Journal of NeuroEngineering and Rehabilitation

RESEARCH

Open Access

Abnormal arm swing movements in Parkinson's disease: onset, progression and response to L-Dopa

M. Patera[1†], A. Zampogna[1,2†], L. Pietrosanti[3†], F. Asci[1], M. Falletti[1], G. Pinola[1], E. Bianchini[4], G. Di Lazzaro[5], V. Rosati[1], P. Grillo[6,7], F. Giannini[3], F. Fattapposta[1], G. Costantini[3], A. Pisani[6,7], G. Saggio[3] and Antonio Suppa[1,2*]

Abstract

Background Reduced arm swing movements during gait are an early motor manifestation of Parkinson's disease (PD). The clinical evolution, response to L-Dopa and pathophysiological underpinning of abnormal arm swing movements in PD remain largely unclear. By using a network of wearable sensors, this study objectively assesses arm swing movements during gait in PD patients across different disease stages and therapeutic conditions.

Methods Twenty healthy subjects (HS) and 40 PD patients, including 20 early-stage and 20 mid-advanced subjects, underwent a 6-m Timed Up and Go test while monitored through a network of wearable inertial sensors. Arm swing movements were objectively evaluated in both hemibodies and different upper limb joints (shoulder and elbow), using specific time-domain (range of motion and velocity) and frequency-domain measures (harmonics and total harmonic distortion). To assess the effects of L-Dopa, patients under chronic dopaminergic therapy were randomly examined when OFF and ON therapy. Finally, clinical-behavioral correlations were investigated, primarily focusing on the relationship between arm swing movements and cardinal L-Dopa-responsive motor signs, including bradykinesia and rigidity.

Results Compared to HS, the whole group of PD patients showed reduced range of motion and velocity, alongside increased asymmetry of arm swing movements during gait. Additionally, a distinct increase in total harmonic distortion was found in patients. The kinematic changes were prominent in the early stage of the disease and progressively worsened owing to the involvement of the less affected hemibody. The time- and frequency-domain abnormalities were comparable in the two joints (i.e., shoulder and elbow). In the subgroup of patients under chronic dopaminergic treatment, L-Dopa restored patterns of arm swing movements. Finally, the kinematic alterations in arm swing movements during gait correlated with the clinical severity of bradykinesia and rigidity.

Conclusions Arm swing movements during gait in PD are characterized by narrow, slow, and irregular patterns. As the disease progresses, arm swing movements deteriorate also in the less affected hemibody, without any

[†]M. Patera, A. Zampogna and L. Pietrosanti contributed equally to this work.

*Correspondence:
Antonio Suppa
antonio.suppa@uniroma1.it

Full list of author information is available at the end of the article

joint specificity. The positive response to L-Dopa along with the significant correlation between kinematics and bradykinesia/rigidity scores points to the involvement of dopaminergic pathways in the pathophysiology of abnormal arm swing movements in PD.

Keywords Parkinson's disease, Arm swing, Wearable sensors, Bradykinesia, Rigidity

Introduction

Patients with Parkinson's disease (PD) may manifest an impairment of arm swing movements which become slow and reduced in range and amplitude [1–4]. Abnormal arm swing movements often occur early in PD and frequently lead patients to prompt their first medical assessment [5]. The early and asymmetric presentation of abnormal arm swing movements may give the appearance of *gunslingers* to PD patients, with one hand swinging freely and the other fixed and near the holster [6]. Despite several previous investigations, the detailed and systematic characterization of clinical and kinematic features of abnormal arm swing movements in PD is still lacking [2]. Moreover, the pathophysiological underpinning of abnormal arm swing movements in PD remains unclear. Further advances in the field would require a more systematic investigation of arm swing movements in a large cohort of PD patients through advanced methodologies.

A possible approach is to apply a network of wearable sensors to achieve detailed kinematic data, including information on the range, amplitude, velocity, and movement frequency [7, 8]. Wearable sensors are accurate tools for measuring physiological and pathological movement patterns both in laboratory and domestic environments [9–11]. Wearable devices are ideal tools to examine arm swing movements unobtrusively in PD patients [12].

Previous studies adopting wearable technologies to assess arm swing movements in PD reached controversial findings concerning the overall clinical evolution of arm swing movements over the disease progression [13, 14]. Furthermore, none has clarified whether abnormal arm swing movements in PD show specific topographic changes across the major upper limb joints. It is well established that motor symptoms in PD can respond differently to treatment depending on the affected body region. For instance, appendicular regions generally show a better response to levodopa than axial regions [15]. Regarding arm swing, alterations in shoulder dynamics (reflecting the motor control of the most proximal portion of the upper limb, which plays a key role in initiating and coordinating movement) have been well documented in PD [2]. In contrast, far less attention has been given to elbow movement alterations, limiting our understanding of how the involvement of specific joints affects arm swing mechanics during gait. Moreover, whether dopaminergic therapy improves arm swinging in PD is still controversial as well as the contribution of cardinal L-Dopa-responsive motor signs, including bradykinesia and rigidity [13, 16, 17]. To clarify the pathophysiology of abnormal arm swing movements in PD, it would be necessary to systematically address all the above-mentioned unresolved questions by applying innovative techniques and new analytical approaches in a large cohort of PD patients, in different disease stages and therapeutic conditions.

In this study, we instrumentally evaluated arm swing movements in a large cohort of PD patients and age-matched healthy subjects (HS), using a network of wearable sensors. To assess the contribution of disease stage, we compared kinematic data between early and mid-advanced PD patients. Still, to verify whether abnormal arm swing movements reflect specific topographic changes, we assessed body asymmetry and different upper-limb joints, including shoulder and elbow. Furthermore, to clarify the impact of dopaminergic therapy, we compared patients under and not under L-Dopa. Lastly, to further unveil the pathophysiological underpinning of abnormal arm swing movements in PD, we investigated the contribution of bradykinesia and rigidity to abnormal arm swinging by assessing clinical-behavioural correlations. In addition to the standard analysis of the range and velocity of arm swing movements, we also performed a frequency-domain analysis of all kinematic data, integrating information about the rhythm and cadence of motion. Frequency-domain variables are underexplored measures reflecting dynamic change and smoothness of movements, thereby potentially providing new pathophysiological insights on arm swing movements in PD [18].

Materials and methods

Subjects

Forty PD patients and twenty age-matched healthy subjects (HS) were recruited in the Movement Disorders outpatient clinic of Sapienza University of Rome, IRCCS Neuromed Institute and Tor Vergata University of Rome, Italy. The sample size was calculated based on an error margin of 20–30%, derived from available data from small studies on HS, with a target 95% confidence interval [19]. All participants were enrolled according to the following inclusion criteria: diagnosis of idiopathic PD based on current consensus criteria and follow-up clinical evaluations [20]; Hoehn and Yahr scale (H&Y) ≤ 3 [21]; 3) ability to maintain the upright stance and walk independently;

absence of disabling L-Dopa-induced dyskinesia, dementia (i.e., Montreal Cognitive Assessment– MoCA > 23 [22, 23]) and comorbidities affecting gait or arm movements. The patients were divided into two subgroups based on the disease stage: 20 subjects with a recent diagnosis of PD and no previous exposure to L-dopa (early PD), and 20 patients with longer disease duration under chronic dopaminergic treatment (mid-advanced PD). All early PD underwent longitudinal follow-up for a minimum of two years after the study enrolment to evaluate their response to dopaminergic therapy and rule out the development of atypical features. All patients underwent a clinical assessment through a battery of standardized scales. In detail, we employed the H&Y scale, the Movement Disorders Society-unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) [24], MoCA and Frontal Assessment Battery (FAB) [25]. Mid-advanced PD patients were evaluated in two sessions according to the therapeutic condition: OFF (i.e., after drug withdrawal for at least 12 h) and ON state of therapy (i.e., one hour after taking the 150% of their usual L-Dopa dose). We calculated the L-Dopa equivalent daily dose (LEDD), according to standardized procedures, in all mid-advanced PD patients [26]. Table 1 and 2 summarizes patients' demographic and clinical features. All the enrolled subjects have given written informed consent to the study which was approved by the institutional review board following the Declaration of Helsinki.

Experimental setting

Motor task

All participants were asked to perform a modified "Timed Up and Go" test (TUG test) [27] while wearing a network of wearable sensors. Accordingly, subjects were asked to rise from an armchair, walk forward at a comfortable speed for 6 m, turn around, walk back to the chair, and sit down. The gait task was illustrated to each participant by a health professional. Patients were not explicitly instructed to swing their arms during the walking tasks to allow for natural gait patterns. The participants repeated the modified TUG test twice. Two trials were performed to increase the number of recorded events, balancing patient tolerance and minimizing fatigue, which could introduce bias, especially in individuals with advanced motor impairment. Mid-advanced PD performed two separate evaluations according to the therapeutic state (OFF and ON state).

Kinematic data acquisition

For the kinematic evaluation, we adopted five lightweight (< 20 g each), small (4 cm × 3 cm × 1.5 cm) wearable devices (Movit G1 system by Captiks Srl, Rome, Italy), positioned on the trunk and upper limbs of each participant, as shown in Fig. 1. To assess the clinical progression

Table 1 Demographic and clinical features of participants (mean and standard deviation)

	Participants	Age	Height	BMI	Disease duration	H&Y		MoCA	FAB	MDS-UPDRS-III		LEDD
						OFF	ON			OFF	ON	
HS	20	65.2 (9.3)	165.4 (11.5)	25.1 (3.0)	-	-	-	-	-	-	-	-
Early PD	20	61.1 (8.9)	168.6 (7.6)	25.0 (2.1)	1.7 (1.3)	1.4 (0.5)	-	26.6 (2.1)	15.8 (1.6)	19.3 (5.1)	-	-
Mid-advanced PD	20	70.6 (8.1)	169.9 (10.6)	24.3 (3.3)	4.3 (4.2)	2.2 (0.4)	1.9 (0.3)	26.7 (1.8)	15.7 (1.9)	31.9 (9.9)	17.6 (8.0)	502.9 (219.9)

FAB, Frontal Assessment Battery; HS, healthy subjects; H&Y, Hoehn and Yahr scale; LEDDs, L-Dopa Equivalent Daily Dose; MoCA, Montreal Cognitive Assessment; MDS-UPDRS-III, Movement Disorder Society - Unified Parkinson's Disease Rating Scale part III; PD, Parkinson's disease

Table 2 Kinematic data of arm swing movements (median and interquartile range)

	HS	PD	Early PD	Mid-advanced PD	
				OFF	ON
Shoulder ROM	22.61 (14.09)	15.05 (11.84)	14.58 (9.04)	16.92 (12.18)	20.26 (14.78)
Shoulder velocity	69.42 (40.40)	55.85 (28.93)	49.74 (23.29)	61.18 (37.41)	67.41 (66.46)
Elbow ROM	13.70 (6.63)	7.01 (4.41)	7.17 (5.01)	6.79 (4.48)	8.41 (9.66)
Elbow velocity	55.49 (26.10)	35.67 (17.71)	37.40 (17.13)	34.08 (18.04)	40.46 (39.37)
Shoulder Asym	0.23 (0.20)	0.40 (0.27)	0.41 (0.27)	0.35 (0.30)	0.30 (0.28)
Elbow Asym	0.41 (0.33)	0.46 (0.30)	0.51 (0.36)	0.45 (0.19)	0.36 (0.34)
THD_A	0.25 (0.25)	0.28 (0.24)	0.29 (0.36)	0.26 (0.18)	0.27 (0.17)
THD_F	0.37 (0.02)	0.53 (0.38)	0.53 (0.57)	0.53 (0.31)	0.46 (0.31)
Asym-THD_A	0.08 (0.19)	0.11 (0.16)	0.12 (0.30)	0.11 (0.13)	0.07 (0.13)
Asym-THD_F	0.10 (0.15)	0.15 (0.28)	0.19 (0.55)	0.17 (0.27)	0.10 (0.25)

Asym-, asymmetry index; HS, healthy subjects; OFF, not under dopaminergic therapy; ON, under dopaminergic therapy; ROM, range of motion; PD, all enrolled PD patients; THD_A, total harmonic distortion of the upper arm; THD_F, total harmonic distortion of the forearm

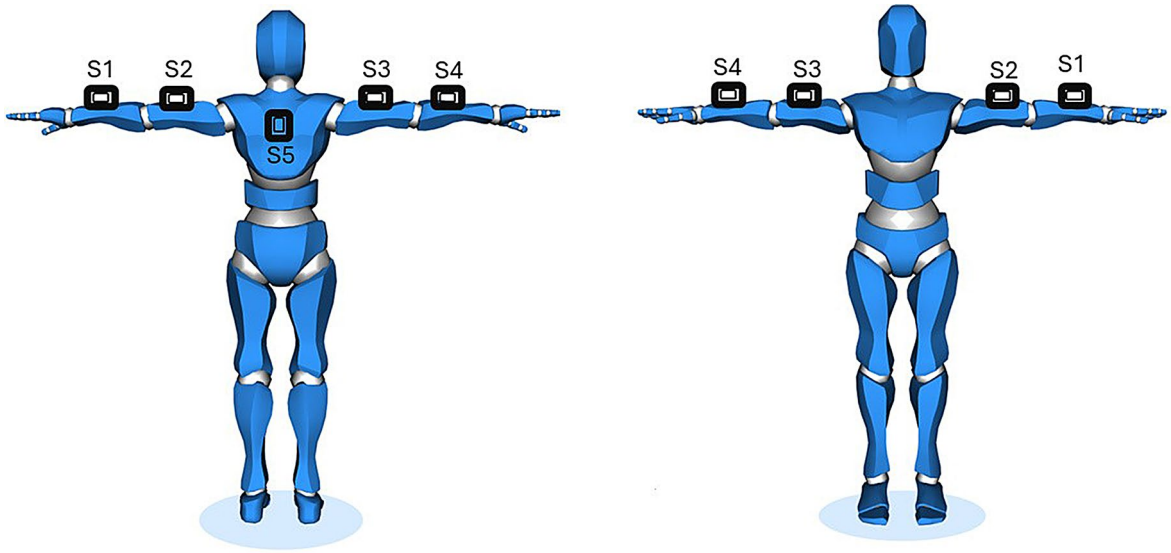

Fig. 1 Wearable sensors placement. Arm swing movements were recorded using five sensors positioned on the forearms (S2, S5), upper arms (S3, S4), and trunk (S1)

of arm swing movements according to body topography, two distinct devices were placed over the upper arms and forearms allowing for the separate recording of movements at the shoulder and elbow joints. Each Movit G1 hosted inertial measurement units with a triaxial accelerometer and a triaxial gyroscope, validated to the optoelectronic gold standard system (Vicon, by Oxford Metrics) [28], to collect kinematic data (i.e., acceleration, angular velocity, and orientation) from different anatomic segments. The accelerometer configuration was to ± 8 g with 16.384 least significant bit per g (LSB/g) sensitivity and the gyroscope to ± 2000°/s with 32.8 LSB/°/s sensitivity. Signals were acquired at a sampling rate of 52 Hz and sent to a receiver connected to a laptop. All data were processed with a dedicated program named Motion Studio (by Captiks Srl, Rome, Italy). To avoid artifacts, obtained signals were filtered with a six-order low-pass elliptic filter with a cut-off frequency of 3 Hz.

Moreover, the recorded signal length was standardized at 1024 samples, to guarantee the same frequency resolution for each recording. All data were processed with Matlab (by Matworks).

Outcome measures

The sensor-based outcome measures encompassed both time-domain and frequency-domain measurements. For both the time- and frequency-domain analysis, we considered the more affected side of PD patients (i.e., the side with the highest MDS-UPDRS-III score). Both sides of the body were considered only for calculating the asymmetry index. In the case of HS, where slight asymmetry may exist [19], we accounted for the side with the lower shoulder range of motion (ROM).

Concerning the time-domain analysis, the following spatiotemporal parameters were extracted: (i) ROM of the shoulder and elbow; (ii) arm swing velocity of the shoulder and elbow (shoulder velocity and elbow velocity, respectively), calculated as the median value of the peak velocity of each oscillation; (iii) asymmetry index of the shoulder and elbow (shoulder Asym and elbow Asym, respectively), calculated as the difference in angular flexion range between the wider and the smaller arm swing divided by the larger value (lv%) [29].

Regarding the frequency-domain analysis, after performing a Fast Fourier Transform (FFT) on gyroscope data, we obtained the oscillation spectrum of specific arm segments. The first harmonic is the fundamental frequency, representing the main swing velocity of the arm during gait. If the arm swing is perfectly sinusoidal like a pendulum, the spectrum consists only of the fundamental frequency. The presence of higher harmonics indicates signal distortion and suggests some restraints limiting arm oscillation. This model applies to any swinging arm segment, allowing us to extract harmonic contents from both the upper arm and forearm. In our frequency-based analysis, we extracted the amplitude of the fundamental harmonics of the upper arm and forearm, as well as the second and third harmonics. To understand the abnormal frequency content distribution in participants, we calculated the "total harmonic distortion" (THD) for both the upper arm (THD_A) and forearm (THD_F), as the ratio of the sum of the higher harmonics' amplitudes to the fundamental. Variations in the frequency content of movement signals reflect changes in dynamics, such as acceleration, deceleration, and direction changes. Temporal aspects are also encoded in the frequency domain. Lower THD suggests more coordinated and rhythmic upper limb movement during walking, while higher values may indicate less regular and smooth movement patterns.

To evaluate any degree of asymmetry between the THD of both sides, we calculated the THD asymmetry index, for both shoulder and elbow. The THD asymmetry index was calculated as the difference between the THD of each side.

Statistical analysis

Since our data did not meet the assumptions of parametric tests, including normal distribution at the Shapiro-Wilk test, we adopted non-parametric tests for statistical analysis. Specifically, the Kruskal-Wallis test and the Mann-Whitney U test were used to compare anthropometric data (age, height, BMI) and clinical features (disease duration, H&Y, MDS-UPDRS-III, MoCA, FAB) among participants. The Kruskal-Wallis test and the Mann-Whitney U test were also used to compare kinematic data among subgroups (HS vs. all PD; HS vs. early PD; HS vs. mid-advanced PD; early PD vs. mid-advanced PD - multiple independent groups and continuous, non-normally distributed variables). The Wilcoxon signed-rank test was used to investigate the effect of dopaminergic treatment on clinical features (e.g., MDS-UPDRS-III) and to compare kinematic measurements in mid-advanced PD, OFF and ON states (dependent and non-normally distributed variables). Finally, the Spearman rank correlation test was used to assess possible correlations between kinematic data and the sum of all upper limb MDS-UPDRS-III sub-items for rigidity, bradykinesia, and tremor (i.e., items 3.3, 3.4, 3.5, 3.6, 3.15, 3.16, 3.17) as well as the specific score for each of the cardinal motor signs of PD, assessed as follows: MDS-UPDRS-III item 3.3 for upper limb rigidity; the sum of items 3.4, 3.5, and 3.6 (i.e., "arm bradykinesia composite score") for bradykinesia (ordinal and non-normally distributed variables). For all analyses, p-values less than 0.05 were deemed statistically significant (two-tailed). To control for false discovery rate due to multiple comparisons (HS vs. all PD; HS vs. early PD; HS vs. mid-advanced PD; early PD vs. mid-advanced PD) and ensure reliable results while minimizing Type I errors, the Benjamini-Hochberg correction was applied. We applied the Benjamini-Hochberg correction also in the correlation analyses. Lastly, the Cliff's Delta effect size and rank-biserial correlation coefficient were used to assess the effect sizes for comparisons between independent groups (HS, all PD, early PD, mid-advanced PD) and dependent variables (mid-advanced PD OFF and ON state of therapy), respectively.

Results

Clinical features

The demographic and anthropometric variables were comparable between HS and PD patients, and between early PD and mid-advanced PD (all $p > 0.05$) except for older age in mid-advanced PD than early PD ($U = 78.5$, $p = 0.001$). While MoCA and FAB scores were comparable

among the two subgroups of patients ($p > 0.05$), mid-advanced PD showed higher disease duration (U = 97, $p = 0.004$), H&Y (U = 72.5, $p < 0.001$), and MDS-UPDRS-III OFF (U = 53.5, $p < 0.001$) than early PD. Finally, the MDS-UPDRS-III significantly improved with the dopaminergic therapy, as demonstrated by lower scores in PD patients ON than those OFF state (U = 606; $p < 0.001$).

Onset and progression

Considering the time-domain analysis, significant differences were found in shoulder ROM ($H_{(2)} = 8.824$, $p = 0.012$), shoulder velocity ($H_{(2)} = 6.430$, $p = 0.04$), elbow ROM ($H_{(2)} = 13.598$, $p = 0.001$) and elbow velocity ($H_{(2)} = 12.646$, $p = 0.002$). More in detail, the whole cohort of PD patients showed lower shoulder ROM (U = 216, $p = 0.004$, corrected $p = 0.008$, $r = 0.372$), shoulder velocity (U = 258, $p = 0.026$, corrected $p = 0.05$, $r = 0.287$), elbow ROM (U = 165, $p < 0.001$, corrected $p = 0.002$, $r = 0.425$) and elbow velocity (U = 175, $p < 0.001$, corrected $p = 0.002$, $r = 0.425$) than HS (Fig. 2a-d). When comparing HS and early PD, shoulder ROM (U = 94, $p = 0.004$, corrected $p = 0.008$, $r = 0.455$), shoulder velocity (U = 105, $p = 0.01$, corrected $p = 0.04$, $r = 0.407$), elbow ROM (U = 79, $p = 0.001$, corrected $p = 0.002$, $r = 0.520$) and elbow velocity (U = 70, $p < 0.001$, corrected $p = 0.002$, $r = 0.520$) were lower in patients than controls. Similar results were found when comparing HS and mid-advanced PD, OFF state. Indeed, mid-advanced PD OFF state showed lower

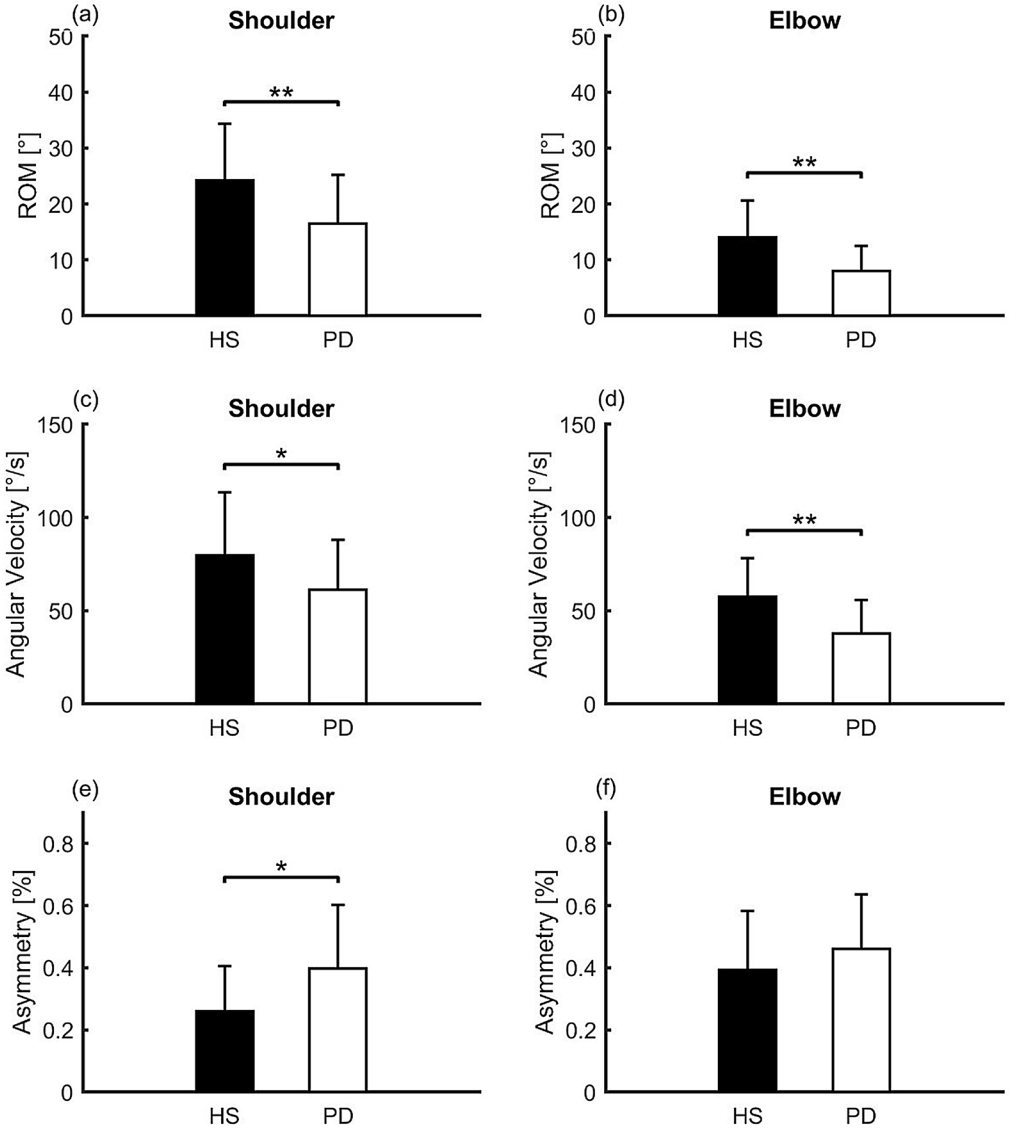

Fig. 2 Time-domain analysis of arm swing movements. The figure depicts the spatiotemporal parameters of arm swing movements in healthy subjects (HS) and all patients with Parkinson's disease (PD). (**a**) Shoulder range of motion (ROM) comparison; (**b**) Elbow ROM comparison; (**c**) Shoulder swing velocity comparison; (**d**) Elbow swing velocity comparison; (**e**) Shoulder asymmetry comparison; (**f**) Elbow asymmetry comparison. Error bars represent the standard deviation. *$p < 0.05$, **$p < 0.01$

shoulder ROM (U = 122, $p = 0.035$, corrected $p = 0.046$, $r = 0.333$), elbow ROM (U = 86, $p = 0.002$, corrected $p = 0.003$, $r = 0.489$), elbow velocity (U = 105, $p = 0.01$, corrected $p = 0.013$, $r = 0.407$) than HS. Also, the comparison between early PD and mid-advanced PD OFF state showed no differences in time-domain measures (all $p > 0.05$) (Fig. 3a-d).

Concerning frequency-domain parameters, significant differences were found among subgroups for THD_F ($H_{(2)=}8.718$, $p = 0.013$). By contrast, THD_A did not show significant differences ($H_{(2)=}1.260$, $p = 0.533$). Specifically,

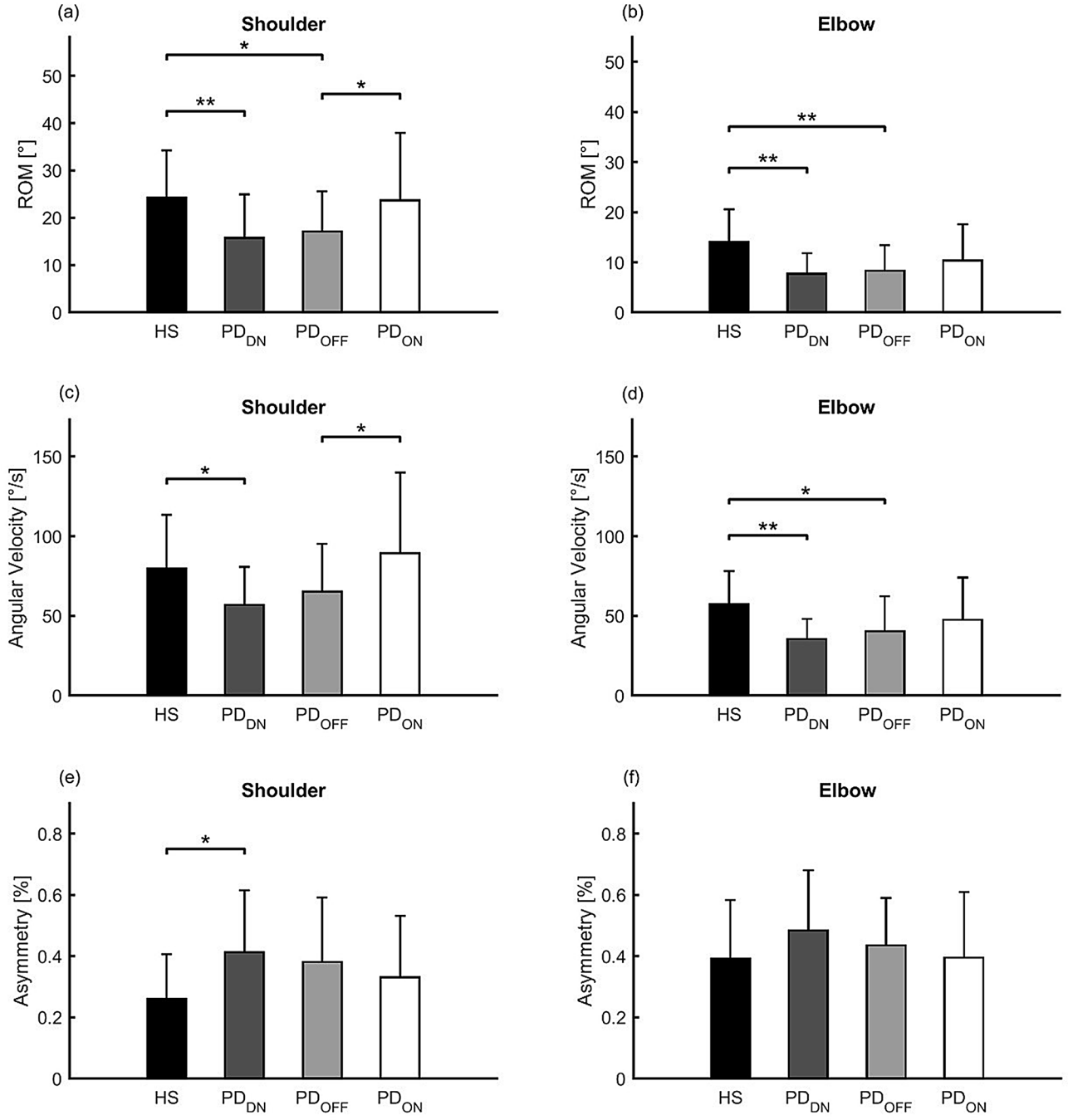

Fig. 3 Subgroup time-domain analysis of arm swing movements. The figure depicts the spatiotemporal parameters of arm swing movements in healthy subjects (HS) and subgroups of patients with Parkinson's disease, including drug naïve early-stage patients (PD_{DN}), mid-advanced PD patients under (PD_{ON}) and not under (PD_{OFF}) dopaminergic therapy. (**a**) Shoulder range of motion (ROM) subgroup comparison; (**b**) Elbow ROM subgroup comparison; (**c**) Shoulder swing velocity subgroup comparison; (**d**) Elbow swing velocity subgroup comparison; (**e**) Shoulder asymmetry subgroup comparison; (**f**) Elbow asymmetry subgroup comparison. Error bars represent the standard deviation. *$p < 0.05$, **$p < 0.01$

the whole cohort of PD patients showed higher THD_F (U = 1408, $p = 0.003$, corrected $p = 0.040$, $r = 0.383$) than HS (Fig. 4b). THD_F was also higher in early PD (U = 500, $p = 0.015$, corrected $p = 0.030$, $r = 0.385$) as well as mid-advanced PD, OFF state (U = 508, $p = 0.008$, corrected $p = 0.030$, $r = 0.419$) than in HS (Fig. 4d). Lastly, when comparing early PD with mid-advanced PD, OFF state, no significant differences in frequency parameters were found ($p > 0.05$) (Fig. 4c-d).

Body topography: asymmetry and joint specificity

When examining asymmetry indices in the time-domain analysis, shoulder Asym significantly differed ($H_{(2)} = 6.520$, $p = 0.038$) while elbow Asym was similar ($H_{(2)} = 2.540$, $p = 0.281$) among subgroups. Specifically, shoulder Asym was higher in the whole cohort of PD patients than HS (U = 241, $p = 0.012$, corrected $p = 0.030$, $r = 0.324$) (Fig. 2e). Similarly, early PD also presented higher shoulder Asym than controls (U = 111, $p = 0.015$, corrected $p = 0.030$, $r = 0.385$), while no differences were found in asymmetry indices between HS and mid-advanced PD, OFF state of therapy (all $p > 0.05$) (Fig. 3e).

Concerning the frequency-domain analysis, again significant differences were found in the Asym-THD_F ($H_{(2)} = 4.889$, $p = 0.027$), but not in the Asym-THD_A ($H_{(2)} = 0.498$, $p = 0.480$). More in detail, Asym-THD_F was higher in the whole cohort of PD patients than HS (U = 1361, $p = 0.028$, $r = 0.284$) (Fig. 4b). Similarly, early PD also presented higher Asym-THD_F than controls (U = 489, $p = 0.034$, $r = 0.335$). However, after applying the Benjamini-Hochberg correction for repeated measures, these comparisons no longer reached statistical significance (both corrected $p = 0.068$). No differences were found in asymmetry indices between HS and mid-advanced PD, OFF state (all $p > 0.05$) (Fig. 4e).

The effects of L-Dopa

No significant differences were found both in time- and frequency-domain measures, including asymmetry indices, between HS and mid-advanced PD ON state as well as between early PD and mid-advanced PD ON state (all $p > 0.05$) (Figs. 3a-f and 4c-f).

When comparing mid-advanced PD OFF and ON states, L-Dopa increased shoulder ROM (Z = 38, $p = 0.011$, $r = 0.402$) and shoulder velocity (Z = 47, $p = 0.030$, $r = 0.343$) in mid-advanced PD ON state of therapy, while did not change other time-domain measures, including asymmetry indices ($p > 0.05$) (Fig. 3a-f). Concerning the frequency-domain analysis, L-Dopa reduced THD_F (Z = 158, $p = 0.048$, $r = 0.313$), while no effects of L-Dopa were observed on THD_A or in the THD asymmetry content ($p > 0.05$) (Fig. 4c-f).

Clinical-behavioral correlations

The overall motor impairment of the upper limb, assessed by the MDS-UPDRS-III, demonstrated negative correlations with shoulder ROM (ρ=-0.396, $p < 0.001$, corrected $p = 0.002$), shoulder velocity (ρ=-0.346, $p = 0.002$, corrected $p = 0.004$), elbow ROM (ρ=-0.451, $p < 0.001$, corrected $p = 0.002$), and elbow velocity (ρ=-0.448, $p < 0.001$, corrected $p = 0.002$), and positive correlations with THD_A (ρ = 0.373, $p < 0.001$, corrected $p = 0.002$), and THD_F (ρ = 0.331, $p = 0.003$, corrected $p = 0.005$). Furthermore, the severity of upper limb rigidity (subitem 3.3 of the MDS-UPDRS-III) exhibited inverse correlations with shoulder ROM (ρ=-0.221, $p = 0.049$, corrected $p = 0.049$), shoulder velocity (ρ=-0.250, $p = 0.026$, corrected $p = 0.032$), elbow ROM (ρ=-0.250, $p = 0.025$, corrected $p = 0.032$), elbow velocity (ρ=-0.233, $p = 0.038$, corrected $p = 0.043$), and positive correlation with THD_F (ρ = 0.222, $p = 0.047$, corrected $p = 0.049$). Additionally, the severity of upper limb bradykinesia (i.e., arm bradykinesia composite score) correlated negatively with shoulder ROM (ρ=-0.347, $p = 0.002$, corrected $p = 0.004$), shoulder velocity (ρ=-0.288, $p = 0.01$, corrected $p = 0.014$), elbow ROM (ρ=-0.454, $p < 0.001$, corrected $p = 0.002$), elbow velocity (ρ=-0.364, $p = 0.001$, corrected $p = 0.002$), whereas it was positively associated with THD_A (ρ = 0.398, $p < 0.001$, corrected $p = 0.002$), and THD_F (ρ = 0.325, $p = 0.003$, corrected $p = 0.005$).The main clinical-behavioral correlations are illustrated in Fig. 5.

Discussion

In this study, the application of a modern network of wearable sensors coupled with advanced analytical approaches allowed us to demonstrate that PD patients manifest early alterations in arm swing movements, both in terms of time-domain (i.e., range and velocity of movement) and frequency-domain changes (i.e., harmonic distortion). Furthermore, we have clarified the clinical evolution of this disorder, showing how it changes across different disease stages and according to body topography. Lastly, we have provided new pathophysiological insights into abnormal arm swing movements in PD by clarifying the response to dopaminergic therapy and the relationship with cardinal L-Dopa-responsive motor signs of the disease, including bradykinesia and rigidity.

The strict clinical inclusion criteria and methodological precautions adopted in this study allowed us to avoid confounding possibly leading to misinterpretation of results. First, we excluded patients presenting conditions other than PD and likely affecting arm swing movements during gait, such as orthopedical and rheumatological comorbidities, and cognitive impairment. Second, according to the well-known impact of ageing on arm swing dynamics [30], we recruited age-matched control subjects ensuring comparability in our study population.

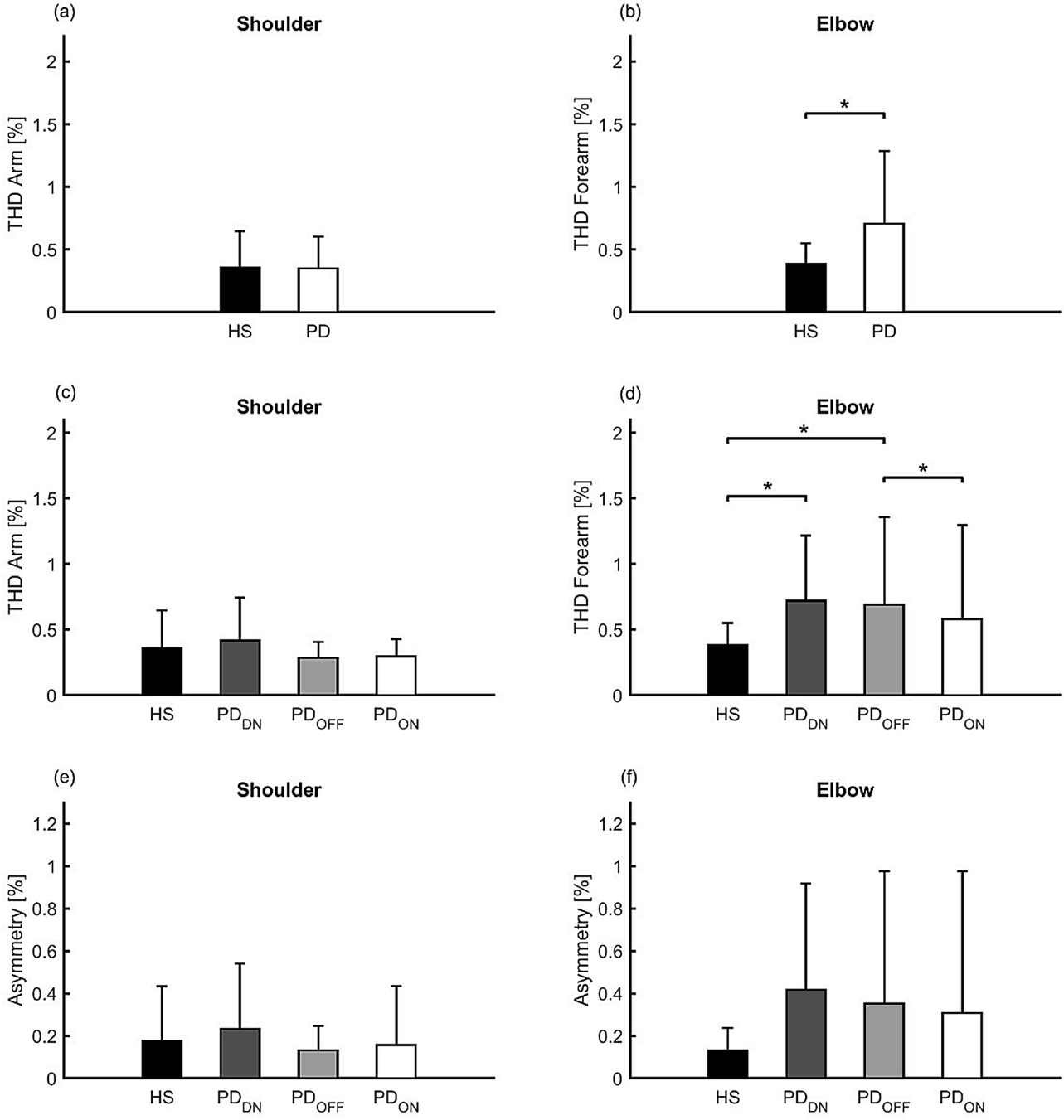

Fig. 4 Frequency-domain analysis of arm swing movements. The figure depicts the total harmonic distortion (THD) of arm swing movements in healthy subjects (HS), all patients with Parkinson's disease (PD), drug-naïve early-stage individuals (PD_{DN}), mid-advanced PD patients under (PD_{ON}) and not under (PD_{OFF}) dopaminergic therapy. (**a**) Shoulder THD PD vs. HS comparison; (**b**) Elbow THD PD vs. HS comparison; (**c**) Shoulder THD subgroup comparison; (**d**) Elbow THD subgroup comparison; (**e**) Shoulder THD subgroup comparison; (**f**) Elbow THD subgroup comparison. Error bars represent the standard deviation. *$p < 0.05$, **$p < 0.01$

Lastly, we evaluated patients in the ON state of therapy after administering 150% of the usual L-Dopa dose to exclude that arm swing movements responsiveness to dopaminergic stimulation requires higher doses than those used for improving cardinal motor signs in PD.

Arm swing movements in PD: clinical onset and progression

PD patients manifested altered arm swing movements during gait compared to HS. In line with previous literature, our results confirm the presence of diminished shoulder ROM [14, 31–34] and swing velocity in arm

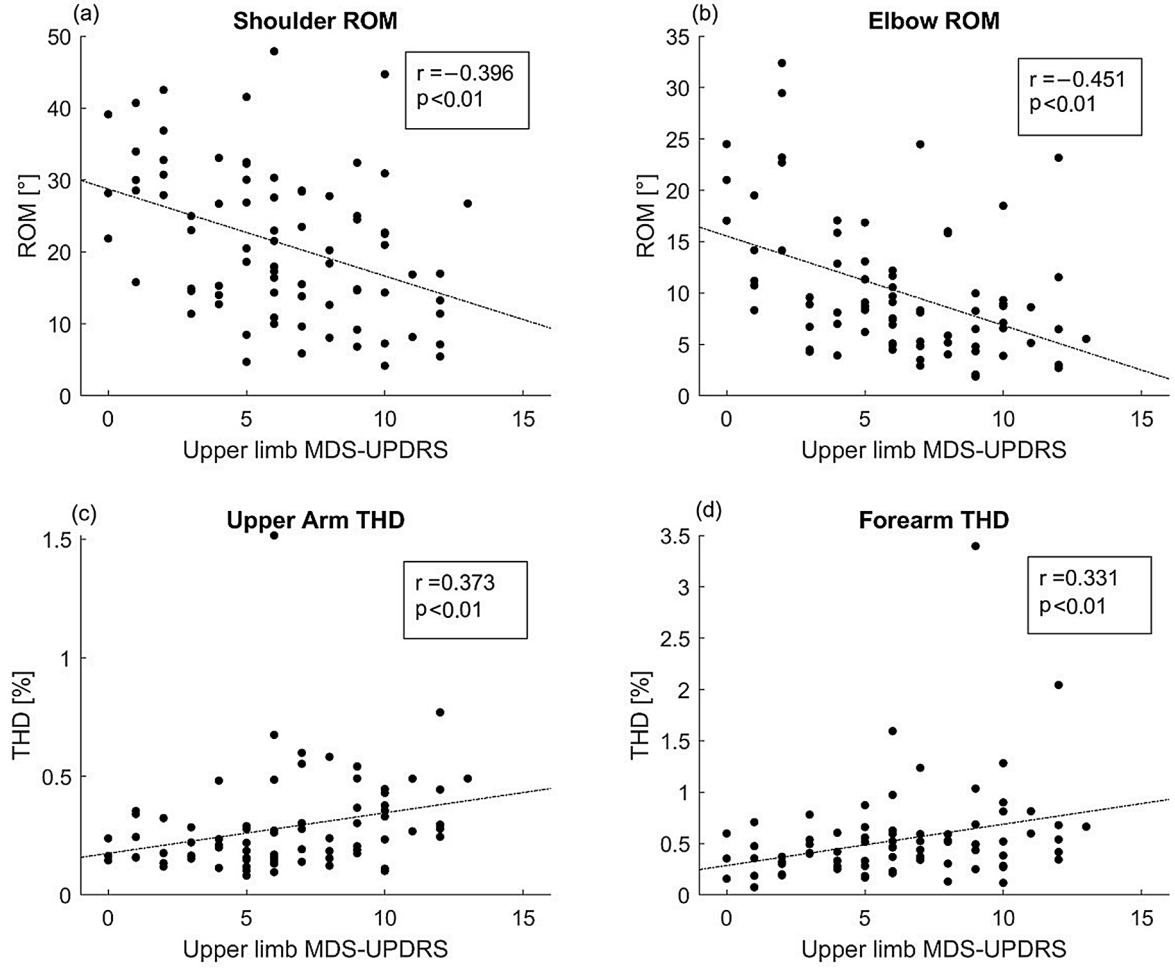

Fig. 5 Clinical-behavioral correlations. The scatterplot diagrams report clinical-behavioral correlation between kinematic parameters and upper limb motor impairment as reflected by MDS-UPRDS-III scores. (**a**) Shoulder range of motion (ROM) correlation; (**b**) Elbow range of motion (ROM) correlation; (**c**) Total harmonic distortion (THD) correlation; (**d**) Forearm total harmonic distortion (THD)

swing of PD patients [32, 35]. Furthermore, these changes occur early throughout the disease and persist in mid-advanced stages, as demonstrated by the comparison of HS with early PD and mid-advanced PD, OFF state. The early reduction of ROM and velocity of arm swing movements we found is fully in line with time-domain measures reported in preliminary studies in small cohorts of patients with early PD [1, 13, 36]. Therefore, our observations suggest decreased upper limb mobility during gait in PD. To our knowledge, our study is the first to analyze the harmonic content of arm swing during gait in PD patients. By reflecting the dynamic changes of movements, our innovative frequency-domain analysis provided further evidence of abnormal arm swinging during gait in PD in addition to the static time-domain features. Indeed, we found that a distinct increase of the THD_F occurred in the whole cohort of PD patients, as well as in early PD and mid-advanced PD, OFF state, compared to HS. This finding points to a lack of upper limb movement rhythmicity and smoothness in PD patients during walking suggesting impaired synchronization of arm swing movements with gait.

When specifically investigating the impact of disease progression, arm swing movements on the more affected body side did not change between early and mid-advanced PD patients. This observation is in agreement with a previous study showing comparable arm swing ROM and velocity in PD patients with different disease stages [14]. Notably, in this research, all the examined gait parameters worsened according to the disease progression except for arm swing ROM and velocity [14]. This observation suggests that, following the first occurrence of abnormal arm swing movements, the more affected body side does not worsen further in PD. Hence, as the disease progresses, abnormal arm swinging during gait endures with reduced amplitude, diminished velocity, and decreased smoothness, as evidenced by both spatiotemporal measurements and frequency-domain

features. This finding might suggest that the disruption of the dopaminergic pathway alone might not be sufficient to explain the arm swing reduction in PD. More complex networks, such as supraspinal projections or intraspinal interneuronal circuits, may stabilize the progressive alteration of arm swing movements along disease progression, as previously suggested [37, 38].

Under physiological conditions, arm swing movements are not merely passive pendulum-like motions of the upper limbs but reflect the activation of distinct motor sequences [39]. As in quadrupedal gait, the human bipedal gait displays a distinct four-limb pattern, with arm swinging occurring in anti-phase with lower limb oscillations at the same frequency. By producing propulsive forces, optimizing stability, and minimizing energy consumption, arm swinging enhances the biomechanical efficiency of the human gait [40]. Accordingly, the kinematic abnormalities we reported in our cohort of patients may substantially affect gait and overall mobility in PD [41–44] by disrupting walking rhythm and coordination and leading to irregular gait patterns as well as increased risk of falls [45].

Body topography: asymmetry and joint specificity

Compared to HS, the whole group of PD patients manifested an asymmetrical pattern of arm swing movements, as shown by the time- domain analysis. More in detail, PD patients exhibited a reduced amplitude of arm swinging during gait predominantly on one body side, in line with previous studies [5, 33, 46]. Although the kinematic changes were evident in the whole cohort of PD patients, when considering the two patients' subgroups, we confirmed increased asymmetry only in early PD. While a certain level of asymmetry is linked to physiological ageing [47, 48], our findings support asymmetrical arm swing movements as a distinct characteristic of the early stages of PD [1, 13, 35, 46, 49, 50]. Fully consistent with this hypothesis, previous authors have proposed arm swing asymmetry as a potential prodromal indicator of PD which is present even in pre-symptomatic subjects carrying LRRK2 genetic mutations [51]. Asymmetrical arm swing movements might also contribute to the differential diagnosis of parkinsonian syndromes since atypical parkinsonisms are usually associated with a more symmetrical pattern of arm swinging during gait [52]. However, it should be considered that some non-neurological conditions, like the frozen shoulder syndrome, can result in noticeable unilaterally reduced arm swing movements during gait [53].

As the disease progresses, arm swing movements also deteriorate on the less affected body side, as indicated by similar asymmetry indices between mid-advanced PD and HS. This finding aligns with the well-known progression of motor symptoms in PD, initially manifesting unilaterally and then spreading to the contralateral hemibody and axial regions, ultimately resulting in a more symmetric distribution of motor impairment [5, 54, 55]. Asymmetric arm swing movements in PD could stem from the imbalanced nigro-striatal degeneration in the two hemispheres at the disease onset [56, 57]. Hence, the decreased asymmetry in arm swing movements in mid-advanced patients may reflect the progression of nigro-striatal degeneration to a more homogeneous and bilateral involvement [58, 59]. Nevertheless, most PD patients usually present a mild asymmetric distribution of motor symptoms even in more advanced stages of the disease [60]. Indeed, despite a trend towards reduced asymmetry indices and similar parameters to HS, our mid-advanced PD did not exhibit statistically significant differences in these measures compared to the early PD.

Concerning upper-limb joint specificity, we found concordant time- and frequency-domain measures at shoulder and elbow joints during gait, both in early PD and mid-advanced PD, except for an increased harmonic distortion in forearm movements (THD_F) possibly reflecting restrained mobility due to the typical elbow flexed posture in PD. Overall, the findings we reported in our cohort of PD patients point to a similar contribution of shoulder and elbow changes in abnormal arm swinging during gait at disease onset as well as in more advanced stages of the disease. Accordingly, our results highlight the need for targeted rehabilitation strategies addressing not only shoulder dynamics but also elbow mobility, which could help improve gait symmetry and overall motor function in PD patients while walking.

The effect of L-Dopa

L-DOPA improved arm swing movements during gait in PD patients by increasing their ROM, velocity and smoothness, suggesting that abnormal arm swinging in PD reflects neurodegeneration in dopaminergic pathways, in agreement with some previous studies [13, 14, 37, 61]. Previous nuclear medicine investigations have disclosed a direct correlation between dopaminergic depletion in the nigro-striatal pathway and impairment of arm swing movements in PD [31]. Moreover, we found that L-Dopa does not change the degree of asymmetry in mid-advanced PD, as previously suggested [14]. Nevertheless, it should be considered that our mid-advanced PD presented a pattern of symmetry comparable to HS likely due to the progressive impairment of arm swing movements in the less affected body side. We speculate that since L-Dopa comparably acts on both hemibodies, dopaminergic stimulation would not modify asymmetry measures in mid-advanced PD. Accordingly, when evaluating the degree of asymmetry in arm swing movements, it is crucial to consider the patients' disease stage. In line with this observation, most previous researchers who

have documented notable enhancements in arm swing asymmetry primarily focused on patients in the early stages of PD, where the asymmetry is more pronounced [13, 32]. Lastly, we did not find differences between shoulder and elbow joints in mid-advanced PD, OFF and ON states, pointing to the beneficial effects of L-Dopa regardless of body topography.

Pathophysiological implications

In our cohort of PD patients, we found a significant association between kinematic measures of arm swing movements and cardinal L-Dopa responsive motor signs, including bradykinesia and rigidity, in line with some previous authors [17]. Our findings suggest that abnormal arm swinging in PD reflects neurodegeneration in dopaminergic pathways at least partly overlapping those contributing to bradykinesia and rigidity [62]. In line with this observation, previous studies found significant correlations between arm swing asymmetry and dopaminergic striatal denervation via nuclear imaging [31]. Also, further supporting our hypothesis, L-Dopa administration restored abnormal arm swinging in PD patients again pointing to the functional role of basal ganglia in regulating amplitude, rhythm, and automaticity of arm movements during human gait. Notably, a previous study in patients treated with subthalamic nucleus DBS (STN-DBS) has confirmed the pathophysiological involvement of basal ganglia motor circuits in arm swinging during gait in PD [37].

Arm swing movements represent a phylogenetically preserved aspect of locomotion across mammals and, specifically, primates representing an evolutionary adaptation from quadrupedal locomotion [63–66]. The complex and stereotyped muscle contractions in human gait mirror the synchronized movements seen in quadrupedal locomotion, generated by spinal central pattern generators (CPGs) [67–69]. Experimental studies in animals have induced walking motor patterns at the 4 limbs following electric stimulation of specific midbrain and cerebellar nuclei, in an intensity-dependent manner, strongly demonstrating that specific supraspinal regions modulate spinal CPGs [70]. Among them, the mesencephalic locomotor region (MLR), including the pedunculopontine nucleus (PPN), integrates inputs from various brain regions and activates in turn the reticulospinal pathway that finally projects to spinal CPGs [3, 67, 71, 72]. In PD, prior fMRI studies reported reduced basal ganglia activity and increased cortical motor area activation in patients with upper limb motor blocks and altered motor timings [73–75]. Additionally, functional and structural alterations have been found in the MLR and PPN, particularly in patients with more severe gait disturbances [76]. Accordingly, we speculate that the abnormal arm swinging observed in PD would result from dopaminergic denervation-induced functional changes in the cortico-basal ganglia-thalamo-cortical motor inputs to supraspinal generators including the MLR, in line with previous neuroimaging studies [71, 77–79].

When evaluating the present study some limitations should be considered. First, our cross-sectional study design cannot provide detailed information on disease progression in PD as in the case of a longitudinal study. Second, given that we did not systematically collect nuclear medicine measures in our patients with PD, we cannot provide direct evidence for our speculation about the strict involvement of dopaminergic pathways in the pathophysiology of abnormal arm swing movements in PD. Lastly, our experimental setting did not allow us to exclude the possible impact of participants' attention to their movement during direct medical observation. Hence, to obtain more ecologically valid data, future studies should examine arm swinging in PD patients in real-world settings.

Conclusions

Using a network of wearable sensors and advanced analytical methods, the present study demonstrates that abnormal arm swing movements during gait occur early in PD, worsen along with disease progression by affecting both body sides, and improve following L-Dopa. Our observations, including the association with cardinal L-Dopa responsive signs, support the involvement of dopaminergic pathways in the pathophysiology of abnormal arm swing movements in PD. Given that abnormal arm swing movements directly impact the dynamic postural stability of gait and increase the risk of falls [80], addressing this issue would promote a new rehabilitative strategy in PD patients [41, 81, 82].

Abbreviations

Asym-THD_A	Asymmetry in Total Harmonic Distortion of the Upper Arm
Asym-THD_F	Asymmetry in Total Harmonic Distortion of the Forearm
CPG	Central Pattern Generator
FAB	Frontal Assessment Battery
FFT	Fast Fourier Transform
H&Y	Hoehn and Yahr scale
HS	Healthy Subjects
LEDD	Levodopa Equivalent Daily Dose
MDS-UPDRS-III	Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III
MLR	Mesencephalic Locomotor Region
MoCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PPN	Pedunculopontine Nucleus
ROM	Range of Motion
STN-DBS	Subthalamic Nucleus Deep Brain Stimulation
THD	Total Harmonic Distortion
THD_A	Total Harmonic Distortion of the Upper Arm
THD_F	Total Harmonic Distortion of the Forearm
TUG test	Timed Up and Go test

Acknowledgements
The authors express their sincere gratitude to all the voluntary subjects who participated in this study as well as to Ralpharma for their unconditional support of the research.

Author contributions
M.P, A.Z., L.P., G.S., and A.S. contributed to the conception, organization and execution of the study, as well as the statistical analysis of data and manuscript drafting. M.P., A.Z. and L.P. wrote the main manuscript test. M.P. and L.P. prepared figures and tables. F.A., M.F., G.P., E.B., G.D.L., V.R., P.G., F.G., F.F., G.C., and A.P. contributed to the acquisition of data and manuscript revision for intellectual content.

Funding
A.Z.'s research activity was supported by the European funding "PNRR-MR1-2022-12376921, Next Generation EU - PNRR M6C2 - Investment 2.1 Enhancement and strengthening of biomedical research of the NHS". The funder played no role in study design, data collection, analysis and interpretation of data, or the writing of this manuscript.

Data availability
Data is provided within the manuscript and additional data will be provided on reasonable request.

Declarations

Ethical approval
All participants provided written informed consent, and the study received approval from the institutional review board in compliance with the 1964 Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
[2]IRCCS Neuromed, Pozzilli (IS), Italy
[3]Department of Electronic Engineering, University of Rome Tor Vergata, Rome, Italy
[4]Department of Neuroscience, Mental Health, and Sensory Organs (NESMOS), Sapienza University of Rome, Rome, Italy
[5]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[6]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
[7]IRCCS Mondino Foundation, Pavia, Italy

Received: 29 November 2024 / Accepted: 24 February 2025
Published online: 04 March 2025

References

1. Lewek MD, Poole R, Johnson J, Halawa O, Huang X. Arm swing magnitude and asymmetry during gait in the early stages of Parkinson's disease. Gait Posture Febbraio. 2010;31(2):256–60.
2. Navarro-López V, Fernández-Vázquez D, Molina-Rueda F, Cuesta-Gómez A, García-Prados P, Del-Valle-Gratacós M, et al. Arm-swing kinematics in Parkinson's disease: A systematic review and meta-analysis. Gait Posture Ottobre. 2022;98:85–95.
3. Meyns P, Bruijn SM, Duysens J. The how and why of arm swing during human walking. Gait Posture Settembre. 2013;38(4):555–62.
4. Nieuwboer A, Weerdt WD, Dom R, Lesaffre E. A frequency and correlation analysis of motor deficits in Parkinson patients. Disabil Rehabil Gennaio. 1998;20(4):142–50.
5. Espinoza-Araneda J, Caparrós-Manosalva C, Caballero PM, Da Cunha MJ, Marchese RR, Pagnussat AS. Arm swing asymmetry in people with Parkinson's disease and its relationship with gait: A systematic review and meta-analysis. Braz J Phys Ther Novembre. 2023;27(6):100559.
6. Araújo R, Ferreira JJ, Antonini A, Bloem BR. «Gunslinger's gait»: a new cause of unilaterally reduced arm swing. BMJ. 14 dicembre 2015;351:h6141.
7. Zampogna A, Mileti I, Palermo E, Celletti C, Paoloni M, Manoni A et al. Fifteen Years of Wireless Sensors for Balance Assessment in Neurological Disorders. Sensors. 7 giugno. 2020;20(11):3247.
8. Zampogna A, Manoni A, Asci F, Liguori C, Irrera F, Suppa A. Shedding Light on Nocturnal Movements in Parkinson's Disease: Evidence from Wearable Technologies. Sensors. 10 settembre. 2020;20(18):5171.
9. Zampogna A, Mileti I, Martelli F, Paoloni M, Del Prete Z, Palermo E, et al. Early balance impairment in Parkinson's disease: evidence from Robot-assisted axial rotations. Clin Neurophysiol Off J Int Fed Clin Neurophysiol Ottobre. 2021;132(10):2422–30.
10. Di Castelli Gattinara F, Menna G, Mileti I, Zampogna A, Asci F, Paoloni M et al. Machine Learning and Wearable Sensors for the Early Detection of Balance Disorders in Parkinson's Disease. Sensors. 16 dicembre. 2022;22(24):9903.
11. Bianchini E, Galli S, Alborghetti M, De Carolis L, Zampogna A, Hansen C et al. Four Days Are Enough to Provide a Reliable Daily Step Count in Mild to Moderate Parkinson's Disease through a Commercial Smartwatch. Sensors. 4 novembre. 2023;23(21):8971.
12. Di Lazzaro G, Ricci M, Saggio G, Costantini G, Schirinzi T, Alwardat M, et al. Technology-based therapy-response and prognostic biomarkers in a prospective study of a de Novo Parkinson's disease cohort. NPJ Park Dis 17 Settembre. 2021;7(1):82.
13. Sterling NW, Cusumano JP, Shaham N, Piazza SJ, Liu G, Kong L, et al. Dopaminergic modulation of arm swing during gait among Parkinson's disease patients. J Park Dis. 2015;5(1):141–50.
14. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa I s a D ouble- E Dged S word for B Alance and G Ait in P Eople W Ith P Arkinson's D isease. Mov Disord Settembre. 2015;30(10):1361–70.
15. Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. Nat Rev Neurol Febbraio. 2015;11(2):98–110.
16. Kwon KY, Kim M, Lee SM, Kang SH, Lee HM, Koh SB. Is reduced arm and leg swing in Parkinson's disease associated with rigidity or bradykinesia? J Neurol Sci Giugno. 2014;341(1–2):32–5.
17. Winogrodzka A, Wagenaar RC, Booij J, Wolters EC. Rigidity and bradykinesia reduce interlimb coordination in parkinsonian gait. Arch Phys Med Rehabil Febbraio. 2005;86(2):183–9.
18. Pietrosanti L, Calado A, Verrelli CM, Pisani A, Suppa A, Fattapposta F et al. Harmonic Distortion Aspects in Upper Limb Swings during Gait in Parkinson's Disease. 2023.
19. Plate A, Sedunko D, Pelykh O, Schlick C, Ilmberger JR, Bötzel K. Normative data for arm swing asymmetry: How (a)symmetrical are we? Gait Posture. gennaio. 2015;41(1):13–8.
20. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease: MDS-PD clinical diagnostic criteria. Mov Disord Ottobre. 2015;30(12):1591–601.
21. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurol Maggio. 1967;17(5):427–427.
22. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc Aprile. 2005;53(4):695–9.
23. Carson N, Leach L, Murphy KJ. A re-examination of Montreal cognitive assessment (MoCA) cutoff scores. Int J Geriatr Psychiatry Febbraio. 2018;33(2):379–88.
24. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 15 Novembre. 2008;23(15):2129–70.
25. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: A frontal assessment battery at bedside. Neurol 12 Dicembre. 2000;55(11):1621–6.
26. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of Levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 15 Novembre. 2010;25(15):2649–53.
27. Podsiadlo D, Richardson S. The timed up & go: A test of basic functional mobility for frail elderly persons. J Am Geriatr Soc Febbraio. 1991;39(2):142–8.
28. Saggio G, Tombolini F, Ruggiero A. Technology-Based complex motor tasks assessment: A 6-DOF Inertial-Based system versus a Gold-Standard Optoelectronic-Based one. IEEE Sens J 15 Gennaio. 2021;21(2):1616–24.
29. Ricci M, Di Lazzaro G, Pisani A, Mercuri NB, Giannini F, Saggio G. Assessment of motor impairments in early untreated Parkinson's disease patients: the wearable electronics impact. IEEE J Biomed Health Inf Gennaio. 2020;24(1):120–30.

30. Ortega JD, Fehlman LA, Farley CT. Effects of aging and arm swing on the metabolic cost of stability in human walking. J Biomech Dicembre. 2008;41(16):3303–8.
31. Isaias IU, Volkmann J, Marzegan A, Marotta G, Cavallari P, Pezzoli G. The Influence of Dopaminergic Striatal Innervation on Upper Limb Locomotor Synergies. Sgambato-Faure V, curatore. PLoS ONE. 7 dicembre. 2012;7(12):e51464.
32. Gera A, O'Keefe JA, Ouyang B, Liu Y, Ruehl S, Buder M, et al. Gait asymmetry in glucocerebrosidase mutation carriers with Parkinson's disease. McKay JL, curatore. PLOS ONE 24 Gennaio. 2020;15(1):e0226494.
33. Koh SB, Park YM, Kim MJ, Kim WS. Influences of elbow, shoulder, trunk motion and temporospatial parameters on arm swing asymmetry of Parkinson's disease during walking. Hum Mov Sci Dicembre. 2019;68:102527.
34. Mian OS, Schneider SA, Schwingenschuh P, Bhatia KP, Day BL. Gait in SWEDDs patients: comparison with Parkinson's disease patients and healthy controls: gait in SWEDDS patients. Mov Disord Giugno. 2011;26(7):1266–73.
35. Ospina BM, Chaparro JAV, Paredes JDA, Pino YJC, Navarro A, Orozco JL. Objective Arm Swing Analysis in Early-Stage Parkinson's Disease Using an RGB-D Camera (Kinect®).
36. Huang X, Mahoney JM, Lewis MM, Guangwei Du, Piazza SJ, Cusumano JP. Both coordination and symmetry of arm swing are reduced in Parkinson's disease. Gait Posture Marzo. 2012;35(3):373–7.
37. Crenna P, Carpinella I, Lopiano L, Marzegan A, Rabuffetti M, Rizzone M, et al. Influence of basal ganglia on upper limb locomotor synergies. Evidence from deep brain stimulation and L-DOPA treatment in Parkinson's disease. Brain 1 Dicembre. 2008;131(12):3410–20.
38. Dietz V, Michel J. Locomotion in Parkinson's disease: neuronal coupling of upper and lower limbs. Brain 1 Dicembre. 2008;131(12):3421–31.
39. Pontzer H, Holloway JH, Raichlen DA, Lieberman DE. Control and function of arm swing in human walking and running. J Exp Biol Febbraio. 2009;212(Pt 4):523–34.
40. Collins SH, Adamczyk PG, Kuo AD. Dynamic arm swinging in human walking. Proc Biol Sci 22 Ottobre. 2009;276(1673):3679–88.
41. Hill A, Nantel J. The effects of arm swing amplitude and lower-limb asymmetry on gait stability. PLoS ONE. 2019;14(12):e0218644.
42. Bruijn SM, Meijer OG, Beek PJ, van Dieën JH. The effects of arm swing on human gait stability. J Exp Biol 1 Dicembre. 2010;213(Pt 23):3945–52.
43. Punt M, Bruijn SM, Wittink H, van Dieën JH. Effect of arm swing strategy on local dynamic stability of human gait. Gait Posture Febbraio. 2015;41(2):504–9.
44. Ferraris C, Amprimo G, Masi G, Vismara L, Cremascoli R, Sinagra S, et al. Evaluation of arm swing features and asymmetry during gait in Parkinson's disease using the Azure kinect sensor. Sens 21 Agosto. 2022;22(16):6282.
45. Bondi M, Zeilig G, Bloch A, Fasano A, Plotnik M. Split-arm swinging: the effect of arm swinging manipulation on interlimb coordination during walking. J Neurophysiol 1 Agosto. 2017;118(2):1021–33.
46. Liu P, Yu N, Yang Y, Yu Y, Sun X, Yu H, et al. Quantitative assessment of gait characteristics in patients with Parkinson's disease using 2D video. Parkinsonism Relat Disord Agosto. 2022;101:49–56.
47. Kuhtz-Buschbeck JP, Brockmann K, Gilster R, Koch A, Stolze H. Asymmetry of arm-swing not related to handedness. Gait Posture Aprile. 2008;27(3):447–54.
48. Mirelman A, Bernad-Elazari H, Nobel T, Thaler A, Peruzzi A, Plotnik M et al. Effects of Aging on Arm Swing during Gait: The Role of Gait Speed and Dual Tasking. Balasubramaniam R, curatore. PLOS ONE. 25 agosto. 2015;10(8):e0136043.
49. Roggendorf J, Chen S, Baudrexel S, Van De Loo S, Seifried C, Hilker R. Arm swing asymmetry in Parkinson's disease measured with ultrasound based motion analysis during treadmill gait. Gait Posture Gennaio. 2012;35(1):116–20.
50. Huang X, Mahoney JM, Lewis MM, Guangwei Du null, Piazza SJ, Cusumano JP. Both coordination and symmetry of arm swing are reduced in Parkinson's disease. Gait Posture. marzo. 2012;35(3):373–7.
51. Mirelman A, Bernad-Elazari H, Thaler A, Giladi-Yacobi E, Gurevich T, Gana-Weisz M, et al. Arm swing as a potential new prodromal marker of Parkinson's disease. Mov Disord Off J Mov Disord Soc Ottobre. 2016;31(10):1527–34.
52. Fearon C, Bhowmick SS, Tosserams A, Di Luca DG, Liao J, Nonnekes J, et al. Arm swing while walking and running: A new clinical feature to separate Parkinson's disease from functional parkinsonism. Mov Disord Clin Pract Febbraio. 2024;11(2):166–70.
53. Millar NL, Meakins A, Struyf F, Willmore E, Campbell AL, Kirwan PD, et al. Frozen shoulder. Nat Rev Dis Primer 8 Settembre. 2022;8(1):59.
54. Marinus J, Van Hilten JJ. The significance of motor (A)symmetry in Parkinson's disease. Mov Disord Marzo. 2015;30(3):379–85.
55. Zampogna A, Cavallieri F, Bove F, Suppa A, Castrioto A, Meoni S, et al. Axial impairment and falls in Parkinson's disease: 15 years of subthalamic deep brain stimulation. NPJ Park Dis 24 Settembre. 2022;8(1):121.
56. Tamás G, Kelemen A, Radics P, Valálik I, Heldman D, Klivényi P, et al. Effect of subthalamic stimulation on distal and proximal upper limb movements in Parkinson's disease. Brain Res 1 Ottobre. 2016;1648(Pt A):438–44.
57. Halliday GM, Macdonald V, Henderson JM. A comparison of degeneration in motor thalamus and cortex between progressive supranuclear palsy and Parkinson's disease. Brain J Neurol Ottobre. 2005;128(Pt 10):2272–80.
58. Rousseaux MWC, Marcogliese PC, Qu D, Hewitt SJ, Seang S, Kim RH, et al. Progressive dopaminergic cell loss with unilateral-to-bilateral progression in a genetic model of Parkinson disease. Proc Natl Acad Sci U S 25 Settembre. 2012;109(39):15918–23.
59. Yagi S, Yoshikawa E, Futatsubashi M, Yokokura M, Yoshihara Y, Torizuka T, et al. Progression from unilateral to bilateral parkinsonism in early Parkinson disease: implication of mesocortical dopamine dysfunction by PET. J Nucl Med Off Publ Soc Nucl Med Agosto. 2010;51(8):1250–7.
60. Monje MHG, Sánchez-Ferro Á, Pineda-Pardo JA, Vela-Desojo L, Alonso-Frech F, Obeso JA. Motor onset topography and progression in Parkinson's disease: the upper limb is first. Mov Disord Off J Mov Disord Soc Aprile. 2021;36(4):905–15.
61. Warmerdam E, Romijnders R, Hansen C, Elshehabi M, Zimmermann M, Metzger FG, et al. Arm swing responsiveness to dopaminergic medication in Parkinson's disease depends on task complexity. NPJ Park Dis 5 Ottobre. 2021;7(1):89.
62. Zampogna A, Suppa A, Bove F, Cavallieri F, Castrioto A, Meoni S et al. Disentangling Bradykinesia and Rigidity in Parkinson Disease: Evidence from Short- and Long-Term Subthalamic Nucleus Deep Brain Stimulation. Ann Neurol. 9 maggio. 2024.
63. Dietz V. Quadrupedal coordination of bipedal gait: implications for movement disorders. J Neurol Agosto. 2011;258(8):1406–12.
64. Pearcey GEP, Zehr EP. We are Upright-Walking cats: human limbs as sensory antennae during locomotion. Physiol 1 Settembre. 2019;34(5):354–64.
65. Dietz V. Do human bipeds use quadrupedal coordination? Trends Neurosci Settembre. 2002;25(9):462–7.
66. Granatosky MC, Schmitt D. The mechanical origins of arm-swinging. J Hum Evol Maggio. 2019;130:61–71.
67. Frigon A. The neural control of interlimb coordination during mammalian locomotion. J Neurophysiol 1 Giugno. 2017;117(6):2224–41.
68. Kudo N, Yamada T. Locomotor activity in a spinal cord-indlimb muscles Preparation of the newborn rat studied in vitro. Neurosci Lett Marzo. 1987;75(1):43–8.
69. Duysens J, Van De Crommert HWAA. Neural control of locomotion; part 1: the central pattern generator from cats to humans. Gait Posture Marzo. 1998;7(2):131–41.
70. Ryczko D, Dubuc R. The multifunctional mesencephalic locomotor region. Curr Pharm Des. 2013;19(24):4448–70.
71. Jahn K, Deutschländer A, Stephan T, Kalla R, Wiesmann M, Strupp M, et al. Imaging human supraspinal locomotor centers in brainstem and cerebellum. NeuroImage 15 Gennaio. 2008;39(2):786–92.
72. Winn P. Experimental studies of pedunculopontine functions: are they motor, sensory or integrative? Parkinsonism Relat Disord Luglio. 2008;14:S194–8.
73. Vercruysse S, Spildooren J, Heremans E, Wenderoth N, Swinnen SP, Vandenberghe W, et al. The neural correlates of upper limb motor blocks in Parkinson's disease and their relation to freezing of gait. Cereb Cortex 1 Dicembre. 2014;24(12):3154–66.
74. Jahanshahi M, Jones CRG, Zijlmans J, Katzenschlager R, Lee L, Quinn N, et al. Dopaminergic modulation of striato-frontal connectivity during motor timing in Parkinson's disease. Brain 1 Marzo. 2010;133(3):727–45.
75. Wu T, Wang L, Hallett M, Li K, Chan P. Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease. Brain 1 Agosto. 2010;133(8):2394–409.
76. Bharti K, Suppa A, Tommasin S, Zampogna A, Pietracupa S, Berardelli A, et al. Neuroimaging advances in Parkinson's disease with freezing of gait: A systematic review. NeuroImage Clin. 2019;24:102059.
77. Hellstrand E. Brain metabolism and human gait-a PET study. Acta Physiol Scand Novembre. 1985;125(3):555–6.
78. Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, et al. Brain functional activity during gait in normal subjects: a SPECT study. Neurosci Lett Giugno. 1997;228(3):183–6.

79. Jahn K, Deutschländer A, Stephan T, Strupp M, Wiesmann M, Brandt T. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. NeuroImage Agosto. 2004;22(4):1722–31.
80. Siragy T, Nantel J. Absent arm swing and dual tasking decreases trunk postural control and dynamic balance in people with Parkinson's disease. Front Neurol. 2020;11:213.
81. Weersink JB, Maurits NM, van Laar T, de Jong BM. Enhanced arm swing improves parkinsonian gait with EEG power modulations resembling healthy gait. Parkinsonism Relat Disord Ottobre. 2021;91:96–101.
82. Zampier VC, Vitório R, Beretta VS, Jaimes DAR, Orcioli-Silva D, Santos PCR, et al. Gait bradykinesia and hypometria decrease as arm swing frequency and amplitude increase. Neurosci Lett 20 Novembre. 2018;687:248–52.

Publisher's note