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# Harmonic ratio is the most responsive trunk-acceleration derived gait index to rehabilitation in people with Parkinson's disease at moderate disease stages

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ABSTRACT

*Background:* Harmonic ratios (HRs), recurrence quantification analysis in the antero-posterior direction ($RQA_{detAP}$), and stride length coefficient of variation (CV) have recently been shown to characterize gait abnormalities and fall risk in people with Parkinson's disease (pwPD) at moderate disease stages.
*Research question:* This study aimed to i) assess the internal and external responsiveness to rehabilitation of HR, $RQA_{detAP}$, and CV, ii) identify the baseline predictors of normalization of the gait stability indexes, and iii) investigate the correlations between the gait indexes modifications (Δ) and clinical and kinematic Δs in pwPD at Hoehn and Yahr disease staging classification 3.
*Methods:* The trunk acceleration patterns of 21 pwPD and 21 age- and speed-matched healthy subjects (HSmatched) were acquired during gait using an inertial measurement unit at baseline (T0). pwPD were also assessed after a 4-week rehabilitation period (T1).
Each participant's HR in the antero-posterior ($HR_{AP}$), medio-lateral ($HR_{ML}$), and vertical directions, $RQA_{detAP}$, CV, spatio-temporal, and kinematic variables were calculated.
*Results:* At T1, $HR_{AP}$ and $HR_{ML}$ improved to normative values and showed high internal and external responsiveness. Lower HRs and higher pelvic rotation values at baseline were predictors of ΔHRs. A minimal clinically important difference (MCID) $\geq$ 21.5 % is required to normalize $HR_{AP}$ with 95 % probability. MCID $\geq$ 36.9 % is required to normalize $HR_{ML}$ with 92 % probability. $\Delta HR_{AP}$ correlated with $\Delta HR_{ML}$ and both correlated with Δstride length and Δpelvic rotation, regardless of Δgait speed. RQAdetAP and step length CV were not responsive to rehabilitation.
*Significance:* When using inertial measurement units, $HR_{AP}$ and $HR_{ML}$ can be considered as responsive outcome measures for assessing the effectiveness of rehabilitation on trunk smoothness during walking in pwPD at moderate disease stages.

## 1. Introduction

People with Parkinson's disease (pwPD) can benefit from gait rehabilitation to improve their gait and normalize some of their abnormal gait parameters [1,2]. Many clinical tools have been developed to detect unbalance in pwPD [3,4]. Nonetheless, because of their higher sensitivity, technology-based objective measures may represent appropriate outcome measures for assessing the effects of gait rehabilitation [5,6]

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and tailoring the rehabilitation program based on the participants' baseline prognostic characteristics [7]. The use of mobile inertial measurement units (IMU) represents a viable and clinically applicable technique of gait analysis to assess gait impairment in pwPD [8,9]. Because of their affordability and ease of use, IMUs may represent the ideal tools to support clinical decisions, monitor the effectiveness of neurorehabilitation in outpatient facilities, and deliver home-based interventions [5,9,10]. A single IMU at the lower back level can accurately measure dynamic trunk behavior and spatiotemporal gait parameters based on trunk acceleration patterns during gait [11]. A series of quantitative trunk-acceleration derived measures has been proposed to quantify gait imbalance in pwPD [11]. Recently, the ability of a set of trunk acceleration-derived gait stability indexes to characterize the severity of gait alteration and the risk of fall of pwPD has been reported: 12] i) the Harmonic Ratio (HR), a measure of smoothness of the trunk acceleration patterns that captures the ability to synchronize changes in trunk mechanics with those in the lower limbs;[11] ii) the percent determinism in the antero-posterior direction of the accelerative pattern ($RQA_{detAP}$), an index that expresses the predictability of acceleration trajectories during the gait; and iii) the coefficient of variation of the stride length (CV), an index that reflects the continuous step-to-step adjustments of the gait strategy due to the adoption of adaptive mechanisms during the gait. These indexes showed to accurately characterize the gait of pwPD with a mild-to-moderate disability, as defined by a Hoehn and Yahr (HY) score of 3, regardless of the gait speed [12]. Moreover, the HR in the antero-posterior direction ($HR_{AP}$) was found to be a potential marker of fall risk and to correlate with trunk rigidity and a decrease in pelvic motion [12]. These clinical features are common in pwPD with mild-to-moderate disability [13] and may represent clinical outcomes of gait rehabilitation [14,15]. Therefore, the aforementioned gait instability indexes could represent useful outcome measures for assessing the effectiveness of rehabilitative interventions. However, before recommending these indexes as outcome measures in a clinical setting, their responsiveness, defined as their ability to meaningfully change over time and to parallel clinical modifications following a rehabilitation intervention [16], should be investigated. Moreover, identifying clinical and kinematic characteristics that predict and reflect the improvements in the responsive gait stability indexes may provide clinicians a tool to improve the therapeutic indications and set up personalized exercise interventions for pwPD. Therefore, the primary aim of our study is to assess the internal responsiveness to rehabilitation of HR, RQAdetAP, and CV, namely the magnitude of changes after rehabilitation. Moreover, we aim to determine: i) the external responsiveness of the gait stability indexes, along with the minimal clinically important differences that characterize pwPD who near the normative values after rehabilitation; ii) the baseline gait parameters that predict the improvements of the gait stability indexes; and iii) the spatio-temporal and kinematic gait parameters that correlate with the improvements in the gait stability indexes following rehabilitation in pwPD with a mild-to-moderate disability.

## 2. Methods

### 2.1. Subjects

We collected data samples from 21 subjects diagnosed with idiopathic PD (9 females and 12 males, aged 74 ± 5.83 years, disease duration: 9 ± 6.47 years, levodopa equivalent dose: 530.38 ± 234.84 mg) who underwent an outpatient rehabilitation period at "ICOT" in Latina, Italy, and at "IRCCS Mondino Foundation" in Pavia, Italy. The inclusion criteria were: i) a diagnosis of idiopathic Parkinson's disease (PD) based on UK bank criteria;[17] ii) HY stage 3; iii) the ability to walk repeatedly without assistance for at least 10 walking strides without exhibiting gait freezing; [18–20] and iv) a stable and accustomed drug program for at least two weeks before baseline. Subjects with cognitive deficits (Mini Mental State Examination < 26) [21], moderate-to-severe depression (Back Depression Inventory > 17) [22], orthopedic and/or other gait-affecting diseases, including other neurological diseases, clinically defined osteoarthritis referring pain in hip or knee joints, reduced hip internal rotation, visible anatomic abnormalities of the joints, or total hip joint replacement [23], were all ruled out.

The severity of PD was assessed using the HY disease staging system and the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) at baseline (T0) and after (T1) the rehabilitation period. Subjects were assessed by expert neurologists who were unaware of the gait stability indexes reports.

For group comparison, a 1:1 optimal data matching procedure using propensity score difference method [24] was performed to match pwPD with a dataset of 89 walking trials recorded in healthy subjects (HS). To reduce the influence of gait speed on the other speed-dependent gait parameters and to collect the largest possible sample size for speed-matched comparisons [14,25], each HS was asked to repeat the gait task twice by walking at both self-selected speed and slower directed speed. The propensity scores were computed using logistic regression analysis with age and speed as covariates [26,27]. Following the matching procedure, 21 age-and-speed-matched healthy subjects ($HS_{matched}$), aged 69.25 ± 6.61 years, were included as a control group. An independent sample t-test confirmed the effectiveness of the matching procedure.

Informed consent was obtained from all participants in compliance with the Helsinki Declaration and local ethics committee approval was obtained (CE Lazio2, protocol number: 0053667/2021).

### 2.2. Procedures

To acquire data, an inertial sensor (BTS GWALK, BTS, Milan, Italy) was placed at the level of the fifth lumbar vertebra (L5) using an ergonomic belt placed around the pelvis. The inertial sensor was connected to a laptop via Bluetooth for data recording and offline analysis. This sensor incorporates a tri-axial accelerometer (16 bit/axis), tri-axial magnetometer (13 bits), and tri-axial gyroscope (16 bit/axes). At a sampling rate of 100 Hz, linear trunk accelerations and trunk angular velocities in the anterior-posterior (AP), mediolateral (ML), and vertical (V) directions were recorded. The "Walk+ " protocol of the G-STUDIO software (G-STUDIO, BTS, Milan, Italy) was used to detect trunk acceleration patterns, right and left heel strikes, toe-off, spatiotemporal parameters, and pelvic kinematics.

Before the experimental session, the participants were asked to walk on the ground along a predetermined pathway to become acquainted with the procedure. pwPD were asked to walk at their self-selected speed along a corridor (approximately 3 m wide and 30 m long) with no external sensory cues to interfere with their pacing and rhythm. pwPD were assessed before (T0) and at the end (T1) of their scheduled rehabilitation period during their "ON phase".

The rehabilitation protocol consisted of a 60-min session/day, performed 3 days/week, for 4 consecutive weeks. According to the European Physiotherapy guidelines for PD [28], the intervention focused on the prevention of inactivity and management of fear of falls, maintenance or improvement of global motor activities, improvement of physical performance, improvement of transfer abilities, balance, manual activities, and gait, and consisted in trunk mobility, muscle stretching, balance training, and gait exercises, with and without external auditory or visual cueing [2,29–31]. HRs in the three spatial directions, $RQA_{detAP}$, and CV were calculated using MATLAB (MATLAB 7.4.0, MathWorks, Natick, MA, USA) [12] at T0 and T1. Details on the calculation of the indexes are described in the Supplementary material.

Walking trials with at least 10 consecutive correctly recorded strides [12,18–20] were input into the analyses.

### 2.3. Statistical analysis

Based on a previous study [12] that identified a medium effect size of

0.74 to be the magnitude of significant differences in gait stability indexes between pwPD and age-and-speed matched HS ($HS_{matched}$), a sample size of at least 17pwPD was calculated to identify significant improvements in pwPD that could approach the values of $HS_{matched}$ at the final evaluation in a paired-samples comparison. The power and statistical significance were set at 80 % and 95 %, respectively. After checking for the normality of the distributions through the Shapiro-Wilk test, a paired T-test or Wilcoxon test was performed to identify significant modifications in clinical and gait parameters at T1. Cohen's *d* with Hedge's correction [32] was calculated to assess internal responsiveness [16].

Unpaired t-test or Mann-Whitney test was used to identify significant differences between pwPD and $HS_{matched}$ at T0 and normalization at T1.

Changes in gait variables and UPDRS-III scores at T1 were expressed as delta (Δ) values according to the following formula:

$$\Delta = 100 \bullet \frac{value_{T1} - value_{T0}}{value_{T0}}$$

Multiple linear regression analysis with "backward" procedure was performed to identify the clinical and gait parameters that predicted the improvements of the gait stability indexes.

Spearman's correlation coefficients were calculated to identify the correlations between the Δs of the modified gait stability indexes and the Δs of the clinical, spatio-temporal, and kinematic gait parameters. To exclude a carry-over effect of Δgait speed on the Δgait stability indexes [33], partial correlation analysis adjusting for the Δgait speed was also performed.

An anchor-based method was used to assess the external responsiveness of the normalized parameters [16]. AUCs were calculated to assess the ability of the correlated Δs to identify the subjects who improved and normalized the modified stability indexes, using the normalization of the gait stability indexes as the anchor. Each improved subject with PD was individually categorized as having the gait stability indexes "normalized" at T1 if the thresholds characterizing pwPD at HY3 had been exceeded. The minimally clinically important differences (MCID) were calculated as the Δvalues that maximize the sum of sensitivity and specificity. Positive and negative likelihood ratios (LRs) were calculated at the MCID value and transformed into post-test probabilities through Fagan's nomograms. The probability to be identified as pwPD by the threshold values was used as pre-test probabilities [12].

All the statistical tests were set at 95 % significance level and 80 % power. Statistical analyses were performed using the IBM SPSS ver. 27 and NCSS 2019 software.

## 3. Results

### 3.1. Internal responsiveness findings

Table 1 summarizes the results of the assessments. After the matching procedure, no differences in age and gait speed between pwPD and $HS_{matched}$ were found.

At T0, there were significant differences in HRs, CV, stride length, and pelvic rotation between pwPD and $HS_{matched}$. After rehabilitation, pwPD improved in $HR_{AP}$, $HR_{ML}$, gait speed, stride length, cadence, pelvic obliquity, pelvic rotation, and UPDRS-III, with medium-to-large effect sizes. At T1, $HR_{AP}$, $HR_{ML}$, stride length, and pelvic rotation were no longer different from $HS_{matched}$, suggesting a normalization of these parameters.

### 3.2. Predictors of responsiveness findings

According to the multiple linear regression analysis models, lower HRs values, and higher pelvic rotation values at baseline predicted $\Delta HR_{AP}$ and $\Delta HR_{ML}$ (Table 2).

**Table 1**
Results of the assessments at baseline and at T1 in pwPD and comparison with $HS_{matched}$.

| HSmatched | | pwPD | | p-value T0 vs. T1 | d |
|---|---|---|---|---|---|
| | | T0 | T1 | | |
| UPDRSIII | – | 43.85 (16.28) | 30.80 (10.30) | **0.00** | **0.97** |
| Speed (m/s) | 0.80 (0.21) | 0.71 (0.21) | 0.85 (0.26) | **0.01** | **0.65** |
| HRAP | 2.00 (0.48) | 1.55 (0.35) * | 1.81 (0.35) | **0.00** | **0.82** |
| HRML | 1.90 (0.38) | 1.54 (0.30) * | 1.67 (0.24) | **0.03** | **0.52** |
| HRV | 2.02 (0.44) | 1.61 (0.37) * | 1.70 (0.32) * | 0.22 | 0.28 |
| RQAdetAP | 40.56 (28.51) | 34.12 (23.44) | 30.45 (27.27) | 0.71 | 0.03 |
| CV | 25.11 (10.47) | 39.26 (20.63)* | 36.87 (18.02)* | 0.58 | 0.12 |
| Stance duration (%) | 62.32 (4.63) | 61.45 (2.48) | 61.01 (1.91) | 0.46 | 0.17 |
| Swing duration (%) | 37.67 (4.63) | 38.57 (2.32) | 38.85 (2.09) | 0.61 | 0.12 |
| DS (%) | 12.22 84.54) | 11.30 (2.51) | 10.80 (2.07) | 0.35 | 0.21 |
| SS (%) | 38.06 (4.42) | 38.53 (2.49) | 38.99 (1.92) | 0.42 | 0.18 |
| Stride duration (s) | 1.31 (0.23) | 1.25 (0.27) | 1.24 (0.41) | 0.90 | 0.03 |
| Stride length (m) | 1.10 (0.19) | 0.85 (0.22) * | 0.98 (0.25) | **0.01** | **0.62** |
| Cadence (steps/min) | 95.48 (13.77) | 98.60 (23.35) | 105.08 (22.63) | **0.02** | **0.49** |
| Pelvic Tilt (°) | 2.76 (0.77) | 3.01 (1.15) | 3.46 (1.08) * | 0.13 | 0.36 |
| Pelvic Obliquity (°) | 4.02 (1.39) | 3.28 (2.38) | 3.80 (2.10) | **0.02** | **0.43** |
| Pelvic Rotation (°) | 7.00 (4.41) | 4.44 (2.28) * | 6.29 (3.55) | **0.01** | **0.70** |

*Significant difference between pwPD and $HS_{matched}$ ($p < 0.05$); pwPD, persons with Parkinson Disease; $HS_{matched}$, age-and-speed matched healthy subjects; T0, baseline assessment; T1, assessment at the end of the rehabilitation period; AP, antero-posterior direction; ML, medio-lateral direction; V, vertical direction; HR, harmonic ratio; RQAdet, %determinism in the recurrence quantification analysis; CV, step length coefficient of variation; DS, double support phase; SS, single support phase; p-value, 95 % significance level of the paired samples tests; d, Cohen's effect size.

**Table 2**
Multiple regression analysis findings.

| | Baseline variables | B | SE | *b* | t | p |
|---|---|---|---|---|---|---|
| $\Delta HR_{AP}$ | Constant | 69.75 | 25.63 | | 2.72 | 0.01 |
| $R^2_{adj}$: 0.43, | $HR_{AP}$ | -25.55 | 13.60 | -0.57 | -3.32 | 0.00 |
| F = 8.34, | pelvic rotation | 5.71 | 2.39 | 0.41 | 2.38 | 0.03 |
| p = 0.00 | | | | | | |
| $\Delta HR_{ML}$ | Constant | 57.85 | 17.23 | | 3.36 | 0.00 |
| $R^2_{adj}$: 0.45, | $HR_{ML}$ | -40.57 | 10.52 | -0.66 | -3.85 | 0.00 |
| F = 8.92, | pelvic rotation | 3.19 | 1.51 | 0.36 | 2.11 | 0.05 |
| p = 0.00 | | | | | | |

The multiple regression analysis took in consideration: independence of residuals, homoscedasticity, absence of multicollinearity and significant outliers, and normal distribution of residuals verified through graphical visualizations and Durbin-Watson, tolerance, and variance inflation factor calculations.
Δ, difference between T1 and T0 values; $HR_{AP}$, harmonic ratio in the antero-posterior direction; $HR_{ML}$, harmonic ratio in the medio-lateral direction; B, unstandardized coefficients of regression; b: standardized coefficients; SE: standard error.

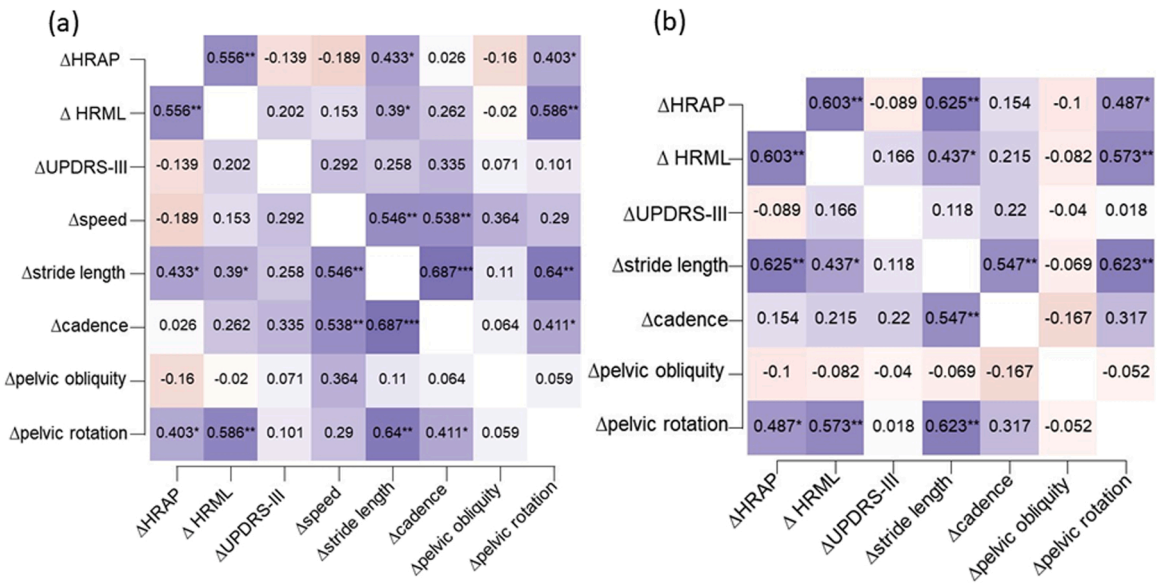


**Fig. 1.** a) Spearman's correlation coefficients between the improvements in gait parameters; b) Partial Spearman's correlation coefficients excluding the effects of the improvements in gait speed.

### 3.3. Correlation findings

Fig. 1 summarizes the results of the correlation analyses. $\Delta HR_{AP}$ correlated with $\Delta HR_{ML}$, and both were positively correlated with Δstride length and Δpelvic rotation, regardless of Δgait speed.

### 3.4. External responsiveness findings

Assuming the normalization of the gait stability indexes as anchor, $HR_{AP}$, $HR_{ML}$, stride length, and pelvic rotation revealed good-to-optimal responsiveness to rehabilitation (Table 3). Eight (38 %) and 6 (28 %) pwPD normalized their $HR_{AP}$ and $HR_{ML}$ values at T1, respectively. At the analysis of MCID, $\Delta HR_{AP} \geq 21.47$ %, $\Delta HR_{ML} \geq 11.31$ %, Δstride length $\geq 10.09$ %, and Δpelvic rotation $\geq 8.59$ % were needed to normalize $HR_{AP}$ with 95 %, 88 %, 74 %, and 81 % probability, respectively (Table 3). $\Delta HR_{ML} \geq 36.94$ %, $\Delta HR_{AP} \geq 16.79$ %, Δstride length $\geq 22.67$ %, and Δpelvic rotation $\geq 37.67$ %, were needed to normalize $HR_{ML}$ with 92 %, 71 %, 73 %, and 90 % probability, respectively (Table 3).

## 4. Discussion

The purpose of this study was to evaluate the responsiveness of four trunk-acceleration-derived gait stability indexes in a sample of pwPD with mild-to-moderate disability (HY = 3), by determining the magnitude of their modification and quantifying the minimal improvements required to approach HS values after a rehabilitation program. We also aimed to identify the baseline predictors of improvement of the gait stability indexes, as well as to identify the correlations between Δstability indexes and Δclinical and kinematic gait variables.

We found that the $HR_{AP}$ and the $HR_{ML}$, two measures of smoothness of the trunk acceleration patterns in the antero-posterior and medio-lateral planes, respectively, can significantly improve up to normative values after rehabilitation (Fig. 2, Table 1), with medium-to-high internal ($0.52 > d < 0.82$, Table 1), and optimal external ($0.87 > AUCs < 0.90$, Table 3) responsiveness. Improvements in $HR_{AP}$ and $HR_{ML}$ of at least 21.5 %, and 36.9 %, respectively, resulted in the normalization of the smoothness of trunk while walking. By measuring the smoothness of trunk acceleration patterns during walking, the HRs mirrors the ability to coordinate trunk and lower extremity mechanics [11]. These parameters reflect the appearance of postural instability, possibly leading to falls and correlating with axial rigidity in pwPD [12]. A previous study [12] showed that HRs were accurate and speed-independent markers of gait alteration in pwPD at HY = 3. Expanding on those findings, the present study allows to consider the $HR_{AP}$ and $HR_{ML}$ as the most suitable outcome measures, among the trunk-acceleration-derived gait stability indexes, for the assessment of the level of gait instability and for assessing the effectiveness of the gait rehabilitation of pwPD at HY = 3.

Our results are consistent with previous studies reporting the $HR_{AP}$ and the $HR_{ML}$ to significantly improve after rehabilitation [31,34]. Lowry et al. [35] showed that internal cognitive and verbal amplitude-based cueing aiming to increase stride length is effective in

**Table 3**
External responsiveness and minimal clinically important differences (MCID) analysis of normalized parameters.

| Criterion | | AUC (95 % CI) | MCID | Se (95 % CI) | Sp (95 % CI) | LR+ | LR- | PTP+ | PTP- |
|---|---|---|---|---|---|---|---|---|---|
| $HR_{AP}$ normalization | $\Delta HR_{AP}$ | 0.87 (0.52–0.97) | ≥ 21.47 % | 0.66 (0.22–0.98) | 0.92 (0.64–0.98) | 8.67 | 0.36 | 95 % | 42 % |
| | $\Delta HR_{ML}$ | 0.84 (0.53–0.95) | ≥ 11.31 % | 0.83 (0.36–0.99) | 0.77 (0.46–0.94) | 3.61 | 0.21 | 88 % | 30 % |
| | Δstride length | 0.63 (0.42–0.78) | ≥ 10.09 % | 0.87 (0.47–0.93) | 0.59 (0.21–0.80) | 1.37 | 0.21 | 74 % | 34 % |
| | Δpelvic rotation | 0.70 (0.50–0.83) | ≥ 8.59 % | 0.87 (0.47–0.99) | 0.58 (0.28–0.85) | 2.10 | 0.21 | 81 % | 30 % |
| $HR_{ML}$ normalization | $\Delta HR_{ML}$ | 0.90 (0.64–0.97) | ≥ 36.94 % | 0.60 (0.14–0.95) | 0.94 (0.70–0.99) | 9.60 | 0.42 | 92 % | 33 % |
| | $\Delta HR_{AP}$ | 0.74 (0.42–0.89) | ≥ 16.79 % | 0.80 (0.28–0.99) | 0.62 (0.35–0.85) | 2.13 | 0.32 | 71 % | 27 % |
| | Δstride length | 0.76 (0.44–0.90) | ≥ 22.67 % | 0.66 (0.27–0.96) | 0.71 (0.42–0.92) | 2.33 | 0.46 | 73 % | 35 % |
| | Δpelvic rotation | 0.81 (0.43) | ≥ 37.67 % | 0.60 (0.14–0.95) | 0.94 (0.70–0.99) | 7.50 | 0.38 | 90 % | 38 % |

Δ, difference between T1 and T0 values; HRAP, harmonic ratio in the antero-posterior direction; HRML, harmonic ratio in the medio-lateral direction; AUC, area under the receiver operating characteristics curve; CI, confidence interval; MCID, minimal clinically important difference; Se, sensitivity; Sp, specificity; LR+ , positive likelihood ratio; LR-, negative likelihood ratio; PTP+ , positive post-test probability; PTP-, negative post-test probability.

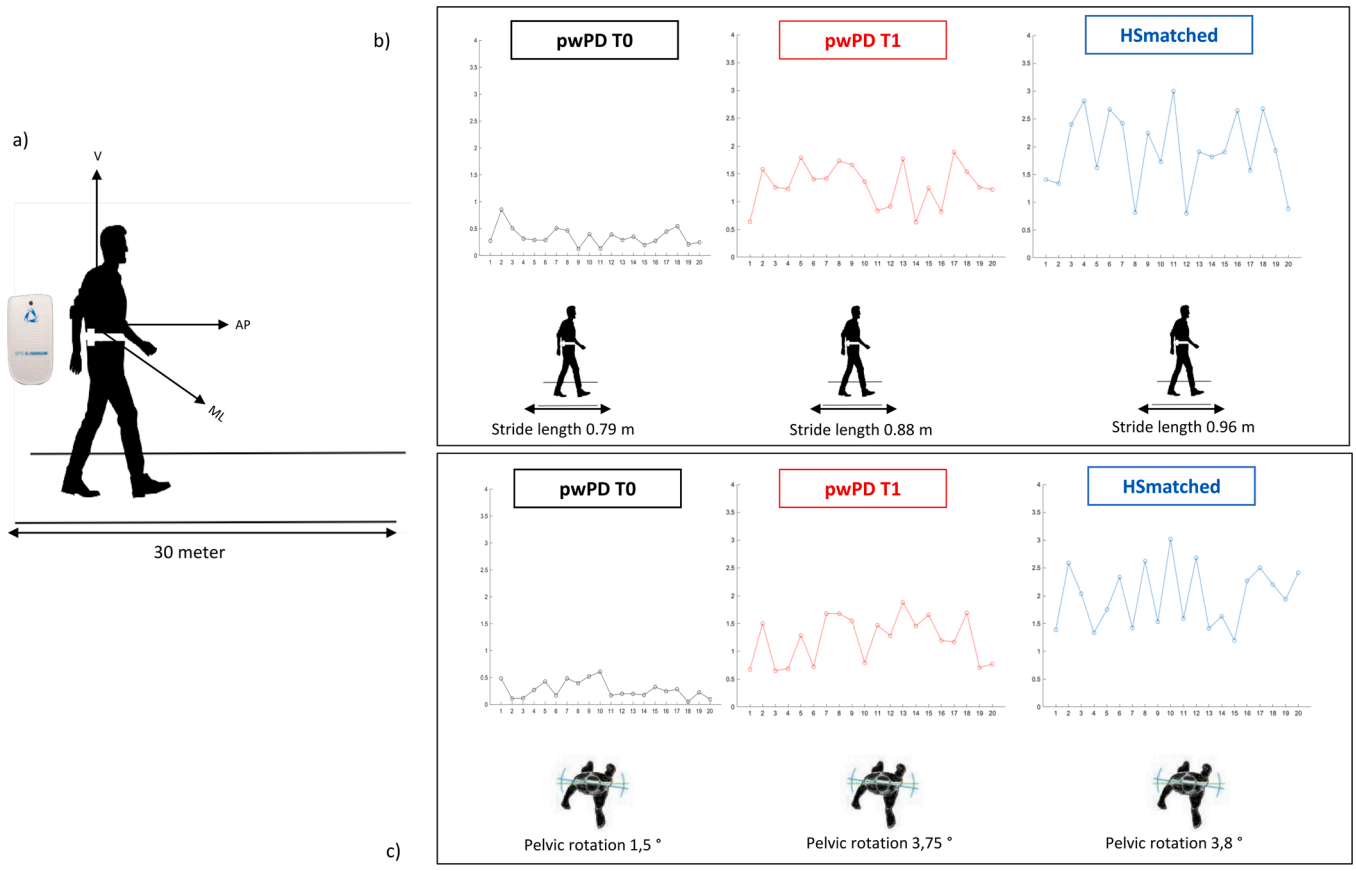


**Fig. 2.** a) graphical representation of the acquisition procedure; b) graphical representation of the Harmonic Ratios in the antero-posterior directions of a representative age-and-speed-matched healthy subject (blue) and a subject with PD at Hoehn and Yahr stage = 3 at baseline evaluation (black) and after rehabilitation (red). Stride length values of the healthy subject and the subject with PD at baseline and after rehabilitation and are reported. C) graphical representation of the Harmonic Ratios in the medio-lateral direction of a representative age-and-speed-matched healthy subject (blue) and a subject with PD at Hoehn and Yahr stage = 3 at baseline evaluation (black) and after rehabilitation (red). The pelvic rotation values of the healthy subject and the subject with PD at baseline and after rehabilitation and are reported.

improving HRs. Because Δstride length correlated with ΔHRs in our study, it is possible to argue that the HRs are responsive to exercises aimed at improving stride length, such as lower limb stretching exercises and visual cueing gait exercises [2]. Noteworthy, Lowry et al. (2010) found that cueing exercises alone were not effective in improving HRs in subjects at HY = 3. The gait alteration of pwPD at HY= 3 is characterized by a decreased trunk rotation during walking [15], which has proven to be an effective and responsive outcome measure in pwPD [14]. In our study, we found that pelvic rotation values improved up to normative values after rehabilitation and that improvements in HRs were predicted by pelvic rotation values at baseline (Table 2) and were related to both Δstride length and Δpelvic rotation (Fig. 1), with Δpelvic rotation ≥ 8.59 % and ≥ 37.67 % leading to the normalization of $HR_{AP}$ and $HR_{ML}$ with 81 % and 90 % probability, respectively (Table 3). As a result, consistent with other studies reporting the beneficial effects of trunk-focused exercises on HRs [31] and kinematic gait parameters [2], it is conceivable that HRs are responsive to exercises aimed at improving both trunk and pelvic mobility, with the latter enhancing the impact of stride length improvements. However, these hypotheses deserve to be confirmed by further clinical trials investigating the effects of specific rehabilitation exercises on each responsive target variable.

$RQA_{detAP}$ and step length CV did not show significant modifications after the rehabilitation period.

To the best of our knowledge, this is the first study to assess the responsiveness to rehabilitation of RQA, and our results do not allow it to be considered as an outcome measure in rehabilitation trials and clinical contexts.

Previous studies found no improvements in step length CV during gait tasks when different methods of external [35,36] or internal [37,38] cueing were used. In our study, subjects were only administered external cueing during the gait rehabilitation exercises. Because internal cueing, such as singing, showed to reduce step length variability [37], we cannot exclude that stride length variability may be responsive to gait rehabilitation exercises other than external cueing. Further studies are needed to address this issue.

Although we found a correlation between ΔUPDRS-III and Δcadence after rehabilitation (Fig. 1), ΔUPDRS-III did not correlate with ΔHRs. Considering that the comprehensive evaluation of UPDRS-III included a variety of symptoms other than gait impairment and that the adequacy of its content validity for assessing gait impairment is debated [4], the lack of correlation with the improvements in gait-oriented measures is reasonable [39].

In conclusion, when assessing the effectiveness of rehabilitation on the trunk smoothness during gait using a single lumbar-mounted IMU, $HR_{AP}$ and $HR_{ML}$ can be considered as responsive speed-independent outcome measures. In this study, we also identified: i) the baseline predictors of improvement of HRs; and ii) the kinematic and spatio-temporal improvements correlated with the normalization of the trunk-acceleration derived gait stability indexes, providing predictive thresholds and MCIDs. The findings of this study could provide engineers and clinicians with useful information for optimizing gait analysis software and designing personalized rehabilitative interventions based on the individual features of the patients.

This study presents some limitations. Although the small sample size

was adequate to detect the improvements in HRs, it may have limited the interpretation of the external responsiveness results. To overcome this limitation and improve the generalizability of the results, we used the pre-test probabilities from a larger sample to calculate the probability to normalize HRs at the MCIDs [12,40]. Furthermore, because we wanted to avoid potential bias in the interpretation of the results due to symptoms other than PD, we excluded subjects with neuropsychiatric and cognitive symptoms, freezing of gait, orthopedic and peripheral conditions. Therefore, we cannot extend the results on the responsiveness of the HRs to pwPD who present the aforementioned symptoms.

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## CRediT authorship contribution statement

**Stefano Filippo Castiglia:** Writing – original draft, Conceptualization, Data curation, Formal analysis. **Dante Trabassi:** Conceptualization, Data curation, Formal analysis. **Roberto De Icco:** writing – review & editing, Investigation. **Antonella Tatarelli:** Data curation, Investigation. **Micol Avenali:** Data curation, Investigation. **Michele Corrado:** Data curation, Investigation. **Valentina Grillo:** Data curation, Investigation. **Gianluca Coppola:** writing – review & editing, Investigation. **Alessandro Denaro:** Resources, investigation. **Cristina Tassorelli:** Writing – review & editing, Resources, Conceptualization, Supervision. **Mariano Serrao:** Writing – original draft, Conceptualization, Investigation, Resources, Supervision.

## Conflict of interest statement

The authors declare no conflicts of interest.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gaitpost.2022.07.235.

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