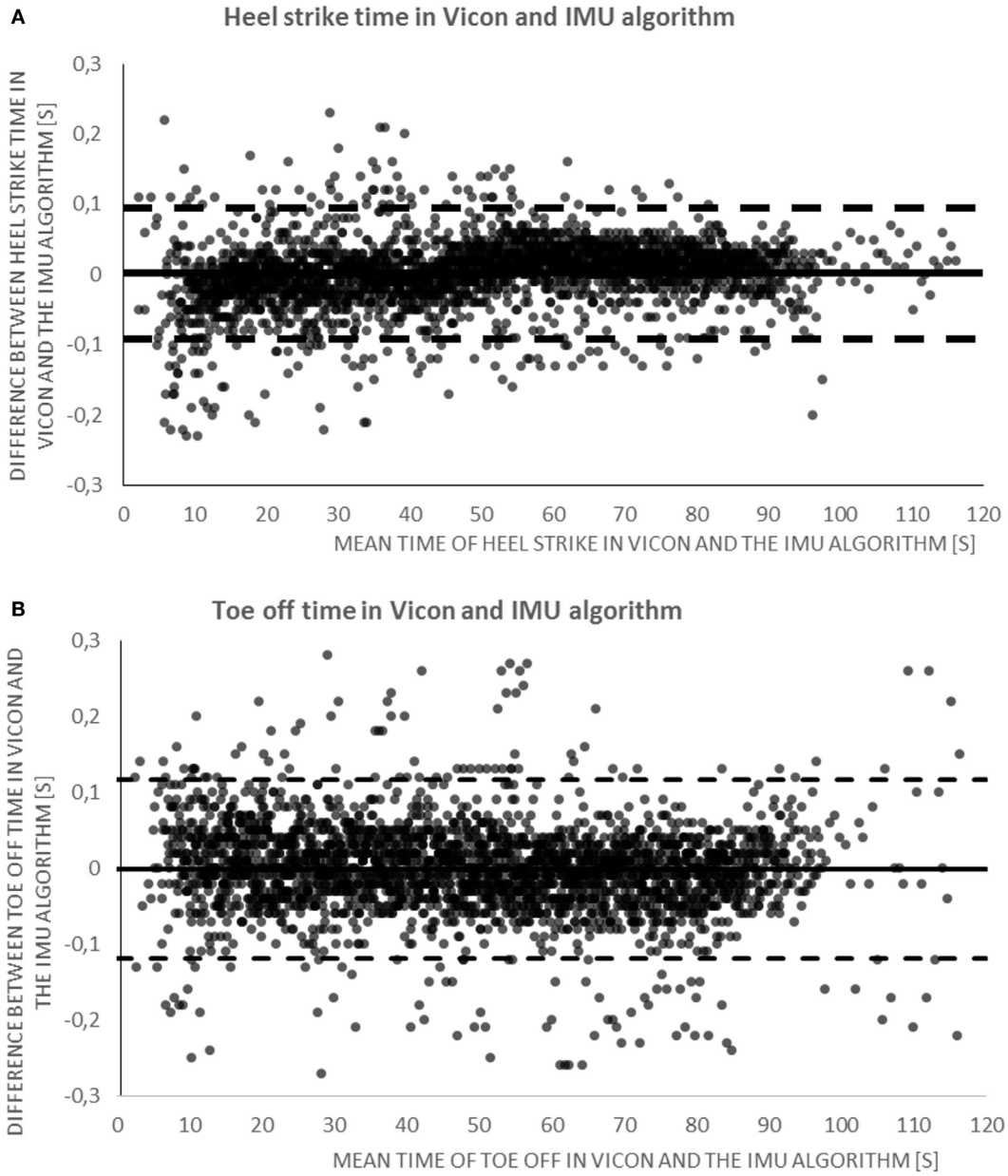

FIGURE 4 | **(A)** Bland–Altman plot illustrating the agreement for time of heel strike detection between the algorithm and the gold standard. The continuous line is the mean, and dashed lines are the 95% confidence intervals (CIs) of step observation difference (in seconds). **(B)** Bland–Altman plot illustrating the agreement for time of toe off detection between the algorithm and the gold standard. The continuous line represents the mean, and dashed lines are the 95% CI of step observation difference (in seconds). IMU, inertial measurement unit.

the IMU detected 5,020 steps. During non-turning episodes, the total number of steps detected by clinical observers was 19,885, and from IMU data it was 21,313. During turning episodes, we obtained accuracies for step detection by IMU of 88% for PD patients and 89% for older adults. The corresponding accuracy values for non-turning episodes were 91 and 91%, respectively. **Table 2** provides detailed information about the validation values for these analyses.

DISCUSSION

We present in this paper an algorithm for step detection during non-turning walking episodes on a treadmill and during turning and non-turning walking episodes in a home-like assessment, using a single IMU worn at the lower back. The algorithm was tested in PD patients and older adults and yielded very good accuracy. It might thus provide a valuable tool for future daily-life-like assessments of gait in these cohorts.

One of the major advantages of the algorithm is the consideration of steps during turning. Assessment of steps during turning episodes is frequently omitted in current research (12, 23). Although the accuracy values for step detection during turning were slightly lower than during straight walking episodes (88% compared to 91%), results are still promising and indicate the suitability of the algorithm for gait assessment in daily-life conditions. Moreover, the algorithm showed high accuracy during non-turning episodes, which included stepping on the spot and walking backwards.

This algorithm is reliable in both, lab assessments and home environment, with the adaptation of the used wavelet types. We think that such adaptation of algorithms can substantially increase their validity, and even might be promising when used at an individual level. Such approaches have already been introduced in commercially available step detection systems used in the health and fitness sector, and validated for questionnaire-based assessment in diseases such as cerebral palsy (32, 33). Previous studies demonstrated the frequent challenge to compare results from the lab versus the home environments, as the patients behave differently and show more complex movements in the home environment (18, 34–36). The reliability of the current algorithm in home-like environment indicates its applicability in future assessments of PD patients and older adults in more natural unobtrusive surroundings.

The higher accuracy of the algorithm in the lab assessment versus the home-like environment might not only be due to more regular and "simpler" stepping patterns on the treadmill compared to free living-like movements, but also to the higher accuracy of the gold standard in the lab assessment [Vicon (37, 38) versus video observation, visual classification of a step belonging to a turn or non-turn episode]. Assessment based on clinical observers bears several limitations, e.g., that clinical observers can inaccurately define a step as part of a turning episode (39).

Our algorithm showed comparable validity in our average moderately affected PD patients and in older adults. This finding implies that motor impairments, in particular gait deficits, do not limit the reliability of our algorithm given that individuals can walk without aid. This aspect may be essential to the applicability of the algorithms in different healthy and pathological conditions. Previous algorithms used the vertical acceleration for step detection (12, 30). However, we opted to applying the AP acceleration, which is also an established method, already used in previous studies (23, 40, 41). The vertical acceleration may have better accuracy, but it yielded a more complex pattern in our training dataset in particular in the home-like environment data, which reduced the signal's regular consistency (40).

The following limitations should be considered in future studies and algorithm development. In the home-like assessment, the gold standard (videotaping) allowed only the validation of step occurrence, but not of HS and TO. Therefore, it was not possible to validate qualitative step parameters (for example, step time, stance time, and swing time), although the algorithm provides these data. Based on the very good results from the treadmill evaluation, we are optimistic that HS and TO parameters extracted from the algorithm in the home-like assessment would also be valid. This hypothesis has to be evaluated in future studies using, e.g., instrumented shoes and insoles. Instrumented shoes with feet IMUs (23) and instrumented insoles (42) provide HS and TO event detection and can be used in home-like conditions (23, 42). Another

TABLE 2 | Validation values for steps detection in the home-like assessment.

Cohorts	Cohen's kappa (%)	Acc (%)	Sens (%)	Spec (%)	NPV (%)	PPV (%)	Steps detected by algorithm	Steps detected by clinical observers	True positive steps	False positive steps	False negative steps	True negative steps
Turning episodes												
Overall cohort	73	88	90	85	78	94	5,020	4,831	4,517	314	503	1,730
PD patients	70	88	90	83	75	94	3,618	3,484	3,257	227	361	1,083
Controls	77	89	90	88	82	94	1,402	1,347	1,260	87	142	647
Non-turning episodes												
Overall cohort	72	91	91	90	69	98	21,313	19,885	19,429	456	1,884	4,096
PD patients	71	91	91	90	67	98	15,522	14,493	14,181	312	1,341	2,738
Controls	74	91	91	90	71	97	5,791	5,392	5,248	144	543	1,358

Acc, accuracy; NPV, negative predictive value; PD, Parkinson's disease; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

limitation is the choice of wavelet types and thresholds for step detection. We made these choices of the wavelet types and threshold based on visual inspection of the AP acceleration in the training groups. It is still possible that other wavelet shapes and threshold values yield even better accuracy in these populations and activities. Furthermore, it is worth noting that the error of 0.1 s in HS and TO detection was not negligible if we want to estimate stride time variability. Although some variation may be explained by physiological differences (e.g., feet and lower back may not always be synchronized), further efforts should be undertaken to reduce this variation and increase the sample size to improve the statistical power and reduce the error of such outliers. Moreover, the sample size could be expanded in future studies to test the validity of the algorithm in a bigger cohort.

This study presents and validates an algorithm for step detection during treadmill walking, during turning and non-turning walking episodes based on data extracted from an IMU at the lower back, for PD patients and older adults. The algorithm was tested with different validation methods: optical markers and videotaping. While the results are promising, future work has to investigate the validity of the algorithm in different disease phases of PD including the prodromal phase and potentially also phases in which patients use walking aids.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Medical Faculty at the University of Tübingen, protocol number 602/2012BO1, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Faculty at the University of Tübingen.

AUTHOR CONTRIBUTIONS

MP and WM were responsible for the conception and design of the study. KS, TH, MS, CB, and WM contributed to acquisition of data. MP, ME, LH, SD, LR, GS, and WM were involved in analysis and interpretation of data. MP and WM drafted the first version of the article. MP, ME, LH, SD, KS, MS, MH, GF, CH, DS, JF, DB, AS-F, JD, CB, LR, GS, and WM revised it critically for important intellectual content. All the authors gave final approval of the version to be submitted.

ACKNOWLEDGMENTS

The authors thank all individuals who took part in the study.

FUNDING

The study was supported by the EU project FAIR-PARK II, funded under the Horizon2020 Program of the European commission (grant no. 633190, PHC13 2014–2015; NCT02655315) and by Lundbeck. The funding sources did not have any role in conception and design of the study, acquisition, analysis, and interpretation of data, and in writing of the manuscript. The authors acknowledge financial support by Land Schleswig-Holstein within the funding program Open Access Publikationsfonds. SD and LR are supported by the Newcastle Biomedical Research Centre (BRC) and Unit (BRU) based at Newcastle upon Tyne and Newcastle University. They are also supported by the NIHR/Wellcome Trust Clinical Research Facility (CRF) infrastructure at Newcastle upon Tyne Hospitals NHS Foundation Trust. KS and MS received financial support from the Forschungskolleg Geriatrie of the Robert Bosch Foundation, Stuttgart, Germany. All opinions are those of the authors and not the funders.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer, FC, and handling editor declared their shared affiliation.

frontiers in Neurology

ORIGINAL RESEARCH
published: 14 August 2017
doi: 10.3389/fneur.2017.00406

L-DOPA and Freezing of Gait in Parkinson's Disease: Objective Assessment through a Wearable Wireless System

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Freezing of gait (FOG) is a leading cause of falls and fractures in Parkinson's disease (PD). The episodic and rather unpredictable occurrence of FOG, coupled with the variable response to L-DOPA of this gait disorder, makes the objective evaluation of FOG severity a major clinical challenge in the therapeutic management of patients with PD. The aim of this study was to examine and compare gait, clinically and objectively, in patients with PD, with and without FOG, by means of a new wearable system. We also assessed the effect of L-DOPA on FOG severity and specific spatiotemporal gait parameters in patients with and without FOG. To this purpose, we recruited 28 patients with FOG, 16 patients without FOG, and 16 healthy subjects. In all participants, gait was evaluated clinically by video recordings and objectively by means of the wearable wireless system, during a modified 3-m Timed Up and Go (TUG) test. All patients performed the modified TUG test under and not under dopaminergic therapy (ON and OFF therapy). By comparing instrumental data with the clinical identification of FOG based on offline video-recordings, we also assessed the performance of the wearable system to detect FOG automatically in terms of sensitivity, specificity, positive and negative predictive values, and finally accuracy. TUG duration was longer in patients than in controls, and the amount of gait abnormalities was prominent in patients with FOG compared with those without FOG. L-DOPA improved gait significantly in patients with PD and particularly in patients with FOG mainly by reducing FOG duration and increasing specific spatiotemporal gait parameters. Finally, the overall wireless system performance in automatic FOG detection was characterized by excellent sensitivity (93.41%), specificity (98.51%), positive predictive value (89.55%), negative predictive value (97.31%), and finally accuracy (98.51%). Our study overall provides new information on the beneficial effect of L-DOPA on FOG severity and specific spatiotemporal gait parameters as objectively measured by a wearable sensory system. The algorithm here reported potentially opens to objective long-time sensing of FOG episodes in patients with PD.

Keywords: Parkinson's disease, freezing of gait, wireless sensors, L-DOPA, inertial measurement unit, gait analysis

OPEN ACCESS

Edited by:
Maurizio Ferrarin, Fondazione Don Carlo Gnocchi Onlus (IRCCS), Italy

Reviewed by:
Massimiliano Pau, Università degli studi di Cagliari, Italy
Martina Mancini, Oregon Health & Science University, United States

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *29 April 2017*
Accepted: *28 July 2017*
Published: *14 August 2017*

Citation:
Suppa A, Kita A, Leodori G, Zampogna A, Nicolini E, Lorenzi P, Rao R and Irrera F (2017) L-DOPA and Freezing of Gait in Parkinson's Disease: Objective Assessment through a Wearable Wireless System. Front. Neurol. 8:406. doi: 10.3389/fneur.2017.00406

INTRODUCTION

Freezing of gait (FOG) is an episodic gait disorder with the paroxysmal interruption of stride or marked reduction in forward feet progression (1), severely affecting quality of life and increasing risk of falls and fractures in patients with Parkinson's disease (PD) (2, 3). In patients with PD, the pathophysiological investigation of FOG is rather challenging since FOG is crucially influenced by a number of cognitive, attentional, emotional, and even ecological factors (4–6). The current clinical evaluation of FOG severity is mainly based on patients' subjective self-reported data that are largely affected by recall bias, thus precluding a clear interpretation of this disorder (7). A further important aspect in the clinical management of PD patients with FOG concerns the response of FOG to L-DOPA that is known to be rather complex and unpredictable. Although FOG most commonly manifests in patients not under dopaminergic treatment, in a number of patients with PD, FOG may persist or even worsen after acute L-DOPA administration (8–12). The objective evaluation of FOG and the response to L-DOPA are therefore critical clinical challenges with relevant impact in the current therapeutic management of patients with PD.

Over recent years, wearable technologies based on inertial measurement units (IMUs) have been increasingly used for the objective evaluation of specific motor symptoms including FOG in patients with PD (13, 14). Objective detection of FOG is currently achieved by using a various number of wearable IMUs with algorithms specifically designed, with time domain or frequency domain approaches, to detect or even predict FOG episodes in PD (13, 15–29). Previous studies have demonstrated that, due to the unobtrusive and wearable features, IMUs are optimal solutions for objective long-term monitoring of FOG in patients with PD, even in a domestic environment (13, 30). Hence, IMUs are also optimal candidates for objective evaluation of FOG response to L-DOPA in patients with PD.

So far, although a number of studies in PD have used IMUs to detect objectively FOG episodes, very few have objectively measured the effect of L-DOPA on FOG by using IMUs and only in relatively small cohorts of patients with PD (31). Moreover, none have used IMUs to compare spatiotemporal gait parameters between patients with and without FOG, under and not under dopaminergic therapy to clarify the pathophysiology of FOG (32–37). Filling in these gaps would help in better understanding the phenomenology of FOG in PD and its relationship with dopaminergic therapy. We here tested the hypothesis that L-DOPA influences spatiotemporal gait parameters differently in patients with and without FOG.

Abbreviations: ACC, accuracy; ANOVA, analysis of variance; BAI, Beck Anxiety Inventory; FAB, Frontal Assessment Battery; FI, freezing index; FOG, freezing of gait; FOG-Q, freezing of gait questionnaire; H&Y, Hoehn and Yahr; HAM-D, Hamilton Rating Scale for Depression; IMU, inertial measurement unit; MDS-UPDRS, Movement Disorders Society—Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; NPV, negative predictive value; PD, Parkinson's disease; PPV, positive predictive value; SE, sensitivity; SP, specificity; PI, proportional integral; PIGD, postural instability and gait difficulty; TUG, Timed Up and Go test.

In this study, we investigated gait clinically and objectively, by means of IMUs, in a large cohort of patients with PD, with and without FOG, and compared all measures with those obtained in a cohort of healthy subjects. Participants were evaluated while performing a modified Timed Up and Go (TUG) test, a motor task designed to evaluate dynamic balance and functional mobility (19, 21, 24, 38). To clarify the effect of L-DOPA on FOG, we examined gait in patients with and without FOG, while performing the modified TUG test, under and not under dopaminergic therapy. We also specifically compared spatiotemporal gait parameters in patients with and without FOG, excluding FOG episodes from gait analysis. Finally, we examined the performance of a new algorithm for automatic FOG detection and thus suitable for objective long-term monitoring of FOG in patients with PD.

MATERIALS AND METHODS

Subjects

Twenty-eight PD patients with FOG (18 men and 10 women, mean age 70.3 ± 7.30 years, mean disease duration 11.6 ± 6.70 years), 16 patients without FOG (14 men and 2 women, mean age 71.8 ± 6.45 years, mean disease duration 8.3 ± 5.37 years), and 16 age-matched healthy subjects (4 men and 12 women, mean age 69.7 ± 4.43 years) were recruited from the movement disorder outpatient clinic of the Department of Neurology and Psychiatry, Sapienza, University of Rome, and from IRCCS Neuromed Institute (Italy). The diagnosis of idiopathic PD was made according to current consensus criteria, and in all patients, the diagnosis was confirmed by follow-up clinical evaluations (39, 40). Patients with FOG were selected when showing a paroxysmal interruption of stride or marked reduction in forward feet progression during the clinical examination finalized to patients' recruitment (1). Patients were clinically evaluated before starting each experimental session. The clinical assessment of motor symptoms included the following scales: Hoehn and Yahr (H&Y) (41) and Movement Disorders Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (42). FOG and other axial symptoms were evaluated by using the FOG-Q (43) and the Postural Instability and Gait Difficulty (PIGD) score, calculated as the sum of items 2.12, 2.13, 3.10, 3.11, and 3.12 of the MDS-UPDRS (44). Cognitive evaluation included the Mini-Mental State Examination (MMSE) (45) and the Frontal Assessment Battery (FAB) (46). Mood and anxiety disorders were assessed by means of the Hamilton Rating Scale for Depression (HAM-D) (47) and the Beck Anxiety Inventory (BAI) (48). Inclusion criteria included a diagnosis of idiopathic PD, ability to walk independently, absence of comorbidities possibly affecting gait, including diabetes, rheumatic, or orthopedic disorders, and a MMSE score >24, thus excluding dementia. Patients were first studied after drug withdrawal for at least 12 h (OFF therapy) and then 1 h after the administration of their usual dopaminergic treatment (ON therapy) in the same experimental session. For each patient, the L-DOPA Equivalent Daily Doses (LEDDs) were calculated according to standardized procedures (49). None of the patients received other neuropsychiatric medications at the

time of the study. Demographic and clinical features of patients, with and without FOG, are summarized in **Table 1**. All the subjects gave a written informed consent, and the experimental procedures have been approved by the institutional review board of Sapienza University of Rome, Italy, in agreement with the Declaration of Helsinki.

Experimental Session

The experimental session consisted of anthropometric (height) and clinical data collection and then the execution of a motor task, a modified 3-m TUG test (38). Given the known unusual presentation of FOG, which is common in home environment but not under medical observation as in a research laboratory (50), in this study, the modified TUG test was carried out in a specific setting, reproducing a domestic environment. In detail, the route of 3 m of the modified TUG test involved the passage from a spacious room to a narrow corridor with the interposition of a door, reflecting a more ecological environment for FOG occurrence. Subjects were asked to rise from an armchair, walk forward at comfortable speed for 3 m, turn around, walk back to the chair, and sit down. Differently from the standard TUG, the point of turning was marked on the wall. Subjects were asked to perform the modified TUG test two times according to right-side or left-side turning (randomly selected) and both OFF and ON therapy (a total of two TUG tests for each healthy subject and two TUG tests for each subject with PD and state of therapy). To recognize specific FOG subtypes in relation to the effect of L-DOPA (i.e., OFF FOG, unresponsive FOG, pseudo-ON FOG, and finally ON FOG) (9), in patients manifesting poor response of FOG to their usual L-DOPA dose, we also used a supratherapeutic (double) dose of L-DOPA. The response of FOG to L-DOPA was clinically evaluated in terms of improvement in FOG duration during the modified TUG test. Patients were all videotaped while performing the modified TUG, with a camera standing at the end of the path in front of the patient. Video recordings of TUG trials allowed the offline evaluation by two independent neurologists, experts in movement disorders, blinded for state of therapy, serving as a gold standard for FOG detection. In this regard, FOG was defined as paroxysmal interruption of stride or marked reduction in forward feet progression. The two raters separately evaluated video recordings and assessed occurrence and duration of FOG episodes for each trial. FOG duration was defined as the sum of all FOG episodes (in seconds) within trials in the same state of therapy (OFF and ON). In case of discrepancy in FOG assessment between the two raters, a common assessment was performed to resolve the ambiguity. TUG duration was measured by a stopwatch considering the initial "GO" command and final patient's contact with the chair at the end of modified TUG test.

Wearable Sensing System

Hardware

The core of the wearable wireless system used for FOG detection and gait analysis consisted of two Inertial Measurements Units (IMUs) placed on the shins (**Figure 1**) (51, 52). The prototype IMU board was designed for processing signals in real time. It

TABLE 1 | Demographic and clinical features of PD patients with and without FOG.

Subjects	Sex	Age	Disease duration (years)	Phen	H&Y	UPDRS-III		MMSE	FAB	HAM-D	BAI	Years after FOG onset	FOG-Q	PIGD	LEDDs
						ON	OFF								
PD patients with FOG (n = 28)	18 M	70.3 ± 7.30	11.6 ± 6.70	24A/R, 4 Trem	2.6 ± 0.84	30.7 ± 13.70	39.7 ± 13.85	28.3 ± 19.60	14.6 ± 2.53	15.4 ± 7.76	12.7 ± 8.05	4.6 ± 4.51	15.4 ± 4.57	11.1 ± 4.38	797.7 ± 285.94
PD patients without FOG (n = 16)	14 M	71.8 ± 6.45	8.3 ± 5.37	11A/R, 5 Trem	2.0 ± 0.38	20.8 ± 10.54	28.2 ± 12.22	28.2 ± 1.90	15.1 ± 2.64	13.2 ± 5.69	11.7 ± 6.80			2.7 ± 2.54	700.4 ± 466.98

Phen, phenotype; H&Y, Hoehn and Yahr scale; UPDRS-III, Unified Parkinson's Disease Rating Scale—part III; MMSE, Mini-Mental State Evaluation; FAB, Frontal Assessment Battery; HAM-D, Hamilton Rating Scale for Depression; BAI, Beck Anxiety Inventory; FOG-Q, freezing of gait questionnaire; PIGD, Postural Instability and Gait Difficulty; LEDDs, L-Dopa Equivalent Daily Dose; PD, Parkinson's disease.

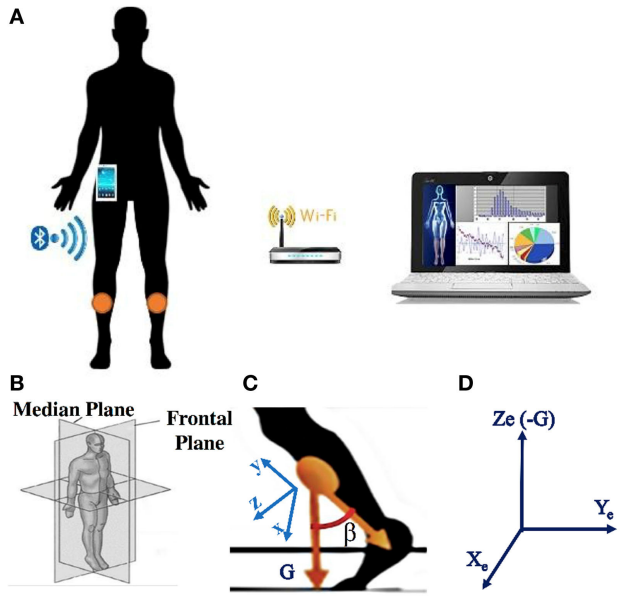

FIGURE 1 | **(A)** Sketch of the system: the two sensors are positioned on the shins, a smartphone is used as portable receiver, a PC is connected to the smartphone *via* the Wi-fi or *via* Bluetooth; **(B)** representation of the reference systems where the gait takes place: median and frontal planes; **(C)** representation of the sensor reference system, with G the gravity direction; **(D)** representation of the earth reference system, in which the sensor reference system rotates.

included the IMU LSM9DS0 integrating a ±16 g (g-force) 3D accelerometer and a ±2,000 dps 3D gyroscope in a 4 mm × 4 mm Land Grid Array package. Wireless communication was supported by a Bluetooth V3.0 module using the Serial Port Profile. The processing unit was an ultralow-power 32-bit microcontroller, with a 33.3 DMIPS peak computation capability and an extremely low power consumption scalable down to 233 uA/MHz. The Cortex™ M3 architecture along with the 32 MHz clock frequency makes this microcontroller suitable for advanced and low-power embedded computations. An USB 2.0 interface was present for battery recharge. The board including the battery has a total dimension of 25 mm × 30 mm × 4 mm. The offline postprocessing was performed by a PC, which realized an individual electronic diary where the information and data statistics in time are stored.

Algorithm for FOG Detection

Ad hoc algorithms were used to detect and classify FOG episodes in all participants. The recognition algorithm was based on a time domain analysis of sensor signals. The raw signals of accelerometer and gyroscope were fused together by using an orientation estimation algorithm proposed by Mahony et al. (53). To eliminate the gyroscope drift and to provide the sensor orientation in space, Mahony et al. (53) used a correction vector provided by a proportional integral (PI) controller, where the error vector ε driving the PI controller is determined from the previously estimated attitude and the accelerometer vector a. Mahony et al. (53) suggested to use $\varepsilon = a \times d$, where d is the direction of the gravity vector as given by the estimated attitude. Regarding the PI controller, the value of the integral coefficient is $K_i = 0.0025$, while the proportional coefficient is $K_p = 0.5$. A quaternion-based representation of the limbs orientation and position was calculated, and a 3D vector representing the limbs was generated. The sampling frequency (f_s) was 60 Hz (51) using a PC for the postprocessing, while it can be better set at 25 Hz (52) using a smartphone as a portable receiver. Reducing the sampling frequency has a benefit in that the number of transmitted data and operations per unit time becomes lower, thus improving the sensors and smartphone battery life. In turn, setting $f_s = 25$ Hz does not present any drawbacks in the detection since the characteristic band of FOG in PD lies below 12 Hz (21). The sensors were positioned on the shins. Gait direction was in the median plane represented in **Figure 1B**. The x-y-z sensor reference system is sketched in **Figure 1C**. **Figure 1D** shows the Xe-Ye-Ze earth reference system in which the sensor reference system rotates. Ze coincides with negative G axis. The angle β sketched in **Figure 1C** is used for the FOG detection, and it is calculated as the angle formed between two 3D vectors: the negative y-axis and the gravity axis (G). It is worth noticing that the angle β is solid and, therefore, does not lie in the median plane. To detect FOG and calculate all the gait statistics, we need to analyze the projection of the β angle onto the median plane. In this way, any information on the rotation around the G axis is ignored. Eventual discontinuities of the β angle when it changes the sign, and consequent problems in angle derivation, can be easily overcome by conventional mathematical techniques.

The angular velocities ω_{right}, ω_{left} obtained after the β angle derivation were used as the input for the FOG detection algorithm. That algorithm calculated the first-order low-pass filtered angular velocities. We defined as ω_t and k_t, respectively, as the right/left angular velocity and the low-pass filter measured at time t, k_{t-1} the value of k at the previous step, α the smoothing coefficient set by the cutoff frequency (f_{cutoff}):

$$K_{right} = \text{lowpass}(|\omega_{right}|) \quad (1a)$$

$$K_{left} = \text{lowpass}(|\omega_{left}|) \quad (1b)$$

$$K_t = (1-\alpha)\cdot\omega_t + \alpha\cdot k_{t-1} \quad (1c)$$

$$\alpha = (1 + 2\pi\cdot f_{cutoff} / f_s)^{-1}, \quad (1d)$$

where $f_{cutoff} = 0.83$ Hz (51). A K index was calculated and defined as:

$$K = K_{right} + K_{left}. \quad (1e)$$

Once the values of T1 and T2 were fixed for a certain patient, they remained unchanged for the whole duration of the monitoring. To further implement algorithm and reduce false positives and negatives in FOG detection, especially during voluntary step shortening and slowing during turning, we also introduced a threshold T_{turn} and a K_{turn} index, defined as follows:

$$K_{turn} = \text{lowpass}(|\omega_y|) \quad (2a)$$

$$K' = K + K_{turn} \text{ for } K_{turn} > T_{turn} \quad (2b)$$

$$K' = K \text{ for } K_{turn} \leq T_{turn}. \quad (2c)$$

A K_{swing} index was also introduced to definitely distinguish leg tremor due to body swinging and leg tremor during FOG, by using the following formula:

$$K_{swing} = \text{lowpass}(|\omega_Z|). \quad (3)$$

In summary, algorithm operations were the following: K, K_{turn}, and K_{swing} indices were first calculated, K_{turn} index was compared with the threshold T_{turn} and, only in the case $K_{turn} > T_{turn}$, K' index was calculated (Eqs 2b and 2c). K' index was then compared with K_{swing} index and, if $K' > K_{swing}$, the algorithm could exclude a body swing and classify a specific gait state. If $K' < K_{swing}$, leg movement was interpreted as a body swing (**Figure 2**). A practical application of the final algorithm is shown in **Figure 3**, where angle β, angular velocity ω, K index, and clinical report in a sample test are reported. During this sample test (**Figure 3**), very different behaviors of the angle β, angular velocity ω, and K index traces could be recognized. The traces of angle β and angular velocity ω clearly showed an oscillatory behavior during regular gait, such as in the time intervals 0–4 and 32–39 s, whereas they became flat traces during voluntary rest position when the subject was standing up at the end of the test. However, the traces of angle β and angular velocity ω were irregular and unpredictable when FOG episodes occurred, such as in the time intervals 4–32 and 39–46 s. On the contrary, the dynamic range of K index, that was rather wide, helped in the correct identification of every different gait behavior, also when FOG episodes occurred. In particular, clinical report of FOG episodes allowed to define two threshold values of K index (T1 and T2), which automatically classified three stationary states: regular gait, FOG state, and rest state, respectively, defined by K > T2, T2 > K > T1, and K < T1. Accordingly, in this specific sample test, clinical report agreed on the exact timing of three FOG episodes in the time intervals 4–32 and 39–46 s. An illustrative comparison of K index in a healthy subject, a PD patient without FOG, and a PD patient with FOG is shown in **Figure 4**.

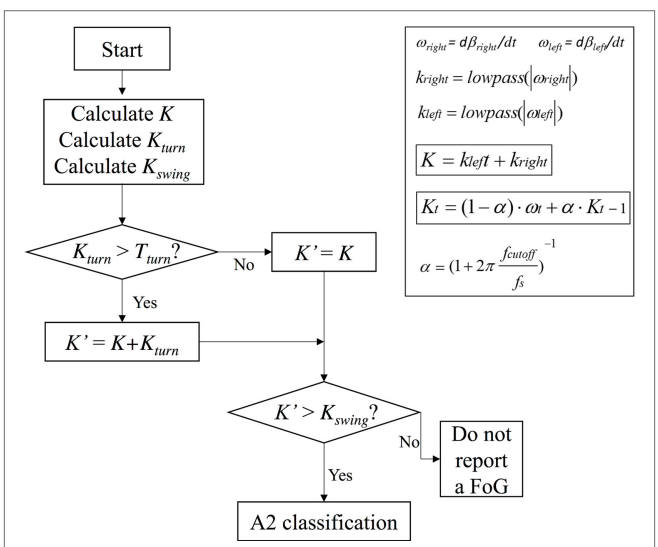

FIGURE 2 | Block scheme of algorithm operations.

Wireless Sensor-Based Gait Analysis

Gait analysis was performed in all participants except for seven patients with FOG. Gait analysis included the measurement of step velocity, stride length, stride time, and cadence as main spatiotemporal gait parameters in healthy subjects and in patients, OFF and ON therapy. Our analysis also included the evaluation of gait symmetry by comparing spatiotemporal gait parameters of the right and left leg. Step velocity (centimeters per second) was defined as the distance covered by the leg in time unit; stride length (centimeters), the distance between two consecutive heel strike of the same foot; stride time (seconds), the time from initial contact of one foot to subsequent contact of the same foot; and finally, cadence (steps per minute) was defined as the number of steps per minute. Spatiotemporal gait parameters were all expressed as the weighted average of right and left leg measures except for assessment of gait symmetry. In patients with FOG, sensor-based gait analysis included spatiotemporal gait parameters with the exclusion of FOG episodes. We have previously compared spatiotemporal gait parameters measured by means of our IMUs and by a standardized gait analysis lab based on an optoelectronic system (SMART analyzer motion system; BTS Bioengineering, Milan, Italy), and we have calculated a maximum error of ±2% (data not shown).

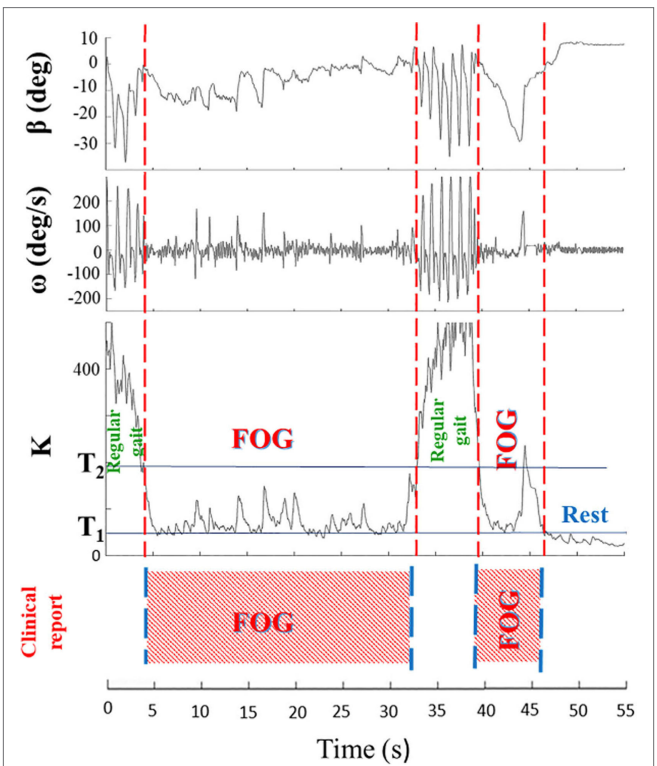

FIGURE 3 | Angle β, angular velocity ω, K index, and clinical report during a sample test are shown. Clinical report allows to define two threshold values (T1 and T2) of K index, which automatically classify three stationary states: regular gait (K > T2), rest state (K < T1), and freezing of gait (FOG) episodes (T2 > K > T1). The wide dynamic range of the K index easily identifies distinct regions with different gait behaviors.

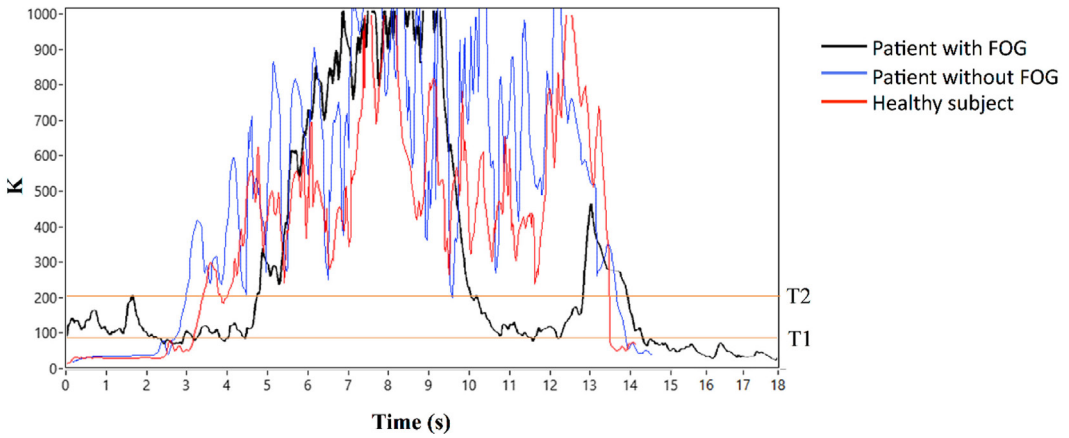

FIGURE 4 | *K* index in a healthy subject, a Parkinson's disease (PD) patient without freezing of gait (FOG), and a PD patient with FOG.

Statistical Analysis

The Mann–Whitney *U* test was used to compare anthropometric data (height) in all participants and clinical features (age, disease duration, H&Y, UPDRS-III OFF and ON therapy, MMSE, FAB, HAM-D, BAI, PIGD score, and dopaminergic treatment as calculated by LEDDs), between patients with and without FOG. The Mann–Whitney *U* test was also used to compare TUG duration between healthy subjects and the whole group of patients. Finally, the Mann–Whitney *U* test was used to compare TUG duration in healthy subjects and in patients with and without FOG, OFF and ON therapy. The Wilcoxon signed-rank test was used to investigate the effect of dopaminergic treatment on UPDRS-III scores and TUG duration in patients with and without FOG and finally on FOG duration in patients with FOG. The Wilcoxon signed-rank test was also used to compare the number of FOG episodes at gait initiation, during straight passage through a narrow space, during turning, and finally during turn-to-sit, in patients with PD, OFF and ON therapy. Unpaired Student's *t*-test was used to compare spatiotemporal gait parameters (step velocity, stride length, stride time, and cadence) between healthy subjects and patients with and without FOG, OFF and ON therapy. To compare all spatiotemporal gait parameters between patients with and without FOG, OFF and ON therapy, we used separate between-group analyses of variances (ANOVAs) with factors "Group" (patients with versus patients without FOG) and "dopaminergic therapy" (patients OFF versus ON therapy) as main factors of analysis. To evaluate gait symmetry in patients with and without FOG, OFF and ON therapy, we also used separate between-group ANOVAs with factors "Group" and "Side" (right versus left leg) as main factors of analysis. Tukey Honestly Significant Difference test was used for all *post hoc* analyses. Finally, Spearman rank correlation test was used to assess correlation between patients' clinical features, FOG severity (as measured by years after FOG onset, scores at FOG-Q, FOG duration during TUG), TUG duration, and spatiotemporal gait parameters, in patients with and without FOG, OFF and ON therapy.

P values less than 0.05 were considered to indicate statistical significance.

The performance of the wearable sensing system to identify FOG episodes (presence or absence) was evaluated in terms of sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) compared to the clinical identification of FOG based on offline video-recordings (gold standard).

RESULTS

The Mann–Whitney *U* test showed comparable anthropometric data (height) in healthy subjects and in patients with and without FOG ($P > 0.05$ for all comparisons) and comparable age, disease duration, and MMSE, FAB, HAM-D, and BAI scores ($P > 0.05$ for all comparisons) in patients with and without FOG. Conversely, the Mann–Whitney *U* test showed higher H&Y ($z = -2.06$; $P = 0.045$), UPDRS-III OFF ($z = -2.42$; $P = 0.02$) and UPDRS-III ON ($z = -2.45$; $P = 0.001$), PIGD scores ($z = 5.01$; $P < 0.001$), and finally, LEDDs ($z = -2.1$; $P = 0.04$) in patients with FOG than in those without FOG. The Wilcoxon signed-rank test showed that dopaminergic treatment improved UPDRS-III scores in the whole patients group ($z = 5.45$; $P < 0.001$) as well as in patients with FOG ($z = 4.22$; $P < 0.001$) and without FOG ($z = 3.52$; $P < 0.001$).

Modified TUG Test

Clinical assessment of video recordings reported that 25 of 28 patients with definite FOG manifested at least 1 FOG episode while performing the modified TUG test, overall experiencing 152 FOG episodes (102 FOG episodes OFF therapy and 50 ON therapy). The Wilcoxon signed-rank test showed comparable number of FOG episodes in patients OFF and ON therapy at gait initiation, during straight passage through a narrow space, and finally during turn-to-sit (all $P > 0.05$ for all comparisons). By contrast, the number of FOG episodes differed during turning in patients OFF and ON therapy ($z = -2.89$; $P < 0.01$). During the modified TUG test in patients OFF therapy, FOG was elicited more frequently, respectively, by turning (41 FOG episodes, 40.2%), straight passage through a narrow space (21 FOG episodes,

20.6%), gait initiation (20 FOG episodes, 19.6%), and turn-to-sit (20 FOG episodes, 19.6%). Similarly, during the modified TUG test in patients ON therapy, FOG was elicited more frequently, respectively, by turning (22 FOG episodes, 44%), gait initiation (13 FOG episodes, 26%), turn-to-sit (10 FOG episodes, 20%), and straight passage through a narrow space (5 FOG episodes, 10%). Most of the patients with FOG manifested "OFF FOG" episodes because of the improvement or even the disappearance of FOG when ON therapy. Conversely, six patients presented "unresponsive FOG" given the absence of FOG improvement after administration of a supratherapeutic dose of L-DOPA. A single patient showed an ambiguous response to L-DOPA, with an apparent worsening of FOG, suggesting a case of "ON FOG."

When comparing TUG duration in healthy subjects and in the whole group of patients with PD, the Mann–Whitney *U* test showed longer TUG duration in patients OFF ($z = -3.34$; $P < 0.001$) as well as ON therapy ($z = -2.68$; $P < 0.01$) than in controls. Patients with FOG had longer TUG duration compared with controls in OFF ($z = -3.56$; $P < 0.001$) and ON therapy ($z = -3.23$; $P = 0.001$). By contrast, patients without FOG had longer TUG duration compared with controls in OFF ($z = -2.04$; $P < 0.04$) but not in ON state of therapy ($z = -1.06$; $P = 0.29$). When comparing patients with and without FOG, TUG duration differed in OFF ($z = -2.29$; $P = 0.02$) but not in ON state of therapy ($z = -1.76$; $P = 0.08$). The Wilcoxon signed-rank test showed that dopaminergic treatment decreased TUG duration in the whole patients group ($z = 5.34$; $P < 0.001$) as well as in patients with ($z = 4.28$; $P < 0.001$) and without FOG ($z = 3.52$; $P < 0.001$). Finally, dopaminergic treatment also decreased FOG duration in patients with FOG ($z = 2.27$; $P = 0.02$) (**Table 2**).

Wireless Sensor-Based Gait Analysis

When comparing spatiotemporal gait parameters between healthy subjects and the whole group of PD patients, OFF and ON therapy, unpaired Student's *t*-test showed higher step velocity and stride length in controls than in patients ON therapy (step velocity: $t = 3.48$; $P = 0.001$; stride length: $t = 3.00$; $P = 0.004$) and OFF therapy (step velocity: $t = 4.76$; $P < 0.001$; stride length: $t = 3.49$; $P = 0.001$), whereas stride time and cadence were comparable in the two study groups ($P > 0.05$ for all comparisons) (whole group of PD patients OFF: step velocity: 74.02 ± 26.62; stride length: 48.70 ± 25.76; stride time: 0.80 ± 0.16; cadence: 101.48 ± 19.10; PD patients ON: step velocity: 87.15 ± 26.99; stride length: 54.96 ± 21.82; stride time: 0.81 ± 0.15; cadence: 105.83 ± 20.58; **Table 2**; Figure S1 in Supplementary Material).

When comparing healthy subjects and patients with FOG, unpaired Student's *t*-test again showed higher step velocity and stride length in controls than in patients with FOG in OFF (step velocity: $t = 3.72$; $P < 0.001$; stride length: $t = 3.20$; $P = 0.003$) and ON therapy (step velocity: $t = 2.07$; $P < 0.05$; stride length: $t = 2.0$; $P < 0.05$). Differently, stride time was comparable in controls and patients with FOG, OFF and ON therapy ($P > 0.05$ for all comparisons). Finally, patients with FOG had a lower cadence than controls in OFF ($t = 2.52$; $P = 0.02$), but not in ON therapy ($P > 0.05$) (**Table 2**).

When comparing healthy subjects and patients without FOG, unpaired Student's *t*-test showed higher step velocity and stride length in controls than in patients in OFF (step velocity: $t = 4.32$; $P < 0.001$; stride length: $t = 2.58$; $P = 0.01$) and ON therapy (step velocity: $t = 4.16$; $P < 0.005$; stride length: $t = 3.06$; $P = 0.005$), whereas stride time and cadence were comparable in the two study groups ($P > 0.05$ for all comparisons) (**Table 2**).

When testing all spatiotemporal gait parameters in patients with and without FOG, OFF and ON therapy, between-group ANOVA showed a non-significant effect of the factor "Group" for step velocity ($F_{1.35} = 2.48$; $P = 0.12$), stride length ($F_{1.35} = 0.14$; $P = 0.72$), stride time ($F_{1.35} = 1.66$; $P = 0.21$), and cadence ($F_{1.35} = 0.86$; $P = 0.36$), whereas the factor "dopaminergic therapy" was significant only for step velocity ($F_{1.35} = 15.6$; $P < 0.001$), but not for stride length ($F_{1.35} = 3.42$; $P = 0.07$), stride time ($F_{1.35} = 1.35$; $P = 0.94$), and cadence ($F_{1.35} = 1.21$; $P = 0.28$). ANOVA also showed a significant interaction between factors "Group" and "dopaminergic therapy" for step velocity ($F_{1.35} = 7.84$; $P < 0.01$), stride length ($F_{1.35} = 12.58$; $P < 0.001$), and stride time ($F_{1.35} = 4.78$; $P = 0.04$), but not for cadence ($F_{1.35} = 1.75$; $P = 0.19$). *Post hoc* analysis demonstrated higher step velocity and stride length in patients with FOG than in patients without FOG ON ($P < 0.01$) but not OFF therapy ($P > 0.05$), whereas stride time was lower in patients with FOG than patients without FOG OFF ($P = 0.003$), but not ON therapy ($P = 0.86$). Dopaminergic therapy increased step velocity and stride length in patients with FOG ($P = 0.001$) but not in patients without FOG ($P > 0.05$), whereas it left stride time unchanged in patients with and without FOG ($P = 0.39$ and 0.46, respectively) (**Table 2**; Figure S2 in Supplementary Material).

When comparing gait symmetry in patients with and without FOG, OFF and ON therapy, ANOVA showed a non-significant effect of the factors "Group" and "Side" for step velocity, stride length, stride time, and cadence ($P > 0.05$ for all comparisons).

TABLE 2 | Average (±SD) Timed Up and Go (TUG) duration, total freezing of gait (FOG) duration, step velocity, stride length, stride time, and cadence in healthy subjects and Parkinson's disease (PD) patients with and without FOG, OFF and ON therapy.

Subjects	State of therapy	TUG duration (s)	FOG duration (s)	Step velocity (cm/s)	Stride length (cm)	Stride time (s)	Cadence (steps/min)
Healthy subjects		18.6 ± 5.7		118.7 ± 37.17	77.7 ± 32.11	0.8 ± 0.10	111.2 ± 14.25
PD patients with FOG	OFF	49.9 ± 38.18	39.5 ± 63.50	76.0 ± 32.55	45.7 ± 28.49	0.8 ± 0.17	97.3 ± 18.18
	ON	31.4 ± 17.24	22.9 ± 48.37	96.6 ± 28.03	60.3 ± 20.74	0.8 ± 0.13	105.5 ± 22.67
PD patients without FOG	OFF	24.4 ± 7.79		71.4 ± 22.50	52.6 ± 21.25	0.9 ± 0.13	107.0 ± 18.83
	ON	21.5 ± 6.56		74.7 ± 19.61	48.0 ± 21.17	0.8 ± 0.17	106.2 ± 17.62

Clinical-Behavioral Correlations

When assessing clinical-behavioral correlations in patients with FOG, Spearman rank correlation test found a positive correlation between years after FOG onset and LEDDs ($R = 0.52$; $P = 0.005$), and between FOG-Q and UPDRS-III ON therapy ($R = 0.47$; $P = 0.01$), PIGD scores ($R = 0.71$; $P < 0.001$), and FOG duration during TUG in patients OFF ($R = 0.57$; $P = 0.002$) and ON therapy ($R = 0.62$; $P < 0.001$). Spearman rank correlation test also found a positive correlation between FOG-Q and TUG duration in patients with FOG OFF ($R = 0.59$; $P < 0.001$) and ON therapy ($R = 0.55$; $P = 0.003$) and a positive correlation between TUG duration and FOG duration OFF ($R = 0.59$; $P < 0.001$) and ON therapy ($R = 0.66$; $P < 0.001$) (**Figure 5**).

Performance of the Wearable System in FOG Detection

The performance of the wearable sensing system in automatic FOG detection, compared to the clinical identification of FOG based on offline video recordings (gold standard), showed the

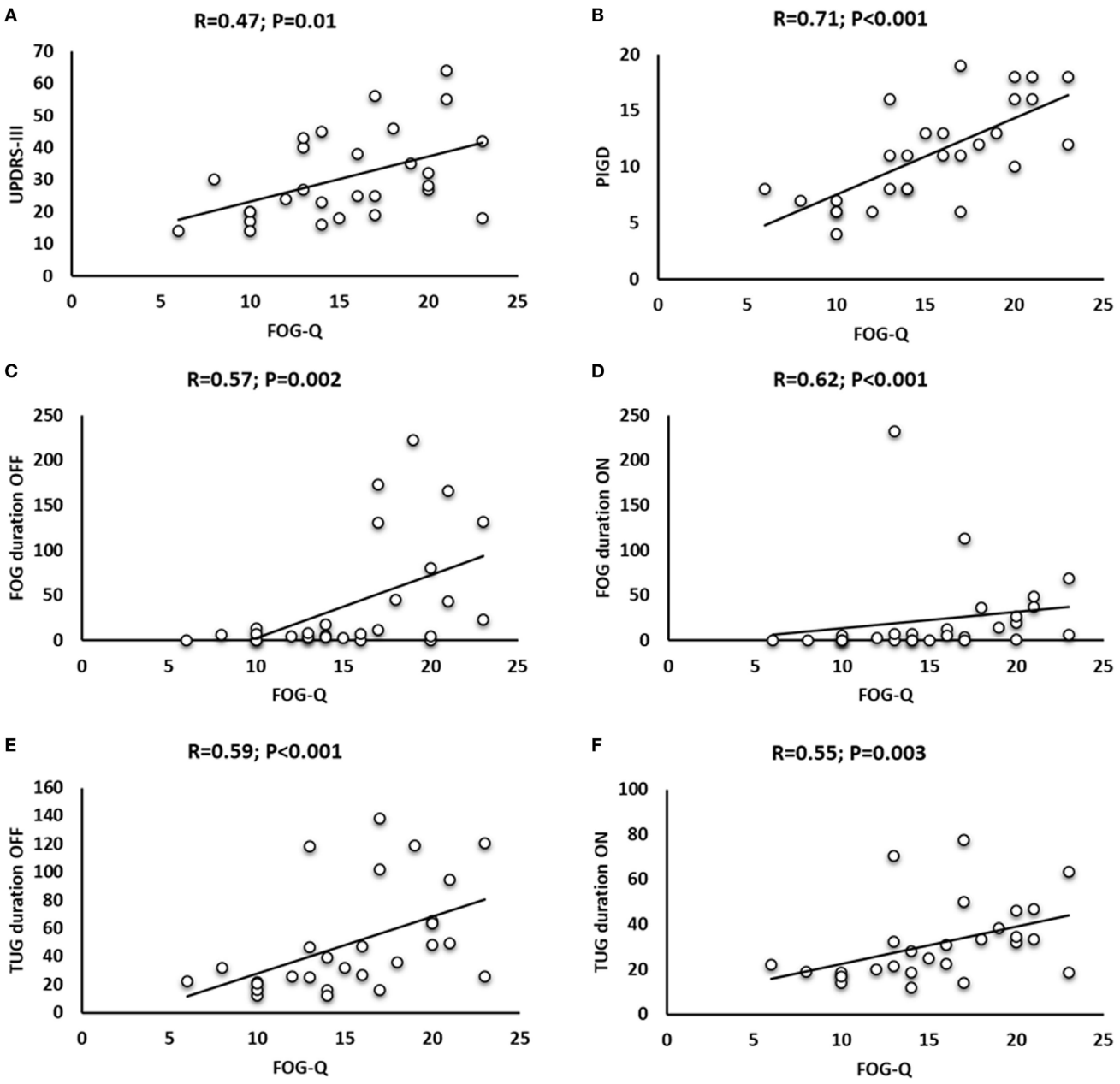

FIGURE 5 | Correlation analysis in patients with freezing of gait (FOG) between freezing of gait questionnaire (FOG-Q) and Unified Parkinson's Disease Rating Scale (UPDRS)-III ON therapy **(A)**, FOG-Q and Postural Instability and Gait Difficulty (PIGD) **(B)**, FOG-Q and FOG duration OFF **(C)** and ON therapy **(D)**, and FOG-Q and Timed Up and Go (TUG) duration OFF **(E)** and ON therapy **(F)**.

following average measures in 25 patients presenting FOG during the modified TUG test: SE 93.41%; SP 97.24%; PPV 89.55%; NPV 97.31%; and ACC 97.23% (**Table 3**), obtained with a latency of 400 ms. When considering PD patients not manifesting FOG during the modified TUG test and healthy subjects, the wearable sensing system showed 99.42% of SP and ACC. Accordingly, considering all the subjects participating to the study, the overall performance of the adopted wearable sensing system, using the proposed FOG detection algorithm, was the following: SE 93.41%; SP 98.51%; PPV 89.55%; NPV 97.31%; and ACC 98.51%.

DISCUSSION

We here report a detailed clinical and objective analysis of gait by means of IMUs, in a relatively large cohort of patients with PD, with and without FOG. We also provide new data on the effect of L-DOPA on clinical measures (modified TUG test) and spatiotemporal gait parameters, in patients with PD, with and without FOG. Finally, we here propose a new algorithm for automatic FOG detection in patients with PD and report the excellent performance of this new, unobtrusive, wearable sensing system.

Strict inclusion criteria allowed us to exclude a number of methodological factors possibly leading to misinterpretation of data. The clinical diagnosis of PD was made according to the current standardized criteria (39, 40), thereby reducing the possibility that our cohort included patients affected by neurological disorders other than PD such as atypical parkinsonism. We carefully excluded patients with comorbidities possibly affecting gait including diabetes, rheumatic, or orthopedic disorders. We enrolled patients without dementia as reflected by MMSE scores >24. To clarify motor response to dopaminergic treatments in patients with and without FOG, OFF and ON therapy, we examined each patient after 12 h of drug withdrawal (OFF), 1 h after acute administration of the best medical treatment (ON), and finally, in selected patients with poor response of FOG to L-DOPA, after a supratherapeutic (double) dose of L-DOPA (9).

TABLE 3 | Performance of the wearable sensing system in FOG detection in PD patients presenting FOG during motor task.

Case	SE	SP	PPV	NPV	ACC
1	97.20	95.23	92.35	98.29	96.36
2	98.95	94.60	98.18	96.84	98.05
3	100.00	97.15	88.15	100.00	97.65
4	99.30	96.20	99.20	96.66	98.76
5	96.80	96.20	94.00	98.00	96.70
6	99.05	93.10	93.70	98.95	96.10
7	90.40	97.75	94.45	96.01	95.75
8	91.00	100.00	100.00	98.09	98.40
9	86.90	97.00	91.40	95.28	95.70
10	84.85	98.65	92.85	96.92	94.40
11	100.00	98.25	77.35	100.00	97.15
12	60.00	96.67	54.50	97.32	97.20
13	94.10	96.20	86.40	98.45	95.80
14	89.23	98.40	95.00	96.41	97.10
15	81.25	98.00	96.05	89.72	96.73
16	94.43	99.10	99.35	92.43	96.40
17	92.80	98.60	98.30	94.01	97.30
18	100.00	98.90	66.70	100.00	98.90
19	100.00	97.70	66.70	100.00	97.70
20	94.40	97.30	89.50	98.62	97.00
21	100.00	100.00	100.00	100.00	100.00
22	92.85	97.30	92.85	97.30	95.57
23	100.00	100.00	100.00	100.00	100.00
24	91.68	91.28	88.98	93.46	98.22
25	100.00	97.53	82.85	100.00	97.80
AV	93.41	97.24	89.55	97.31	97.23

SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; AV, average; FOG, freezing of gait; FOG-Q, freezing of gait questionnaire; PD, Parkinson's disease.

The first finding in this study is that, although disease duration was comparable in the two patients' subgroups (patients with and without FOG), patients with FOG had higher H&Y and UPDRS-III scores than patients without FOG, suggesting greater disease severity and progression. We also found higher LEEDs patients with FOG than in patients without FOG in agreement with previous observations (54–56). Finally, PIGD scores were also greater in patients with FOG than in patients without FOG and correlated significantly with FOG-Q scores confirming the association between the amount of axial impairment and severity of FOG in PD (55).

Previous clinical observations have raised the hypothesis that FOG reflects changes in frontal executive functions (57–60). However, when comparing patients enrolled in the present study, with and without FOG, we found similar FAB scores in the two patients' subgroups, thus making unlikely the hypothesis that in our cohort of patients, a frontal disexecutive syndrome contributed significantly to the occurrence of FOG. Similarly, we found comparable HAM-D and BAI scores in patients with and without FOG, excluding that mood changes or anxiety disorders played a major role in the pathophysiology of FOG in our cohort of patients with FOG (61–64). Our clinical observations, however, do not exclude that possible changes in frontal executive functions and mood or anxiety disorders may further deteriorate FOG in patients with PD (57–64).

In line with previous studies (50, 65–68), during our modified TUG test, FOG occurred more frequently during postural transitions (turning and turn-to-sit), probably due to prominent axial impairment in patients with FOG, as demonstrated by higher H&Y and PIGD scores than patients without FOG. The other prevalent situation eliciting FOG occurrence during our modified TUG test was gait initiation, reflecting the complex motor and cognitive interaction to prepare and execute the first step, by performing adequate anticipatory postural adjustments (69, 70). Finally, the observation of a number of FOG episodes in the straight passage through a narrow space confirms the importance of ecological circumstances in triggering FOG (4, 5). This finding supports the hypothesis that, in patients with PD, abnormal visuospatial abilities lead to FOG occurrence by interfering with the online adjustment of gait pattern to environmental changes, such as the narrowing of the path (71–73). Finally, when examining the effect of dopaminergic treatment on the number of FOG episodes in patients with PD at gait initiation, during straight passage through a narrow space, during turning, and finally during turn-to-sit, we found that L-DOPA decreased significantly FOG episodes during turning likely by improving patients' axial mobility. It is known that FOG is associated with

akinetic-rigid phenotype (74), contributing to difficulties in change of direction.

Gait in Patients with and without FOG, OFF Therapy

When clinically evaluating gait in the whole group of patients with PD and controls, while performing the modified TUG test, as expected, patients had longer TUG duration than controls confirming a number of previous observations (75, 76). When examining gait by means of our sensor-based analysis, we found that the longer TUG duration in patients with PD than in controls reflected changes in specific spatiotemporal gait parameters. Patients showed decreased step velocity and reduced stride length fully in agreement with several previous observations in PD (77–79). When comparing the whole group of patients with healthy subjects, our sensor-based gait analysis also showed similar cadence and stride time in patients and controls, confirming a previous hypothesis that in PD cadence increases to compensate for decreased step velocity and reduced stride length (80).

When we clinically evaluated gait, in patients with and without FOG, while performing the modified TUG test, TUG duration was significantly longer in patients with FOG than in those without FOG. However, when examining gait objectively, our sensor-based gait analysis disclosed comparable spatiotemporal gait parameters (when excluding FOG episodes) in the two patients' subgroups. Our observation of comparable stride length in patients with and without FOG agrees with a previous study using IMUs (81) but apparently contrasts with others using pressure measurement systems, which showed shorter stride length in patients with FOG than in those without FOG (82, 83). The different methodology used to examine gait objectively, in patients with PD, including the path length and the measurement system likely explains such inconsistency. We therefore conclude that the longer TUG duration in patients with FOG than in those without FOG coupled with the observation of comparable spatiotemporal gait parameters (when excluding FOG episodes) in the two patients' subgroups, specifically reflected the occurrence of FOG episodes. This conclusion is further supported by our observation of a positive correlation between TUG duration and FOG-Q scores as well as between TUG duration and FOG duration in patients with FOG. A further comment concerns the previously raised hypothesis that abnormal gait symmetry contributes to the pathophysiology of FOG (35, 84). When we compared spatiotemporal gait parameters in the right and left leg, in patients with and without FOG, our sensor-based gait analysis showed similar measures of gait symmetry in the two patients' subgroups. We suggest that this inconsistency between our observations and those of Plotnik et al. (35, 84) might reflect the different degree of asymmetry in parkinsonian features (bradykinesia and rigidity) in the two cohorts of patients studied. In conclusion, our findings overall implying comparable spatiotemporal gait parameters, in patients with and without FOG, might agree with the hypothesis that FOG would reflect the paroxysmal disruption of gait rather than a progressive deterioration of motor control during gait (33–37). This hypothesis fits in well with the well-known existence of typical ecological circumstances implying emotional and attentional demanding tasks able to trigger FOG episodes abruptly (4, 5). Our findings also support the "cross-talk model" hypothesis (32, 85), which interprets FOG as a paroxysmal event. Accordingly, in PD, a functional interference in normally segregated cognitive, motor, and limbic circuits might generate a paroxysmal overactivity in basal ganglia output nuclei (Globus Pallus pars interna and Substantia Nigra pars reticulata) leading to abrupt deactivation of the pedunculopontine nucleus. Finally, a transient disruption of descending inputs from the pedunculopontine nucleus and other structures of the mesenchephalic locomotor region to spinal centers of gait would lead to FOG.

Effect of L-DOPA on Gait in Patients with and without FOG

The clinical evaluation of gait in the whole group of patients with PD, while performing the modified TUG test under dopaminergic therapy, again showed longer TUG duration in patients than in healthy subjects. Hence, although TUG duration improved in patients under dopaminergic therapy, L-DOPA did not restore gait to normal levels in PD. This finding confirms previous observations reported in PD (86–88) and further support the hypothesis that L-DOPA improves the activation of neural circuits responsible for gait control in patients with PD (12, 89). When examining gait objectively, our sensor-based gait analysis again showed lower step velocity and stride length in patients than in controls, whereas stride time and cadence were still comparable in the two groups. This finding is fully in line with previous observations (89, 90), confirming that the inability to generate appropriate stride length is a crucial gait abnormality in PD, probably due to deficient internal cue production (12, 80).

The clinical evaluation of gait in patients with PD with and without FOG disclosed comparable TUG duration in the two patients' subgroups. The observation that TUG duration was longer in patients with FOG than in those without FOG when OFF therapy, whereas it was similar in the two subgroups of subjects with PD when ON therapy, suggests that acute administration of L-DOPA improved gait prominently in patients FOG and such improvement mostly reflected reduced FOG occurrence. Our hypothesis confirms that in PD, FOG is mostly a dopaminergic-responsive gait disorder (3, 10, 91). In addition, when examining gait objectively, our sensor-based gait analysis showed that L-DOPA increased step velocity and stride length predominantly in patients with FOG compared to those without FOG, whereas stride time and cadence remained similar in the two patients' subgroups. As previously discussed in patients OFF therapy, methodological factors likely explain the different stride length reported in patients with and without FOG, ON therapy, when comparing our study with those of Knobl et al. (82) and Barbe et al. (83). We speculate that, following acute administration of L-DOPA, our patients with FOG showed higher step velocity and stride length than patients without FOG probably as a result of increased attention on their walking pattern to support smooth gait and avoid FOG occurrence (80, 92). In conclusion,

overall our findings suggest that the significant gait improvement observed in patients with FOG, ON therapy, reflects at least two factors, reduced FOG duration and improvement of specific spatiotemporal gait parameters.

A further comment concerns mechanisms possibly explaining why some of the patients with FOG here studied manifested a poor response to L-DOPA confirming a rather complex and unpredictable response of FOG to L-DOPA at least in a subgroup of patients with PD (9). Our analysis showed a positive correlation between years after FOG onset and LEDDs, suggesting that as PD progresses and FOG further deteriorates, the response of FOG to L-DOPA might progressively degrade, supporting the hypothesis that additional non-dopaminergic neurotransmitter systems contribute to the pathophysiology of FOG (93–97).

When considering the present findings, however, several limitations should be taken into account. In the present study, the male to female ratio slightly differed when comparing healthy subjects and subjects with PD, with and without FOG, possibly influencing specific spatiotemporal gait parameters (stride length and step velocity) here reported. Moreover, we did not evaluate frontal executive function by means of a detailed neuropsychological examination, thus possibly missing a subtle disexecutive syndrome in patients with FOG. The relatively limited path length of the modified TUG test here used to assess gait might have precluded us to evaluate subtle differences between patients with and without FOG in continuous gait abnormalities due to insufficient number of steps. Moreover, given that FOG often manifests during directional changes (4), our instrumental analysis focused on gait with the exclusion of FOG episodes might have overestimated the spatiotemporal gait parameters examined in patients with FOG. Finally, acceleration changes (gait initiation, turning, and turn-to-sit) due to our modified TUG test could also have influenced measures, thus requiring cautious consideration of absolute values of spatiotemporal gait parameters.

Performance of the Algorithm

We here report systematic tests performed with a new algorithm designed for automatic detection of FOG episodes in patients with PD. Most of the previous studies reported algorithms for FOG detection working in the frequency domain, whereas our algorithm operates in the time domain. In frequency domain, some authors used the freezing index (FI) extrapolation implying the evaluation of the ratio between the power in the FOG band (2–6 Hz) associated to least leg tremor (51) and the power in the rest of the spectrum and comparing this ratio with defined thresholds. In this context, the first detection of FOG episodes was made by monitoring the body acceleration with a three-axis accelerometer (98). The authors applied fast Fourier transform, amplitude, and wavelet analysis performing an offline processing. Later, Moore et al. (21) analyzed offline the accelerometer data collected in 11 patients and detected the frequency components in the 3- to 8-Hz band during a FOG episode, which are not present during regular gait or at rest. Calculating the FI, their algorithm obtained 89% ACC and 89% SE in FOG detection. Following the algorithm proposed by Moore et al. (21), others developed a system for online FOG detection (17) containing three three-axial accelerometers and a wearable computer. The system was able to detect FOG episodes with user-dependent settings, exhibiting a SE of 88.6%, a SP of 92.4% evaluated on a sample of 10 patients, and a latency up to 2 s. Manual adjustment of the algorithm parameters was necessary to achieve optimal results. Other online FOG detection systems based on the FI extrapolation were presented in the studies by Jovanov et al. (16) and Djuric-Jovicic et al. (22). In the study by Jovanov et al. (16), the authors used a three-axis accelerometer and a wearable computer and detected FOG episodes with latency up to 580 ms. In the study by Djuric-Jovicic et al. (22), authors studied a sample of 12 PD patients and evaluated the SE in recognizing the occurrence of a FOG episode (reporting 100% of success), without evaluating the SE to timing and duration of each episode. Other methods of analysis in the frequency domain alternative to the FI extrapolation have been also developed including the algorithm proposed by Sijobert et al. (99) based on the evaluation of the step length and cadence. The authors made a comparison with the FI extrapolation and concluded that their algorithm appeared more accurate in recognizing FOG episodes. Conversely, in pure time domain, the signal amplitude is considered rather than the frequency band, so that a low-pass filter is needed to select the band of interest, and this factor is considered the main drawback of the time domain approach. The time domain analysis has the great advantage of performing a lower number of calculations, which turns into smaller power consumption and longer battery life. So far, very few studies with the pure time domain approach have been reported and among them, the work by Kwon et al. (25), which was based on the use of the root mean square of the accelerometer signal, and our previous work (52), which was based on the fusion of raw accelerometers and gyroscope signals. Both time domain approaches detected FOG episodes through a threshold method (25, 52). Kwon et al. (25) studied 20 patients with PD, obtaining a SE and a SP over 85%, whereas Kita et al. (52) studied 16 patients with PD, obtaining a SE and a SP over 94%. Finally, some work has been carried out in a combination of time and frequency domains, using different methods. Some authors used machine learning techniques (100, 101). SE and SP higher than 98% have been reported in Ref. (100) on a sample of 10 patients, with a latency up to 710 ms. In Pepa et al. (102), fuzzy logic algorithms were applied reporting good SE and SP in a group of 18 patients. More recently, Rezvanian and Lockhart (28) proposed using the continuous wavelet transform to define an index for identifying FOG episodes with good performances evaluated in a cohort of 10 patients. A final comment concerns that while the most used signal fusion algorithm for the calculation of sensor orientation in navigation systems is the Kalman filter (103), in our work, we opted for the algorithm proposed by Mahony et al. (53), which is less computationally expensive and therefore more convenient for wearable applications. By comparing the two algorithms, we got negligible difference in the orientation estimation with a noticeable benefit from the calculation load viewpoint. The reduction in the number of calculations allowed our system to detect FOG with a latency of only 400 ms, significantly lower than those reported in previous studies (16, 17, 100).

CONCLUSION

We here report a detailed clinical and instrumental analysis of gait in a relatively large cohort of patients with PD, with and without FOG, showing that L-DOPA improves FOG duration and specific spatiotemporal gait parameters. We here also propose an unobtrusive wearable, wireless sensor system, including a new algorithm able to detect FOG episodes automatically, possibly helpful for long-term monitoring of FOG in patients with PD.

ETHICS STATEMENT

All participants gave written informed consent and the experimental procedures have been approved by the institutional review board of Sapienza University of Rome, Italy, in agreement with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

AS: conception, design, analysis, data interpretation, drafting, and critical revision of the manuscript. AK and AZ: design, analysis, data interpretation, and drafting of the manuscript. GL, PL, and RR: design, analysis, data interpretation, and critical revision of the manuscript. EN: analysis, data interpretation, and critical revision of the manuscript. FI: conception, design, data interpretation, and critical revision of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00406/full#supplementary-material.

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Conflict of Interest Statement: The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 12 December 2017
doi: 10.3389/fneur.2017.00677

A Perspective on Wearable Sensor Measurements and Data Science for Parkinson's Disease

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Miniaturized and wearable sensor-based measurements enable the assessment of Parkinson's disease (PD) motor-related features like never before and hold great promise as non-invasive biomarkers for early and accurate diagnosis, and monitoring the progression of PD. High-fidelity human movement reconstruction and simulation can already be conducted in a clinical setting with increasingly precise and affordable motion technology enabling access to high-quality labeled data on patients' subcomponents of movement (kinematics and kinetics). At the same time, body-worn sensors now allow us to extend some quantitative movement-related measurements to patients' daily living activities. This era of patient movement "cognification" is bringing us previously inaccessible variables that encode patients' movement, and that, together with measures from clinical examinations, poses new challenges in data analysis. We present herein examples of the application of an unsupervised methodology to classify movement behavior in healthy individuals and patients with PD where no specific knowledge on the type of behaviors recorded is needed. We are most certainly leaving the early stage of the exponential curve that describes the current technological evolution and soon will be entering its steep ascent. But there is already a benefit to be derived from current motion technology and sophisticated data science methods to objectively measure parkinsonian impairments.

Keywords: Parkinson's disease, wearable sensors, data science, biomarkers, biomechanics, clinical decision-making, decision support, motor symptoms fluctuations

OPEN ACCESS

Edited by:
Antonio Suppa,
Università di Sapienza di Roma, Italy

Reviewed by:
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Università di Bologna, Italy
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *30 June 2017*
Accepted: *28 November 2017*
Published: *12 December 2017*

Citation:
Matias R, Paixão V, Bouça R and Ferreira JJ (2017) A Perspective on Wearable Sensor Measurements and Data Science for Parkinson's Disease. Front. Neurol. 8:677. doi: 10.3389/fneur.2017.00677

MOTOR SYMPTOMS ASSESSMENT IN PARKINSON'S DISEASE (PD)

Parkinson's disease is the second most common neurological disorder, caused by the progressive loss of dopaminergic and other subcortical neurons. It is traditionally featured by its motor symptoms, hence its diagnosis is clinical, dependent on the presence of bradykinesia, which is associated with rest tremor, rigidity, and postural instability (1–3).

The classic motor features of PD typically start insidiously and are unilateral and mild, the response to treatment being excellent (3–5). 2–5 years after disease onset, the majority of patients experience wearing-off symptoms, involuntary movements, and other motor complications. Gait and balance disturbances, as well as speech and swallowing difficulties commonly appear, and response

to treatment is only partial (5–8). After 10 years or more, most patients have developed a clearly bilateral disease, OFF states are associated with high disability and dependency, and ON states are also not good. Falls are common, and an increasing number of patients become at least temporarily wheelchair-bound. Dysarthria has a great impact on patients' condition, and hinders communication with caregivers, whereas dysphagia is a frequent cause of choking and aspiration pneumonia, sometimes requiring tube feeding (6, 9).

Parkinson's disease clinical assessment involves subjective patient reports of any changes in status since the last consultation and office-based assessments through clinical scales and traditional patient-reported outcomes (10–12). The use of standardized assessment tools in clinical practice and research is of utmost importance to assess disease progression, evaluate the effect of therapeutic interventions, and to communicate among colleagues (13). The most used instruments for PD assessment are the International Parkinson and Movement Disorder Society Unified Parkinson's disease rating scale (MDS-UPDRS), to evaluate the presence, severity, and progression of PD symptoms, and the Hoehn and Yahr scale, which uses severity levels to evaluate disease progression (10, 11). However, numerous other tests and rating scales have been used, but there is not a consensus on the most suitable screening tools or monitoring outcomes (10, 11, 14).

Parkinson's disease is notorious for its plethora of motor and non-motor features and for considerable inter and intra-subject clinical variability in clinical symptoms, disease progression, and response to medication. This usually reduces clinical visits to brief snapshots of patients' health condition that not always reflects their real health-care status (11, 12, 15, 16). From a scientific and methodological perspective, the current standards of PD clinical evaluations have some limitations: (1) assessments requiring concentration and recall (e.g., fall diaries) are compromised by cognitive impairment, present in 80% of patients in the advanced stage of the disease; (2) the assessment is dependent on clinicians' expertise and individual training; and (3) standard assessments are time consuming and location dependent (7, 11, 15). To obtain an accurate picture of symptoms, a continuous evaluation for prolonged periods of time is, therefore, required (11, 15).

There is a growing awareness that wearable technology, with its ability to capture movement continuously over longer periods of time in controlled and free-living environments, may overcome many of these limitations. It allows a higher sensitivity, accuracy, and reproducibility, and makes it more feasible to objectively capture the full complexity and diversity of changes in motor and non-motor behaviors (12, 15). Therefore, it not only answers to the difficulty to evaluate reliably fluctuating or rare events that, by definition, take place outside clinical visits (i.e., in daily life) but is also able to remotely capture behavioral data and use it to optimize treatment strategies through closed-loop systems (11, 12). Moreover, the use of wearable technology may have an impact on future clinical trials. It may have a significant impact on disease-modifying agents research, since it may offer a way to detect more readily subtle changes that were missed until now. Additionally, with wearable devices' ability to measure outcomes at multiple time points, the statistical power of clinical trials can be enhanced and thus the sample size required to evaluate the effect of therapeutic interventions is reduced (12, 17).

With recent technological advances, a single worn device has the potential to provide a comprehensive picture of the patient within one assessment. A single sensor can quantify macro features, such as walking, sleeping, or sedentary time. It can also be broken down to detect very discrete features (micro features), such as a fall, gait characteristics, turning, and freezing (15). However, despite the variety of commercially available low-cost devices, the use of wearable technology in health care has not yet been established, since algorithm development and data analysis have not kept pace with sensor technology and design advances (15). Also, it is not enough to show that sensor-based technology can measure PD-related features. It is necessary to prove that those features are clinically relevant to patients and clinicians and useful to PD monitoring assessment. A measure is justified if it enhances our understanding of a complex disease or carries the potential to improve disease management as to the need and dose of therapy (11, 12). In order to distinguish relevant from futile technological-based outcome tools, researchers would need to determine: (1) which constructs are clinically relevant; (2) which contribute to an ecologically effective therapeutic decision and provide adequate information about a treatment response or disease course, and finally; (3) which allow an easy and repetitive use (12).

PD PATIENT BIOMECHANICAL ANALYSIS

Biomechanists and mobility researchers have seen human movement analysis evolve from a stick figure representation (18) to accurate real-time 3D movement reconstruction and simulation (19, 20). While such tools support many of today's biomechanical laboratories' services and research, some barriers (e.g., equipment costs and expertise) inhibit their use in clinical practice, and as a result, observation persists as the basis for patient movement analysis.

An increasing body of literature from a range of movement dysfunctions indicates that gait analysis with 3D movement measurements allows a more accurate assessment of gait deviations than visual-based gait analysis (21, 22) and supports its clinical efficacy (23). Musculoskeletal models (19, 24) can be used in clinical settings together with motion capture technology to accurately quantify 3D kinematic variables and complement (or even substitute) observational analysis. Being able to systematically quantify subcomponents of movement (including spatiotemporal variables, joint angles, angular velocity and acceleration, among others) is necessary to ascertain the motor state and monitor patients' specific response to therapeutic interventions (25) and help diminish clinicians' different rating strategies (26). Additionally, clinicians may want to know what were the forces and moment of force for each joint involved in the observed movement (27). This can be indirectly determined from the kinematics, external forces (if applicable), and model inertial properties by a process known as inverse dynamics. In gait analysis, external forces such as the ground reaction forces are collected using force platforms. Recent published literature is paving the way for predicting ground reaction forces based

on measured kinematic data (28) only and by means of artificial neural networks (29). Such solutions will give clinicians access to new subcomponents of movement that are difficult or impossible to measure experimentally and may help overcome the costs and limitations of stationary devices like force platforms. Finally, simulations of human movement (forward dynamics) can be used to help understand what the kinematic results are through a set of given muscle activations. Data from these simulations provide clinicians with a cause-effect framework for analyzing the deviation of a patient's movement pattern from the healthy pattern or from his movement pattern in the past. This type of framework can be used to answer "what if?" questions *via in silico* experiments and help plan therapeutic interventions targeting motor learning and control. Clinicians may access freely available full-body musculoskeletal models for simulations of human gait (30) and use them to synthesize movement patterns with minimum or even absence of experimental data in order to optimally perform a given movement task (often called predictive simulations) (31).

Optical motion capture systems are among the most commonly used solutions for human movement analysis in research laboratories. These systems are used to collect three-dimensional coordinates of special markers (and sometimes clusters) that are placed over the skin of one or more anatomical segments. These segments are tracked throughout the movements and sampled many times per second. To transform the markers' coordinates into body segments' kinematics (e.g., position and orientation), a multi-body chain where each anatomical segment is assumed as a rigid body is generally used. Because skin movements induce displacements in the position of the markers relative to the underlying bones, optimization methods need to be considered to improve segments' pose estimation accuracy in each time frame (32). A new generation of more affordable optical motion capture systems is emerging, proving to be sufficiently accurate and reliable for use in clinical practice (33, 34) and providing a unique opportunity for patients' movement analysis (35, 36) in clinical settings.

One of the major disadvantages of the optical motion capture systems is the limited workspace from where patients' movement can be collected and the time needed for subject instrumentation. Recent advances in microelectromechanical systems provide a new generation of inertial measurement units (IMUs), giving a new surge to human movement analysis clinical and research communities. This new solution has a theoretically unlimited workspace, is cost-effective, and can be successfully used for accurate, non-invasive, and ambulatory motion tracking (37). An independent evaluation of market-available solutions corroborates that low cost and portable IMUs are an attractive solution for patients' evaluation in a clinical setting, when compared to reported accuracy and reliability of optical motion capture systems (38).

Inertial measurement units are probably the most promising candidate for patients' real-life mobility evaluation, extending and complementing the quantitative movement analysis performed in the clinical setting. In line with this, the development of new algorithms for classification of PD patients' motor symptoms fluctuations based on a single IMU has received the attention of many researchers, and promising preliminary results have been published [e.g., Ref. (39)].

As stressed by the Movement Disorders Society Task Force on Technology (12), there is a strong need for a centralized, easy-to-access, and user-friendly platform, capable of merging clinical scores and outcomes, and the biomechanical-related information generated both in the clinical setting and during patients' activities of daily living. With such a myriad of data centralized, sophisticated data science methods can be used to distil the data into knowledge and help support clinical decision-making, as elegantly summarized by Kubota and colleagues (40).

QUANTIFYING MOVEMENT BEHAVIOR IN PATIENTS WITH PD

In 1959, Arthur Samuel stated that "programming computers to learn from experience should eventually eliminate the need for much of this detailed programming effort" (41). Despite this promising claim, researchers that develop and use machine learning pipelines in their research know that it is still a tedious process whose performance depends on manually engineered features or hyperparameter settings and that requires a considerable degree of expertise and programming effort. While researchers are still tackling this and other bottlenecks to reduce the requirement of expert input to a minimum (42), the usage of machine learning has enabled the possibility of detecting new behaviors that were missed by traditional scoring methodologies and may soon allow us to describe and measure the complete behavioral repertoire of a patient (43). This, in turn, will empower clinicians and researchers to correlate the various features of behavior with collected patient data, instead of predicting which particular traits of behavior should be studied. To see how this could be achieved, it is important to understand how behavioral "classifiers" are developed using modern quantitative tools for measuring, describing, and analyzing behavior.

Methods designed to identify predefined blocks of motor behavior are in general incapable of discovering novel ones or new ways in which actions may be executed. One important characteristic of a behavior quantification algorithm should be the capacity of describing the behavior repertoire in its totality, including behaviors not anticipated by the researcher (44). As mentioned, these algorithms must determine explicit intervals of time when a relevant pattern of movement is executed (i.e., an action). These patterns (e.g., walking, running, or sitting) are detected by classifiers: computer algorithms that map input data to a category. A classifier can also distinguish occurrences of a specific action from periods where the action does not occur.

There are two distinct ways to train a classifier: supervised and unsupervised. In a supervised classifier, the behavior blocks are trained by "positive" (where the desired action happens) and "negative" templates (when it does not take place). The distinct actions are recognized by a machine learning algorithm that uses annotated training examples ("ground-truth" labels) to generate a set of rules to discriminate the different actions (44–47). In an unsupervised classifier, on the other hand, no previous assumptions are made about what type of behaviors are occurring.

Only the representative templates with movement information without annotations are presented to the learning algorithm. The algorithm then groups data by its intrinsic structure into discrete units or blocks. The unsupervised classification is driven by the unlabeled data and the result of the procedure used as classifier labels for different sessions and subjects. Using this method, it is possible to generate a continuous unbiased classification of behavioral states.

In the case of PD patients, where disturbance of motor activities rhythmicity is commonly present, mean measures will simply result in averaging out any modifications and may, therefore, be entirely insensitive. Clinicians and researchers should explore all subcomponents of movement and identify those that highlight non-constancy over multiple repetitions and prove to accurately measure variability (48, 49). In the following figures, we present examples of the application of movement behavior classification in healthy individuals (**Figure 1A**) and patients with PD (**Figures 1B** and **2**) with the use of an unsupervised methodology.

The unsupervised clustering approach allowed us to generate a continuous unbiased classification of behavioral states in these examples with healthy individuals and PD patients, even without specific knowledge on the type of behaviors recorded (unlabeled data). In some cases, the found behavior blocks cannot be labeled, either because motor activities are impossible to observe or unknown altogether. Nevertheless, being able to categorize and discriminate these putative actions is important to describe the subject's interaction with the environment, more importantly, so in ambulatory conditions and for long periods of time when direct access to the patient may not be possible (difficult).

Temporal variables that encode patients' movement acquired both in a clinical setting and during patients daily living activities are often accompanied by structured covariates, such as patient demographics and measures from clinical examinations. In most cases, there are interactions and correlations between these movement-related variables and covariates that clinicians would like to understand and leverage. Fiterau and colleagues (52) recently presented a method that incorporates structured covariates into time series deep learning and demonstrated how the method outperforms competing models. Such methods obviate the usually required extensive feature engineering and domain expertise to unveil data interactions and correlations and are becoming increasingly available.

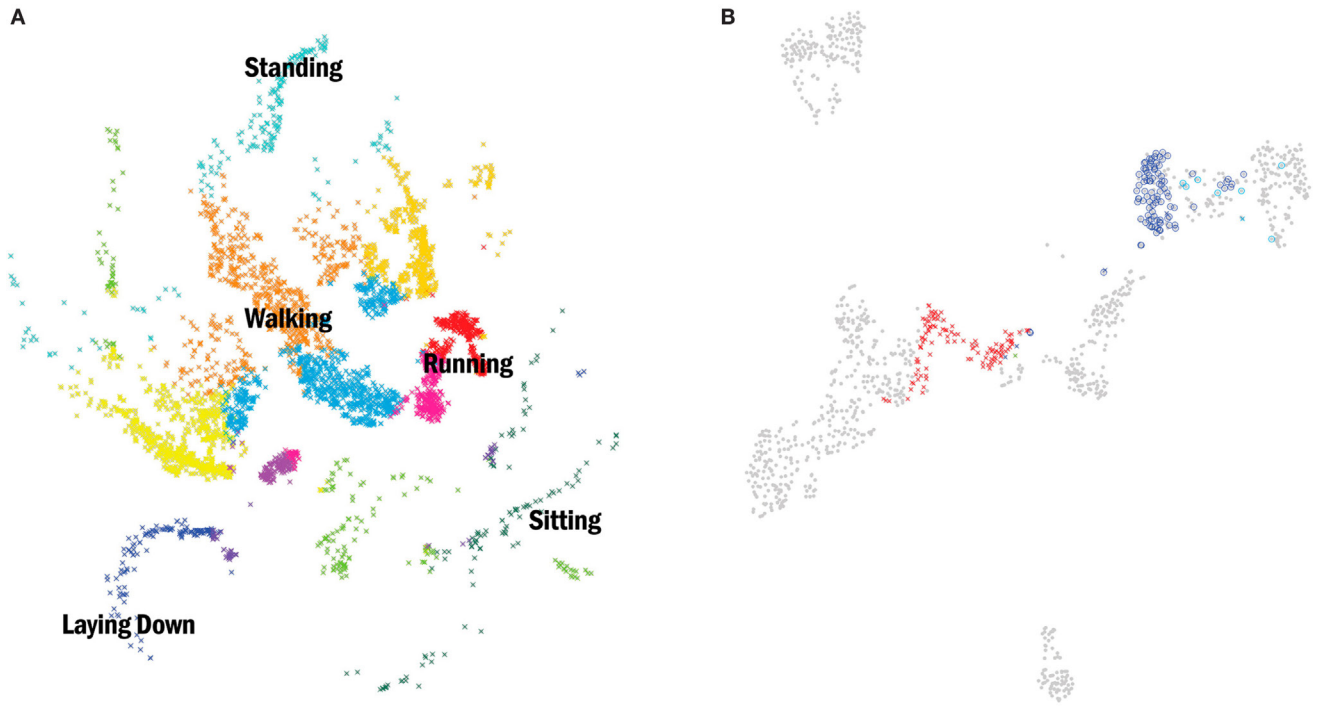

FIGURE 1 | **(A)** (Left) two-dimensional embedding (t-Distributed Stochastic Neighbor Embedding) (50) of acceleration data points from nine healthy subjects performing several daily activities. Data were collected with one inertial measurement unit (IMU) placed over the pelvis with a sample rate of 120 Hz. Each point corresponds to a discretized behavior block obtained with a change-point detection algorithm. Colors correspond to clusters obtained by affinity propagation (51). A subset of clusters was labeled according to the dominant feature (standing, walking, sitting, etc.). **(B)** (Right) shows an example of the same methodology now applied to six patients diagnosed with idiopathic Parkinson's disease (PD) and a Hoehn and Yahr stage less than or equal to 2. Movement data were collected with one IMU placed over the pelvis (sample rate 120 Hz) while patients walked a 10-m corridor, first in their OFF state ("x") and later in their best ON state defined by the Movement Disorder Society Unified Parkinson's disease rating scale ("o"). The gray dots represent all the recorded blocks of behavior from the six PD patients and the color dots the groups related to one patient. Clusters represented in both left and right images are from two independent experiments, thus, the resultant embeddings are not comparable.

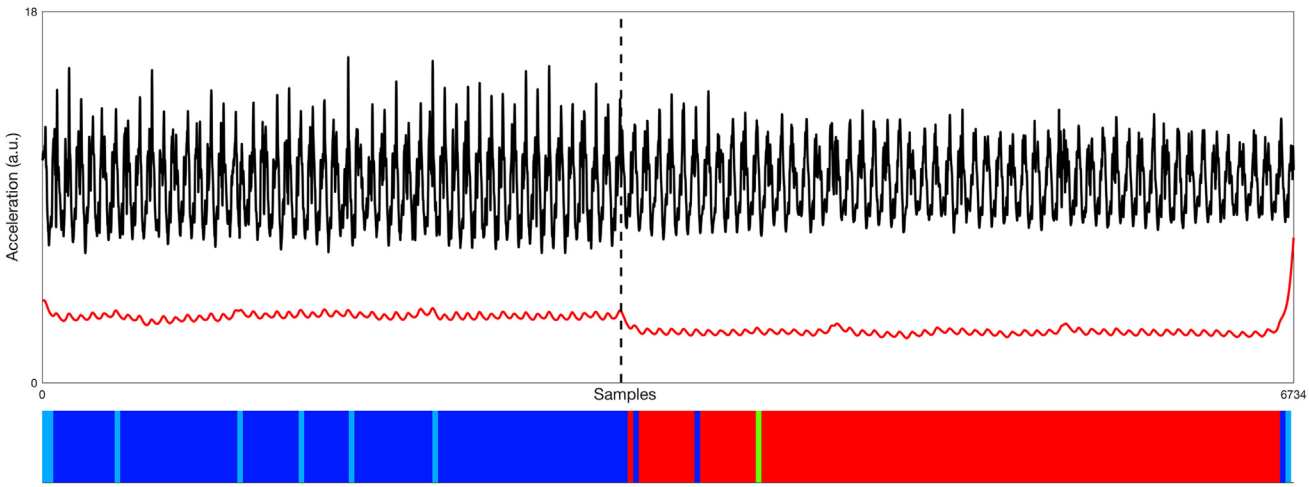

FIGURE 2 | Representative example of data processed from the accelerometer (black signal—raw vertical acceleration; red signal—low-pass filtered posterior–anterior acceleration) used by one of the six Parkinson's disease (PD) patients during two 10-m walk trials, first in his OFF state and later in his best ON state. Time series are two collated non-consecutive segments of data recorded OFF (left) and best ON (right) states of one PD patient, as indicated by the black dashed line. Bottom: the distinction between the OFF and ON states is very clear with this methodology, where the clusters' organization (showed by the color bar) perfectly aligns with the transition of the signals above. Different colors represent found behavioral blocks (same color code as **Figure 1B**).

CONCLUSION

We believe that the technological evolution witnessed in the last decades will allow us to "look" at patients in an unprecedented way, not only because the measurement equipment needed is becoming more accessible (e.g., motion sensors and software) but also because the dedicated expertise once required (e.g., in the form of a staff biomedical engineer) to collect, process, and present the data is nowadays facilitated by highly user-friendly web-based applications leveraged by sophisticated data science methods. The ill-equipped clinician can now be assisted in translating sensors' data into actionable information upon which clinical decisions may be supported. Some of this technology was and continues to be miniaturized and made wearable, leading to a real-time quantified self. This will enable patients with movement disorders to benefit from an analysis that has been limited to academic laboratories and state-of-the-art medical centers. While this patient movement "cognification" is gaining a considerable body of evidence, showing that specific features related to the movement dysfunction can be measured by body-worn sensors, it still needs to prove its clinical impact and usefulness through well-designed studies. Although statistically significant changes may often be seen in movement-related variables in studies aiming to measure change after a given intervention, it is particularly important to determine clinimetric properties, such as the minimum clinically meaningful change, to fully understand its clinical significance.

Machine learning automatic pipelines like the one presented in the previous chapter can be applied to process 3D movement data in a clinical setting and help quantify patterns in the patients' posture, balance, and gait, complementing the information of rating scales such as the MDS-UPDRS. Additionally, from the outcome of the classification, as shown in the previous chapter, we can study the behavior repertoire in real-life scenarios, assessing the micro structure of the continuous movement and behavioral sequences, and quantify transitions and behavior variability, both in the long-term monitoring experiments and also in more conventional tasks. This is of particular interest to track PD motor symptoms fluctuations during patients' daily living activities and help clinicians objectively support decision-making with respect to adjustments to medication type, dose, and timing that we believe will lead to more effective treatments, patient quality of life, and an overall reduction in care-related costs.

It is our belief that the successful integration of miniaturized and wearable sensor-based measurements and data science methods in daily clinical practice will be deeply dependent on a concerted effort of both the research and clinical communities on: (i) guidelines to develop clinically accepted technology-based tools; (ii) promoting research networks and data sharing politics so that others can confirm and extend published results; (iii) learning how data science can and should be applied; (iv) promoting a collective intelligence to exponentially advance the quality of the assessment and management of PD patients.

AUTHOR CONTRIBUTIONS

Conceived and designed the manuscript: RM and JF. Data processing and interpretation: RM and VP. Wrote the paper and critical review: RM, VP, RB, and JF.

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Conflict of Interest Statement: The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 14 August 2017
doi: 10.3389/fneur.2017.00394

Identification of Characteristic Motor Patterns Preceding Freezing of Gait in Parkinson's Disease Using Wearable Sensors

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OPEN ACCESS

Edited by:
Joan Cabestany, Universitat Politecnica de Catalunya, Spain

Reviewed by:
Francesca Morgante, University of Messina, Italy
Paolo Calabresi, Santa Maria della Misericordia Hospital, Italy
Carlos Pérez López, Universitat Politecnica de Catalunya, Spain

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *26 April 2017*
Accepted: *24 July 2017*
Published: *14 August 2017*

Citation:
Palmerini L, Rocchi L, Mazilu S, Gazit E, Hausdorff JM and Chiari L (2017) Identification of Characteristic Motor Patterns Preceding Freezing of Gait in Parkinson's Disease Using Wearable Sensors. Front. Neurol. 8:394. doi: 10.3389/fneur.2017.00394

Freezing of gait (FOG) is a disabling symptom that is common among patients with advanced Parkinson's disease (PD). External cues such as rhythmic auditory stimulation can help PD patients experiencing freezing to resume walking. Wearable systems for automatic freezing detection have been recently developed. However, these systems detect a FOG episode after it has happened. Instead, in this study, a new approach for the prediction of FOG (before it actually happens) is presented. Prediction of FOG might enable preventive cueing, reducing the likelihood that FOG will occur. Moreover, understanding the causes and circumstances of FOG is still an open research problem. Hence, a quantitative characterization of movement patterns just before FOG (the pre-FOG phase) is of great importance. In this study, wearable inertial sensors were used to identify and quantify the characteristics of gait during the pre-FOG phase and compare them with the characteristics of gait that do not precede FOG. The hypothesis of this study is based on the threshold-based model of FOG, which suggests that before FOG occurs, there is a degradation of the gait pattern. Eleven PD subjects were analyzed. Six features extracted from movement signals recorded by inertial sensors showed significant differences between gait and pre-FOG. A classification algorithm was developed in order to test if it is feasible to predict FOG (i.e., detect it before it happens). The aim of the classification procedure was to identify the pre-FOG phase. Results confirm that there is a degradation of gait occurring before freezing. Results also provide preliminary evidence on the feasibility of creating an automatic algorithm to predict FOG. Although some limitations are present, this study shows promising findings for characterizing and identifying pre-FOG patterns, another step toward a better understanding, prediction, and prevention of this disabling symptom.

Keywords: freezing of gait, wearable sensors, Parkinson's disease, classification, prediction, inertial measurement unit, machine learning, data analysis

INTRODUCTION

Freezing of gait (FOG) is a disabling symptom that is common among patients with advanced Parkinson's disease (PD). FOG is clinically defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (1). It most commonly occurs when a person starts to walk, during turning, when passing through narrow passages, and when approaching a destination such as a chair (1). FOG markedly impairs mobility, it is an important cause of falls (2–4) and reduces quality of life (1). External cues such as rhythmic auditory stimulation (e.g., metronome) and visual cues (e.g., walker or stick projecting a laser line on the floor) (5) can help PD patients experiencing freezing to resume walking.

Recently, several research studies used wearable sensors (mostly accelerometer and gyroscopes) in order to quantify the characteristics of FOG events and to implement systems for effective real-time FOG detection. An updated list of these studies can be found in Ref. (6) and in a recent review (4). The most frequent approach for the detection of FOG events is based on the fact that during FOG the acceleration signals recorded by inertial sensors show a pattern of high frequency movements (mostly given by the trembling behavior of the legs) (4, 6–15).

Automatic FOG detection is paramount for providing a cue (such as rhythmic auditory stimulation) during a FOG episode in order to help the person become free of the motor block. FOG prediction on the other hand refers to the ability of predicting FOG before it occurs. By identifying possible precursor signs of FOG (pre-FOG) the cue could be provided as soon as, or ideally just before, the FOG would begin, which might potentially help to prevent the incoming freezing event. Moreover, understanding the causes and circumstances of FOG is still an open research problem (1, 16–25) and so the characterization of the pre-FOG phase, defined as a time window of a few seconds before FOG occurs, might have an extremely relevant impact.

The pre-FOG phase has been studied using different measurement systems, such as camera-based motion capture systems (26, 27), electromyography (28), electroencephalography (29), functional near infrared spectroscopy (16), electrocardiography (17, 30), and skin conductance (30). To the best of our knowledge, only two exploratory studies have used wearable inertial sensors to analyze the pre-FOG phase (31, 32).

In this study, we aimed to use wearable inertial sensors, specifically accelerometers and gyroscopes, to identify and quantify the characteristics of gait during the pre-FOG phase and compare them with the characteristics of gait that do not precede FOG. The hypothesis of this study is based on the threshold-based model of FOG (23) which suggests that before FOG occurs, there is a degradation of the gait pattern. Once the level of deterioration crosses a critical threshold, FOG occurs (23). A classification algorithm was then developed in order to test if it is feasible to predict FOG (i.e., detect it before it happens). The aim of the classification procedure was to identify the pre-FOG phase. An evaluation of the performance of such classifier is presented.

MATERIALS AND METHODS

Overview of Approach

As an initial step toward identification of the pre-FOG phase, we focus here on FOG episodes that take place during movement, excluding FOG episodes that happen after a period of inactivity (i.e., start hesitation). To compare gait and pre-FOG, an *ad hoc* algorithm was designed and implemented to obtain gait and pre-FOG time windows. Then, features which quantify possible patterns leading to FOG were extracted from the identified windows. Finally, a statistical analysis was performed to identify significant differences between gait and pre-FOG. This analysis was performed for each single feature. We also explored the possibility of combining the information from different features by training a classifier to automatically discriminate between gait and pre-FOG.

All the analyses were performed using Matlab (release 2016b, MathWorks, USA).

Data Set

The CuPiD data set was used for our analyses (30). In this data set, 18 people with PD were monitored during their "ON" medication state using a wearable multisensor setup (30). The study was carried out in accordance with the recommendations of the Ethics Committee of Tel Aviv Sourasky Medical Center with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Tel Aviv Sourasky Medical Center.

The subjects performed several activities which were selected because they are known to frequently induce FOG (e.g., turning, passing narrow corridors, and dual tasking). The recording protocol included resting periods and other conditions such as completing questionnaires and clinical evaluations [MDS-UPDRS (33), NFOG-Q (34)]. These conditions were not considered in this study as we aimed to analyze only conditions associated with motor activities. The considered conditions are reported in **Table 1**.

In this study, data from 11 subjects were analyzed; only those subjects who exhibited at least one FOG episode during the protocol were included. The subject characteristics are reported in **Table 2**. We considered the data registered from the two inertial sensors positioned on the shins right above the ankles and from the inertial sensor positioned on the lower back (see **Figure 1**). The three sensors [ETHOS (35), sampling frequency of 128 Hz] were fixed to the body with straps.

Data Processing

The start and end of each FOG event were identified off-line by two expert clinicians after examining the video recordings [further details in Ref. (30)]. The moment of arrested gait pattern (i.e., stop in alternating left-right stepping) was considered as the start of FOG. The moment when the patient resumed a regular gait pattern was considered as the end of the freezing event.

We defined the period of 2 s before each FOG as the pre-FOG window. We considered 2 s to be the appropriate window length

TABLE 1 | Protocol conditions.

Condition	Description
Ziegler, Single Task Ziegler, Dual Task Ziegler, Triple Task	The Ziegler protocol includes two 360° turns, one 180° turn, and passing through a narrow passage (44). It was performed normally (single task), carrying a glass of water (dual task), and carrying a glass of water while performing serial subtractions (triple task)
Figure of 8, Single Task Figure of 8, Dual Task	The subject is required to walk performing a figure of 8 shape five times in a 3-m area. It was performed normally (single task) and with a cognitive dual task, which required to perform serial subtractions or to enumerate words that start with a specific letter
Straight + Turns, Single Task Straight + Turns, Narrow Corridor Straight + Turns, Dual Task	The subject is required to walk straight for 20 m, turn, and walk again on the opposite direction, for five times. It was performed normally (single task), passing a narrow corridor, and with a cognitive dual task, which required to perform serial subtractions or to enumerate words that start with a specific letter
Circles + Random Turns, First Trial Circles + Random Turns, Second Trial	The subject is required to walk in circles, with random 180° and 360° turns, when asked by the clinicians, for a period of 3 min. The condition was repeated a second time for some subjects (second trial)
Hospital tour	It includes approximately 10 min of free walking through the crowded hall of the hospital. It includes involuntary stops, turns, changes of direction, using the elevator, and passing through narrow spaces

TABLE 2 | Subject characteristics.

Subject ID	Age (years)	Disease duration (years)	NFOG-Q	Hoehn and Yahr	MDS-UPDRS Part III
1	89	13	17	4	43
2	55	14	21	3	38
3	63	4	27	4	55
4	68	7	15	3	24
5	63	5	14	3	54
6	60	10	24	3	36
11	64	5	24	2	38
12	77	17	28	4	55
16	81	12	23	3	43
17	49	3	17	2	44
18	76	10	15	3	42
mean	67.7	9.1	20.5	3.1	42.9
SD	11.9	4.6	5.1	0.7	9.3

NFOG-Q is the new freezing of gait questionnaire (34); MDS-UPDRS Part III is the score of Part III (motor examination) of the MDS-UPDRS (33).

because we were interested in a period of time long enough to capture the last stride before the onset of freezing. In cases where a previous FOG event (or part of it) was present during this 2-s period, the pre-FOG was discarded. This was done because the aim of the work was to study gait before FOG.

To identify gait windows, we first removed the parts of recordings that cannot be considered as gait: pre-FOG windows and FOG events. Then, in the remaining data, we identified continuous portions of at least 2 s. We divided each portion in non-overlapping 2-s windows. In case a portion was not a multiple of 2 s, we discarded an equal period at the beginning and at the end of the portion.

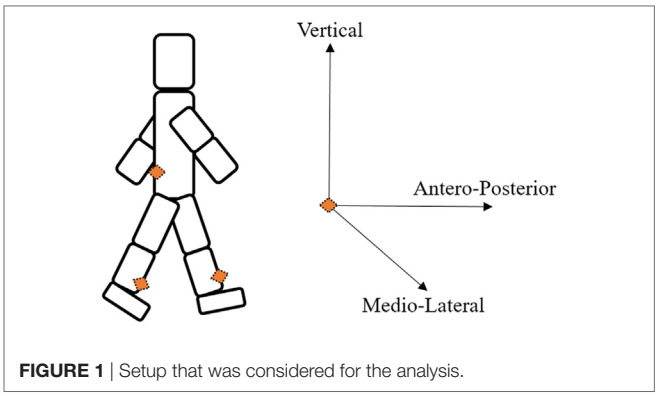

FIGURE 1 | Setup that was considered for the analysis.

For both gait and pre-FOG windows, we only selected windows with sufficient motion.

Consequently, gait windows can be data segments composed of straight walking, curved-path walking (such as the one in the "Figure of 8" and "Circles + Random Turns" conditions), walking through narrow passages, and turns (while walking and in place). The workflow of the identification of gait and pre-FOG windows is presented in **Figure 2**. The check for sufficient motion in a window is as follows.

A window contains insufficient motion if more than 50% of the samples of that window can be considered motionless.

A sample is considered motionless if two conditions are satisfied simultaneously:

(i) Both left and right ankle norms of the gyroscope signals (angular velocities) are less than 0.5 rad/s.
(ii) The norm of the acceleration of the lower back sensor is in a specific range. To compute this range, first a reference value for the norm of the acceleration was computed by averaging the norm of the acceleration in a portion of the recordings at the beginning of the protocol when the subject was not moving. The range was then defined as a "reference value ± 10% of the reference value." The reference value is a value near the gravity acceleration $g = 9.81$ m/s^2 (ideally, it would be exactly g).

From each window with sufficient motion, eight features were computed from the signals recorded by the inertial sensors (see **Table 3**). The features objectively quantify turns (*turning degrees*), gait symmetry (*left-right cross-correlation*, *left-right difference in SD)*, gait amplitude (*left-right average SD*, *lower back SD*), and frequency content (*power in the locomotor band*, *power in the freezing band*, and *freezing index*). These specific features were chosen because we expected them to be sensitive to FOG (1, 23, 36, 37).

The result of this process on a representative example is reported in **Figure 3**, which includes 16 gait windows, six pre-FOG windows, and three windows (which were candidate gait

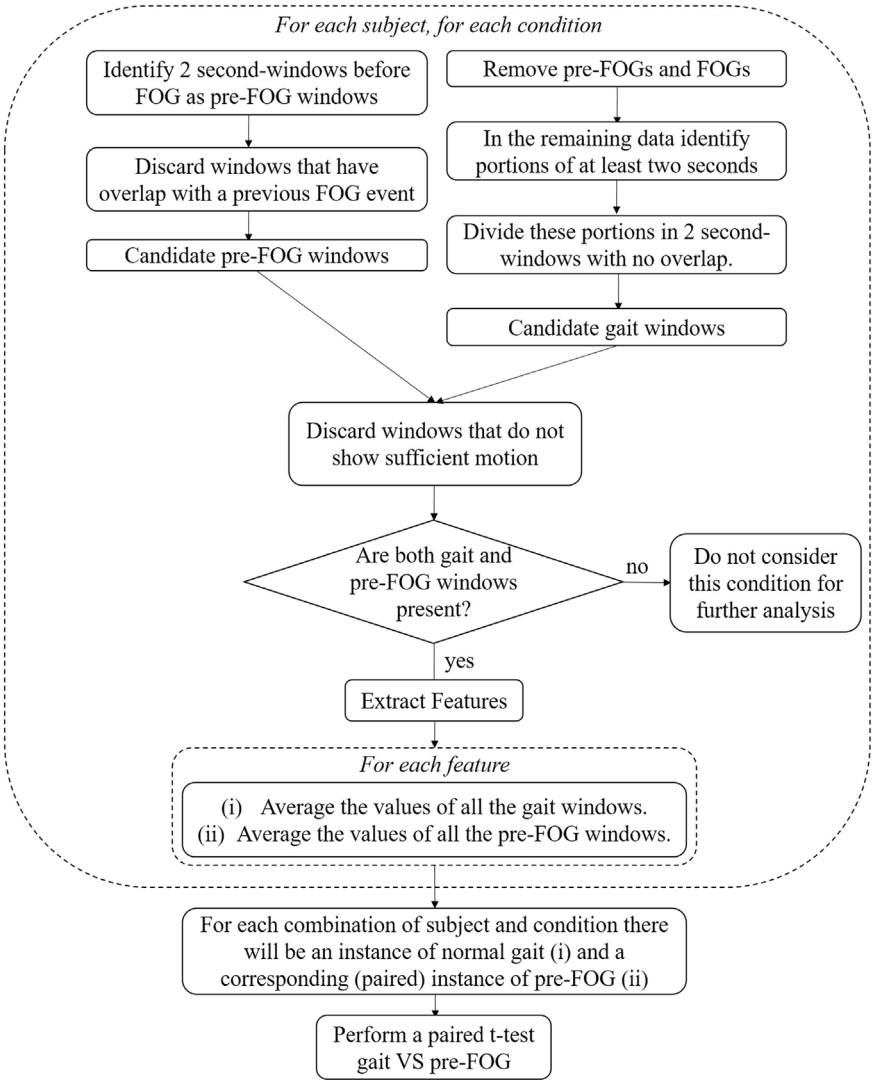

FIGURE 2 | Workflow of data processing.

windows) that were discarded because of insufficient motion. The features extracted from the signals of the 16 gait windows and six pre-FOG windows were then averaged, obtaining a single feature value for gait and a corresponding (paired) single value for pre-FOG, respectively. These two paired values were then considered in the statistical tests.

This process was repeated for each subject, for each condition. Only conditions with both gait and pre-FOG windows were selected for further analysis (see **Figure 2** and **Table 4**).

Statistical Analysis

We considered all the pairs (gait–pre-FOG) obtained from the procedure described above and shown in **Figure 2**. Each pair corresponds to a specific condition of a specific subject. In the pair, the first sample is the average of the feature values of the gait windows, and the second sample is the average of the feature values of the pre-FOG windows in that condition. The paired samples were considered condition by condition to find significant differences that did not depend on the degree of difficulty of a condition. The average was performed to have, for each condition, a single value for gait and a single value for pre-FOG. The averaging allowed for dealing with the imbalance between the number of gait windows and pre-FOG windows. In fact, usually there were more gait windows than pre-FOG windows (see **Figure 3**). Furthermore, both the number of gait windows and pre-FOG windows changed when considering different subjects and conditions.

We used the paired *t*-test to perform the comparison between gait and pre-FOG. The level of significance p was set at $p = 0.05$. Since we performed eight testing procedures (i.e., one for each feature), the results were considered significant if they remained significant after the correction for multiple testing procedures of Benjamini and Yekutieli (38).

TABLE 3 | Features extracted from the recorded signals.

Feature	Sensor	Signal	Direction	Description
Turning degrees	Lower back	Angular velocity	Vertical	In order to obtain the turning degrees, the angular velocity around the vertical axis was low-pass filtered at 1.5 Hz, then integrated, as in Ref. (45)
Left–right cross-correlation	Left and right ankles	Angular velocity	Mediolateral	The cross-correlation between two signals identifies the similarity between them at different lags (shifting in time one signal with respect to the other). This feature is the maximum of cross-correlation between the left and right leg among lags from 0.25 to 1.25 s (this is considered as the period where a pattern of alternate stepping can be in place). If walking is in place there should be a peak of cross-correlation for a lag in that range. As a technical note, the unbiased cross-correlation was performed and the signals were detrended before applying cross-correlation. The angular velocity in the mediolateral direction was chosen because it reflects the leg forward movement during gait for sensors on the ankles (see **Figure 3**)
Left–right average SD	Left and right ankles	Angular velocity	Mediolateral	It is the average between the SD of the signal of the right ankle and the SD of the signal of the left ankle. It is a measure of overall variation and range of leg movement
Left–right difference in SD	Left and right ankles	Angular velocity	Mediolateral	It is the absolute difference between the SD of the signal of the right ankle and the SD of the signal of the left ankle. It is a measure of the difference in ranges between the left and right leg
Lower back SD	Lower back	Acceleration	Anteroposterior	It is a measure of overall variation and range of motion of the trunk. The anteroposterior direction was chosen to reflect forward motion
Power in the locomotor band	Left and right ankles	Acceleration	Anteroposterior	The frequency of walking movements (locomotor activity) is considered to be concentrated around its characteristic periodic patterns, steps, and strides, which are around 2 and 1 Hz, respectively. This feature is the power in the locomotor band, which is defined to be between 0.5 and 3 Hz, as in Ref. (8). This feature was calculated for both left and right ankles and the two values were then averaged
Power in the freezing band	Left and right ankles	Acceleration	Anteroposterior	It was found that leg trembling during freezing is characterized by a higher frequency pattern with respect to the one that is characteristic of walking (7, 8, 14, 15). This feature is the power in this freezing band, which is defined to be between 3 and 8 Hz, as in Ref. (8). This feature was calculated for both left and right ankles and the two values were then averaged
Freezing index	Left and right ankles	Acceleration	Anteroposterior	It is the ratio between the power in the freezing band and the power in the locomotor band (8). It is usually used in studies for detecting freezing of gait with inertial sensors. When freezing is already in place, this index tends to show a high value (8, 14, 15). This feature was calculated for both left and right ankles and the two values were then averaged

Classification

In order to develop the classifier, we selected the three best features in characterizing the differences between gait and pre-FOG from the statistical analysis (the features associated with the lowest *p*-values). Then, we trained a linear discriminant analysis classifier (39). The classifier was trained to discriminate between two classes: gait and pre-FOG. The trained classifier provided the probability that a certain window was gait or pre-FOG. In order to obtain a fair estimation of the accuracy of the classifier, a leave-one-subject-out procedure was performed: when the classifier was tested on a certain subject, all the data from the remaining subjects were used to train the classifier.

The classifier was trained and tested on all of the gait and pre-FOG windows of the conditions selected for the statistical analysis (i.e., the conditions with both gait and pre-FOG windows).

The performance of the classifier, considering the obtained probabilities, is quantified by the area under the curve and the optimal combination of sensitivity and specificity. The latter is calculated with Youden's index (40). The threshold on the probability corresponding to this optimal combination of sensitivity and specificity is also provided in **Table 5**. This threshold is used to classify a window in one of the two classes. So, if the probability of being pre-FOG is higher than the threshold, the window can be classified as pre-FOG (i.e., the classifier predicts an incoming FOG), otherwise the window can be classified as gait.

RESULTS

There was a significant amount of variability with respect to performed conditions in the CuPiD data set (**Table 4**). Not every subject performed the same number of conditions: only one subject (ID 18) performed every condition. The fact that different subjects performed a different number of conditions was mainly due to their health status and disease stage. The clinician decided how many conditions a specific person could perform. For example, the subject who performed the fewest number of conditions (subject 12) was the one with longest PD duration and highest NFOG-Q and MDS-UPDRS Part III scores. The "Straight + Turns, Single Task" condition was the only condition performed by every subject. This condition was likely the easiest to perform (it consists only in straight walking and predefined turns). There was additional intersubject variability with respect to the conditions that had both gait and pre-FOG (i.e., the conditions selected for the analysis). This was due to the episodic nature of FOG as well as due to the fact that different subjects, depending

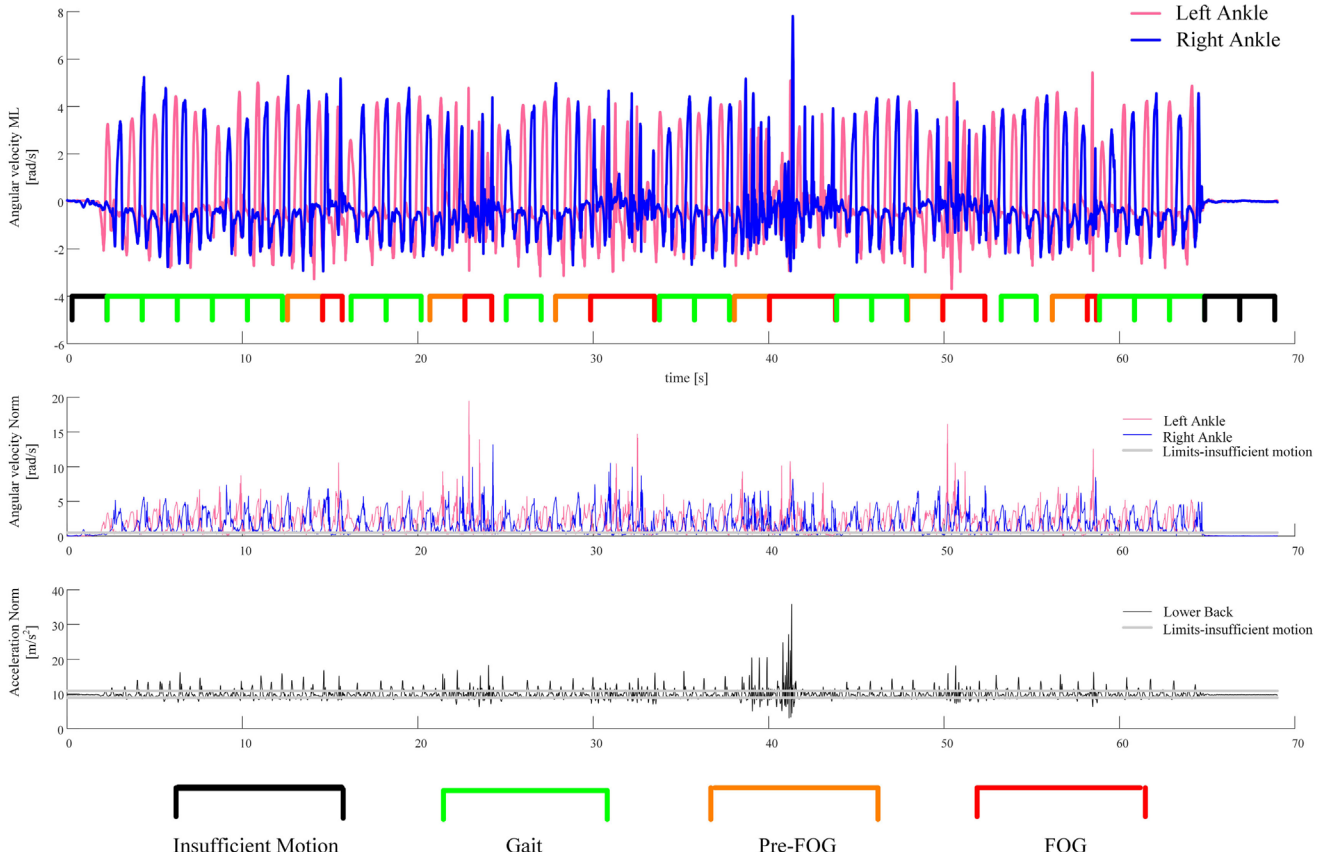

FIGURE 3 | An example of the segmentation of the recorded signal in gait and pre-FOG windows. The first plot from the top shows the recorded angular velocities of the sensors on the left and right ankles together with the segmentation of the windows. The second plot is the norm of the angular velocity of the sensors on the left and right ankles. The third plot is the norm of the acceleration of the sensor on the lower back. These two norms are used to perform the check for sufficient motion in a window.

TABLE 4 | The conditions that were performed by the subjects are highlighted in green.

Condition/subject ID	1	2	3	4	5	6	11	12	16	17	18
Ziegler, Single Task	x	x	x			x			x		x
Ziegler, Dual Task	x					x			x	x	x
Ziegler, Triple Task		x			x	x	x				x
Figure of 8, Single Task	x	x	x		x	x				x	
Figure of 8, Dual Task	x					x				x	
Straight + Turns, Single Task	x		x			x		xx	x	x	
Straight + Turns, Narrow Corridor	x				x	x				x	
Straight + Turns, Dual Task						x					
Circles + Random Turns, First Trial	x	x			x	x		x	x	x	x
Circles + Random Turns, Second Trial									x	x	
Hospital tour				x					x	x	

All the reported conditions were performed a single time with the exception of subject 12 who performed twice the "Straight + Turns, Single Task" condition. The conditions that were selected for the analysis are the ones with at least one gait window and at least one pre-FOG window. They are marked with an "x."

on their disease stage and health status, experienced a different number of FOG episodes.

Fifty paired samples were obtained using the procedure summarized in **Figure 2** (the number of paired samples corresponds to the total number of x marks in **Table 4**). In **Figure 4**, the *p*-values and the significant features (corrected for multiple testing) obtained from the paired *t*-tests are reported. Six out of eight features showed significant differences between gait and pre-FOG. These features were: *turning degrees*, *left-right cross-correlation*, *left-right average SD*, *lower back SD*, *power in the freezing band*, and *freezing index*.

The three features with the lowest *p*-values overall were *left–right cross-correlation*, *left–right average SD*, and *freezing index*. However, the three features selected for the classifier were *left–right cross-correlation*, *turning degrees*, and *freezing index*. *Turning degrees* (the fourth lowest *p*-value) was selected instead of *left–right average SD* because the latter showed high correlation with *left–right cross-correlation* ($r = 0.95$ considering gait windows, $r = 0.94$ considering pre-FOG windows). An example of the application of the classifier is reported in **Figure 5**. The performance of the classifier on each subject is reported in **Table 5**.

TABLE 5 | Performance of the classifier.

Subject ID	1	2	3	4	5	6	11	12	16	17	18	Mean
Area under the curve	0.69	0.66	0.90	0.79	0.69	0.87	0.90	0.75	0.80	0.51	0.75	0.76
Sensitivity	0.56	0.90	0.92	1.00	1.00	0.88	1.00	0.64	0.74	0.73	0.80	0.83
Specificity	0.79	0.41	0.76	0.79	0.41	0.75	0.67	0.83	0.81	0.37	0.75	0.67
Threshold	0.53	0.26	0.22	0.20	0.23	0.49	0.72	0.19	0.59	0.23	0.57	0.38

DISCUSSION

Using inertial sensors, we found evidence that the pre-FOG phase differs from gait in patients with PD who suffer from FOG. This finding is consistent with the threshold model of FOG (23) as it suggests that an abnormal movement occurs before the FOG event.

As expected, the higher *turning degrees* registered in the pre-FOG phase reflect the fact that turning triggers FOG. Plotnik et al. (41) showed that subjects who experience FOG have a poor bilateral coordination of stepping. It was hypothesized that tasks requiring a high degree of left–right coordination (such as turning) could predispose to FOG events (41).

We found the *left–right cross-correlation* to significantly decrease during pre-FOG. This feature quantifies both the temporal symmetry between the two limbs and the movement amplitude of both limbs. Therefore, this result shows a reduction of symmetry between the two limbs and of the overall amplitude (range) of movement. The former is consistent with Plotnik et al. (37), where a reduction in symmetry was found in the gait of subjects who suffered from FOG. Although in Nieuwboer et al. (36) this reduction was not found during pre-FOG. The latter is confirmed by the significant reduction that was found in the forward range of leg movements (*left–right average SD*) and of the trunk (*lower back SD*). These results are consistent with that of Ref. (36), where a pattern of reduced movement amplitude before FOG was reported.

The *left–right difference in SD* was not significant. We decided to quantify a possible difference (asymmetry) in movement amplitude (range) between the left and right leg just before FOG; however, this particular difference was not observed in this study.

In the frequency domain, we sought to test the features that are usually used for FOG detection (i.e., after the FOG episode has begun) to see if there was a similar characteristic pattern in the pre-FOG phase. The *power in the freezing band* and the *freezing index* showed a significant difference between gait and pre-FOG, with higher values associated with the pre-FOG phase. This reflects a pattern of high frequency movements that is not only present when FOG is in place (4, 6–13) but also just before it starts. This is in line with the results by Ferster et al. (32), obtained on a subset of the subjects of this study.

The sensing modality that is more similar to the one used in this study is the camera-based motion capture system. There is a trade-off between the advantages and limitations of the two approaches. On one hand, with motion capture, it is possible to have more detailed information about the movement since it is possible to accurately quantify displacement features (e.g., step and stride length) (26), which are not yet reliably quantifiable with inertial sensors, especially when considering pathological gait such as that observed in people with advanced PD. The important limitation of such system, however, is the constrained laboratory environment and the limited working volume. On the other hand, wearable inertial sensors provide the possibility of quantifying relevant features in diverse environments, shifting from laboratory to unconstrained environments, and real-life conditions. For example, Weiss et al. (42) showed that subjects with PD suffering from FOG, who were recorded continuously for 3 days during daily community living, have altered gait variability and consistency with respect to subjects not suffering from FOG. In this study, wearable sensors provided the possibility to test subjects in a series of diverse conditions, the hospital tour being the one most similar to daily living activities. Difference between laboratory and unconstrained activity monitoring is particularly important in FOG, where it is common to find subjects who are reporting freezing events at home, but do not experience FOG in the laboratory (43).

In the previous work by Nieuwboer et al. (26) that used motion capture and found spatiotemporal abnormalities of gait, only FOG events without direction change were selected for the analysis. In contrast, all FOG events, except for those occurring at gait initiation [which were not considered in Ref. (26) either], were considered in this study. We did this because we were interested in quantifying the effect of turning as a trigger of FOG and turning is one of the main activities performed at the time of FOG onset (25). Another difference, which is a limitation of this study, is that subjects of the CuPiD data set did not perform *ad hoc* tasks of voluntary stops. Therefore, we were unable to compare the degradation of gait specific to pre-FOG with gait characteristics prior to voluntary stops.

Classification

The idea behind the use of the classifier was to replicate the threshold model of FOG (23), by identifying when the combination of values of three gait features changes over a critical threshold. The performance of the classifier varied across subjects. For most subjects, the performance was acceptable, for some subjects (such as the one presented in **Figure 5**), the performance was good, while for one subject (subject 17), the performance was not better than random classification (**Table 5**).

The optimal threshold of the classifier reported in **Table 5** and **Figure 5** can be interpreted as an estimate of the critical threshold of gait degradation of the threshold model of FOG. The optimal threshold varies among subjects, suggesting that different subjects may have different critical levels of gait degradation leading to imminent FOG. This is possibly connected to the

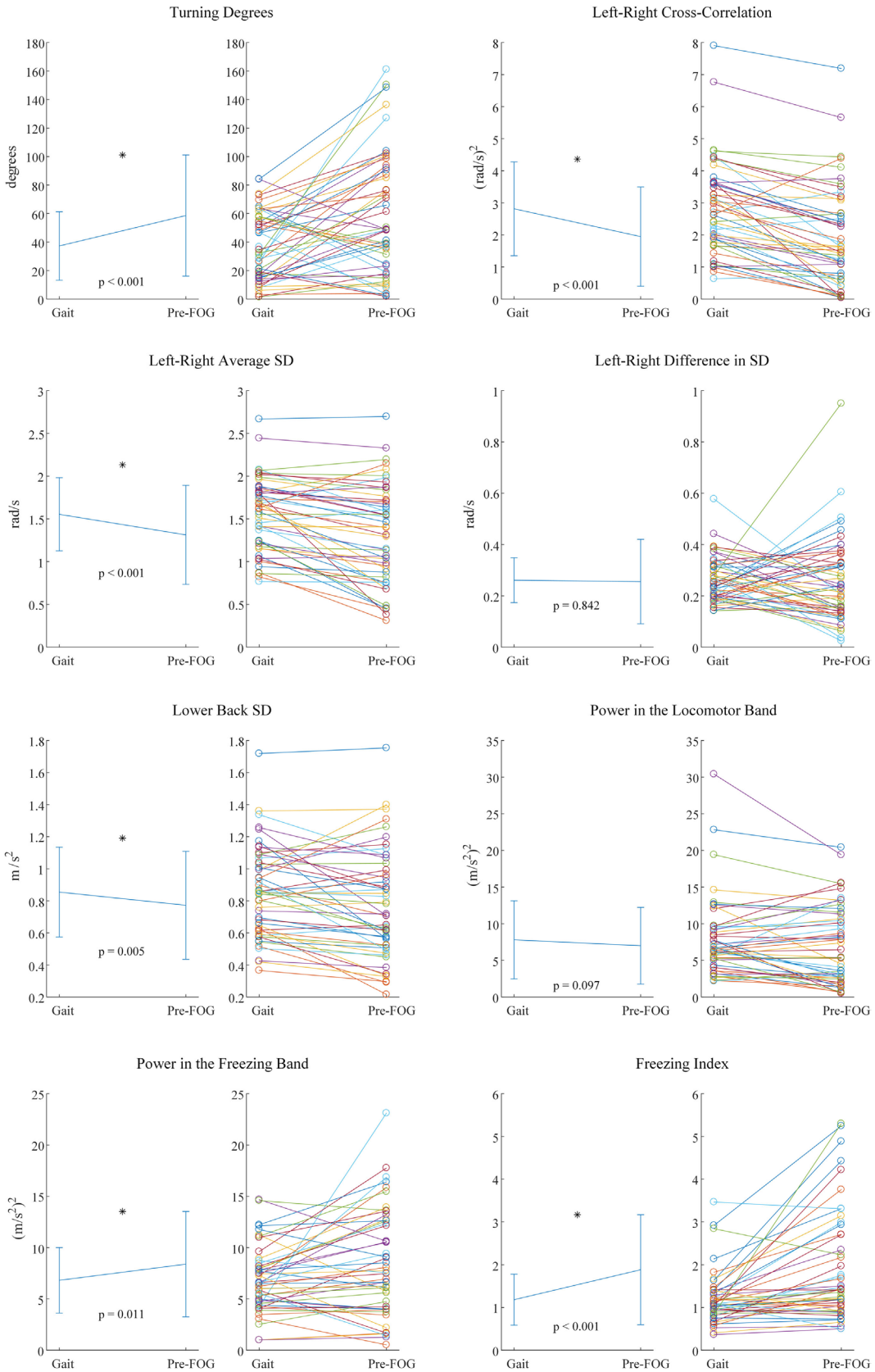

FIGURE 4 | Paired *t*-test results for each feature. For each feature, two plots are present. On the left the mean and SD values are reported, together with corresponding *p*-value and statistical significance (*). On the right, the values of each pair that was considered in the statistical testing are reported.

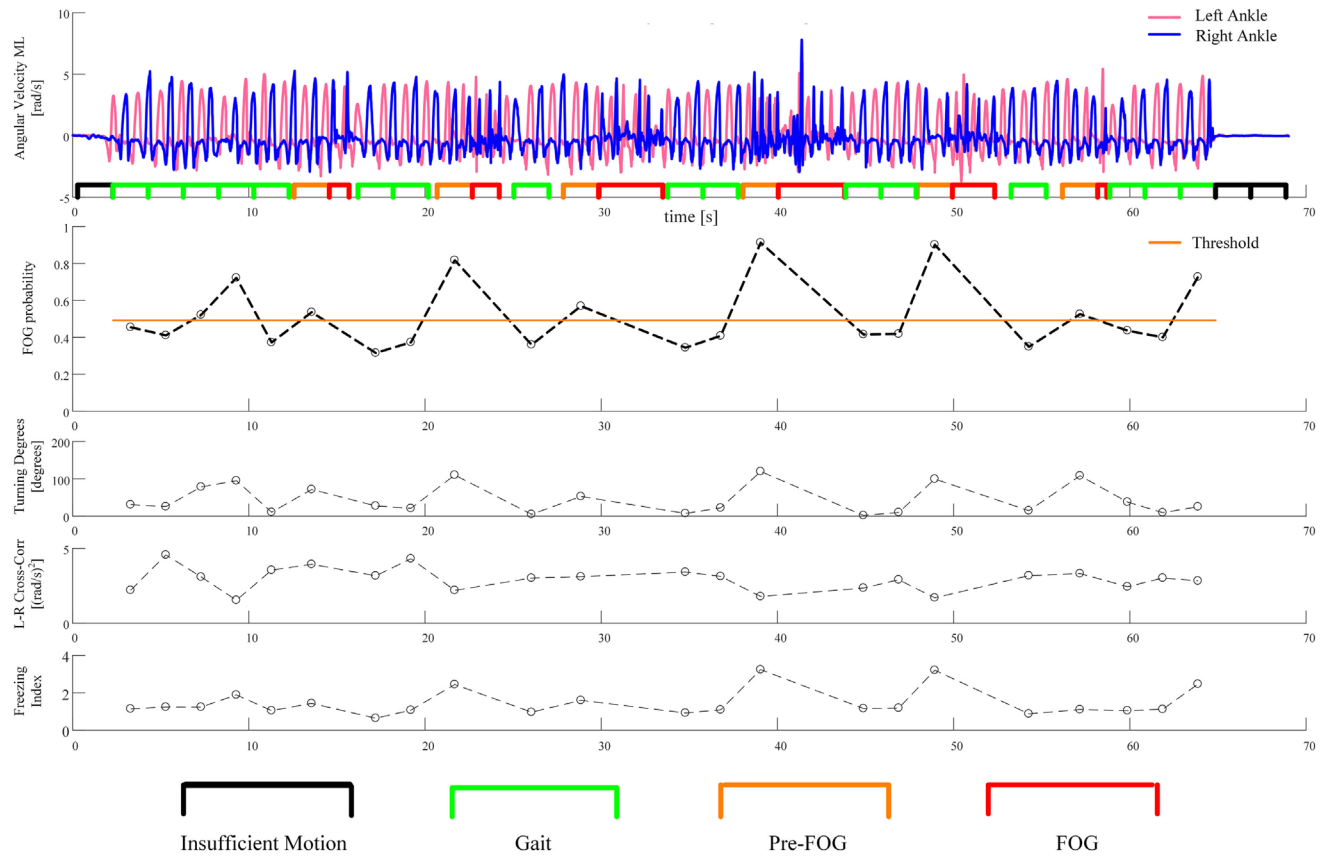

FIGURE 5 | An example of the application of the classifier. The first plot from the top shows the recorded angular velocities of the left and right ankles together with the segmentation of the windows, as in **Figure 3**. The second plot reports the probability of incoming FOG, as predicted by the classifier. This probability is computed for each gait and pre-FOG window. The threshold on probability is also reported: if the probability is higher than the threshold, then the classifier predicts a FOG (i.e., it identifies the window as pre-FOG), otherwise, the classifier identifies the window as gait. In the last three plots, the values of the three features which are used in the classifier are reported.

different disease stages and functional state. Different optimal thresholds also imply different trade-offs between sensitivity and specificity.

The example in **Figure 5** shows that high *turning degrees*, low *left–right cross-correlation*, and a high *freezing index* contribute to an increase in the probability of an incoming FOG episode. In particular, it can be seen that all FOGs are correctly predicted (the first and last one by a small margin). On the other hand, there are three false positives (i.e., windows predicted to be FOG that are actually gait). The first two false positives take place during a turn of approximately 100° (see **Figure 5**, third plot from the top). The high value of *turning degrees*, together with the reduction in *left–right cross-correlation*, pushes the probability over the threshold. A FOG episode, however, does not occur. The third false positive is at the end of the "Figure of 8," when the subject stops. Here, the value of *turning degrees* is low and the *left–right cross-correlation* shows an average value. However, the value of *freezing index* is particularly high. This combination of feature values still pushes the probability of incoming FOG over the threshold, but the subject just stops her/his gait (the freezing episode does not occur).

Limitations and Future Developments

The main limitation of this study is the small number of subjects involved (11 subjects). Another limitation is that subjects with different disease stages performed a different number and type of conditions. In addition, subjects did not experience FOG in every condition that they performed. This was due to both the episodic nature of FOG and the fact that subjects were tested during their "ON" medication (resulting in better than usual gait performance and fewer FOG events).

A consequence of these limitations is that different subjects had a different number of conditions considered in the statistical analysis (**Tables 4** and **6**). Another consequence is that, for each condition, the number of gait windows that were averaged was higher than the number of pre-FOG windows. In total (considering all subjects, all conditions with both gait and pre-FOG) there were 2,128 gait windows and 137 pre-FOG windows (**Table 6**). The imbalance between the number of gait and pre-FOG windows may also be attributed to the fact that there were often long periods of straight walking that did not elicit FOG events.

In future studies subjects should also be tested during their "OFF" medication state. In this case, we expect to see an increased

TABLE 6 | Detailed number of gait and pre-freezing of gait (FOG) windows for each subject.

Subject ID	Gait windows	Pre-FOG windows	Conditions with both gait and pre-FOG
1	204	16	7
2	111	10	4
3	21	12	3
4	184	1	1
5	162	4	4
6	236	33	9
11	12	4	1
12	275	11	3
16	407	19	6
17	435	22	8
18	81	5	4
Total	2,128	137	50
Mean	193.5	12.5	4.5
SD	139.9	9.5	8.5

average FOG probability (i.e., the corresponding dotted line in **Figure 5** would shift upwards) because gait performance would on average be worse without medication (23). An increased average FOG probability would then lead to more events over the critical threshold (and, therefore, to more FOG events).

Specific to the classification procedure, the considered windows do not overlap (see **Figure 5**), so the algorithm was not tested in a situation that fully resembles real-time. Then, in order to consider a real-time application, the processing time of feature extraction and classification on a mobile system should also be evaluated. The performance of the classification algorithm was acceptable for some subjects but not satisfactory for others. In this study, we used a simple classifier in order to find a linear relation between the extracted features. The use of more sophisticated machine learning techniques (which will require larger data sets), together with personalization of the algorithms, will probably yield better performance.

In the study by Mazilu et al. (30), which was performed on the same subjects of this study, it was shown that skin conductance is promising for the identification of pre-FOG phase. Combining this additional data source with movement data could also help to improve the performance in FOG prediction.

We considered a time window of 2 s before FOG as the pre-FOG phase. The previous studies on pre-FOG implemented different window durations. Further studies should analyze what is the most appropriate window duration for analyzing pre-FOG and how (and if) this could change among subjects. It should be further studied whether and to what extent the classifier and the statistical analysis are specific to pre-FOG (e.g., with respect to voluntary stops). For future studies, we would suggest to: (a) select subjects with similar disease stages (possibly stratifying by clinical FOG severity); (b) select a limited number and type of conditions; and (c) include a condition with voluntary stops. This may help to more fully match real-world conditions.

CONCLUSION

This work leverages wearable inertial sensors to study the patterns leading to FOG (i.e., the pre-FOG phase). The results indicate that there is a degradation of gait that occurs before freezing, suggesting that there are some identifiable and quantifiable precursors to the event itself. Future work should more fully investigate what factors lead to the observed changes in the movement pattern and how the pre-FOG phase evolves into FOG. The work also presents preliminary evidence for the feasibility of automatic FOG prediction using wearable inertial sensors and classification algorithms. Although some limitations are present, this study shows promising results for characterizing and identifying pre-FOG movement patterns, a first step toward a better understanding, prediction, and prevention of this disabling symptom.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of Tel Aviv Sourasky Medical Center with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Tel Aviv Sourasky Medical Center.

AUTHOR CONTRIBUTIONS

LP, LR, and LC conceived and designed the study. SM and EG carried out data collection and data preprocessing. LP carried out data analysis and statistical analysis. LP wrote the manuscript. JH and LC supervised the study. All the authors revised and approved the final manuscript.

ACKNOWLEDGMENTS

The authors would like to thank Julia Marshall Leach for the English revision of the manuscript.

FUNDING

The research leading to these results has been funded by the European Union-Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 288516 (CuPiD project).

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Conflict of Interest Statement: LP and LC have a significant financial interest in mHealth Technologies, a company that may have a commercial interest in the results of this research. All other authors declare no competing interests.

The reviewer, CL, and handling editor declared their shared affiliation and previous collaboration, and the handling editor states that the process nevertheless met the standards of a fair and objective review.

frontiers in Neurology

ORIGINAL RESEARCH
published: 06 April 2017
doi: 10.3389/fneur.2017.00128

Prolonged Walking with a Wearable System Providing Intelligent Auditory Input in People with Parkinson's Disease

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Rhythmic auditory cueing is a well-accepted tool for gait rehabilitation in Parkinson's disease (PD), which can now be applied in a performance-adapted fashion due to technological advance. This study investigated the immediate differences on gait during a prolonged, 30 min, walk with performance-adapted (intelligent) auditory cueing and verbal feedback provided by a wearable sensor-based system as alternatives for traditional cueing. Additionally, potential effects on self-perceived fatigue were assessed. Twenty-eight people with PD and 13 age-matched healthy elderly (HE) performed four 30 min walks with a wearable cue and feedback system. In randomized order, participants received: (1) continuous auditory cueing; (2) intelligent cueing (10 metronome beats triggered by a deviating walking rhythm); (3) intelligent feedback (verbal instructions triggered by a deviating walking rhythm); and (4) no external input. Fatigue was self-scored at rest and after walking during each session. The results showed that while HE were able to maintain cadence for 30 min during all conditions, cadence in PD significantly declined without input. With continuous cueing and intelligent feedback people with PD were able to maintain cadence ($p = 0.04$), although they were more physically fatigued than HE. Furthermore, cadence deviated significantly more in people with PD than in HE without input and particularly with intelligent feedback (both: $p = 0.04$). In PD, continuous and intelligent cueing induced significantly less deviations of cadence ($p = 0.006$). Altogether, this suggests that intelligent cueing is a suitable alternative for the continuous mode during prolonged walking in PD, as it induced similar effects on gait without generating levels of fatigue beyond that of HE.

Keywords: Parkinson's disease, gait, fatigue, auditory cue, attentional strategy, verbal feedback, wearable sensors

OPEN ACCESS

Edited by:
Antonio Suppa, Sapienza University of Rome, Italy

Reviewed by:
Angelo Quartarone, University of Messina, Italy
Graziella Madeo, National Institutes of Health (NIH), USA

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *17 October 2016*
Accepted: *20 March 2017*
Published: *06 April 2017*

Citation:
Ginis P, Heremans E, Ferrari A, Dockx K, Canning CG and Nieuwboer A (2017) Prolonged Walking with a Wearable System Providing Intelligent Auditory Input in People with Parkinson's Disease. Front. Neurol. 8:128. doi: 10.3389/fneur.2017.00128

INTRODUCTION

Continuous rhythmical auditory cueing (ConCue) is a well-accepted tool to improve gait in people with Parkinson's disease (PD). Several reviews reported the immediate (1, 2) and long-term training (3, 4) effects of ConCues on spatiotemporal gait outcomes such as improved cadence, gait speed and step length, and a reduction in gait variability. However, auditory cueing was mainly studied during short-term gait trials in a laboratory setting (5). Furthermore, some side effects of ConCue have been identified. People with PD demonstrated cue dependency, expressed as a movement decline after cue removal (6–8). In addition, walking with ConCues required more metabolic energy and may thus be more fatiguing than walking without cues in both PD and healthy elderly (HE)

(9, 10). Fatigue is a prevalent disabling non-motor symptom in PD (11). The mechanisms of fatigue are ill understood, but it has been associated with gait problems (12) and may have an impact on rehabilitation (13). Attentional strategies by means of verbal instructions were proposed as an alternative method for cues and were shown to have similar short-term effects (14–16). A potential drawback of verbal instruction might be that it requires more attention and translation into action than cueing and therefore increases performance variability and fatigue (17).

With the emergence of wearable technology, alternatives to ConCues are now possible. Espay et al. tested a performance-based system, which in real-time tracked the walking rhythm and modulated cueing accordingly (18). Cues no longer served as a reference target but rather as feedback on the produced stepping rhythm, requiring the person to detect and respond to the rhythm change. Although an overall cadence improvement was found after 2 weeks, results were equivocal, possibly due to the fact that abnormal cadence was supported instead of corrected by the system. More recently, a novel wearable approach was proposed, which also provided performance-based feedback, but in an intelligent rather than a continuous way (19). This system first recorded the personal optimal gait parameters, registered during a 1 min reference walk. If the selected gait parameter deviated from the individual's optimum, corrective verbal feedback was provided through headphones. Effectiveness of this intelligent wearable system was shown following 6 weeks of at-home training, and results were retained after 4 weeks follow-up (20). Not only feedback but also auditory cueing can be provided intelligently (IntCue). It is presently unclear whether delivering IntCue is as effective as providing verbal feedback (IntFB) whereby the required stepping decrement or increment is made explicit by verbal messages such as "speed up" or "slow down." In summary, the effects of personalized alternatives for standard cue provision need to be further investigated, including their potential effects on exertion and fatigue.

The European evidence-based guideline for physiotherapy recommends that people with PD should have daily walks of 30 min (21). Therefore, the central research question of this study was to compare the immediate effects of different cueing and feedback strategies (ConCue, IntCue, and IntFB) during a 30 min walk in people with PD. Additionally, the potential effects of these external input strategies on physical fatigue were assessed. Given the novelty of investigating a prolonged walk, a control condition without cueing or feedback and an HE control group were included. First, we hypothesized that, in contrast to HE, people with PD would have more gait difficulties during prolonged walking. We also expected that IntCue and IntFB would be as or even more effective than ConCue, as we presumed that fatigue would be reduced and that the intermittent nature of the intelligent input would be extra stimulating. Finally, we assumed that 30 min walking would induce more physical fatigue in PD compared to HE.

MATERIALS AND METHODS

Participants

People with PD were randomly recruited from the Movement Disorders clinic of the University Hospitals Leuven based on the following inclusion criteria: (1) idiopathic PD, diagnosed according to the UK Brain Bank criteria; (2) Hoehn and Yahr stage I–III, and (3) stable PD medication for the past month and anticipated to remain so for the following 2 months. Exclusion criteria were: (1) cognitive impairment (Mini Mental State Examination score <24); (2) subjectively unable to walk unassisted for 30 min; (3) fluctuating response to levodopa, which would interfere with 30 min gait tests; (4) musculoskeletal or neurological conditions other than PD affecting gait; (5) severe hearing problems precluding headphone use for auditory information. All people with PD were tested in their subjective ON-state of the PD medication, on average 1 h after intake. HE were age matched and recruited from a database of voluntary study participants.

Protocol

Participants performed four walks spread over a period of 6 weeks with at least 1 week interval between walks. All walks were performed in the same hall at the same time and day of the week to minimize the effects of time and PD medication. Demographic information and clinical tests were collected systematically over the four sessions prior to commencing the 30 min walk. Participant demographics, Multidimensional Fatigue Inventory (MFI) (22, 23), LASA Physical Activity Questionnaire (LAPAQ) (24), and Walk-12G (25) were collected at session 1. The Movement Disorders Society Unified Parkinson's Disease Rating Scale—Motor Part (MDS-UPDRS III) (26) was rated at session 2. The Montreal Cognitive Assessment (MoCA) (27) was collected at session 3, and the Scale for Outcomes in Parkinson's disease-Cognition (SCOPA-Cog) (28) was completed at session 4. After collecting demographics and clinical information, participants were provided with 5 min of rest after which they self-scored physical fatigue on a 10 cm long visual analog scale, ranging from "No fatigue" to "Maximal fatigue."

Before every 30 min walk, participants performed a 1 min comfortable reference walk along a 24 m × 9 m elliptical walking trajectory (**Figure 1A**) comprising of wide curves to minimize the turning impact. Reference walks were recorded by two foot-mounted inertial measurement units (IMUs, EXLs1, EXEL srl, Italy), and the mean cadence was used as the reference for the subsequent 30 min walk. Each 30 min walk was performed while wearing headphones (Sennheiser RS160, Sennheiser, Germany) and in one of the following four conditions offered in a randomized order: (i) continuous cueing (ConCue), (ii) intelligent cueing (IntCue), (iii) intelligent feedback (IntFB), and (iv) no information (NoInfo). During ConCue, participants received an auditory rhythm generated by an adaptive cueing system (see Materials and Outcome Measures). The auditory rhythm was set at the mean cadence of the reference walk. Participants were instructed to follow the rhythm by stepping to the beat. During IntCue, participants received an auditory rhythm consisting of 10 beats upon real-time detection of a cadence deviation from the reference. A deviation was defined as when the mean cadence of five consecutive left and right strides deviated more than 5%. These settings were based on prior pilot work. During IntFB, participants received verbal feedback to "speed up" or "slow down" upon the real-time detection of a cadence deviation using the

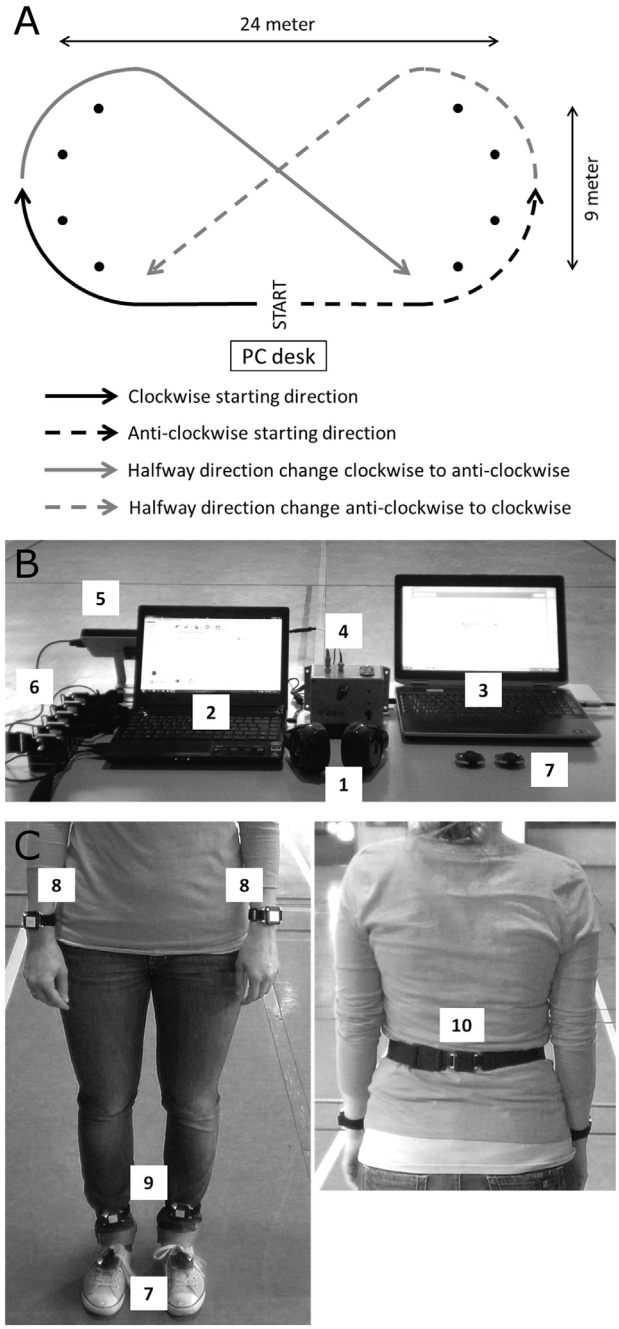

FIGURE 1 | **(A)** The walking trajectory including its dimensions, randomized starting directions, and halfway direction changes. **(B)** The computerized setup with the (1) wearable headphone; (2) mobility lab computer; (3) computer with the custom MATLAB program providing the external auditory information; (4) sound synchronization box to APDM sensor system; (5) APDM antenna; (6) OPAL wearable inertial measurement units (IMUs) in their docking station; (7) EXLs1 foot-mounted wearable IMUs. **(C)** The (7) EXLs1 IMUs placed on the feet and the placement of the OPAL IMUs at the (8) wrists, (9) ankles, and (10) lower back.

same criteria as in IntCue. Verbal messages were prerecorded in the local language (Dutch). During NoInfo, no external information was given during the entire walk.

Participants started their 30 min walk either in clock- or anticlockwise direction, whereby the direction was kept identical per participant over the four sessions but was randomized between persons. To counterbalance the possible effect of disease dominance, participants had to cross the walking trajectory diagonally after walking 15 min and continue the rest of the walk in the opposite direction (**Figure 1A**). Immediately after the walk, participants scored physical fatigue as well as their subjective rating of perceived exertion on a 6–20 Borg scale (29).

Materials and Outcome Measures

Two foot-mounted IMUs containing a triaxial accelerometer, gyroscope, and magnetometer were attached on top of the shoes using Velcro straps. Raw angular velocities were sampled at 100 Hz and wirelessly streamed using Bluetooth to a computer (**Figure 1B**). A custom MATLAB (MathWorks Inc., USA) software application processed the raw data in real-time computing cadence and its deviations from the prerecorded reference during the 30 min. The algorithm to obtain cadence from the feet raw data was described elsewhere (19) and validated for PD (30). During all conditions, deviations were detected in real-time and stored for data analyses. Spatiotemporal gait variables were measured with the Mobility Lab OPAL system (APDM, USA) consisting of five IMUs attached at the participant's wrists, ankles, and lumbar region using elastic Velcro straps (**Figure 1C**). The auditory information was delivered through wearable headphones.

Cadence was the primary outcome as cueing and feedback conditions targeted this gait parameter. Secondary spatiotemporal outcomes were stride length, double support time, arm swing range of motion, stride length asymmetry, and variability of cadence expressed as the coefficient of variability (%CV = SD/average × 100). These spatiotemporal gait variables were selected based on their significance for representing gait in PD (31, 32). Physical fatigue and perceived exertion were assessed as secondary outcomes using the abovementioned visual analog and Borg scale.

Statistical Analysis

After checking data normality and homogeneity, independent *T*-tests identified differences between people with PD and HE for normally distributed descriptive data. Non-normally distributed data were analyzed using Mann–Whitney *U* tests and chi-square statistics for frequency data. Intraclass correlation coefficients ($ICC_{3,4}$) were used to assess the agreement between the four 1-min reference walks.

The 30 min walks were split into six blocks of 5 min, and both averages and coefficients of variability of each variable per time block were calculated. A 2 group by 4 condition by 6 time-block ANOVA was used to investigate differences in spatiotemporal outcomes between groups and conditions over time, using Bonferroni corrected *post hoc* testing. Additionally, physical fatigue scores at rest and their change scores (after 30 min walking—rest) as well as Borg scores were analyzed in each condition between groups by Mann–Whitney *U* tests and in each group between conditions using Friedman tests. In case

of significant Friedman tests, *post hoc* analyses were performed using Bonferroni corrected Wilcoxon Rank tests.

"Deviators" were defined as participants who deviated at least once from their reference cadence per walk. The proportion of deviators was compared in each condition and between groups using chi-square statistics. For condition differences per group, Cochran's *Q* tests with Bonferroni corrected *post hoc* analyses were applied. The number of deviations was compared in deviators only using non-parametric Mann–Whitney *U* and Friedman tests. SPSS version 23 (IBM, USA) was used for all statistical analyses with $\alpha = 0.05$.

RESULTS

Thirty-one people with PD and 14 age-matched HE participated in this study. All participants could perform the 30 min prolonged walk without interruptions. Data of one HE and one PD participant were excluded due to technical malfunctioning, which induced incorrect cue rhythms during their IntCue session. In addition, two PD participants were excluded because cadence deviated from the reference more than 95% of the time during ConCue, reflecting a complete inability to match the cued rhythm. Cadence of one of these participants was systematically higher than the cue rhythm, while it was systematically lower in the other. Interestingly, during IntCue, IntFB, and NoInfo both participants' cadence did not deviate at all. Further analysis revealed that both persons were only mildly affected by the disease (H&Y I and II; LEDD 360 mg/day).

Both groups were well matched for age, body height, body weight, cognitive ability (MoCA), total self-reported daily physical activity (LAPAQ Total), and self-reported daily walking time (LAPAQ Walking) (**Table 1**). The test–retest agreement between the four reference minutes for cadence was excellent [$ICC_{3,4}$ of 0.98 (95% CI 0.95–0.99)] indicating that condition effects were not confounded by reference walk instability (see Table 1 in Supplementary Material for all ICC values).

Effects of Walking Condition on Spatiotemporal Outcomes

Figure 2A shows the average cadence during the four conditions in both groups over the full 30 min. A group × condition × time interaction effect was found for cadence [$F_{(15,585)} = 2.35$, $p = 0.04$]. *Post hoc* analysis revealed that cadence in the PD group was significantly higher in the last three 5 min time blocks during ConCue compared to NoInfo ($\Delta_{T4} = 2.16$ steps/min, $p = 0.03$; $\Delta_{T5} = 2.25$ steps/min, $p = 0.04$; and $\Delta_{T6} = 2.34$ steps/min, $p = 0.03$). Additionally, in the PD group, cadence was significantly higher in the last two 5 min time-blocks during IntFB compared to NoInfo ($\Delta_{T5} = 2.26$ steps/min, $p = 0.03$ and $\Delta_{T6} = 2.29$ steps/min, $p = 0.04$) (see **Figure 2B**). All spatiotemporal outcomes are provided in Supplementary Material Table 2.

As for the secondary spatiotemporal gait outcomes, a main time effect [$F_{(5,195)} = 8.23$, $p = 0.001$] was found for stride length, whereby the stride length during the first 5 min was significantly shorter than that of the last 5 min ($\Delta_{T1-T6} = -0.015$ m, $p = 0.04$) (see **Figure 2C**). Furthermore, stride length during the second time block was significantly shorter than those during the last three time blocks ($\Delta_{T2-T4} = -0.010$ m, $p = 0.007$; $\Delta_{T2-T5} = -0.011$ m, $p = 0.009$; and $\Delta_{T2-T6} = -0.013$ m, $p = 0.02$). A main time effect [$F_{(5,195)} = 12.74$, $p < 0.001$] was also found for arm range of motion, whereby range of motion during the first two time blocks was significantly smaller than during the last three time blocks (all *post hoc* *p*-values ≤ 0.03).

TABLE 1 | Participant characteristics.

	Parkinson (*N* = 28)	Healthy elderly (*N* = 13)	Significance
Age (years)	62.04 (6.91)	60.23 (6.07)	$p = 0.42$
Gender (M/F)[b]	23/5	7/6	$p = 0.07$
Body weight (kg)	82.73 (15.83)	74.39 (14.63)	$p = 0.12$
Body height (cm)	174.00 (8.37)	169.85 (7.99)	$p = 0.14$
Leg length left (cm)	92.54 (5.99)	90.15 (4.20)	$p = 0.21$
Leg length right (cm)	92.14 (5.77)	90.46 (4.35)	$p = 0.36$
Disease duration (years)	10.57 (6.71)	/	/
Hoehn and Yahr (1/2/2.5/3)	1/12/7/7	/	/
MDS-UPDRS III (0–132)	34.57 (14.37)	/	/
LEDD (mg/24 h)	517.42 (312.97)	/	/
MoCA (0–30)	26.36 (2.18)	27.46 (2.22)	$p = 0.14$
Scale for Outcomes in Parkinson's disease-Cognition (0–42)[a]	29.50 (26.00–31.25)	34.00 (32.00–35.00)	**$p = 0.001$**
Multidimensional Fatigue Inventory (MFI) general fatigue (4–20)[a]	13.00 (9.75–15.00)	4.00 (4.00–7.00)	**$p < 0.001$**
MFI physical fatigue (4–20)[a]	12.00 (8.75–14.25)	6.00 (5.00–8.00)	**$p < 0.001$**
MFI reduced activity (4–20)[a]	11.50 (9.00–14.25)	6.00 (5.00–7.00)	**$p < 0.001$**
MFI reduced motivation (4–20)[a]	9.00 (6.75–12.00)	4.00 (4.00–9.00)	**$p = 0.02$**
MFI mental fatigue (4–20)[a]	11.50 (7.75–14.25)	5.00 (4.00–7.00)	**$p = 0.002$**
LASA Physical Activity Questionnaire (LAPAQ) walking (min/day)[a]	14 (5–30)	11 (7–21)	$p = 0.71$
LAPAQ total (min/day)[a]	127 (56–198)	207 (105–326)	$p = 0.14$
12 G (0–87)[a]	9.50 (5.75–14.50)	0 (0–0)	**$p < 0.001$**

Results are reported as mean (SD) in case of parametric statistics and as median (quartile 1–quartile 3) in case of non-parametric statistics.

[a]*Non-parametric statistics were applied.*

[b]*Chi-squared statistic.*

Statistically significant differences ($p < 0.05$) are marked in bold.

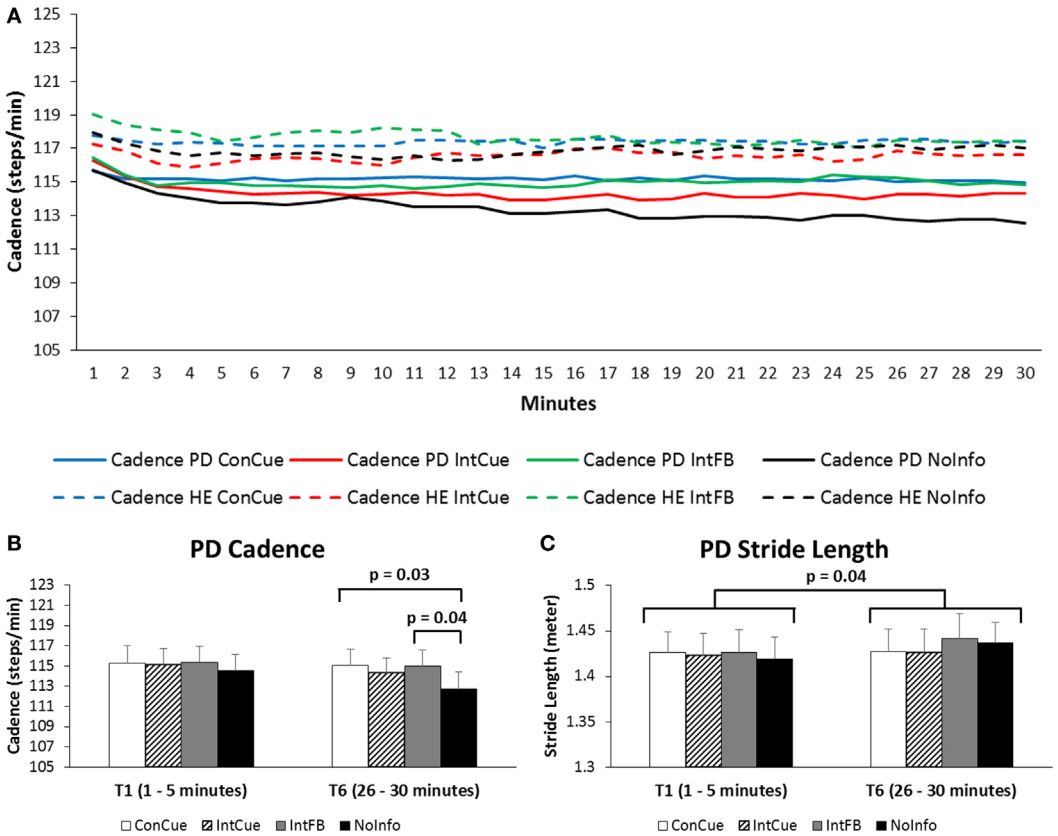

FIGURE 2 | **(A)** Progression of cadence over the 30 min in the Parkinson's disease (PD) and healthy elderly (HE) groups during the four different conditions. Full lines represent the PD group, and dotted lines represent the HE group. Averages of each minute are displayed for the full group. SDs are not displayed for reasons of clarity. See Supplementary Material Table 2 for means and SDs displayed for each 5 min interval. **(B)** Cadence of the PD group during the first and last time blocks for the four different conditions. Means and SEs (error bars) are displayed. **(C)** Stride length of the PD group during the first and sixth time blocks for the four different conditions. Means and SEs (error bars) are displayed.

With respect to cadence CV, there was a significant group × condition interaction effect [$F_{(3,117)} = 3.07$, $p = 0.04$]. *Post hoc* analyses revealed that cadence CV was significantly higher during IntFB in PD compared to HE ($\Delta = 0.6\%$, $p = 0.02$). There was also a main time effect for cadence CV [$F_{(5,195)} = 2.90$, $p = 0.04$]. *Post hoc* tests showed an increased cadence CV during the fourth time block compared to the second time block (Δ_{T2-T4}: $p = 0.01$). No significant results were found for double support time, stride length asymmetry.

Effects of Walking Condition on Deviations

There was no significant difference between groups in the proportion of deviators in any of the four conditions. Only in the HE group, a significantly smaller proportion of deviators was seen during ConCue compared to NoInfo ($p = 0.03$) (**Table 2**). Among the participants who were classified as deviators, the number of deviations is presented in **Table 3**. There were significantly more deviations in PD compared to HE during IntFB and NoInfo (both: $p = 0.04$). Additionally, the number of deviations was smaller during ConCue and IntCue compared to NoInfo in PD ($p = 0.006$).

TABLE 2 | Number and proportion of deviators.

Condition	Parkinson (*N* = 28)	Healthy elderly (*N* = 13)	Group effect
ConCue	15 (54%)	3 (23%)[a]	$p = 0.10$
IntCue	22 (79%)	7 (54%)	$p = 0.15$
IntFB	20 (71%)	5 (38%)	$p = 0.08$
NoInfo	21 (75%)	10 (77%)	$p = 1.00$
Condition effect	$p = 0.08$	**$p = 0.03$**	

Values represent the number of participants (percentage of the group) who at least once deviated from the reference.
[a]*Significantly different from no information (NoInfo).*
Statistically significant differences ($p < 0.05$) are marked in bold.

Effects of Walking Condition on Fatigue

The results on the fatigue scores and the ratings of perceived exertion are presented in **Table 4**. Overall, people with PD were more physically fatigued at the beginning of the sessions than HE, which is in line with the results on the MFI listed in **Table 1**. Thirty minutes of walking increased physical fatigue significantly more in the PD group compared to the HE group during ConCue and IntFB conditions ($p = 0.04$ and $p = 0.004$, respectively). People with PD also rated their exertion as

TABLE 3 | Number of deviations.

	N	Parkinson	*N*	Healthy elderly	Group effect
ConCue	15	3.00 (2.00–8.50)[a]	3	6.00 (3.50–12.50)	$p = 0.82$
IntCue	22	5.00 (2.00–10.00)[a]	7	5.00 (1.00–17.50)	$p = 1.00$
IntFB	20	6.00 (3.75–17.00)	5	3.00 (2.00–5.00)	**$p = 0.04$**
NoInfo	21	25.00 (8.00–83.00)	10	6.00 (4.25–18.75)	**$p = 0.04$**
Condition effect		**$p = 0.006$**		$p = 0.75$	

N reports number of deviators. Number of deviations expressed as median (interquartile range) is reported per group.
[a]Significantly different from no information (NoInfo).
Statistically significant differences ($p < 0.05$) are marked in bold.

TABLE 4 | Fatigue and exertion results.

Outcome	Condition	Parkinson	Healthy elderly	Group effect
Physical fatigue rest (0–100)	ConCue	23.0 (14.5–49.0)	4.0 (0.0–6.0)	**$p < 0.001$**
	IntCue	21.0 (5.0–49.0)	2.0 (0.0–7.0)	**$p = 0.002$**
	IntFB	20.5 (5.5–32.8)	1.5 (0.0–6.0)	**$p = 0.001$**
	No information (NoInfo)	20.0 (6.5–37.0)	3.5 (0.0–5.5)	**$p = 0.01$**
Condition effect		$p = 0.22$	$p = 0.60$	
Physical fatigue change[a] (0–100)	ConCue	11.0 (5.5–25.0)	2.0 (1.0–10.0)	**$p = 0.04$**
	IntCue	12.0 (7.0–26.5)	8.0 (2.0–15.0)	$p = 0.21$
	IntFB	20.0 (10.8–28.5)	3.5 (1.0–7.8)	**$p = 0.004$**
	NoInfo	10.0 (2.5–31.5)	3.0 (1.0–10.8)	$p = 0.11$
Condition effect		$p = 0.68$	$p = 0.14$	
Borg score (6–20)	ConCue	12.5 (11.0–13.0)	8.0 (7.0–9.0)	**$p = 0.001$**
	IntCue	12.5 (11.0–14.0)	9.0 (7.0–11.0)	**$p < 0.001$**
	IntFB	12.5 (10.5–13.3)	9.0 (7.0–11.0)	**$p = 0.007$**
	NoInfo	12.0 (10.0–13.0)	9.0 (7.0–11.0)	**$p < 0.001$**
Condition effect		$p = 0.68$	$p = 0.53$	

Values are expressed as median (interquartile range).
[a]Change = immediately after 30 min walk—rest.
Statistically significant differences ($p < 0.05$) are marked in bold.

significantly higher than HE on the Borg scale following the 30 min of walking under all four conditions (all $p \leq 0.007$). No significant differences between the four conditions were found within the PD or the HE groups for physical fatigue and Borg scores.

DISCUSSION

This study is the first to investigate the effects of different types of auditory cueing and feedback taking into account fatigue, gait stability, and gait quality performed during an extended period of walking in PD. It was found that people with PD were able to better maintain their cadence during a continuously cued walk compared to walking without cues, especially during the last 15 min of the walk. This result illustrates that the response to cueing did not habituate with time, but quite the opposite, it helped to maintain optimal gait when fatigue or waning of attention set in. As well, the number of deviations from the reference was significantly lower during ConCue compared to NoInfo and the number of deviating participants showed a trend toward being smaller in PD. All these results are in line with previous studies showing that goal-directed motor control, elicited by means of an external reference, improved gait in PD (33). Our results extend these findings toward prolonged walking.

We presumed that intelligently provided information would be more effective than continuous cueing as the intermittent nature of the former input would avoid dependency and habituation, previously reported to occur as a result of continuous cueing (6, 7). Furthermore, as performance deviations triggered the onset of information, intelligent solutions might increase the person's alertness avoiding dependency and habituation even more. In fact, we found a similar stabilizing effect on gait for IntCue as for ConCue, even though cues were only presented when gait deviated. Interestingly, the number of deviations was significantly reduced during IntCue whereas this was not the case for IntFB. This may indicate that the actual presence of the target even when applied intermittently is more beneficial for keeping cadence than occasional verbal information, which is less clear about how to change the walking parameters. However, in the last time blocks of the walk, people with PD were better able to increase their cadence in response to IntFB than during IntCue. Along the same lines, there was an overall time effect for stride length improvement mostly seen during IntFB. Taken together, this may indicate that the feedforward action of clear targets, as indicated by cues rather than by verbal feedback, appears more useful to preserve gait stability. In contrast, the feedback approach may be more effective to invigorate gait, maybe driven by the allocation of cognitive resources, as recalling the internal motor plan is needed more without the presence of a target. The fact that cognition and or attention are required more when processing verbal feedback rather than auditory cues is also supported by the finding that a significant increase in cadence variability was apparent in PD and not in HE during IntFB. Hausdorff and colleagues demonstrated that increased gait variability is a marker of heightened attention allocated to gait (34). Another explanation of the differential effects of IntCue and IntFB is that by providing a clear motor target (cue) a limited number of possible movement corrections are indicated. By providing a verbal instruction to speed up or slow down gait, more degrees of freedom are allowed and thus effects may be larger. This is in line with Baker et al. who also found that attentional strategies induced larger effects than auditory cues on gait parameters (14).

In contrast to our hypothesis and previous studies (9, 10), no differences were found between the walking conditions with regard to fatigue and ratings of perceived exertion. It is however noteworthy that the change scores of physical fatigue were significantly higher in PD than in HE during ConCue and IntFB. This suggests that responding to continuous cues as well as reacting to intermittent verbal feedback created an extra burden to people with PD. This pattern fits with the idea that IntFB requires more cognitive load (14). In addition, the fact that ConCue was more burdensome corresponds with the finding that continuous cues during treadmill walking induced a greater metabolic cost than non-cued gait in both PD and HE (9, 10).

Overall, we found strikingly higher fatigue and exertion levels in PD compared to HE during 30 min of walking, which is in line with earlier work (35). Fatigue is one of the most disabling non-motor symptoms in PD and generally defined as a feeling of tiredness, lack of energy, and exhaustion or as a reduced capacity to initiate or sustain voluntary activities (13, 36, 37). Although self-perceived levels of fatigue were high, the measured impact on gait quality was relatively minor as during NoInfo only cadence deteriorated with time.

It is interesting that two persons with PD were unable to follow the rhythm even though cue settings were based on individualized reference walks. This suggests that auditory cueing mechanisms are more complex than merely providing a movement target and underpins earlier findings of individual differences in cue efficacy (5, 38). The fact that two of the least affected persons with PD experienced difficulties with ConCue concurs with earlier work showing that those with more severe disease benefited most from cues (39). Together with the finding that these two persons responded well to the intelligent conditions suggests that persons with mild PD may not benefit from continuous cueing. Another explanation for an individualized response to cueing is the fact that the basal ganglia have a role in rhythm perception (38). However, recent findings point to a facilitating effect of predictive rhythmic stimulation on basal ganglia–premotor cortex interactions (40), despite a potential deficit of rhythm perception in PD (5). In addition, the type of acoustic input may also explain a differential response, the sound of feet walking over gravel was found to be more effective than metronome cues in some people with PD (41, 42).

Surprisingly, we found that stride length and arm swing increased over the 30 min period in both PD and HE. We explain this finding as a possible effect of prolonged walking, whereby the gait pattern gets "into the groove," as also shown in inactive HE (43). Given the strong correlation between arm swing and stride amplitude (44), spontaneous overflow from one parameter to the other may also have occurred. Recent work also showed a significant increase in stride length following a repeated sit-to-stand protocol in both PD and age-matched HE (45). These effects, not demonstrated during short gait trials in gait laboratories, support the European guideline's recommendation to undertake 30 min bouts of brisk walking as a rehabilitation strategy for PD (21).

Our results provide some new clues on how to apply cueing optimally in a rehabilitation context. To obtain positive effects on both gait quality and stability, providing cueing in an intelligent approach alternated with adaptive verbal feedback may prove to be more effective than using continuous cueing and may lead to less overload and fatigue. Given the emergence of smartphone and wearable sensing technology, self-regulating systems to provide external information intelligently are in the making (18, 19, 46), opening their use into daily routine (47). A recent pilot study showed the feasibility and effectiveness of such a wearable system during a home-based minimally supervised training period of 6 weeks in PD (20). While these tools are not widely available yet, physiotherapists can use auditory cues in smartphone apps and verbal instructions intermittently based on clinical observation of gait deterioration. Future studies should test the effectiveness of a combined approach of delivering both IntFB and IntCue, determine which cueing mode is best for different clinical profiles and identify if the benefits can be consolidated during long-term home training. A limitation of this study was the use of self-reported fatigue and exertion scales instead of objective outcomes such as metabolic cost through VO_2 measurement. Another limitation was the significant group differences in fatigue and SCOPA-Cog scores at baseline. The MoCA scores, however, were matched between groups, suggesting that participants were equally capable of processing auditory information.

In conclusion, people with PD show greater cadence deterioration and report more fatigue and exertion during 30 min of walking than healthy age-matched controls. Intelligently applied cueing was most successful in maintaining gait stability. Intelligent feedback led to the best cadence at the end of the walk but also increased cadence variability and fatigue. Although continuous cueing was beneficial for reducing gait deviations, persons with PD reported more fatigue during this cueing mode than HE. We recommend intelligently applied cueing and possibly also adaptive feedback approaches as the most appropriate gait rehabilitation tools for people with PD when undertaking prolonged walking bouts.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethics Committee of the KU Leuven with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the KU Leuven.

AUTHOR CONTRIBUTIONS

PG, EH, CGC, and AN designed the study; AF developed the automated cueing and feedback system; PG and KD collected, processed, and analyzed the data; PG wrote the manuscript; and EH, AF, KD, CGC, and AN revised the manuscript.

ACKNOWLEDGMENTS

This work was supported by the European Union Seventh Framework Programme (FP7/2007-2013) CuPiD project (grant Number 288516). The authors would like to thank all volunteers who were willing to participate in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00128/full#supplementary-material.

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Conflict of Interest Statement: AF has a significant financial interest in mHealth Technologies, a company that may have a commercial interest in the results of this research. All other authors declare no competing interests.

frontiers in Neurology

ORIGINAL RESEARCH
published: 13 June 2017
doi: 10.3389/fneur.2017.00279

Usability of Three-dimensional Augmented Visual Cues Delivered by Smart Glasses on (Freezing of) Gait in Parkinson's Disease

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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 06 April 2017
Accepted: 29 May 2017
Published: 13 June 2017

Citation:
Janssen S, Bolte B, Nonnekes J, Bittner M, Bloem BR, Heida T, Zhao Y and van Wezel RJA (2017) Usability of Three-dimensional Augmented Visual Cues Delivered by Smart Glasses on (Freezing of) Gait in Parkinson's Disease. Front. Neurol. 8:279. doi: 10.3389/fneur.2017.00279

External cueing is a potentially effective strategy to reduce freezing of gait (FOG) in persons with Parkinson's disease (PD). Case reports suggest that three-dimensional (3D) cues might be more effective in reducing FOG than two-dimensional cues. We investigate the usability of 3D augmented reality visual cues delivered by smart glasses in comparison to conventional 3D transverse bars on the floor and auditory cueing *via* a metronome in reducing FOG and improving gait parameters. In laboratory experiments, 25 persons with PD and FOG performed walking tasks while wearing custom-made smart glasses under five conditions, at the end-of-dose. For two conditions, augmented visual cues (bars/staircase) were displayed *via* the smart glasses. The control conditions involved conventional 3D transverse bars on the floor, auditory cueing *via* a metronome, and no cueing. The number of FOG episodes and percentage of time spent on FOG were rated from video recordings. The stride length and its variability, cycle time and its variability, cadence, and speed were calculated from motion data collected with a motion capture suit equipped with 17 inertial measurement units. A total of 300 FOG episodes occurred in 19 out of 25 participants. There were no statistically significant differences in number of FOG episodes and percentage of time spent on FOG across the five conditions. The conventional bars increased stride length, cycle time, and stride length variability, while decreasing cadence and speed. No effects for the other conditions were found. Participants preferred the metronome most, and the augmented staircase least. They suggested to improve the comfort, esthetics, usability, field of view, and stability of the smart glasses on the head and to reduce their weight and size. In their current form, augmented visual cues delivered by smart glasses are not beneficial for persons with PD and FOG. This could be attributable to distraction, blockage of visual feedback, insufficient familiarization with the smart glasses, or display of the visual cues in the

Abbreviations: PD, Parkinson's disease; FOG, freezing of gait; OFF, smart glasses switched OFF; CB, conventional bars; CM, conventional metronome; AB, augmented bars; AS, augmented staircase.

central rather than peripheral visual field. Future smart glasses are required to be more lightweight, comfortable, and user friendly to avoid distraction and blockage of sensory feedback, thus increasing usability.

Keywords: Parkinson's disease, freezing of gait, wearables, smart glasses, augmented reality, external cueing, visual cues

INTRODUCTION

In advanced disease stages, most persons with Parkinson's disease (PD) experience freezing of gait (FOG): sudden paroxysmal gait arrests preventing effective forward movement (1, 2). FOG negatively impacts mobility and independence and is associated with falls, fall-related injuries, and emotional stress in social situations, resulting in a reduced quality of life (3, 4). Tight turns, narrow passages, gait initiation, and approaching a destination are well-known triggers for FOG (1). Apart from episodes of FOG, persons with PD and FOG (PD-FOG) display continuous gait abnormalities such as increased stride variability (5).

External cues (i.e., transverse bars on the floor or walking at the rhythm of a metronome) are well-known strategies to reduce FOG (6) and improve speed, cadence (7–9), and stride length variability (10–12), with an additional increase in step length for visual cues (7–9). Despite their potential effectiveness, the use of cues is limited by practical constraints such as a lack of portability and hindrance of bystanders (e.g., housemates). Smart glasses, also called augmented reality (AR) glasses, have the potential to provide portable, personalized cues in an AR overlay on top of a user's visual field. Smart glasses have been welcomed as an assistive technology to facilitate daily living by a majority of respondents in a user requirement survey amongst persons with PD (13, 14).

A previous study compared the effects of rhythmic flashes, a visual flow, and a static placebo delivered by virtual reality glasses with transverse lines on the floor on FOG and gait parameters. This study found a deterioration of gait with rhythmic flashes, a marginal improvement only of task completion time with the virtual visual flow, and the largest improvement of FOG and gait parameters with transverse lines on the floor (15). In another study, three types of external cues (a metronome, flashing light, and optic flow) delivered *via* the Google Glass reduced the variability of cadence and stride length, suggesting a more stable gait pattern (12). There was no significant effect on FOG, possibly due to a low overall number of FOG episodes. Some participants disliked the placement of the display in the right upper corner, and instead suggested a binocular projection focally in the visual field. To avoid distraction, it is important to minimize interference of augmented visual cues with normal visual perception. Therefore, visual cues should be displayed as if they are part of the environment, e.g., augmented bars (AB) that are displayed as if they are placed on the floor. This demands that the position and size of the augmented cues are updated in real time, depending on the position and orientation of the head and the walking speed. Also, it requires the smart glasses to have a sufficiently wide field of view. In addition, to enable users to adjust their steps to augmented visual cues, the augmented cues should start close to the user's body. Furthermore, previous reports (16, 17) suggested that three-dimensional (3D) cues might be more effective in reducing FOG than two-dimensional cues, as were used in previous studies (12, 15). Equally spaced transverse bars on the floor as well as a staircase, either real or as painted optical illusion (17), can constitute such 3D cues. Whether the presentation of transverse bars and staircases *via* AR influences FOG and gait still needs to be explored. However, smart glasses with displays that are binocular (to enable 3D cues), tiltable and with a sufficient field of view (to allow for display of the cues close to the user), are not yet commercially available. For this purpose, we developed a prototype of custom-made smart glasses and software to provide 3D transverse bars or a staircase in AR. For augmented visual cues to be useful, they should be at least as effective as commonly applied cueing strategies such as conventional 3D transverse bars on the floor (16) or auditory cueing *via* a metronome (18). It should be carefully investigated whether wearing smart glasses, even when switched off, interferes with the effects of external cues. Possibly, augmented visual cues might not only affect FOG provoked by spatially demanding situations such as gait initiation but also those provoked by temporal triggers such as turning while walking. Originally, visual cues were thought to provide spatial information that could aid patients in scaling their movements (18), while auditory cues are considered to provide an external rhythm to which movements can be coupled to in the presence of a disrupted internal rhythm (18–20). Interestingly, moving visual targets have also been shown to improve motor timing in finger tapping tasks in healthy individuals, thereby activating regions in the basal ganglia which are associated with motor control and temporal processing (21, 22). Whether moving visual cues, such as augmented visual cues updated in real time, can reduce both spatially and temporally triggered FOG is not yet known. In addition to their effectiveness, user satisfaction should be carefully investigated to assess the usability of 3D augmented visual cues delivered by smart glasses.

The present study investigates the usability of 3D augmented visual cues delivered by smart glasses in comparison to conventional 3D transverse bars on the floor and auditory cueing *via* a metronome in reducing the occurrence of FOG, the percentage of time spent on FOG, and the variability of stride length and cycle time.

MATERIALS AND METHODS

Participant Selection

This study was performed in accordance with the guidelines of the Declaration of Helsinki (1964) and was approved by the medical ethics committee Twente. All subjects provided written informed

consent prior to their inclusion in the study. Persons aged over 18 years, with PD according to the UK Brain Bank criteria (23), and subjective presence of FOG [score 1 on question 1 from the New Freezing of Gait Questionnaire (NFOGQ) (24)] more than once per day (score 3 on question 2 from the NFOGQ) were eligible for inclusion. Exclusion criteria were stroke in the medical history, psychiatric disease interfering with assessment of FOG, severe uncorrected visual or hearing impairments disabling the participant to perceive visual or auditory cues, comorbidity limiting ambulation, inability to walk unaided, a deep brain stimulator or apomorphine pump, jejunal levodopa gel infusion, and severe cognitive impairments [mini-mental state examination (MMSE) <24 at the moment of inclusion]. As in several previous studies (12, 25), participants were tested at the end of their regular dopaminergic medication cycle (i.e., while experiencing the end-of-dose phenomenon), because this closely resembles the real-life situation where the most FOG occurs during an OFF state when the dopaminergic medication has been wearing off. Thus, participants were tested at the time when they would normally take their (after-) noon levodopa and were instructed to postpone this levodopa intake until after the walking trials. Prior to testing, the following questionnaires were taken: NFOGQ (24), MMSE (26, 27), frontal assessment battery (28), and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (29).

Smart Glasses System

A prototype of custom-made smart glasses (Cinoptics, Maastricht, the Netherlands) was used to display the augmented cues and was worn throughout the experiment (**Figure 1**). These binocular smart glasses contained two CE-certified see-through optical color displays (organic light-emitting diodes, with 1,280 × 720 pixel resolution, a 60 Hz refresh rate, and a diagonal field of view of 45°), which could be tilted up to 30°. The participant's head orientation was measured with an inertial measurement unit (IMU) with a sampling frequency of 160 Hz. The displays were mounted in a black frame attached to adjustable head straps, weighting 530 g altogether. The smart glasses were connected with a Microsoft Surface Pro 4 tablet carried inside a mesh pack worn on the participant's back. In addition, participants wore an MVN Awinda motion capture system (Xsens, Enschede, the Netherlands) for collection of motion data. This system consisted of 17 IMUs with 3D gyroscopes, accelerometers, and magnetometers (60 Hz sampling frequency, 30 ms latency) attached to the feet (2), lower legs (2), upper legs (2), pelvis (1), hands (2), forearms (2), upper arms (2), sternum (1), shoulders (2), and head (1) with Velcro straps. The sensors were calibrated without the participant wearing the smart glasses (to avoid magnetic disruption of orientation) at the start of the experiment and recalibrated during the experiment if the sensor orientation was disrupted. The motion data were transmitted *via* a wireless local area network to a laptop with the MVN studio 4.2.0 software installed, and then to the tablet. Custom-made software on the tablet used the incoming data from the IMUs of the smart glasses and the motion capture system to update the position of the augmented cues displayed by the smart glasses in real time. This resulted in the augmented cues being displayed as if they were placed on the floor.

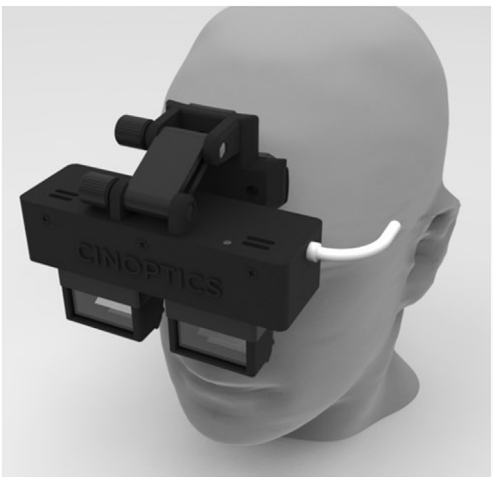

FIGURE 1 | Smart glasses. Illustration of the prototype of custom-made smart glasses (Cinoptics, Maastricht, the Netherlands) on a model. The prototype is specifically designed for a large field of view and adjustable angle to allow augmented reality visual cues to be presented as if they are placed on the floor. Binocular see-through displays are mounted in a black frame attached to adjustable head straps (not shown here).

Cues

The following five conditions were tested: 3D augmented transverse bars (AB) (see Video S1 in Supplementary Material for an illustration), 3D augmented staircase (AS) (Video S2 in Supplementary Material), equally spaced transverse conventional bars (CB) on the floor, auditory cueing *via* a conventional metronome (CM) and no cues (OFF). The smart glasses were worn during all conditions. The dimensions of the AB were set to match those of the CB, which measured 914 mm (width) × 19 mm (depth) × 19 mm (height) with a distance in between the bars of 40% of the participant's height rounded to the nearest 5 cm, based on previous studies (9, 15, 30). The AS was set to match a real staircase measuring 914 mm (width) × 254 mm (depth) × 196 mm (height). The position of the AB and staircase was adjusted in real time according to the walking speed and head orientation of the participant. The bars in conditions CB and AB and the staircase in condition AS were all colored white. The metronome in condition CM was played *via* speakers at a clearly audible volume, at 110% of a participant's preferred cadence (25, 31–33).

Walking Courses

The walking trajectory consisted of a 15 m walking track along an empty corridor at the University of Twente, with a passage at 7.5 m made-up by two chairs placed 50 cm apart (**Figure 2**). Three different walking courses were performed along this walking trajectory. In the "walking straight" (−) course, participants walked along the walking trajectory without any additional task. In the "stop and start" (S) course, prerecorded voice commands signaled the participants to stop walking at three random distances along the track; they were instructed beforehand to resume walking on their own initiative. In the "turning" (T) course, participants were signaled by prerecorded voice commands to make a full 360°

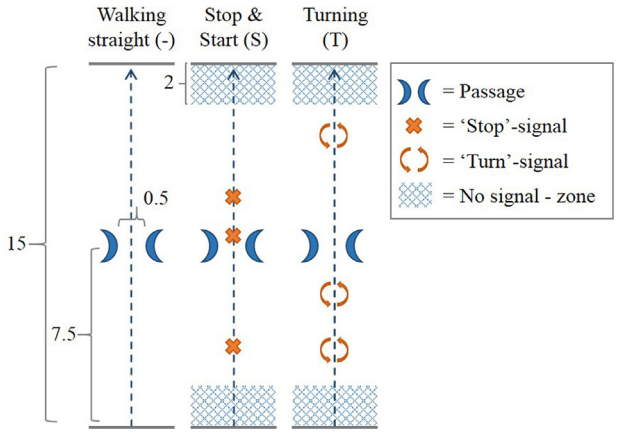

FIGURE 2 | Walking courses. In each of three walking courses, the participant walked across a 15 m long walking trajectory with a passage at the middle of the trajectory created by two chairs 0.5 m apart. In the walking straight (–) course, no additional task was performed. In the "stop and start" (S) course, prerecorded voice commands signaled the participants to stop walking at three random distances along the track. Participants were instructed to resume walking on their own initiative. In the "turning" (T) course, participants were signaled by prerecorded voice commands to make a full 360° turn at three random distances along the track. No stop-signals or turn-signals were given in the "no signal—zone" at the first and last 2 m of the walking trajectory. All measures in **Figure 2** are given in meters.

turn at three random distances along the track. No stop-signals or turn-signals were given in the "no signal—zone" at the first and last 2 m of the walking trajectory.

The experiment consisted of two sessions separated by a half an hour break. Each session consisted of five "blocks" with one condition (AB, AS, CB, CM, or OFF) per block. A block included all the walking courses (–, S, T) performed once. Hence, each condition–course combination was performed once per session. In between blocks, participants were offered to rest as long as needed. The order of the conditions (AB, AS, CB, CM, OFF), the courses (–, S, T) and the timing of the "stop" and "turn" signals were balanced by the experiment control software on the laptop. Experiments were performed in a single visit, lasting on average 2.5–3 h.

Prior to the experiment, participants familiarized themselves with the smart glasses, the augmented cues, and the CB. Each walking course was explained, shown, and practiced until performed correctly. Participants were not instructed in explicit detail on how to handle the cues. After the first session, participants were asked whether they wanted to continue with the second session after the break, or quit (for example, because of tiredness).

User Interview

A semi-open structured interview was performed after the walking trials to assess participants' experience with the smart glasses and cues (Table S1 in Supplementary Material). This interview encompassed questions and statements regarding the use of technical devices, usefulness of the four different cues (AB, AS, CB, and CM), ease of use and learning, satisfaction with the glasses and cues, preferences, and suggestions regarding the glasses and cues. Participants were asked to rate on a 5-point Likert scale (1 representing "totally disagree," 5 "totally agree") how much they agreed with the statements and were invited to elaborate on their answer. For question 7, which asked for cueing condition preferences, the condition preferred the most (question 7.1) was assigned 5 "preference points," the second most preferred condition (question 7.2) 4 preference points, and so on up to the least preferred condition (question 7.5). Preference points were summed per condition.

Data Analysis

A video recorder at each end of the walking trajectory recorded all trials on video for *post hoc* analysis of FOG. In accordance with the current working definition, FOG was defined as "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (1). Two independent raters (Sabine Janssen and Jorik Nonnekes) were blinded for the condition (except for the CB) and scored the videos for number and duration of FOG per trial. Discrepant ratings were discussed until consensus was reached. Motion data from the Awinda motion capture system were wirelessly transmitted to MVN studio version 4.2.0. Orientation and position data, calculated by MVN studio, together with raw accelerometer and gyroscope data were exported to Matlab R2014b (Mathworks, Inc., Natick, MA, USA) for the offline calculation of gait parameters as previously described (12).

Primary performance measures were the number of FOG episodes, the percentage of time spent on FOG, and the variability (represented by the SD) of the stride length and cycle time. Secondary performance measures were the stride length, cycle time, cadence, and speed.

All statistical tests were performed in IBM SPSS version 24. An alpha of 0.05 was applied for all two-sided tests. Normality of distributions was tested with the Shapiro–Wilk test. Central tendency and statistical dispersion are given as the mean and SD if distributions were normally distributed, and otherwise as the median and interquartile range. The number of FOG episodes and the percentage of time spent on FOG (calculated as the cumulative duration of FOG divided by the summed duration of trials multiplied with 100, per individual and per condition) were compared in participants who experienced at least one FOG episode throughout the experiment. Sub-analyses were performed for FOG episodes occurring during turning and during non-turning events. In addition, sub-analyses were performed for the number of FOG episodes and the percentage of time spent on FOG in the participants who experienced the most FOG episodes (defined as a total number of FOG episodes above the median number of FOG episodes in all participants with at least one FOG episode).

The mean and SD of the step length and of the time to complete one gait cycle (cycle time), cadence, and walking speed were analyzed exclusively for the "walking straight" courses, in all participants. Kinematic parameters were calculated as the median values per participant, per condition, and then compared across participants for each cueing condition. A one-way repeated measures ANOVA was applied in the case of normally distributed data. If the assumption of sphericity, as assessed by Mauchly's test of sphericity, was violated, a Greenhouse–Geisser correction was applied. The non-parametric Friedman test was

used in case of non-normality. All *post hoc* pairwise comparisons were performed with a Bonferroni correction for multiple comparisons.

From the exit interview, median scores are reported for questions answered on a 5-point Likert scale. Questions with open answers and elaborations on the closed questions were qualitatively assessed.

RESULTS

Clinical characteristics of the participants are summarized in **Table 1**. All 25 participants completed the first session. Five participants did not perform the second session because of physical tiredness, resulting in 20 participants who completed both sessions. The results of the statistical tests on FOG and gait parameters are summarized in **Table 2**.

TABLE 1 | Clinical characteristics of the participants ($N = 25$).

	Median	Range
Age (years)	72	65–79
Gender (% male)	76	
Height (cm)	171	159–189
Body mass index (kg/m^2)	27.1	21.7–37.2
Disease duration (years)	11	3–20
Years since FOG (years)	2	0.25–12
Daily levodopa dosage (mg/day)	750	0–1,200
UPDRS-part III	34	10–61
UPDRS-PIGD	6	2–12
Hoehn and Yahr	2	2–3
MMSE	28	19–30
NFOGQ	18	8–28
FAB	14	5–26

FOG, freezing of gait; UPDRS-part III, Unified Parkinson's Disease Rating Scale part III: motor examination; UPDRS-PIGD, Unified Parkinson's Disease Rating Scale—postural instability and gait disorder (question 3.9 up to 3.13 from UPDRS-part III); MMSE, mini-mental state examination; NFOGQ, New Freezing of Gait Questionnaire; FAB, frontal assessment battery.
All questionnaires, including the UPDRS, were rated while participants were end-of-dose.

Freezing of Gait

There was a high degree of consensus between raters (Sabine Janssen and Jorik Nonnekes) on the rating of number [$r_s(23) = 0.979$, $p < 0.0005$] and total duration of FOG episodes [$r_s(23) = 0.974$, $p < 0.0005$] per participant. In 19 out of 25 participants, at least one FOG episode occurred during the experiment, with a total of 300 FOG episodes for all persons together. Of these, 18 participants experienced a total of 224 FOG episodes during turning, and 8 participants experienced FOG during walking straight (20 episodes), gait initiation (18 episodes), passing the passage (21 episodes), or upon coming to a standstill (17 episodes). Only participants in whom at least one FOG episode occurred ($N = 19$) were included in the analysis of the effect of cues on FOG. The number of FOG episodes (**Figure 3A**) and the percentage of time spent on FOG (**Figure 3B**) were non-normally distributed, hence the Friedman test was used. Although there was a statistically significant difference amongst the various cues for number of FOG episodes, pairwise comparisons failed to show a significant difference. There was no statistically significant difference in the percentage of time spent on FOG amongst the different cues. Results were similar when performing a sub-analysis for FOG episodes occurring during turning (representing temporally triggered FOG) and during non-turning events (representing spatially triggered FOG). Sub-analyses among participants with the greatest number of FOG episodes ($N = 10$) again showed no statistically significant difference in number of FOG episodes nor in the percentage of time spent on FOG across the five conditions.

TABLE 2 | FOG and gait parameters per condition.

Parameter	Condition					*p*-Value
	OFF	CB	CM	AB	AS	
FOG parameters[a]						
Mean number of FOG per trial	0.08 (0.11)	0.10 (0.08)	0.09 (0.14)	0.11 (0.19)	0.13 (0.15)	0.042$^{\dagger A}$
% Time spent on FOG	9.05 (12.11)	12.73 (13.08)	12.34 (16.86)	12.41 (15.28)	15.56 (13.68)	0.090†
Gait parameters[b]						
Stride length variability	0.17 (0.12)	**0.21 (0.10)^{B}**	0.17 (0.13)	0.16 (0.14)	**0.15 (0.07)^{B}**	0.001*
Cycle time variability	0.24 (0.06)	0.31 (0.27)	0.24 (0.12)	0.24 (0.12)	0.21 (0.13)	0.117*
Stride length (m)	0.92 (0.35)	**1.19 (0.57)^{C,D}**	0.94 (0.37)	**0.93 (0.32)^{C}**	**0.86 (0.37)^{D}**	0.001*
Cycle time (s)	**1.15 (0.16)^{E}**	**1.60 (0.33)^{E,F,G,H}**	**1.15 (0.16)^{F}**	**1.18 (0.25)^{G}**	**1.18 (0.16)^{H}**	<0.0005†
Cadence (steps/min)	**102.76 (13.88)^{I}**	**74.41 (15.83)^{I,J,K,L}**	**102.81 (14.38)^{J}**	**100.40 (19.63)^{K}**	**99.85 (13.41)^{L}**	<0.0005†
Speed (m/s)	**0.83 (0.41)^{M}**	**0.72 (0.44)^{M,N}**	**0.84 (0.42)^{N}**	0.78 (0.34)	0.75 (0.40)	0.001†

[a]FOG parameters in mean (SD), in participants with more than one FOG episode throughout the experiment (N = 19); all walking courses.
[b]Gait parameters in median (interquartile range), in all participants (N = 25); during "straight-walking" courses.
FOG, freezing of gait; OFF, smart glasses switched OFF; CB, conventional bars; CM, conventional metronome; AB, augmented bars; AS, augmented staircase.
p-Values for within group differences are calculated with a one-way repeated measures ANOVA (*) or Friedman test (†). Statistically significant differences (adjusted $p < 0.05$, two-sided tests) between pairs of cues are printed bold, with the test statistic and p-value given in the legend. [A]Upon post hoc pairwise comparisons no statistically significant differences between cue-pairs. [B]χ^2 2.048, $p < 0.0005$. [C]χ^2 1.571, $p = 0.013$. [D]χ^2 1.762, $p = 0.003$. [E]$p < 0.0005$, 95% CI difference CB–OFF 0.30–0.55. [F]$p < 0.0005$, 95% CI difference CB–CM 0.31–0.54. [G]$p < 0.0005$, 95% CI difference CB–AB 0.26– 0.49. [H]$p < 0.0005$, 95% CI difference CB–AS 0.27–0.52. [I]$p < 0.0005$, 95% CI difference CB–OFF −32.42 to −18.56. [J]$p < 0.0005$, 95% CI difference CB–CM −31.88 to −20.07. [K]$p < 0.0005$, 95% CI difference CB–AB −30.09 to −15.19. [L]$p < 0.0005$, 95% CI difference CB–AS −30.99 to −17.02. [M]$p = 0.019$, 95% CI difference CB–OFF −0.23 to −0.02. [N]$p = 0.007$, 95% CI difference CB–CM −0.22 to −0.03.

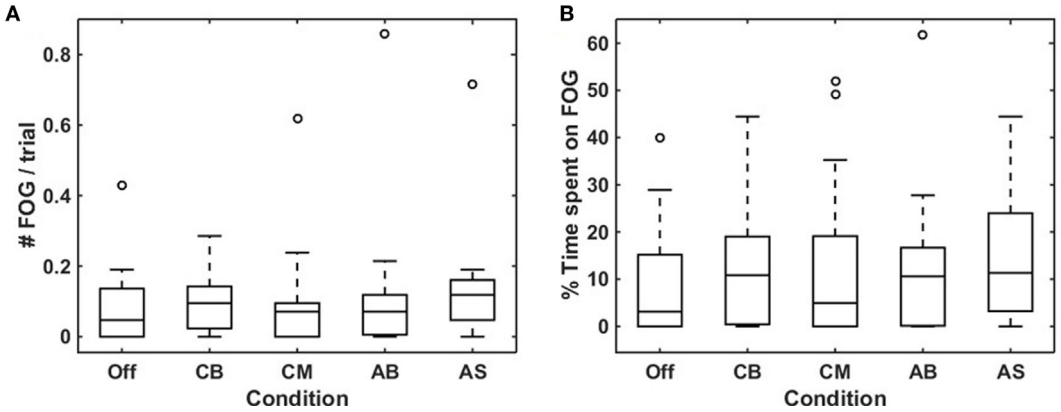

FIGURE 3 | Effects of conditions on freezing of gait (FOG) occurrence. Boxplots visualizing the effect of the five conditions on mean number of FOG episodes per trial **(A)** and percentage of time spent on FOG **(B)** for each condition in participants who experienced more than one FOG episode throughout the experiment ($N = 19$). Off, smart glasses worn but switched off; CB, conventional bars; CM, conventional metronome; AB, augmented bars; AS, augmented staircase.

Gait Variability

The median stride length variability was statistically significant higher for the CB compared to the AS (**Figure 4A**; **Table 2**). There was no statistically significant difference in cycle time variability amongst the various conditions (**Figure 4B**; **Table 2**).

Stride Length and Cycle Time

The stride length was statistically significant larger for the conservative bars compared to the AB and the AS (**Figure 4C**; **Table 2**). The median cycle time showed one outlier for the no cue condition; exclusion of the outlier did not change the results, hence the outlier was included in the analysis. The assumption of sphericity was violated [$\chi^2(9) = 28.564$, $p = 0.001$], and therefore a Greenhouse–Geisser correction was applied ($\varepsilon = 0.555$). The median cycle time was statistically significant higher for the CB when compared to the no cue condition, the CM, the AB, and the AS (**Figure 4D**; **Table 2**).

Cadence and Speed

Cadence showed no outliers, and the assumption of sphericity was not violated [$\chi^2(9) = 13.979$, $p = 0.124$]. The median cadence was lower for the CB compared to the no cue condition, the CM, the AB, and the AS (**Figure 4E**; **Table 2**). For speed, the assumption of sphericity was violated [$\chi^2(9) = 24{,}325$, $p = 0.004$], hence a Greenhouse–Geisser correction was applied ($\varepsilon = 0.594$). The median speed was lower for the CB compared with the no cue condition and the CM (**Figure 4F**; **Table 2**).

User Experience

Overall, the CM was preferred the most (99 preference points), followed by the CB (80 preference points), AB (77 preference points), no cues (61 preference points), and AS (58 preference points). Participants indicated they could walk better with cues (AB/AS/CB/CM 4), that all cues except the AS made walking easier (AS 3; AB/CB/CM 4), and that they considered all cues except the AB useful (AB 3; AS/CB/CM 4). The metronome was considered the most well-suited cue to provide more control over daily life activities (CM 4; AB/AS/CB 3) and met participants' needs (CM 4; AB 2; AS/CB 3) and expectations (CM 4; AB/AS 3; CB 2) the most. The AB and CB were considered less distracting than the AS and CM (AB/CB 4; AS/CM 3). Ease of use, usability, and willingness to use the smart glasses in everyday life were rated low (2). The use of smart glasses did not require additional effort (3), and walking with smart glasses was considered easy to learn (4). Participants suggested to improve the comfort, esthetics, usability, field of view, and stability of the smart glasses on the head and to reduce their weight and size. With regard to the augmented cues, three participants suggested to experiment with softer colors than the current white, and three participants suggested to broaden the augmented cues, and one participant wished for footsteps on the AS.

DISCUSSION

The present study investigated the usability of 3D augmented visual cues delivered by smart glasses, conventional 3D bars on the floor, a metronome or no cues on the occurrence of FOG, the percentage of time spent on FOG, the (variability of) stride length and cycle time, cadence, and speed. Note that the smart glasses were worn during all conditions, but only switched on for the AB and staircase. Neither the AB and staircase, the CB on the floor, nor the metronome reduced the number of FOG episodes or the percentage of time spent on FOG. Results were similar in the subset of FOG episodes occurring during spatially demanding situations, when the FOG episodes triggered by turning were excluded. The CB caused an increase in stride length, cycle time and stride length variability, and a decrease in cadence and speed. There was no effect of the other cues on gait parameters.

That the CB on the floor and the metronome failed to reduce FOG contradicts studies reporting a reduction in FOG by visual (16, 34) or auditory (34, 35) cues. The influences of CB on gait parameters could be attributable to the distance between the bars depending on the participant's height (leading to larger and

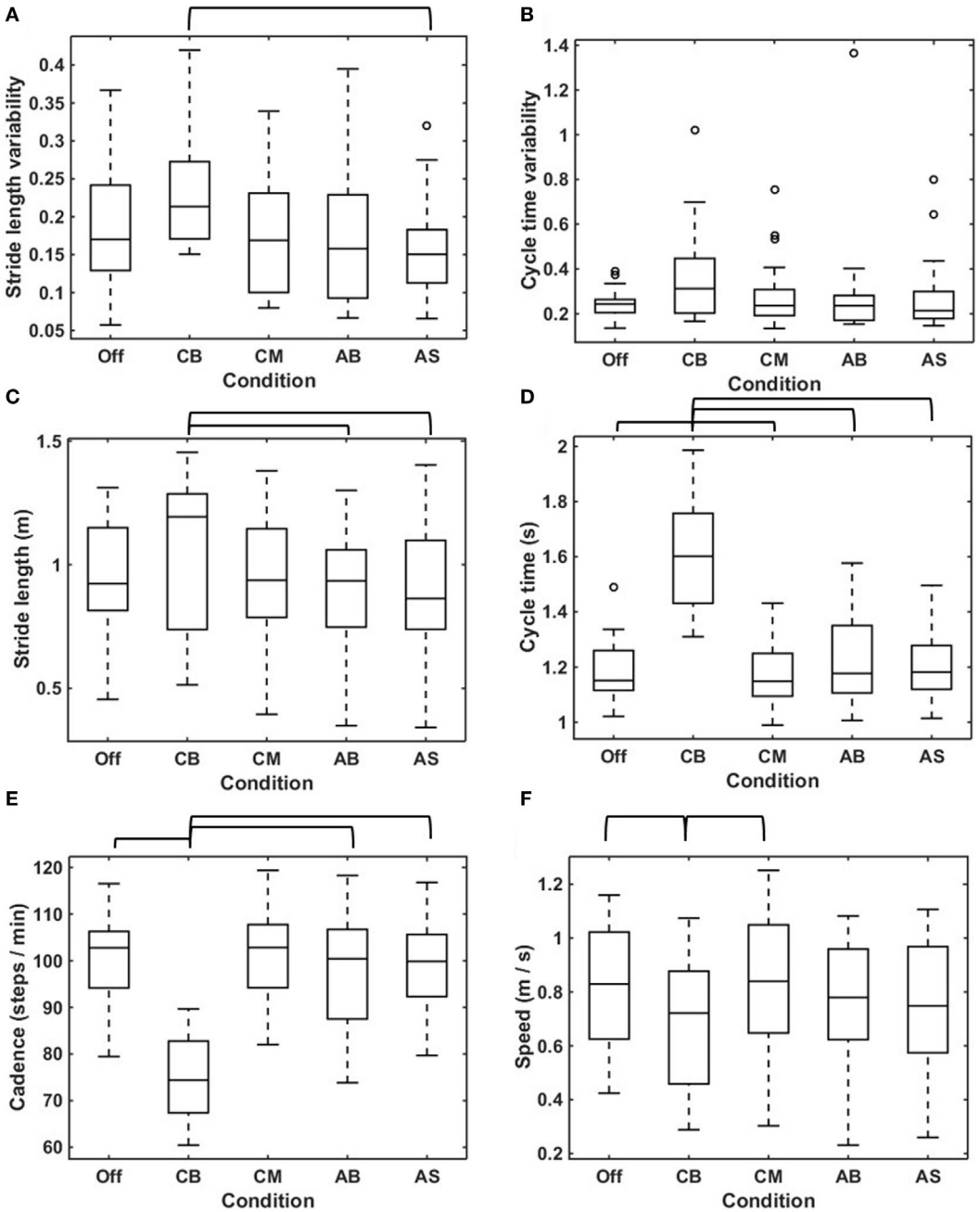

FIGURE 4 | Effects of conditions on gait parameters. Boxplots visualizing the effects of the five conditions on stride length variability **(A)**, cycle time variability **(B)**, mean stride length **(C)**, mean cycle time **(D)**, cadence **(E)**, and speed **(F)** calculated in straight-walking trials in all participants ($N = 25$). The brackets indicate statistically significant differences in the parameters concerned between conditions ($p < 0.05$). The statistical test values are given in **Table 2**.

slower steps if the distances between the bars were larger than a participants' preferred uncued step length), and the observation that participants varied the number of steps in between two bars, increasing stride length variability. That other cues did not alter gait parameters does not correspond to earlier studies (7, 10, 11).

We propose several possible explanations for the lack of effects of cues on FOG and gait parameters. First, participants were not used to walking with smart glasses, and this novel experience, together with their experience of the smart glasses being quite heavy and uncomfortable, might have caused distractions. It is well recognized that dividing attention is impaired in PD-FOG (36), and FOG severity has been correlated with difficulties in switching attention (37). Dual tasks, which also require switching or dividing attention, are known to deteriorate FOG (38) and to counteract the FOG-alleviating effects of visual cues (39). Considering that FOG occurrence did not differ amongst

conditions (including with the smart glasses switched off), the smart glasses themselves rather than the cues might have caused distraction. This may have canceled out the FOG-ameliorating effect of cues. With regard to gait parameters, dual tasks are known to decrease step length, walking speed (39), and increase cadence (38) and step length variability (39) in PD-FOG, effects which are undone in the presence of visual cues (39). Because a condition without smart glasses was not included, we cannot rule out that the smart glasses induced distraction, similar to a dual task, altering these gait parameters. However, the previous observation that dual task-induced gait alterations could be reversed by visual cues (39) was not found in our study. The rather "bulky" design of this prototype of smart glasses was due to technical constraints raised by the requirements to deliver 3D augmented cues as if placed in the real environment. Second, the duration of the experiment might have been insufficient for participants to familiarize themselves with the smart glasses and cues. Indeed, in former studies, immediate effects of cues were variable, while longer periods of cueing training were thought to be more effective (18). Third, the frame of the smart glasses blocked part of the peripheral visual field. This might have reduced the visual feedback which persons with PD-FOG are more reliant on due to impaired propriocepsis (40–43). A previous study showed that blocking the view of the lower limbs caused an increase in FOG, which visual cues did not prevent (39). Hence, the frame of the smart glasses might have reduced visual sensory feedback, thereby increasing FOG occurrence in all conditions, which was not reversed by visual cues. In addition, blockage of the visual field has previously shown to decrease step length, velocity, and cadence, which was reversible with visual cues in one (39), but not in another study (41). Such difference in gait parameters between visually cued and un-cued conditions could not be confirmed in our study. Fourth, the augmented visual cues as well as the CB were all perceived in the central visual field. It has been suggested that the integration of information from the central and peripheral visual fields is important for the perception of self-movement (44) and that typically a stationary center with a moving periphery induces a sense of self-movement. Moving visual cues in the central visual field, such as in our experiment, constitute the opposite situation. This might influence the sense of self-motion, thereby affecting motor planning and potentially contributing to the occurrence of FOG (45). However, currently used visual cues such as bars on the floor or laser lights (46–48) are predominantly presented in the central visual field, while an enhanced peripheral optic flow delivered *via* Google Glass did not reduce FOG (12). Fifth, dopaminergic medication levels at the end-of-dose might have interfered with the effects of cueing. Studies finding no effects of cues on FOG and gait parameters were predominantly performed in the ON state (15, 49–52). However, rather than that medication interferes with the effects of cues, these studies might have been underpowered to find effects of cues on gait parameters that (due to the symptomatic effect of medication) were less severely disturbed than in the OFF state. Positive effects of cues have been reported by studies performed in the OFF (15, 34, 35, 52, 53), ON (6, 10) as well as the end-of-dose state (25). The role of medication state on response to cues remains to be established.

A limitation of this study is the absence of a control condition without smart glasses and cues, which would have allowed to distinguish distraction by the smart glasses, as discussed above. Furthermore, 224 out of 300 FOG episodes occurred during turning, which might be more receptive to temporal than spatial cues. The remaining 76 non-turn FOG episodes, which could potentially be more sensitive to visual cues, might have been too few to find a statistically significant effect.

In conclusion, 3D augmented visual cues delivered by customized smart glasses did not improve FOG nor gait stability in persons with PD-FOG. Adjustments to smart glasses are prerequisite to turn them into effective cueing devices, amongst others by a more lightweight, comfortable, and user friendly design, a wider field of view and less interference with sensory visual feedback. Future research should investigate whether, and through which mechanisms, 3D cues are more effective than 2D cues; whether novel cues affect FOG provoked by spatial as well as temporal triggers; and whether visual cues should be presented in the central or peripheral visual field. Furthermore, it is of particular interest whether a larger effect of augmented visual cues can be obtained with a longer habituation period, or when cues are provided "on demand." Ideally, future studies should include healthy control individuals to assess whether cues affect gait parameters differently in persons with PD and healthy controls. To avoid a "trial-and-error"-based development of new cueing devices, it is important to deepen our insights into the characteristics of effective cues, requirements for new cueing devices, and the neuronal mechanisms underlying externally cued (freezing of) gait.

ETHICS STATEMENT

This study was performed in accordance with the guidelines of the Declaration of Helsinki (1964) and was approved by the medical ethics committee Twente. All subjects provided written informed consent prior to their inclusion in the study.

AUTHOR CONTRIBUTIONS

SJ contributed to the study design and to the acquisition, analysis, and interpretation of the data, drafted the manuscript, and edited the final manuscript for submission. BB contributed to the concept and design of the study, to the development of the software investigated in the study, and to the critical appraisal of the manuscript. JN was involved in the conception and design of the current work, in the acquisition and interpretation of data and critically revised the manuscript. MB was involved in the acquisition of the data and critically appraised the manuscript. BRB contributed to the study design and revision of the manuscript. TH, YZ, and RW were involved in the conceptual design and setup of this study, in the interpretation of the data, and in the critical revision of the manuscript. All the authors gave their approval of the final manuscript.

ACKNOWLEDGMENTS

The authors are grateful to Lucille D. A. Dorresteijn, Agnes A. A. C. M. Wertenbroek, Henk-Willem Nijmeijer, Jeroen P. P. van

Vugt, and Marleen C. Tjepkema-Cloostermans for their help in recruiting participants, and their insights in the study setup and discussion of the results. The authors thank Anja van Gestel for her assistance during the participant measurements. The authors are thankful to Erwin E. H. van Wegen for his help with the study design. The authors thank the "Parkinson Vereniging" for their support in the recruitment of participants.

FUNDING

This work is funded by a research grant (058-14-001) under the Light, Cognition, Behaviour and Health call, a joint initiative of the Netherlands Organisation for Scientific Research, the Netherlands Organisation for Health Research and Development (ZonMw), and the National Initiative Brain & Cognition (NIHC). In addition, this study was funded by the Fonds NutsOhra (1303-071), the EU INTERREG/MIND project, and the MIRA Institute of the University of Twente (Pioneers in Healthcare Innovation Fund and MIRA voucher).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00279/full#supplementary-material.

VIDEO S1 | Illustration of the simulation of three-dimensional (3D) transverse bars displayed in augmented reality (AR) perceived through the smart glasses. The upper half of the screen represents a top view of the walking direction of the user; here walking forward, turning 90° to the left and resuming to walk forward. The lower half of the screen represents the AR display. White 3D transverse bars are updated in real time upon movement of the user. The black area represents the part of the display where no AR images are being displayed, and the "real environment" is transmitted to be perceived by the user.

VIDEO S2 | Illustration of the simulation of a three-dimensional (3D) staircase displayed in augmented reality (AR) perceived through the smart glasses. The upper half of the screen represents a top view of the walking direction of the user; here walking forward, turning 90° to the left and resuming to walk forward. The lower half of the screen represents the AR display. A white 3D staircase is updated in real time upon movement of the user. The black area represents the part of the display where no AR images are being displayed, and the "real environment" is transmitted to be perceived by the user.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer, DR-M, and handling editor declared their shared affiliation and the handling editor states that the process nevertheless met the standards of a fair and objective review.

frontiers in Neurology

ORIGINAL RESEARCH
published: 05 February 2018
doi: 10.3389/fneur.2018.00035

Levodopa-Induced Changes in Electromyographic Patterns in Patients with Advanced Parkinson's Disease

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Levodopa medication is the most efficient treatment for motor symptoms of Parkinson's disease (PD). Levodopa significantly alleviates rigidity, rest tremor, and bradykinesia in PD. The severity of motor symptoms can be graded with UPDRS-III scale. Levodopa challenge test is routinely used to assess patients' eligibility to deep-brain stimulation (DBS) in PD. Feasible and objective measurements to assess motor symptoms of PD during levodopa challenge test would be helpful in unifying the treatment. Twelve patients with advanced PD who were candidates for DBS treatment were recruited to the study. Measurements were done in four phases before and after levodopa challenge test. Rest tremor and rigidity were evaluated using UPDRS-III score. Electromyographic (EMG) signals from biceps brachii and kinematic signals from forearm were recorded with wireless measurement setup. The patients performed two different tasks: arm isometric tension and arm passive flexion–extension. The electromyographic and the kinematic signals were analyzed with parametric, principal component, and spectrum-based approaches. The principal component approach for isometric tension EMG signals showed significant decline in characteristics related to PD during levodopa challenge test. The spectral approach on passive flexion–extension EMG signals showed a significant decrease on involuntary muscle activity during the levodopa challenge test. Both effects were stronger during the levodopa challenge test compared to that of patients' personal medication. There were no significant changes in the parametric approach for EMG and kinematic signals during the measurement. The results show that a wireless and wearable measurement and analysis can be used to study the effect of levodopa medication in advanced Parkinson's disease.

Keywords: Parkinson's disease, levodopa challenge test, medication, EMG, kinematic, wearable, PCA

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *25 April 2017*
Accepted: *15 January 2018*
Published: *05 February 2018*

Citation:
Ruonala V, Pekkonen E, Airaksinen O, Kankaanpää M, Karjalainen PA and Rissanen SM (2018) Levodopa-Induced Changes in Electromyographic Patterns in Patients with Advanced Parkinson's Disease. Front. Neurol. 9:35. doi: 10.3389/fneur.2018.00035

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease mainly among the old with increasing incidence with age (1, 2). There is no cure for PD. The main symptoms of PD are rigidity, rest tremor, bradykinesia, and postural instability (3). Majority of patients with PD experience rest tremor during their course of disease. Rest tremor can be present either in the beginning or a latter

phase of the disease, or the whole time. Rigidity is characterized by increased resistance in the limbs. Along with rest tremor, rigidity hinders activity of daily living (ADL) in PD. With appropriate treatment, it is possible to relieve the symptoms of the disease and thus improve ADL of PD patients to maintain their active life several years longer.

The symptoms of PD can be alleviated with multiple types of medication. Levodopa medication is currently the most efficient treatment for PD, and it alleviates the motor symptoms. COMT-inhibitors are often used to enhance the duration of levodopa treatment effect. Mild symptoms of PD can be treated with a combination of other medication, such as dopamine agonists and MAO-B inhibitors, alone or in combination (4). This allows delaying of levodopa treatment, because duration and dose of levodopa treatment are associated with appearance of dyskinesia and motor fluctuations. Up to 50% of PD patients experience dyskinesia or motor fluctuations within 5 years from the onset of levodopa medication (4).

When motor symptoms can no longer be adequately controlled with medication, deep-brain stimulation (DBS) can be introduced. Electrodes are implanted in either subthalamic nucleus (STN) or internal segment of globus pallidus (5, 6) for dyskinesia and motor symptoms or to ventral intermediate thalamic nucleus (VIM) (7) for tremor control, to give continuous electrical stimulation via stimulation device. DBS has been shown to be more efficient than optimal medication to control motor fluctuations and dyskinesias, when the patient selection is done correctly (8). Levodopa challenge test is the most important single test to assess efficacy of DBS in advanced PD. Positive levodopa challenge test predicts successful outcome from DBS treatment (5, 9).

The symptoms of PD can be assessed by using Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS is a well-established rating scale to assess the multitude of PD symptoms. The third part, UPDRS-III, is based on motor assessment (0–108 points). Levodopa challenge test can be used to determine the effect of levodopa in patients with PD. The UPDRS-III score is determined before the dosage and approximately 30–60 min after the dosage of levodopa, when the medication effect is maximal. Over 30% decrease of UPDRS-III score in challenge test is generally regarded positive to introduce DBS in PD (5, 9).

Surface electromyographic (EMG) and kinematic methods have been established during last two decades for the clinical research of PD, and they can extract multitude features (10). It has been shown that the EMG signals of PD patients have different characteristics compared to healthy controls. The complexity of signals is reduced (11, 12), and more rhythmic bursts and pattern like behavior has been observed (13). Kinematic measurements are sensitive for tremor patterns. EMG and kinematic based analyses have been used to observe gait (14), REM sleep (15), medication response (13, 16–18), and DBS treatment (17, 19, 20) in PD. During recent years, the measurement devices have become smaller, portable, and wireless. This has made the measurements more feasible, thus longer and more measurements are available. Methods to classify parkinsonian symptoms during unconstrained activity have been presented (21–23). EMG and kinematic methods have been used to recognize levodopa-induced dyskinesias during medication response (24–26).

Traditional methods for analyzing the EMG and the kinematic signals include amplitude and spectral-based measures. These methods allow for the determination of the strength of muscle activation, muscle conduction velocity, firing rate of motor units, and fatigue. The kinematic signals can be quantified with amplitude and power measures. There are newer techniques for analyzing the EMG and the kinematic signals that include linear and non-linear parametrizations as well as methods which are statistics related. These methods focus more on the morphology of the EMG signal than amplitude and frequency. The EMG and the kinematic signals in PD have been studied with amplitude and spectral based methods (15, 17, 27–31), wavelet-based approaches (32–34), linear and non-linear parameters (11, 20), EMG-burst shape analysis (13, 35, 36) and principal component approach (37, 38).

In this study, we measure and analyze EMG and kinematic signals during isometric arm tension task with linear and non-linear methods as they have been proven to be effective for analyzing signals from patients with PD (12). For analyzing EMG signals during passive flexion–extension of arm, we use spectrum-based methods since they are well established and robust enough to analyze non-stationary signals during arm movement. There are two purposes for the present study: to devise a method that consists of measurements and analysis to objectively assess the levodopa challenge test and to prove that a wearable and wireless measurement can be used for monitoring the treatment of PD.

2. MATERIALS AND METHODS

2.1. Subjects

After a written informed consent, EMG and kinematic signals of 12 (8 males, 4 females) patients with advanced PD were measured (**Table 1**). The UPDRS-III score was determined during the measurement to estimate the benefit of DBS for the patient. The patients had DBS later if they met all the selection

TABLE 1 | Patient demographic and medication data.

#	Sex	Age	Dur.	H and Y	UPDRS-III	UPDRS-III	LEDD	Test
				Med off	Med off	Med on		Dose
1	F	48	11	3	25	3	1,250	150
2	M	46	5	2	33	11	700	150
3	F	47	14	3	0	0	1,600	150
4	F	63	8	3	37	14	935	150
5	M	56	9	3	43	16	1,175	300
6	M	60	9	3	33	17	1,030	200
7	M	44	7	2	43	18	1,030	300
8	F	62	14	3	30	8	520	75
9	M	55	8	3	37	10	1,695	300
10	M	52	6	4	55	20	1,780	400
11	M	58	10	3	38	9	1,355	250
12	M	62	11	2	35	14	1,153	200

Hoehn and Yahr stage was determined on range 1–5. UPDRS-III was determined with and without medication during the study. UPDRS-III is missing for the patient 3 due to interrupted measurement. The levodopa equivalent doses for medication of each patient has been calculated according to Ref. (39). The test dose was 50% higher than the patients' normal medication dose.

criteria. The study was approved by human ethics committee of the Kuopio University Hospital. The age of the patients was (58 ± 7) (mean ± SD) years and they had had the PD diagnosis (9 ± 3) years before the measurement. The UPDRS-III score for the patients was (37 ± 8) before the administration and (13 ± 5) after 60 min of administration of levodopa.

All measurements were done in the morning when the patients had been about 10–12 h without antiparkinsonian medication. The patients did neither have breakfast nor coffee before the measurement. UPDRS-III score was determined by an experienced neurologist. The rigidity and rest tremor assessments during the measurements were conducted by the measurement person.

All parts of the measurements were done while the patient was sitting upright, with their feet on the ground, on a wooden stool which had no armrests. The condition of patients was adequate when taking into account the UPDRS-III score and thus all of them were able to sit throughout the measurement. The patients were let to rest on their hospital bed between the measurement phases if needed.

2.2. Measurement Protocol

EMG and kinematic measurements were used to observe effects of levodopa during the levodopa challenge test. Before attaching the EMG electrodes, the surface of the skin beneath was properly cleaned with ethanol wetted cotton pads. Disposable Ag/AgCl surface electrodes (Medicotest M-00-S) were placed on top of left and right biceps brachii muscle, below the belly of the muscle with interelectrode distance 3 cm. The reference electrode was placed to an inactive point on the lateral side of brachium, 6–7 cm from the recording electrodes. The whole measurement was done without detaching the electrodes in between. For recording arm kinematics, triaxial accelerometers (MEAC-X, ±10 g Mega Electronics) were attached to anterior side of forearm, halfway between the wrist and the elbow of both arms, to record the movement of arms during the measurement. The signals were recorded with wireless ME6000 biosignal monitor (Mega Electronics Ltd., Kuopio, Finland) with sampling rate 1,000 Hz. The resolution was 1 μV for EMG acquisition and 2 milligravity for acceleration acquisition. The wireless measurement provides a shield from unwanted noise in the signals.

The measurement took place four times in total: before levodopa dose (phase I), 30 min after levodopa dose (phase II), 60 min after levodopa dose (phase III). After the levodopa challenge test was over, the patient was guided how to return into his daily medication rhythm depending on the medication response he was having. One more measurement (phase IV) was done 60 min after the patient had taken his personal medication dose.

2.2.1. Task 1: Isometric Elbow Flexion

The patient was asked to hold his elbows in 90° angle with palms facing upwards. The elbows were not allowed to be supported by body sides. The patient held arms in this position for 30 s and was advised to not restrict possibly emerging tremor during the task.

2.2.2. Task 2: Passive Elbow Flexion–Extension

The patient was asked to relax his arms on top of his feet. Then the patients' elbow joint was flexed and extended periodically by holding other hand on the elbow joint and another on patients hand to allow natural track of movement. The patient was advised to not act or counteract with the movement. The measurement started after the patient relaxed his arm completely and did not perform any voluntary movements. The flexion–extension movement was repeated 9–10 times for each arm separately.

2.3. Analysis

The tasks were segmented from the measurement and the signals checked for artifacts and inconsistencies. The measurement of one patient was interrupted by other treatment and could not be proceeded along the protocol. The patient was omitted from the analysis.

The EMG and the kinematic signals were preprocessed for the analysis by removing possible baseline drift with smoothness priors method (40). The method resembled a high pass filter with cut off frequency 10 Hz for the EMG and 2 Hz for the kinematic signals. Then the EMG and kinematic signals were divided to short epochs of 1,024 ms with overlap 768 ms for isometric elbow flexion and 512 ms with overlap 384 ms for passive flexion–extension measurement. In the following analyses, the parameters and the histograms are first calculated for the epochs separately and then averaged over the epochs.

2.3.1. Task 1: Isometric Elbow Flexion

Parameters characterizing EMG and kinematic signals were calculated for the signals measured during the isometric elbow flexion. The parameters were calculated in similarly to Ref. (11, 12). EMG shape characterizing parameters kurtosis (KURT), SD, root mean-square value (RMS), median frequency (MDF), sample entropy (SampEn), correlation dimension (D2), determinism (DET), and recurrence of bursts (REC) were determined for EMG signals. Further, parameters characterizing kinematic signals, root mean-square value (ARMS), sample entropy (ASampEn), and cross sample entropy (CSampEn), were determined. The group mean and SD over patients were calculated for each phase.

The analysis was expanded by calculating 50 bin sample histograms for the EMG signals. Then the left and right side EMG histogram were concatenated for each patient and each measurement resulting four histogram-vectors for each patient, a total of 11×4 vectors.

These vectors are used as the feature vectors of principal component approach. In this analysis, the directions in which the data has the greatest variance are determined.

The feature vectors z_j can be modeled with linear model,

$$z_j = H\theta_j + v_j, \tag{1}$$

where H is the model matrix containing the basis vectors $\phi_1 \ldots \phi_k$ as columns. The basis vectors are the directions in which the data has the greatest variance. The parameter θ_j contains the principal components. The parameter V_j contains the model error. Each feature vector can be expressed as a linear combination of basis vectors multiplied by principal components

$$z_j = \phi_1\theta_j(1) + \phi_2\theta_j(2) + \cdots + \phi_k\theta_j(K) + v_j. \tag{2}$$

The linear model can be presented in matrix form if the data set consists of multiple measurements or patients. In this work, feature matrix Z is formed from feature vectors of every subject and every measurement (11 × 4 feature vectors). Now a corresponding linear model can be written

$$Z = H\theta + v, \tag{3}$$

where θ is the matrix of principal components and v the matrix of errors. The basis vectors were selected so that they are the eigenvectors of experimental correlation matrix

$$R = \frac{1}{M}\Sigma_{j=1}^{M} z_j z_j^T = \frac{1}{M} ZZ^T. \tag{4}$$

With this selection, the first basis vector ϕ_1 is the best mean-square fit for the data set Z, the vector ϕ_2 is the best mean-square fit for the residual of the first fit and further. Four basis vectors $\phi_1 \cdot \phi_4$ (BV1–BV4 from this on) of largest principal components were chosen to represent the original feature vectors. The principal components can be solved from the linear model in the least-squares sense

$$\theta = (H^T H)^{-1} H^T Z = IH^T Z. \tag{5}$$

Since the eigenvectors of R are orthonormal, $H^T H$ is a unit matrix.

2.3.2. Task 2: Passive Elbow Flexion–Extension

The EMG signals during passive elbow flexion–extension were analyzed with time dependent spectrum approach. The epoch length was 512 ms with 386 ms overlap. Short time Fourier transform was calculated for the epochs with the spectrogram function of MATLAB (MathWorks, USA). The frequency range was set between 0 and 200 Hz, since the spectral power above 200 Hz was non-significant. The spectrum was observed visually and quantified by calculating mean power spectral density for each measurement. The values for the phases II, III, and IV were normalized with each patients phase I value to make the values comparable to other patients.

2.3.3. Statistical Tests

All statistical tests were performed so that the phases of each patient were compared to the phase I. Wilcoxon signed rank test was used to determine the significance of changes in the principal components, the spectrum means and the EMG and the kinematic parameters.

3. RESULTS

3.1. UPDRS-III

During the levodopa challenge test, UPDRS-III score of the patients changed from (37 ± 8) to (13 ± 5) indicating significant improvement of motor symptoms (**Table 2**). The decrease ranged from 48 to 88% in individuals and is considered a positive outcome for DBS installation. Rigidity was the most common symptom among the patients, but a majority showed also rest tremor. The **Table 3** shows the group mean of the upper limb rigidity and rest tremor which were graded with UPDRS-III scale.

TABLE 2 | UPDRS-III score and limb rest tremor and rigidity during the measurement phases I–IV.

	UPDRS-III	Tremor	Rigidity
Range	**0–108**	**0–16**	**0–16**
I	37.2 ± 7.9	1.9 ± 2.4	6.9 ± 3.2
II	–	0.4 ± 0.5	3.0 ± 3.2
III	12.7 ± 5.0	0.0 ± 0.0	2.0 ± 2.5
IV	–	0.5 ± 1.2	3.5 ± 2.4

The whole UPDRS-III was done in phases I and III, the limb rigidity and rest tremor assessment were done in each phase I–IV. The maximum of each item in UPDRS-III is 4, though the whole range of limb tremor and rigidity is 0–16.

Before the levodopa administration (phase I) the rigidity differed only slightly between the left and the right hand whereas the rest tremor seemed to be stronger on the right side. The rigidity and the rest tremor decreased already 30 min after the administration of levodopa (phase II). The effect became stronger and alleviated the rest tremor totally in the phase III, also the rigidity continued to decrease. In the last phase, the rigidity and the rest tremor began to increase indicating that the levodopa dosage given in levodopa challenge relieves the motor symptoms of the disease more than the patients' personal medication.

3.2. Task 1: Isometric Elbow Flexion

The EMG and the kinematic signals for a single patient are shown in Figure S1 in Supplementary Material. There were some differences in the EMG signals between the different phases. In the phase I, the left hand EMG contained bursts which decreased in the phases II–IV. On the right hand side, the signal amplitude increased from the phase I to the phase III. The kinematic signals showed slightly less changes between the phases I–IV. The amplitude was greatest in the phase II, but the frequency was slightly high (around 9 Hz) compared to typical Parkinsonian rest tremor (4–6 Hz).

The calculated EMG and kinematic parameters (**Table 3**) differed slightly between the phases. However, the deviation was high and there were no statistically significant changes either in the EMG or the kinematic parameters. According to the UPDRS-III score, majority of the patients suffered from rest tremor. Traditionally this is easily picked up by kinematic measurement. However, in this study, the kinematic measurement and the signal RMS values showed that rest tremor is generally very low.

The characterization of the EMG signals was taken further by including principal component analysis. The basis vectors for characterization of the histograms are presented in Figure S2 in Supplementary Material. The first and the second BV characterized the histogram height and width, which are closely related to the EMG signal characteristics in PD. The third BV characterized the side differences in histogram peak height, whereas the fourth BV was a mixture of peak width and side differences. The principal components which showed the greatest difference between the phases, PC1 and PC2, are shown in Figure S3 in Supplementary Material. These two principal components are related to the signal burstiness. It is seen that in the phase II there are varying responses between the patients. While the PC1 decreases and the PC2 increases for most patients, opposite paths are observed also.

TABLE 3 | Parameters of isometric tension task.

	I		II		III		IV	
	Left	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
UPDRS-III of upper limb								
Rigidity	2.00 ± 1.34	1.82 ± 0.98	1.00 ± 1.34	0.64 ± 1.03**	0.45 ± 0.93**	0.27 ± 0.90**	1.27 ± 1.56*	0.82 ± 0.60*
Tremor	0.50 ± 0.67	1.08 ± 1.31	0.08 ± 0.29	0.33 ± 0.65	0.00 ± 0.00	0.00 ± 0.00	0.25 ± 0.45	0.25 ± 0.62
EMG-parameters								
KURT	4.79 ± 1.66	4.33 ± 0.65	4.42 ± 0.60	4.20 ± 0.66	4.49 ± 0.71	4.18 ± 0.55	4.34 ± 0.68	4.14 ± 0.49
DEV	0.34 ± 0.03	0.35 ± 0.03	0.34 ± 0.02	0.35 ± 0.02	0.34 ± 0.02	0.35 ± 0.03	0.35 ± 0.03	0.36 ± 0.02
RMS	46.8 ± 27.8	36.9 ± 10.1	65.1 ± 55.9	69.2 ± 75.7	67.7 ± 34.0	70.2 ± 58.5	49.4 ± 20.0	64.0 ± 37.9
MDF	71.0 ± 18.5	66.2 ± 14.8	67.3 ± 11.0	67.4 ± 15.3	66.0 ± 12.7	68.4 ± 13.5	69.0 ± 16.8	67.6 ± 16.9
REC	8.2 ± 3.5	8.9 ± 5.3	7.5 ± 2.9	9.0 ± 7.2	8.0 ± 3.0	6.9 ± 2.8	8.0 ± 2.9	8.6 ± 5.3
DET	9.7 ± 6.2	15.3 ± 15.6	9.7 ± 4.2	15.3 ± 15.8	11.9 ± 9.1	10.6 ± 9.4	10.5 ± 5.1	14.7 ± 14.1
SampEn	1.11 ± 0.26	1.16 ± 0.24	1.15 ± 0.13	1.17 ± 0.26	1.11 ± 0.22	1.20 ± 0.20	1.15 ± 0.19	1.18 ± 0.21
D2	6.23 ± 0.83	6.21 ± 1.03	6.40 ± 0.48	6.23 ± 1.30	6.26 ± 0.64	6.55 ± 0.69	6.26 ± 0.53	6.28 ± 1.11
Kinematic parameters								
ARMS	0.06 ± 0.02	0.08 ± 0.09	0.06 ± 0.03	0.09 ± 0.11	0.08 ± 0.05	0.06 ± 0.04	0.09 ± 0.08	0.10 ± 0.08
ASampEn	1.14 ± 0.28	1.00 ± 0.37	1.11 ± 0.30	1.02 ± 0.36	1.11 ± 0.44	1.10 ± 0.26	0.97 ± 0.47	0.86 ± 0.37
CSampEn	1.28 ± 0.21	1.20 ± 0.32	1.25 ± 0.21	1.22 ± 0.26	1.26 ± 0.31	1.28 ± 0.14	1.23 ± 0.24	1.16 ± 0.20
PCA of EMG								
PC1	0.50 ± 0.26		0.29 ± 0.20		0.22 ± 0.13*		0.32 ± 0.22**	
PC2	0.65 ± 0.30		0.85 ± 0.15		0.91 ± 0.08*		0.80 ± 0.19**	
PC3	0.39 ± 0.28		0.32 ± 0.18		0.25 ± 0.21		0.35 ± 0.33	
PC4	0.62 ± 0.27		0.62 ± 0.15		0.58 ± 0.11		0.62 ± 0.14	

*UPDRS-III score for arm rigidity and rest tremor decreased in the phases I–III and increased in the phase IV compared to phase III. There were only slight changes in EMG and kinematic parameters between the phases, none of which was significant. The principal component approach showed significant difference between the phases I and III and between the phases I and IV. Values presented in format (mean ± SD). Significant change to first measurement *p < 0.05, **p < 0.01.*

In the phase III, the effect of medication is more homogeneous, nearly all of the patients experience decrease in the PC1 and increase in the PC2. In the phase IV, the response is similar to the phase III, but milder. Means and SDs of the coefficients PC1–PC4 are shown in **Table 3**. For the PC1 and the PC2, it indicates the same results than the Figure S2 in Supplementary Material. It is seen that the PC3 changes similarly than the PC1, indicating that there is a decrease in side difference, but not significant. There was practically no change in the PC4 between the phases.

3.3. Task 2: Passive Extension–Flexion Task

The time dependent spectrum of EMG activation during the passive flexion–extension task showed muscle activity even though the patients were not voluntarily tensing their muscles. The involuntary muscle activity was strongest in the phase I, while a decreasing trend was observed toward phases II and III. In the phase IV, a slight increase in activity compared to phase III is observed. Muscle activation in phases I and III for both hands of each patient is shown in Figure S4 in Supplementary Material. The decrease in involuntary activity is clear in most of the patients. We hypothesize that this is an indication of Parkinsonian rigidity. The EMG amplitudes are not directly comparable between the patients. However, the amplitudes can be compared between the measurement phases of one patient, since all the phases were measured in the same session without moving or detaching the electrodes in between. The normalized mean power spectral density decreased to (0.88 ± 0.40, 0.63 ± 0.31**) (left, right) in the phase II (not shown in the figure), to (0.62 ± 0.39*, 0.51 ± 0.21**) in the phase III and increased again to (0.65 ± 0.40*, 0.68 ± 0.28**) in the phase IV (not shown in the figure). The change was significant compared to the phase I in the phases III and IV on the left arm, and in the phases II-IV on the right arm. Significances $^{**}p < 0.01$, $^{*}p < 0.05$.

4. DISCUSSION

In this study, 12 patients with advanced PD went through tests to determine their applicability for DBS treatment. During the levodopa challenge test, the muscle activity and arm movements of the patients were measured, and 11 of them were analyzed. The results of the study proved that a wireless and wearable device combined with the presented analysis can be used to objectively monitor the muscle activity during levodopa challenge test.

The main finding of the study is that levodopa challenge test changes the characteristics of EMG and kinematic signals in patients with advanced PD. The proposed principal component approach suggests that the morphology of EMG changes due to levodopa administration so that the EMG histogram peak lowers and widens. The clinical indication of this is the alleviation of PD symptoms. Variation in the phase II suggests that the begin of medication response varies between the patients. The third PC shows slight decline in side difference, but the change was non significant. PD typically begins unilaterally and these results suggest that even though medication relieves the symptoms bilaterally, it failed to lessen the side difference between the left and the right arm. The nearly absent change in PC4 indicates that most of the differences in histograms are

described already by the three first PC's and it is only used to fine tuning the histogram shape. The strength of the principal component approach is in the core of the method. It relies on determining the directions of data variation in the data set and thus is tailored to find the differences in that particular data set. This is a slight shortcoming of the method at the same time. The method needs a training set and it cannot be used for a single measurement.

The second main finding is that the effect of levodopa can be seen also in passive flexion–extension task. It was found that levodopa dosage decreases involuntary muscle tone in patients of PD. The results follow trend that is similar to the isometric task. In the phase II, there is more variation in the results, but in the phase III there is a clear decrease in involuntary muscle activation. In the phase IV, it is slightly increased compared to III, but still closer to phase III than phase I. Similar results for measurement during DBS treatment has been observed by Levin et al. (30). When comparing the UPDRS-III limb rigidity, similar trend is observed. We hypothesize that the decrease in rigidity is a result from decreased involuntary muscle activity. Thus, the passive flexion–extension measurement is connected to the Parkinsonian rigidity, and can be used to measure it. We are aware of the difficulties which this method poses: (1) the rate of limb flexion–extension was not controlled precisely and (2) the patients' voluntary movement cannot be perfectly ruled out. The (1) can affect to power spectral density, but we assume that the effect is not significant since the measurement person used same speed for each patient (slightly less than 1/s). Also it can be speculated, that while rigidity could decrease the rate of movement, which would also decrease the difference between phase I and phase III. The (2) can cause false (voluntary) movements during passive flexion–extension cycle. However, the patients were advised to keep their hand in rest while the movement and the measurement was not began before the measurement person felt the patient was not voluntarily contracting their muscles. While it can be argued that patients learn to relax their hand throughout the measurement, this is not the case according to the data: during the fourth phase, most of the patients experienced increased rigidity which is also picked up by EMG measurement.

The third main finding was that unlike in earlier studies, the Parkinsonian symptoms were not visible in the parameters calculated from EMG and kinematic signals during the isometric task. Even patients who presented rest tremor during the UPDRS-III assessment, did not show significant tremor in the kinematic signals. This is an atypical finding since rest tremor is easily picked up by kinematic sensors. Multiple factors can affect to this. It is possible that patients (despite the advice) were restricting their tremor during the isometric measurement. This is quite common along the patients in general. The tremor in PD is mainly rest tremor which disappears during posture or kinetic tasks. It is possible that the isometric tension measurement measures postural tremor and, therefore, is not compatible method to measure rest tremor. However, contrary results have been observed in earlier studies (12, 38). In the third and fourth measurement, rest tremor is absent due to the medication. The patients in this study were going through a series of clinical trials which tell us if the patients would benefit from DBS treatment. Patients older than 70 years may tolerate DBS less well than younger patients like in this study. This affects to our patient selection, and it could be possible that previously mentioned issues are emphasized compared to general population of PD patients. This notion is backed up with the fact that the EMG signals show similar values for parameters for healthy controls as in our earlier study, even when the patients were off-medication. However, principal component approach is more capable to extract information from the EMG signals. In this approach, we see clear changes between the signals during the medication dosage. However, the number of subjects is small for drawing definitive statistical conclusions.

The results of the study indicate that the patients' response to levodopa during levodopa challenge is stronger than the response to their own personal medication. This was an expected result: since the levodopa dosage in levodopa challenge test is 1.5 times the patients' optimal dose, the response is also pronounced. However, this does not imply that the patients' medication dosage is not optimal. When determining suitable medication dose, also the adverse effects have to be taken into account. During this measurement, part of the patients experienced levodopa-induced dyskinesias and some of them were struggling to keep steady during the end of the phase III measurement due to strong medication response.

The strengths of this analysis are the feasible measurements, only the wireless measurement device is needed, as comparison to other methods which typically incorporate special equipment such as manipulators to carry out the measurement. Even though the measurements are currently done with a wireless measurement device which is the size of a scientific calculator, the technology today allows this method to be directly used on even smaller devices. The analysis methods are not computer intensive which enables their use in simpler devices, for example the measurement device. Present method appears to objectively assess the effect of levodopa challenge test on muscle activity and activation patterns in advanced PD. However, there is no restriction for using the method to follow the effects of levodopa during the course of disease. With further research, this method can possibly be used also for analysis of long-time registration of medication response in PD.

ETHICS STATEMENT

This study was approved by the Research Ethics Committee of the Northern Savo Hospital District. All subjects gave a written informed consent in accordance with the Declaration of Helsinki before the measurements.

AUTHOR CONTRIBUTIONS

VR: patient measurements, data analysis, and manuscript writing. EP: management of patient measurements and manuscript writing. OA: study planning and management, funding, and manuscript writing. MK: study planning and manuscript writing. PK: study planning and management, funding, and manuscript writing. SR: study planning, data analysis, and manuscript writing.

FUNDING

The study was partly funded by the Finnish Parkinson Foundation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2018.00035/full#supplementary-material.

FIGURE S1 | Three second segment of EMG and kinematic signals during isometric tension of left and right arm in one patient. EMG bursts decrease in phases I–III on left side, whereas EMG amplitude increases in phases I–IV on right side. There is more tremor-like activity in kinematic signals of phase II than others.

FIGURE S2 | Basis vectors BV1–BV4 of the data set determined by PCA. BV1 denotes EMG histogram peak height, BV2 peak width, BV3 the side differences, and BV4 is a partial mixture of side differences and peak height.

FIGURE S3 | Principal components PC1 and PC2 in phases II–IV, normalized to the phase I. The phase II and the phase III show similar features. The phase IV indicates that the effect of the patients own medication is milder than that of the levodopa test dose (phase III). The phase I for each patient is marked with a solid circle while the hollow circles indicate the change from the phase I.

FIGURE S4 | Left and right arm EMG spectral power during passive extension–flexion task in phases I and III for each patient. White colour denotes higher spectral intensity. The EMG spectral power decreases from the phase I to the phase III in passive extension–flexion task.

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