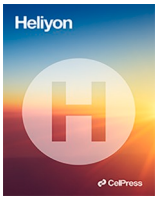
Heliyon 10 (2024) e23740

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



# Gait initiation in Parkinson's disease: comparison of timing and displacement during anticipatory postural adjustments as a function of motor severity and apathy in a large cohort

Ségolène De Waele [a,b,*], Ann Hallemans [c], Emke Maréchal [b,d], Patrick Cras [a,b], David Crosiers [a,b,**]

[a] Translational Neurosciences, Born-Bunge Institute, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[b] Antwerp University Hospital, Department of Neurology, Antwerp, Belgium
[c] Research group MOVANT (Movement Antwerp), Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[d] ZNA Middelheim Hospital, Department of Neurology, Antwerp, Belgium

ARTICLE INFO

*Keywords:*
Parkinson's disease
Gait initiation
Anticipatory postural adjustments
Apathy
Force plate
Gait analysis
Cueing

ABSTRACT

*Introduction:* Gait initiation is preceded by three anticipatory postural adjustment (APA) phases. In Parkinson's disease (PD) generated force, displacement and timing during APA differ from healthy controls. APA might be influenced by disease status, weight or emotion. It is unknown how motor severity, disease duration or presence of apathy influences APA timing and displacement.

*Methods:* We included 99 people with PD and 50 healthy controls (HC) to perform five gait initiation trials following an auditory cue. Force plates measured timing and center of pressure (CoP) displacement during APA phases.

*Results:* Time to gait initiation (tGI) was higher in the PD group ($p < 0.001$, $t = 2.74$, 95%CI (0.008, 0.066)). The first two APA phases (APA1 and APA2a) lasted longer in PD (respectively $p < 0.001$, $t = 3.87$, 95%CI (0.091, 0.28) and $p < 0.001$, $t = 4.1$, 95%CI (0.031, 0.091)). Mean CoP displacement, variability in timing and displacement did not differ. A multiple regression model was used to determine if clinical variables were related to gait initiation parameters. tGI was predicted by age ($p < 0.001$) and weight ($p = 0.005$). The duration of APA1 was predicted by weight ($p = 0.006$) and APA2a by age ($p < 0.001$). Variability in duration of the locomotor phase (LOC) was predicted by age ($p < 0.001$).

*Conclusion:* tGI and initial APA phases are longer in PD than in HC. There are no significant differences in variability of timing or displacement between the two groups. Gait initiation parameters are independent of disease duration, motor severity, medication usage or apathy in PD. Our findings suggest that cueing does not speed up gait initiation but reduces variability.

* Corresponding author. Drie Eikenstraat 655, 2650 Edegem, Belgium.
** Corresponding author. Drie Eikenstraat 655, 2650 Edegem, Belgium.
*E-mail addresses:* segolene.dewaele@uantwerpen.be (S. De Waele), david.crosiers@uantwerpen.be (D. Crosiers).

https://doi.org/10.1016/j.heliyon.2023.e23740
Received 26 June 2023; Received in revised form 14 October 2023; Accepted 12 December 2023
Available online 20 December 2023

## 1. Introduction

Gait initiation is the transition from quiet stance to locomotion, a challenging task for people with Parkinson's disease (PD). The shift from a bipedal to unipedal stance requires the subject to shift their center of mass (CoM) to allow for release of the swing foot [1]. The position of the CoM can be controlled by shifting the center of pressure (CoP). The CoP is the vertical projection of the CoM and the average point where the CoM exerts its force. The CoP can be moved along the antero-posterior (AP) axis through ankle musculature and along the mediolateral (ML) axis through hip musculature control. By shifting the CoP, the position of the CoM can be adapted to free up one foot, allowing for forward motion [2–4]. CoP changes in gait initiation follow a predetermined pattern of displacement that represent the anticipatory postural adjustments (APA) [5,6]. Three APA phases can be distinguished; first the CoP is shifted laterally and posteriorly towards the heel of the swing foot (APA1) to start unloading this foot. Unloading is completed by shifting the CoP medially and anteriorly (APA2a) and loading of the stance foot, the CoP shifts laterally and posteriorly (APA2b). In the final phase, the CoP is shifted along the AP axis towards the front of the stance foot allowing for stance foot release. This is commonly referred to as the locomotor phase (LOC) [7,8]. This pattern is generated before gait initiation, yet it is not a prerequisite thereof. Absence or incomplete APA has been noted in healthy individuals of all ages [7]. Other factors such as age and weight influence CoP displacement and duration of APA [9–11]. CoP displacement is reduced in overweight individuals and decreases with age [1,11].

Similarly to healthy controls (HC), people with PD generate a four-part APA pattern [7,10,12]. The main differences lie within the generated force and duration of the APA and displacement of CoP prior to the first step. Amplitude of APA and their duration is longer and more variable in PD [13–15]. The LOC phase elongation is correlated with the Hoehn and Yahr stage [16]. The displacement of the CoP is decreased and more variable in those with a history of Freezing of Gait (FoG) especially [17]. Large cohorts in-between patients however are lacking; most comparisons have been made to HC of similar ages.

Features which may improve gait initiation are medication usage and cueing [9,10,12,18]. Levodopa administration improves backwards CoP displacement and shortens APA duration [9,10]. Use of auditory cueing improved amplitude and sped up APA phases [12,18]. A single auditory cue can improve generation of APA phases themselves, with fewer trials displaying absence of APA [12]. The emotional state of a subject influences gait initiation as well [19]. In PD, pleasant visual stimuli lead to improved backwards CoP displacement and shorter APA duration [20].

There is ample evidence of the detrimental effect of anxiety and cognitive decline on gait in people with PD [21,22]. Apathy, or a decreased emotional experience, is a frequent neuropsychiatric symptom in PD, linked to worse motor symptoms, increased postural instability and higher risk for motor complications [23,24]. Apathy is often overlooked in PD, and falsely attributed to cognitive decline or depression [25]. Despite its importance, its effect on gait and gait initiation specifically has not yet been examined [26].

We aimed to determine whether gait initiation in PD differed between apathetic and non-apathetic patients. We hypothesized that apathetic patients would be slower to initiate gait following an auditory cue, and would show increased duration of APA phases and decreased displacement. Our secondary aim was to determine which disease parameters (such as motor severity, medication dosage, disease duration and age) influenced duration and displacement of APA, such as motor severity, medication dosage, disease duration and age.

## 2. Methods

### 2.1. Participants

A power analysis (alfa 0.05 and effect size 0.8) using G × Power version 3.1 showed that in total 128 patients would be needed to determine whether apathetic or non-apathetic people with PD would differ in terms of time to gait initiation following a verbal cue. Inclusion was planned to start in March 2020 but was halted due to the covid-19 pandemic. Due to time constraints we only included 99 patients in the end. Patients were recruited through the outpatient clinics of the Antwerp University Hospital of Antwerp and ZNA Middelheim Hospital in Antwerp between June 1, 2020 and December 31, 2021. All people with PD who were fluent in Dutch and could walk unassisted for at least 10 min were asked to participate. Patients suffering from other neurological or orthopedic morbidities affecting their gait were excluded. Patients were included if they had clinically confirmed or probable PD according to the Movement Disorders Society (MDS) Clinical Diagnostic Criteria [27]. Patients were encouraged to follow their usual dopaminergic medication schedule so they were in 'ON' state during examination. If due to a fluctuation an OFF state occurred, data collection was halted until the patient reached an acceptable ON state. We recorded the patients' main demographic variables, i.e. age, sex, date of diagnosis and current medication. Participants were asked to fill out the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II and Non-Motor Symptoms Questionnaire (NMSQuest) independently [28]. MDS-UPDRS parts I and IV were filled out by the investigator during a patient interview. Motor symptoms were assessed using the MDS-UPDRS part III by the same investigator.

Dopaminergic medication was converted to the Levodopa Equivalent Daily Dosage (LEDD) before analysis. Cognitive status was assessed using the Montreal Cognitive Assessment Scale (MoCA). Presence of apathy was determined using the Lille Apathy Rating Scale (LARS), a 33-item questionnaire validated for use in PD. Scores of −21 or above are indicative of apathy [29].

HC were recruited from patients' partners and families, patient organizations and through flyers at our outpatient clinic. Only HC without neurological disorders or orthopedic morbidities affecting their gait were asked to participate. In total 51 H C agreed to participate. For both people with PD and HC, height and weight were measured.

Due to technical difficulties, force plate data on 13 patients and 1 H C was not registered during the trials. This issue became evident during data processing. These 14 participants were contacted and 3 patients agreed to retake the trial. One patient was later excluded

due to a diagnosis of multiple system atrophy during follow-up. In total, data on 88 PD patients and 50 H C was collected.

### 2.2. Gait analysis protocol

Participants were instructed to stand on a force plate (0.4 × 0.5 m, 1000 Hz, ATMI type OR 6–7, Advanced Medical Technology inc., Massachusetts, USA) in a comfortable, upright position. They were allowed to choose how to position their feet. Participants were instructed to start walking at a self-selected walking speed as soon as they received the 'Go' audio cue. Participants were allowed to hear the auditory cue once before starting the trial. In total five trials were performed per patient. Data from the force plate platform was collected through the Nexus software (version 2.8, Vicon, Oxford, UK).

### 2.3. Data processing

Raw force plate data (Fx, Fy, Fz, Mx, My, Mz) were exported to MATLAB version R2021a for further processing (See appendix for code). CoP trajectories along the AP and mediolateral (ML) axis were calculated from the raw force plate data according to formula [1, 2] and where then low-pass filtered to eliminate noise using a second order zero phase-shift Butterworth filter with a cut-off frequency of 12 Hz.

$$COPml = -\left(\frac{(My + (c_1 * Fx))}{Fz}\right) + a_1\ ; \quad [1]$$

$$COPap = \left(\frac{(Mx - (c_1 * Fy))}{Fz}\right) + b_1\ ; \quad [2]$$

where (Fx, Fy, Fz) reflect the forces along the mediolateral, anteroposterior and vertical axis; (Mx, My) reflect the moments of force around the mediolateral and anteroposterior axis; (a1, b1, c1) are the coordinates of the center of the force platform.

The filtered CoPap data were used to determine five time points (Fig. 1): 1) initial CoP position at the instance of the auditory cue (*origin*), 2) minimum posterior position of the CoP on the side of the swing leg (*first minimum*), 3) maximum anterior position of the CoP reflecting the shift from the swing leg to the stance leg (*first maximum*), 4) minimum posterior position of the CoP on the side of the stance leg (*second minimum*) and 5) final CoP position when both feet leave the force platform (*end*). Timepoints were automatically detected in MATLAB using the *findpeaks* function and visually checked by the same researcher. Graphs were evaluated and discernible peaks in the correct direction were considered as APA. In some cases, peaks could not be discerned because of inadequate force generation. Trials in which not all peaks could be discerned were not included in the final analysis.

These five time points were used to distinguish four APA phases: APA1, APA2a, APA2b and LOC. Each phase as shown along the AP axis in time is displayed in Fig. 1 [8]. For each of those four phases both the duration (s) of each phase (*tAPA1, tAPA2a, tAPA2b and*

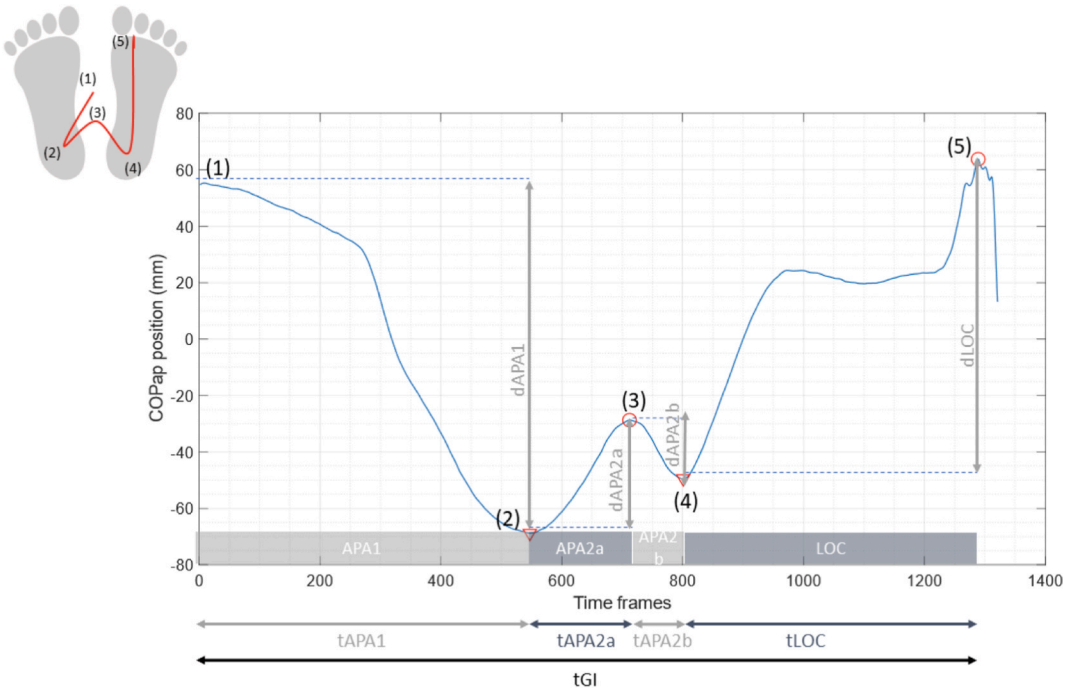



**Fig. 1.** CoP shifts along AP axis during gait initiation.

*tLOC*) and displacement of the COPap (mm) during this phase (*dAPA1, dAPA2a, dAPA2b and dLOC*) was calculated. Additionally, the total time to gait initiation (*tGI*) was calculated as the time difference between *end* and *origin*.

### 2.4. Data analysis

Mean value of all variables were calculated per participant over available trials. In three PD and one HC all three APA could be distinguished in only one trial. In one PD and two HC, no APA or more than three APA could be distinguished. The three APA phases could not be identified in these trials and were excluded from analysis. Therefore, only the variable tGI was retained for analysis for these participants.

We calculated the coefficient of variance (CV) per outcome variable per patient to evaluate within-subject variability [17]. The mean of all CV values of all participants were used to compare PD and HC participants. The tables below present continuous variables as the mean and standard deviation (SD). A Kendall Tau correlation was used to correlate the number of trials excluded with disease variables. Normality was assessed using the Shapiro-Wilk test, kurtosis and skewness values, and visual inspection of the histogram and Q-Q plots. Comparison of the mean of continuous variables between people with PD and HC group was made using the independent student t-test and the Chi-square test for the difference in male-to-female distribution. Bonferroni correction was applied when comparing gait initiation variables (see Supplementary Tables 1 and 2) between the PD and HC group.

A multiple linear regression analysis was used to determine whether LARS scores impacted gait initiation variables. This model allowed us to correct for clinical parameters such as weight, disease duration, age, MDS-UPDRS-II score and LEDD. Assumptions were tested using the Shapiro-Wilk test, visual inspection of the scatter plot for linearity and homoscedasticity. Multicollinearity was assessed by evaluation of the tolerance values ($>0.1$) and VIF ($<10$). Variables were transformed when necessary to fit assumptions. Outliers were detected using the standardized residuals. Cases with residuals above 3 and a Cook's distance larger than 4 were excluded from analysis.

Missing data were excluded from analysis. Data on height and weight was missing in one patient, as well as NMS-Quest score and LEDD in two patients. One patient failed to complete the UPDRS-II completely.

Statistical analyses were performed using SPSS version 26.0 (© IBM) A *P*-value less than 0.05 was considered statistically significant.

## 3. Results

1. APA pattern

Many participants were unable to generate a correct APA pattern during gait initiation. In total 52 PD and 36 H C could generate a correct APA pattern in all five trials. This distribution is equal between groups ($p = 0.087$, $\chi^2 = 2.92$). The number of trials excluded in the PD group was not correlated to age ($\tau_b = 0.158$, $p = 0.053$), weight ($\tau_b = 0.078$, $p = 0.336$), disease duration ($\tau_b = 0.063$, $p = 0.436$), MDS-UPDRS-III score ($\tau_b = 0.-0.05$, $p = 0.535$), LEDD ($\tau_b = 0.085$, $p = 0.299$) or LARS score ($\tau_b = 0.-0.063$, $p = 0.44$).

2. Comparison of PD and HC

In total data on 88 people with PD and 50 H C was evaluated. See Table 1 for the sample description. People with PD were on average 67.2 ± 10.6 years old and had a mean disease duration of 7.9 ± 4.9 years. Age did not differ significantly from the HC (mean age of 65.9 ± 6.7, $p = 0.48$). There were significantly more female participants in the HC group ($p < 0.001$). PD and HC differed significantly in terms of weight ($p = 0.003$, $t = 3.02$, 95%CI (2.7, 13.2). Both groups were similar in terms of age ($p = 0.48$, $t = 0.71$, 95%CI (−2.1, 4.5)) and height ($p = 0.062$, $t = 2.01$, 95%CI (−0.154, 6.46)). In the PD group, 65.9 % reported no history of FoG (n = 58) and 84.1 % (n = 74) reported no falls or near-falls in the last month. In those with FoG the majority reported mild problems (n =

**Table 1**
Descriptive clinical variables of PD patients versus HC.

| | PD (n = 88) | HC (n = 50) | *P*-value |
|---|---|---|---|
| Age (years) | 67.2 (10.6) | 65.9 (6.7) | 0.48 |
| Male/female | 68/20 | 21/29 | **< 0.001** |
| Weight (kg) | 79.9 (15.6) | 71.9 (14.4) | **0.003** |
| Height (cm) | 170.1 (10.2) | 166.9 (7.9) | 0.062 |
| MDS-UPDRS-III score | 28.3 (12.4) | | |
| Disease duration (years) | 7.9 (4.9) | | |
| LEDD (mg) | 791.5 (546.8) | | |
| MoCa | 26.6 (3.05) | | |
| NMSQuest | 8.81 (4.2) | | |
| LARS | −19.4 (7.9) | | |

Variables are displayed as mean (SD). Significant p-values are shown in bold. Abbreviations: MDS-Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III), Levodopa Equivalent Daily Dosage (LEDD), Non-Motor Symptoms Questionnaire (NMSQuest), Lille Apathy Rating Scale (LARS).

25). Only four patients indicated experiencing moderate FoG.

Fig. 2 compares gait initiation variables between PD and HC groups. tGI was higher in the PD group ($p < 0.000$, $t = 2.74$, 95%CI (0.008, 0.066)). Both APA1 and APA2a lasted longer in the PD group as well (respectively $p < 0.000$, $t = 3.87$, 95%CI (0.091, 0.28) and $p < 0.001$, $t = 4.1$, 95%CI (0.031, 0.091)). The mean CoP displacement differed only in the APA2a phase; displacement was higher in the PD group though did not reach significance after Bonferroni correction ($p = 0.025$, $t = 2.26$, 95%CI (2.34, 34.7)). The variability in timing and displacement of APA phases did not reach significance in-between groups. Tables containing all mean values per variable are included in Supplementary Tables 1–3.

3. Linear regression analysis

Multiple linear regression was used to test if the LARS score could predict mean and variability of timing and displacement during different APA phases. We corrected for age, weight, disease duration, motor severity and LEDD. In Table 2 results of the regression analyses are displayed. Only the models for tGI ($R^2 = 0.22$, $F(6, 78) = 3.57$, $p = 0.004$), tAPA1 ($R^2 = 0.22$, $F(6, 78) = 3.66$, $p = 0.003$), tAPA2a ($R^2 = 0.223$, $F(6, 78) = 3.73$, $p = 0.003$), CVtLOC ($R^2 = 0.199$, $F(6,73) = 3.02$, $p = 0.011$) and CVdAPA2a ($R^2 = 0.197$, $F(6, 72) = 2.95$, $p = 0.013$), were statistically significant. These variables were predicted by age ($p < 0.001$ and $p < 0.001$ for tAPA2a and CVtLOC respectively) and weight ($p = 0.005$ and $p = 0.006$ for tGI and tAPA1 respectively). The corresponding B values are displayed in Table 2. The overall model for CVdAPA2b was significant but no separate variables contributed significantly.

## 4. Discussion

To our knowledge, this study is the first to report on gait initiation changes in a large PD cohort. Overall, people with PD take longer to initiate gait following a verbal cue and have an increased duration of APA1 and APA2a compared to healthy controls. Timing of other phases and variability of timing did not differ between PD and healthy controls. The displacement and variability of displacement during APA phases was similar between PD and HC. In the PD group, only weight was a significant predictor of tGI and tAPA1, and increasing age of tAPA2a and CVtLOC. Disease duration, MDS-UPDRS-III and LEDD were not associated with mean or variability of timing or CoP displacement of the APA phases. No link was found between LARS scores and gait parameters.

### 4.1. Performance compared to healthy controls

The prolonged duration of overall gait initiation in people with PD is in line with current literature [14,15]. In our cohort,

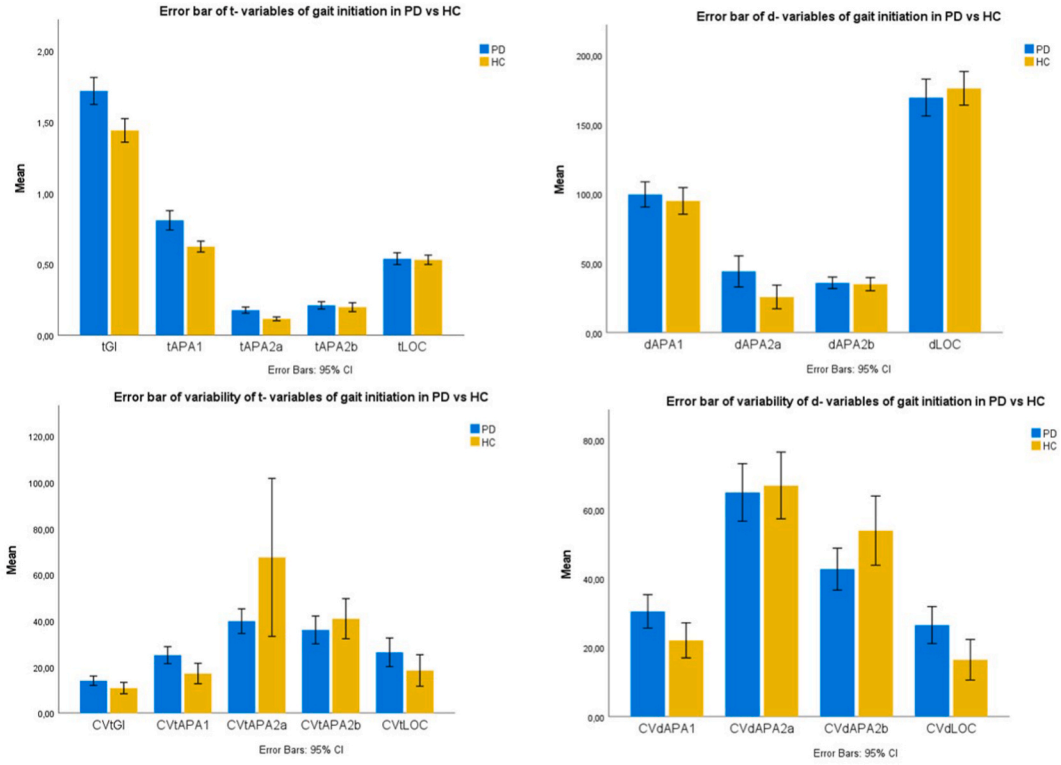



**Fig. 2.** Error bars of mean and CV of all GI variables.

**Table 2**
Results of linear regression analysis.

| Variable | Age | Weight | Disease duration | MDS-UPDRS-III | LEDD | LARS | Model |
|---|---|---|---|---|---|---|---|
| tGI | 0.012 | **0.009**** | −0.001 | 0.006 | 0.008 | −0.007 | $R^2 = 0.215$ p = **0.004** |
| tAPA1 | 0.009 | **0.006**** | −0.001 | 0.006 | 0.004 | 0.004 | $R^2 = 0.220$ p = **0.003** |
| tAPA2a | **0.004***** | 0.001 | <0.000 | <0.000 | 0.003 | −0.005 | $R^2 = 0.223$ p = **0.003** |
| tAPA2b | 0.002 | 0.001 | <0.000 | <0.000 | 0.001 | −0.011 | $R^2 = 0.056$ p = 0.598 |
| tLOC | **−0.001*** | 0.002 | **−0.001*** | <0.000 | <0.000 | −0.001 | $R^2 = 0.088$ p = 0.287 |
| CVtGI | 0.091 | −0.011 | −0.026 | 0.052 | 0.001 | 0.245 | $R^2 = 0.095$ p = 0.254 |
| CVtAPA1 | 0.273 | 0.207 | −0.053 | 0.221 | 0.004 | −0.056 | $R^2 = 0.319$ P = 0.236 |
| CVtAPA2a | 0.302 | −0.152 | 0.045 | 0.132 | 0.004 | 0.051 | $R^2 = 0.260$ p = 0.511 |
| CVtAPA2b | −0.113 | −0.011 | 0.041 | 0.308 | 0.001 | −0.149 | $R^2 = 0.175$ p = 0.887 |
| CVtLOC | **1.125***** | 0.414 | −0.01 | 0.149 | 0.008 | −0.164 | $R^2 = 0.446$ p = **0.011** |
| dAPA1 | 0.653 | −0.004 | 0.009 | 0.166 | 0.008 | 0.330 | $R^2 = 0.226$ p = 0.659 |
| dAPA2a | **1.572*** | 0.04 | 0.057 | 0.162 | 0.017 | −0.036 | $R^2 = 0.362$ p = 0.082 |
| dAPA2b | 0.102 | 0.073 | 0.005 | −0.068 | 0.004 | −0.214 | $R^2 = 0.151$ p = 0.934 |
| dLOC | −0.338 | −0.001 | −0.128 | −0.872 | 0.014 | 0.768 | $R^2 = 0.236$ p = 0.6 |
| CVdAPA1 | 0.163 | 0.0 | 0.022 | **0.51*** | 0.086 | −3.738 | $R^2 = 0.109$ p = 0.192 |
| CVdAPA2a | 0.609 | −0.458 | −0.016 | 0.726 | 0.3 | −0.192 | $R^2 = 0.197$ p = **0.013** |
| CVdAPA2b | −0.075 | −0.035 | −0.022 | 0.173 | −0.002 | 0.872 | $R^2 = 0.072$ p = 0.467 |
| CVdLOC | **0.782**** | 0.2 | −0.013 | 0.424 | 0.005 | −0.074 | $R^2 = 0.147$ p = 0.063 |

Note: Significant B values are displayed in bold, *p < 0.05, **p < 0.01, ***p < 0.001.
The prefix 't-' refers to duration of a phase in seconds, 'd-' to displacement during a phase in mm and 'CV-' to the variability of a variable.
Abbreviations: Time to gait initiation (tGI), anticipatory postural adjustment (APA) and LOC (locomotor phase).

unloading of the swing foot (APA1 and APA2a) was prolonged. Unloading of the stance foot (APA2b and LOC) was similar to HC however. Gantchev and colleagues reached a similar conclusion; the postural phase was elongated in their cohort [14]. Elongation of APA2b and LOC has primarily been noted in patients with advanced disease, suffering from FoG [17]. Auditory cueing and medication use may decrease duration of APA phases to a certain extent; a ceiling effect is likely present however [12,18,30].

The mean displacement was not significantly lower in PD. This is a surprising finding, as current reports almost unanimously agree that displacement is reduced in PD [1,13,15,31]. Only in early stages of the disease, the differences to HC are not yet apparent [32,33]. Differences in displacement are partly reversed by dopaminergic treatment [10]. Our use of an auditory cue may have improved CoP displacement as well. However, Delval et al. did note an improved backwards CoP displacement following an auditory cue, but differences persisted between HC and people with PD [12]. A similar result was found in patients in OFF state [30]. Though in ON state using an auditory cue, lateral displacement of CoP during gait initiation in PD was very similar to those of HC in another cohort [10]. A few other possible explanations remain. Studies tend to recruit HC through community means. These elderly participants are often in good health and tend to volunteer more often [34]. We primarily recruited HC from the patients' families; their primary caregiver, sibling or spouse. Our cohort may be more representative of an elderly population. Displacements of CoP are known to decrease in aging [1]. Furthermore, our cohort is large and may better reflect the heterogeneity of the disease. The previously mentioned studies include much smaller sample sizes of patients. Lastly, at least five trials are necessary to accurately assess gait initiation [35]. The amount of trials performed per study vary, making generalization of results difficult as well.

Another discrepancy in our findings is the variability in duration and displacement, which differed little between PD and HC. Others report increased variability in timing in nearly all phases in people with PD [13,17]. It is possible that medication intake reduces variability in PD [9,10]. Variability in timing however persists even with adequate medication [13,17]. The use of cueing probably had the most significant impact on the variability.

Our findings suggest that cueing does not speed up gait initiation, but reduces variability, allowing for easier weight displacement during this process. This hypothesis however requires further examination, comparing both cueing and self-initiated gait initiation in people with PD, both in ON and OFF state.

### *4.2. Links to clinical parameters*

Our study is the first to compare gait initiation performance in PD as per disease duration and motor severity. Previous reports have compared gait initiation performance to healthy, age-related individuals. Timing and variability in timing of the different APA phases in PD was independent of disease duration, MDS-UPDRS-III or LEDD score. The main determinants of the duration of these phases were age (for tAPA2a) and weight (tGI and tAPA1). Age also determined variability in LOC timing. The link between increasing weight and longer tGI is present in healthy individuals [11]. Elongation of APA phases occurs in healthy aging as well [1]. We had expected that APA duration would steadily increase with disease burden or duration, however we could confirm no such link. Russo et al. found that the larger the UPDRS-III score, the smaller force generated along the ML axis. They however did not correct for clinical confounders [36]. To our knowledge, no other studies have reported on timing and displacement of APA in-between people with PD, with respect to the possible confounding nature of their clinical characteristics. Reports on patients compared to healthy controls found that timing of APA phases are similar in early stages of the disease, but more advanced patients have elongated APA1 and APA2a phases [14,32]. More variable timing of APA phases has been reported in people with PD suffering from FoG [13]. We however found no links between

increasing variability in timing and disease duration. It would prove interesting to further assess the differences between those with and without FoG in our cohort.

Our use of cueing probably had an important impact on our findings. A study by Delval and colleagues showed that auditory cueing was effective in increasing CoP displacement in PD. This effect was more prominent in those without FoG [12]. An additional factor that we did not explore, is generated force. People with PD generate less force when executing APA as compared to HC [10]. UPDRS-III scores are correlated to force generated during APA [36]. During data collection we noticed that many patients had difficulty generating APA, leading to exclusion of trials due to indistinguishable APA patterns. People with PD may either demonstrate a regular APA pattern, absence of APA or multiple APA [37]. Only trials with a regular APA pattern were considered for analysis. The number of participants with inadequate APA patterns was similar between PD and healthy controls. We found no associations between disease parameters and lack of APA pattern generation. Abnormal APA generation is more common in those with FoG [12]. It may prove interesting to further explore this in our cohort and to evaluate how it relates to other clinical parameters.

### *4.3. Links to apathy*

We found no association between the LARS score and gait initiation parameters. Apathetic patients have been reported to suffer more postural symptoms [23]. Due to posture-locomotion coupling, we hypothesized that these postural problems would translate into gait initiation difficulties [38]. Emotion affects gait in people with PD as well, and apathetic patients are slower to respond to cues during tasks [20,39]. We however found no difference in time to gait initiation. The supplementary motor area (SMA) is involved in APA generation and is a therapeutic target for apathy in PD [13,40]. The SMA is involved in self-generated movements and may be bypassed by the premotor cortex when responding to an auditory stimulus [10].

### *4.4. Limitations*

Our study has its limitations as well. Usage of an auditory cue affected our results, as demonstrated above. Using both cued and self-initiated gait would have been preferable. Our patient cohort was in ON state at time of examination. OFF state gait initiation difficulties are also more pronounced, and levodopa has been shown to improve gait initiation performance [9,10]. Furthermore, whilst our cohort was larger than previously reported, PD is a complex and highly variable disease. An even larger sample would be necessary to allow for proper compensation for disease heterogeneity. Recruitment of patients and execution of the gait analysis took place during spring 2020 till the end of 2021. Restrictions in the hospital due to the covid-19 pandemic slowed recruitment. Restrictions also had unforeseen mental health impacts, which possibly increased feelings of apathy in study participants.

Future research should focus on including large cohorts of ambulatory people with PD. Reported clinical variables should not be limited to motor severity and disease duration, but take into account the many factors influencing a patient's condition as we have aimed to. Experimental setup should ideally include both a cued and a self-initiated gait initiation to allow for comparison, as well as testing in both ON and OFF states. We suggest focusing on force generation and APA patterns in-between disease stages.

## 5. Conclusion

Overall duration of gait initiation following a verbal cue, as well as duration of APA1 and APA2a, are longer in people with PD compared to healthy controls. As opposed to previous reports, there are no differences in variability of timing, mean displacement or variability thereof between PD and healthy controls. Duration of APA phases and variability of displacement during these phases are independent of disease duration, motor severity, dopaminergic medication usage or apathy score in PD. Future research should focus on differences in force generated during APA phases and variability of APA patterns in PD in function of disease progression and motor severity.

## Ethical compliance statement

This study was approved by the University Hospital of Antwerp ethics committee on the March 18, 2020 with approval number B3002020000042. Written informed consent was obtained from all patients.

The first phase (APA1) consists of release of the swing foot with CoP displacement along the AP axis; from the origin (displayed as (1) above) to the first minimum (point (2)). APA2a reflects the displacement of CoP towards the middle of the base of support (from point 2 to 3) and APA2b the shift to the stance foot along the ML axis (from point 3 to 4). In the final phase, LOC, the CoP displaces towards the anterior part of the stance foot (from point 4 to 5). The prefix 't-' refers to duration of a phase in seconds and 'd-' to displacement during a phase in mm. Abbreviations: Time to gait initiation (tGI), anticipatory postural adjustment (APA), LOC (locomotor phase) and AP (anteroposterior).

Comparison between PD and HC patients. The prefix 't-' refers to duration of a phase in seconds, 'd-' to displacement during a phase in mm and 'CV-' to the variability of a variable. Abbreviations: Time to gait initiation (tGI), anticipatory postural adjustment (APA) and LOC (locomotor phase).

## Data availability statement

The data that support the findings of this study are available on request from the corresponding author, SDW. The data are not

publicly available due to the nature of the data which may reveal information that could compromise the privacy of research participants.

## CRediT authorship contribution statement

**Ségolène De Waele:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ann Hallemans:** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – review & editing. **Emke Maréchal:** Investigation, Writing – review & editing. **Patrick Cras:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **David Crosiers:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We would like to thank the patient support group 'Move for Parkinson' for their participation in the funding of this study as well all participants of this study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23740.

## References

[1] M. Martin, M. Shinberg, M. Kuchibhatla, L. Ray, J.J. Carollo, M.L. Schenkman, Gait initiation in community-dwelling adults with Parkinson disease, Phys. Ther. 82 (2002) 566–577, https://doi.org/10.1093/ptj/82.12.1264.
[2] D. Knudson, Fundamentals of Biomechanics, Springer US, Boston, MA, 2007, https://doi.org/10.1007/978-0-387-49312-1.
[3] D.A. Winter, Human balance and posture control during standing and walking, Gait Posture 3 (1995) 193–214, https://doi.org/10.1016/0014-5793(86)80927-9.
[4] E. Yiou, T. Caderby, A. Delafontaine, P. Fourcade, J.L. Honeine, Balance control during gait initiation: state-of-the-art and research perspectives, World J. Orthoped. 8 (2017) 815–828, https://doi.org/10.5312/wjo.v8.i11.815.
[5] P. Crenna, C. Frigo, A Motor Programme for the Initiation of Forward-Oriented Movements in Humans, 1991, https://doi.org/10.1113/jphysiol.1991.sp018616.
[6] S. Carlsöö, The initiation of walking, Cells Tissues Organs 65 (1966) 1–9, https://doi.org/10.1159/000142864.
[7] C. Lu, S.L. Amundsen Huffmaster, J.C. Harvey, C.D. MacKinnon, S.L. Amundsen, J.C. Harvey, C.D. MacKinnon, Gait & Posture Anticipatory postural adjustment patterns during gait initiation across the adult lifespan, Gait Posture 57 (2017) 182–187, https://doi.org/10.1016/j.gaitpost.2017.06.010.
[8] V. Cimolin, N. Cau, M. Galli, C. Santovito, G. Grugni, P. Capodaglio, Gait initiation and termination strategies in patients with Prader-Willi syndrome, J. NeuroEng. Rehabil. 14 (2017) 1–8, https://doi.org/10.1186/s12984-017-0257-7.
[9] L. Rocchi, L. Chiari, M. Mancini, P. Carlson-Kuhta, A. Gross, F.B. Horak, Step initiation in Parkinson's disease: influence of initial stance conditions, Neurosci. Lett. 406 (2006) 128–132, https://doi.org/10.1016/j.neulet.2006.07.027.
[10] A. Burleigh-Jacobs, F.B. Horak, J.G. Nutt, J.A. Obeso, Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers, Mov. Disord. 12 (1997) 206–215, https://doi.org/10.1002/mds.870120211.
[11] X. Qu, X. Hu, D. Tao, Gait initiation differences between overweight and normal weight individuals, Ergonomics 64 (2021) 995–1001, https://doi.org/10.1080/00140139.2021.1896788.
[12] A. Delval, C. Moreau, S. Bleuse, C. Tard, G. Ryckewaert, D. Devos, L. Defebvre, Auditory cueing of gait initiation in Parkinson's disease patients with freezing of gait, Clin. Neurophysiol. 125 (2014) 1675–1681, https://doi.org/10.1016/j.clinph.2013.12.101.
[13] J.V. Jacobs, J.S. Lou, J.A. Kraakevik, F.B. Horak, The supplementary motor area contributes to the timing of the anticipatory postural adjustment during step initiation in participants with and without Parkinson's disease, Neuroscience 164 (2009) 877–885, https://doi.org/10.1016/j.neuroscience.2009.08.002.
[14] N. Gantchev, F. Viallet, R. Aurenty, J. Massion, Impairment of posturo-kinetic co-ordination during initiation of forward oriented stepping movements in parkinsonian patients, Electroencephalogr. Clin. Neurophysiol. Electromyogr. Mot. Control 101 (1996) 110–120, https://doi.org/10.1016/0924-980X(95)00253-H.
[15] P. Crenna, C. Frigo, P. Giovanni, I. Piccolo, The Initiation of Gait in Parkinson's Disease, Academic Press Limited, 1990, https://doi.org/10.1016/b978-0-12-089445-1.50019-9.
[16] C.J. Hass, D.E. Waddell, R.P. Fleming, J.L. Juncos, R.J. Gregor, Gait initiation and dynamic balance control in Parkinson's disease, Arch. Phys. Med. Rehabil. 86 (2005) 2172–2176, https://doi.org/10.1016/j.apmr.2005.05.013.
[17] C.-C. Lin, R.A. Creath, M.W. Rogers, Variability of anticipatory postural adjustments during gait initiation in individuals with Parkinson disease, J. Neurol. Phys. Ther. 40 (2016) 40–46, https://doi.org/10.1097/NPT.0000000000000112.
[18] Y. Jiang, K.E. Norman, Effects of visual and auditory cues on gait initiation in people with Parkinson's disease, Clin. Rehabil. 20 (2006) 36–45, https://doi.org/10.1191/0269215506cr925oa.
[19] S.A. Coombes, C.M. Janelle, A.R. Duley, Emotion and motor control: Movement attributes following affective picture processing, J. Mot. Behav. 37 (2005) 425–436, https://doi.org/10.3200/JMBR.37.6.425-436.
[20] K.M. Naugle, C.J. Hass, D. Bowers, C.M. Janelle, Emotional state affects gait initiation in individuals with Parkinson's disease, Cognit. Affect Behav. Neurosci. 12 (2012) 207–219, https://doi.org/10.3758/s13415-011-0071-9.
[21] S. Stuart, S. Lord, E. Hill, L. Rochester, Gait in Parkinson's disease: a visuo-cognitive challenge, Neurosci. Biobehav. Rev. 62 (2016) 76–88, https://doi.org/10.1016/j.neubiorev.2016.01.002.

[22] K.A. Ehgoetz Martens, C.G. Ellard, Q.J. Almeida, Does anxiety cause freezing of gait in Parkinson's disease? PLoS One 9 (2014) https://doi.org/10.1371/journal.pone.0106561.
[23] A. Hassan, S. Vallabhajosula, L.B. Zahodne, D. Bowers, M.S. Okun, H.H. Fernandez, C.J. Hass, Correlations of apathy and depression with postural instability in Parkinson disease, J. Neurol. Sci. 338 (2014) 162–165, https://doi.org/10.1016/j.jns.2013.12.040.
[24] J.T. Hinkle, K. Perepezko, L.L. Gonzalez, K.A. Mills, G.M. Pontone, Apathy and anxiety in De novo Parkinson's disease predict the severity of motor complications, Mov. Disord. Clin. Pract. 8 (2021) 76–84, https://doi.org/10.1002/mdc3.13117.
[25] H.D. Weiss, G.M. Pontone, "Pseudo-syndromes" associated with Parkinson disease, dementia, apathy, anxiety, and depression, Neurol. Clin. Pract. 9 (2019) 354–359, https://doi.org/10.1212/cpj.0000000000000644.
[26] S. De Waele, P. Cras, D. Crosiers, Apathy in Parkinson ' s disease : defining the park apathy subtype, Brain Sci. 12 (2022), https://doi.org/10.3390/brainsci12070923.
[27] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, J. Obeso, K. Marek, I. Litvan, A.E. Lang, G. Halliday, C.G. Goetz, T. Gasser, B. Dubois, P. Chan, B.R. Bloem, C.H. Adler, G. Deuschl, MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1601, https://doi.org/10.1002/mds.26424.
[28] D. Crosiers, B. Pickut, J. Theuns, P.P. De Deyn, C. Van Broeckhoven, P. Martinez-Martin, K.R. Chaudhuri, P. Cras, Non-motor symptoms in a Flanders-Belgian population of 215 Parkinson's disease patients as assessed by the Non-Motor Symptoms Questionnaire, Am. J. Neurodegener. Dis. 1 (2012) 160–167.
[29] P. Sockeel, K. Dujardin, D. Devos, C. Denève, A. Destée, L. Defebvre, The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 77 (2006) 579–584, https://doi.org/10.1136/jnnp.2005.075929.
[30] C. Lu, S.L. Amundsen Huffmaster, P.J. Tuite, J.M. Vachon, C.D. MacKinnon, Effect of cue timing and modality on gait initiation in Parkinson disease with freezing of gait, Arch. Phys. Med. Rehabil. 98 (2017) 1291–1299.e1, https://doi.org/10.1016/j.apmr.2017.01.009.
[31] A. Burleigh-Jacobs, F.B. Horak, J.G. Nutt, J.A. Obeso, M.L. Mille, M.J. Hilliard, K.M. Martinez, T. Simuni, M.W. Rogers, Acute effects of a lateral postural assist on voluntary step initiation in patients with Parkinson's disease, Mov. Disord. 22 (1997) 20–27, https://doi.org/10.1002/mds.870120211.
[32] M. Mancini, C. Zampieri, P. Carlson-Kuhta, L. Chiari, F.B. Horak, Anticipatory postural adjustments prior to step initiation are hypometric in untreated Parkinson's disease: an accelerometer-based approach, Eur. J. Neurol. 16 (2009) 1028–1034, https://doi.org/10.1111/j.1468-1331.2009.02641.x.
[33] I. Carpinella, P. Crenna, E. Calabrese, M. Rabuffetti, P. Mazzoleni, R. Nemni, M. Ferrarin, Locomotor function in the early stage of Parkinson's disease, IEEE Trans. Neural Syst. Rehabil. Eng. 15 (2007) 543–551, https://doi.org/10.1109/TNSRE.2007.908933.
[34] B.A. Golomb, V.T. Chan, M.A. Evans, S. Koperski, H.L. White, M.H. Criqui, The older the better: are elderly study participants more non-representative? A cross-sectional analysis of clinical trial and observational study samples, BMJ Open 2 (2012) 1–6, https://doi.org/10.1136/bmjopen-2012-000833.
[35] J. Seuthe, N. D'Cruz, P. Ginis, R. Blöbaum, B. Weisser, G. Deuschl, A. Nieuwboer, C. Schlenstedt, How many gait initiation trials are necessary to reliably detect anticipatory postural adjustments and first step characteristics in healthy elderly and people with Parkinson's disease? Gait Posture 88 (2021) 126–131, https://doi.org/10.1016/j.gaitpost.2021.05.016.
[36] Y. Russo, S. Stuart, C. Silva-Batista, B. Brumbach, G. Vannozzi, M. Mancini, Does visual cueing improve gait initiation in people with Parkinson's disease? Hum. Mov. Sci. 84 (2022) 102970 https://doi.org/10.1016/j.humov.2022.102970.
[37] J.V. Jacobs, J.G. Nutt, P. Carlson-Kuhta, M. Stephens, F.B. Horak, Knee trembling during freezing of gait represents multiple anticipatory postural adjustments, Exp. Neurol. 215 (2009) 334–341, https://doi.org/10.1016/j.expneurol.2008.10.019.
[38] M.W. Rogers, R. Kennedy, S. Palmer, M. Pawar, M. Reising, K.M. Martinez, T. Simuni, Y. Zhang, C.D. MacKinnon, M.C. Postural, Postural preparation prior to stepping in patients with Parkinson's disease, J. Neurophysiol. 106 (2011) 915–924, https://doi.org/10.1152/jn.00005.2010.
[39] W. Fitts, L. Massimo, N. Lim, M. Grossman, N. Dahodwala, Computerized assessment of goal-directed behavior in Parkinson's disease, J. Clin. Exp. Neuropsychol. 38 (2016) 1015–1025, https://doi.org/10.1080/13803395.2016.1184232.
[40] F.M. Skidmore, M. Yang, L. Baxter, K. von Deneen, J. Collingwood, G. He, R. Tandon, D. Korenkevych, A. Savenkov, K.M. Heilman, M. Gold, Y. Liu, Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease, Neuroimage 81 (2013) 484–495, https://doi.org/10.1016/j.neuroimage.2011.07.012.