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Levodopa is a Double-Edged Sword for Balance and Gait in People with Parkinson's Disease

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Conflict of Interests

OHSU and Dr. Horak have a significant financial interest in APDM, a company that may have a commercial interest in the results of this research and technology. This potential institutional and individual conflict has been reviewed and managed by OHSU.

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Abstract

Background—The effects of levodopa on balance and gait function in people with Parkinson's disease (PD) is controversial. This study compared the relative responsiveness to levodopa on six domains of balance and gait: postural sway in stance, gait pace, dynamic stability, gait initiation, arm swing, and turning in people with mild and severe PD, with and without dyskinesia.

Methods—We studied 104 subjects with idiopathic PD (Hohen & Yahr II (n=52) and III-IV (n=52)) and 64 age-matched controls. Subjects performed a mobility task in the practical OFF state and ON levodopa: standing quietly for 30 seconds, initiating gait, walking 7 meters, and turning 180 degrees. Thirty-four measures of mobility were computed from inertial sensors. Standardized response means were used to determine the relative responsiveness to levodopa.

Results—The largest improvements with levodopa were found for arm swing and pace-related gait measures. Gait dynamic stability was unaffected by PD and not responsive to levodopa. Levodopa reduced turning duration, but only in subjects with severe PD. In contrast to gait, postural sway in quiet standing increased with levodopa, especially in the more severely affected subjects. The increase in postural sway, as well as decrease in turning duration and exaggerated arm swing with levodopa was observed only for subjects with dyskinesia at the time of testing.

Conclusions—The observed spectrum of levodopa responsiveness in balance and gait measures suggests multiple neural circuits control balance and gait. Many of the negative effects of levodopa may be directly or indirectly caused by dyskinesia.

Keywords

Parkinson's disease; levodopa; balance; gait; inertial sensors

Introduction

Gait and balance disturbances are common and important clinical manifestations of idiopathic Parkinson's disease (PD). Nevertheless, the effects of dopamine replacement therapy on gait and balance is unclear. Fragmented knowledge on balance or gait derives mostly from laboratory studies looking at single aspects of gait or balance ON and OFF levodopa. Dopa-responsive characteristics of gait have been widely described as stride length, gait speed, and double support time variability.[1] In contrast, cadence and other temporal characteristics of gait may be dopa-resistant.[1] The effect of dopamine replacement on static balance remains controversial; sway area during quiet standing has been reported to both increase and to decrease after levodopa intake.[2, 3] This discrepancy and others might be explained by differences in disease severity between studies. Other important measures such as anticipatory postural adjustments (APA) prior to step initiation, arm swing, and turning while walking have received scant attention.[4, 5] One reason for the uncertainty about the effects of levodopa on balance and gait is that balance and gait are often considered to be one function. However, physiological and imaging studies provide evidence for separate

supraspinal locomotor and postural control networks in animals and humans.[6] Therefore, to understand the effects of levodopa on the more global function of mobility, it is essential to study the effects of levodopa over a wide spectrum of postural and locomotor tasks, ranging from control of postural sway during quiet standing and steady gait, to movement that requires modulation of stereotypical gait, such as gait initiation and turning. A second reason for the uncertainty about the effects of levodopa on balance and gait is that the effects of levodopa may change with disease progression and presence of dyskinesia. Thus, a large sample of subjects with a wide range of disease severities is required to understand the effects of levodopa on balance and gait in parkinsonism. The purpose of this study was to compare the effects of levodopa across a variety of balance and gait parameters in a large number of people with idiopathic PD and varying disease severity using objective measures from body-worn inertial sensors. We hypothesized that the levodopa responsiveness would differ for different aspects of gait and balance and that disease severity and dyskinesia would influence the levodopa responsiveness.

Methods

Participants

We recruited 104 participants with a clinical diagnosis of idiopathic Parkinson's disease (PD)[7] and undergoing treatment with levodopa, and a group of 64 age-matched healthy control subjects (Table 1). All subjects with PD and controls were free of musculoskeletal and other neurological impairments that could affect gait and balance. Potential PD subjects for this study were approached through advertisement in the clinic, referral through clinicians and recruitment from our database of volunteers. Healthy control subjects were recruited from spouses and caregivers of the participants and our database of healthy volunteers. The protocol was approved by the OHSU Institutional Review Board. All participants gave their informed consent according to the Declaration of Helsinki.

Procedure

The subjects with PD were tested in the morning in their practical OFF state, i.e., at least 12 hours after their last intake of antiparkinsonian medications. Subsequently, they were retested in the ON state, i.e., 1 hour after a levodopa challenge dose that was approximately 1.25 fold of their regular levodopa dose. The healthy control subjects completed the same mobility tests but did not receive the levodopa.

Participants performed 3 trials of the Instrumented Stand and Walk test (ISAW), designed to include several domains of posture and gait.[8] The ISAW consisted of standing quietly for 30 seconds, followed by a verbal instruction to initiate gait with the most involved leg or dominant leg for control subjects, walk 7 meters, turn 180 degree after crossing a line on the ground, and return to the initial starting position (Figure 1). During quiet standing, the subjects were asked to keep their arms at their sides and look straight ahead. A template was used to achieve consistent foot placement with 10 cm between heels and a 30° outward rotation of the feet. Subjects were tested in a quiet hallway of the Oregon Clinical & Translational Research Center at OHSU.

Severity of PD was classified based on the Hoehn & Yahr (H&Y) stage.[9] To prevent rater bias, a clinician, blinded to the ON and OFF states, rated the motor Unified Parkinson's Disease Rating Scale (UPDRS), H&Y scale, and dyskinesia (modified Abnormal Involuntary Movement Scale (AIMS))[10], based on video recordings of the clinical assessments ON and OFF. Rigidity ratings from an UPDRS-trained researcher's scoring were used to complete the otherwise blinded video assessment. The Postural Instability and Gait Difficulty (PIGD) 4-item subscore was calculated from the Motor UPDRS (arising from a chair, standing posture, gait, and postural stability/pull test). The levodopa equivalent daily dose (LEDD) was determined for each of the subjects with PD.[11] Subjects also completed the Activities-specific Balance Confidence (ABC) Scale[12], and the Mobility section of the Parkinson's Disease Questionnaire (PDQ-39)[13]. Finally, subjects reported the number of falls in the previous 12 months.

Equipment

The subjects wore six inertial sensors on: both wrists, both ankles, the sternum and at the 5th lumbar level attached by elastic Velcro straps. The inertial sensors used were either MTX (Xsens, https://www.xsens.com) or Opal (APDM Inc, http://apdm.com). The sensors have similar characteristics; the interchangeability of systems was confirmed though concurrent evaluation (data unpublished). The APDM Mobility Lab software was used to extract all gait and balance parameters.[8]

Outcome Measures

Analysis focused on 34 reliable and valid measures of mobility (Figure 1).[14–17] Based on the results of a factor analysis (in preparation), metrics were categorized into independent domains that were assumed to rely upon different neural networks.[18, 19] Metrics were scaled to body size where appropriate. For a detailed description of the individual metrics and their calculation see (Appendix 1: Nomenclature).[17, 20]

Statistical analysis

The median value for each metric was extracted from the three ISAW trials in the ON and in the OFF states. The responsiveness of the different postural control and gait measures to levodopa was expressed as the standardized response mean (SRM). The SRM was calculated as the mean change between ON and OFF divided by the standard deviation of the change. The responsiveness to levodopa is given as improvement or worsening with respect to healthy control subjects. A SRM value of 0.20 represents a small, 0.50 a moderate, and 0.80 a large responsiveness.

To investigate the effect of disease severity and levodopa on balance and gait, repeated measures ANOVAs were performed. The subjects with PD were divided into two severity groups based on their H&Y stage. PD was considered mild with H&Y I-II (i.e., no clinical signs of postural instability) and severe with H&Y III-IV in the OFF state. PD subjects were also divided into those with a dyskinesia score = 0 and > 0 based on the Dyskinesia Rating Scale. If criteria for normality of data distribution (Kolmogorov–Smirnov test) were not met, data were logarithmically transformed. One-way ANOVAs were used to determine if the subjects with PD performed differently from control subjects. Chi-square test was used to

compare history of falls between subjects with and without dyskinesia. Correlation analyses were performed using Spearman rank correlation. Statistical significance was set to $p<0.05$.

Results

Sixty-four healthy control subjects (age 65.4 ± 6.0 years) and 104 subjects with PD (age 66.5 ± 6.1 years) were tested. Subjects with PD were categorized as either mild (H&Y II, n=52) or severe (H&Y III-IV, n=52). The mean duration of disease was shorter in the subjects with mild PD (7.2 ± 3.9 years) than the subjects with more severe PD (10.4 ± 6.8 years). The subjects with mild PD scored 32.8 ± 10.5 and the subjects with severe PD scored 38.8 ± 11.9 on the motor UPDRS in the OFF state (table 1).

Levodopa improved but did not normalize gait

For the group of subjects with PD as a whole, levodopa induced the largest improvements (SRM>0.5) in pace-related gait metrics (stride velocity, stride length, and lower leg range of motion (RoM leg)), as well as the arm swing RoM, and arm peak velocity during gait (Figures 2, and 3). Yet, even in these most responsive measures, the subjects with PD during their ON state were never within a standard deviation of the control subject values (Appendix 2). Smaller effects (SRM = 0.2 to 0.5) of levodopa included increasing the size of anticipatory postural adjustments (APAs) during step initiation and improving turning measures.

Levodopa worsened balance

Unlike the improvement seen in many gait metrics, levodopa worsened postural sway – sway dispersion (RMS) and sway velocity increased in the ON state, indicating that subjects with PD were less stable when ON than when OFF levodopa.

No changes with levodopa were found in dynamic stability metrics (double support time and swing time) during gait (SRM<0.2). These temporal gait metrics were also not different between subjects with PD and control subjects (Appendix 2).

SRM analysis revealed that motor UPDRS scores and PIGD sub-scores were large to moderately responsive to levodopa (motor UPDRS: SRM=0.81, PIGD: SRM=0.52; Figure 2).

Effects of Severity of PD on Measures of Balance and Gait and Their Response to Levodopa

Most metrics of pace, arm & trunk movement, turning, APA, and sway showed differences between control subjects and subjects with PD in either the ON or OFF state. However, none of the dynamic stability measures during gait detected differences between people with PD and healthy control subjects. As expected, subjects with advanced PD were significantly more impaired than subjects with mild PD in: stride velocity (Figure 3A), stride length (Figure 3B), leg RoM, size of the APA in ML (Figure 3C) and sway in ML direction (Figure 3D, sway RMS ML, sway mean velocity ML, and centroidal frequency ML). Arm swing velocity and range of the most affected arm (Figure 3E) were not significantly different

between subjects with advanced versus mild PD, and arm swing improved equally in both groups. There was an interaction between severity of disease and responsiveness to levodopa on three measures. Only in the more severely affected subjects, postural sway increased (RMS ML in Figure 3D), turning duration was shortened (Figure 3F), and mean step time during turning decreased (Appendix 2, Interaction: L-dopa x Severity).

Levodopa-induced Dyskinesia Increases Postural Instability

Of the 104 subjects with PD, 40 exhibited dyskinesia during testing. The subjects with dyskinesia had a slightly lower ON state motor UPDRS scores (25.3 ± 10.6) than the subjects without dyskinesia (32.3 ± 12.1). Dyskinetic subjects had a larger levodopa-induced improvement of the motor UPDRS (8.5 ± 8.1) than the subjects without dyskinesia (4.3 ± 6.4).

The effects of levodopa on balance and gait were influenced by the presence of dyskinesia. Subjects without dyskinesia showed no changes in speed of turning or in postural sway with levodopa. In contrast, subjects with levodopa-induced dyskinesia had an exaggerated arm swing (p=0.001; Figure 4A) and turned significantly faster in the ON than OFF state (p=0.004; Figure 4B). Dyskinetic subjects swayed significantly more during stance in the ON, compared to OFF state (p<0.001; Figure 4C). The levodopa-induced increase in postural sway correlated with a decrease in turning duration (r= −0.286, p<0.005). Consistent with the larger postural sway in dyskinetic subjects, the percentage of subjects with recurrent falls over the past year (≥2) tended to be higher in the group with dyskinesia (27.5%) than in the group without dyskinesia (12.5%; $\chi^2(1, N=104)=3.709$ p=0.054).

Discussion

Spectrum of Levodopa Responsiveness

This is the first study to compare levodopa responsiveness on balance, gait and postural transitions (gait initiation and turning) in the same large cohort of patients with idiopathic PD. We found a wide spectrum of levodopa-induced changes in mobility measures that ranged from improvement to worsening. The mixed responsiveness of balance and gait to levodopa has two immediate implications. First, it indicates that gait and balance are not a single function; instead, there are distinct, as well as overlapping, multiple neural circuits involved in control of balance and gait, with varying sensitivity to levodopa. Thus, various aspects of gait and balance must be evaluated individually. Successful and safe mobility will be a consequence of the integration of these and other aspects of gait and balance.

Second, the lack of improvement or worsening of some measures with levodopa supports the emerging view of PD as a multisystem failure including degeneration in cholinergic and norepinephrine circuits that may be important for control of balance and gait.[21] Further, recent imaging studies have shown abnormalities in cortical, cerebellar and brainstem nodes of the locomotor networks, as well as in the basal ganglia, in people with PD.[6, 22] Thus, pharmacologic treatment of balance and gait in PD may need to consider manipulating neurotransmitters of cortical and brainstem circuits rather than just focusing on nigrostriatal dopamine replacement therapy.

Improvement of Gait

The measures most improved by levodopa were arm swing range/velocity and gait velocity/stride length, indicating that these metrics would be good to monitor the ON and OFF fluctuations of parkinsonism related to medication cycles. Our results are consistent with previous laboratory studies, showing improvement of pace-related gait measures such as gait velocity and stride length with levodopa.[1, 23] However, it is important to note that even in the "ON" state, these very levodopa-responsive measures did not come within a standard deviation of these measures in control subjects. In addition, step initiation, cadence and turning were improved to a lesser extent by levodopa. This is in accord with a PET study that demonstrated that balance and gait measures of the UPDRS (PIGD) signs were not correlated with dopamine concentration in the putamen, although higher dopamine concentrations were associated with improvement of rigidity and bradykinesia.[24] In contrast, the temporal aspects of gait that determine the amount of time two feet, versus one foot, are on the ground, a sign of dynamic stability, were not impaired in patients with PD and did not change with levodopa.

Worsening of Balance

In the current study, levodopa increased ML and AP postural sway velocity and variability during quiet standing in subjects with H&Y stages III-IV. Postural sway is a well-recognized measure of fall risk in general and also in PD.[25] The deleterious effects of levodopa on postural sway are not an isolated example of exacerbating postural stability in PD. We previously have shown that levodopa worsens postural responses to surface displacements.[26] In contrast to postural sway, balance control during gait (ie; double support time) was not impaired by PD or changed by levodopa. The difference between static and dynamic balance control suggests that these domains of balance depend upon different neural circuits.

Effect of Dyskinesia

Splitting our PD cohort into two groups on the basis of dyskinesia observed during the testing produced two groups with similar disease severity on UPDRS motor scores. However, the increased postural sway with levodopa was confined to the subject group with dyskinesia. Dyskinesia appeared to drive the increase in sway during quiet standing since the extent and frequency of postural sway was related to their clinical dyskinesia ratings. This was not a surprise as we previously found that postural sway velocity and its variability were a sensitive measure of dyskinesia during quiet stance.[27] Dyskinesia increases postural sway by adding higher frequency, involuntary movements to normal, low frequency postural sway.[20] If dyskinesia is not associated with stabilizing anticipatory postural adjustments, these involuntary movements would also increase postural instability.[28] Indeed, dyskinesia was associated with a history of more falls in the previous year in our dyskinetic subjects than the nondyskinetic subjects. As our dyskinetic group did not have more severe disease as judged by the motor UPDRS than those without dyskinesia, our results suggest that dyskinesia itself, contributes to postural instability that could lead to falls. That is, dyskinesia is not simply an indication of more severe disease. An association between dyskinesia and falls has been suggested by other epidemiological studies.[29–31]

In addition to increasing postural sway, levodopa increased turning speed, which may also increase the risk of falls. Other investigators have shown, that subjects with PD turn “en bloc” with a narrow base of support, rather than leading with the eyes and head, regardless of severity of disease or levodopa state.[5] Thus, the sensorimotor strategy for dynamic balance during turning does not appear to be dopa-sensitive although we found that speed of turning is dopa-sensitive. However, because turning speed was increased only in the dyskinetic subjects and related to increased postural sway, it may be that increased turning speed is a product of dyskinesia and not just a direct effect of levodopa.

Like turning, arm swing is also faster in patients with dyskinesia and becomes exaggerated with levodopa in some dyskinetic patients. Exaggerated arm swing may be a sign of excessive motor disinhibition without improvement in motor coordination or postural control. This tradeoff between speeding up gait but increasing risk for falls by impairing postural control is also true for deep brain stimulation in people with PD.[32, 33]

Objective Balance and Gait Measures

Instrumented measures, such as from body-worn, inertial sensors, provide scalable measures of gait and balance dysfunction. Slowness of turning, step initiation, postural sway and reduced arm swing are important measures of PD that are difficult to assess clinically, much less quantify. These objective measures of balance and gait separated the healthy control subjects from subjects with parkinsonism and more severe subjects with PD from milder subjects. Observations from other studies suggest that inertial sensors may be effective for early disease detection,[34] monitoring disease progression,[35] predicting mobility impairment and falls[36] and, as shown in this study, measuring the response to interventions.

Limitations

This large observational study has several limitations. The measures of gait did not include variability in gait (too short gait path) nor width of steps (not measurable with inertial sensors), both features that may relate to dynamic stability. A second drawback was studying the subjects in the same order of OFF, and then ON, making sequence effects or fatigue a possible confounder. A third limitation is that the patient and control subgroups were very different in sex ratio, with more males in the patient group. However, females, who generally have lower gait speed, stride length, etc. than males, predominated in the control group should reduce, rather than enhance, differences in gait characteristics between the control and PD groups. Further, normalizations were applied to correct for potential differences, i.e., stride velocity and stride length were scaled to subjects’ height.[37]

Conclusion

Levodopa is a double-edged sword for treating mobility dysfunction in people with PD. When ON, subjects with PD walk and turn more quickly but became less stable during quiet standing and probably turning. Dyskinesia rather than disease severity accounted for these negative effects of levodopa.

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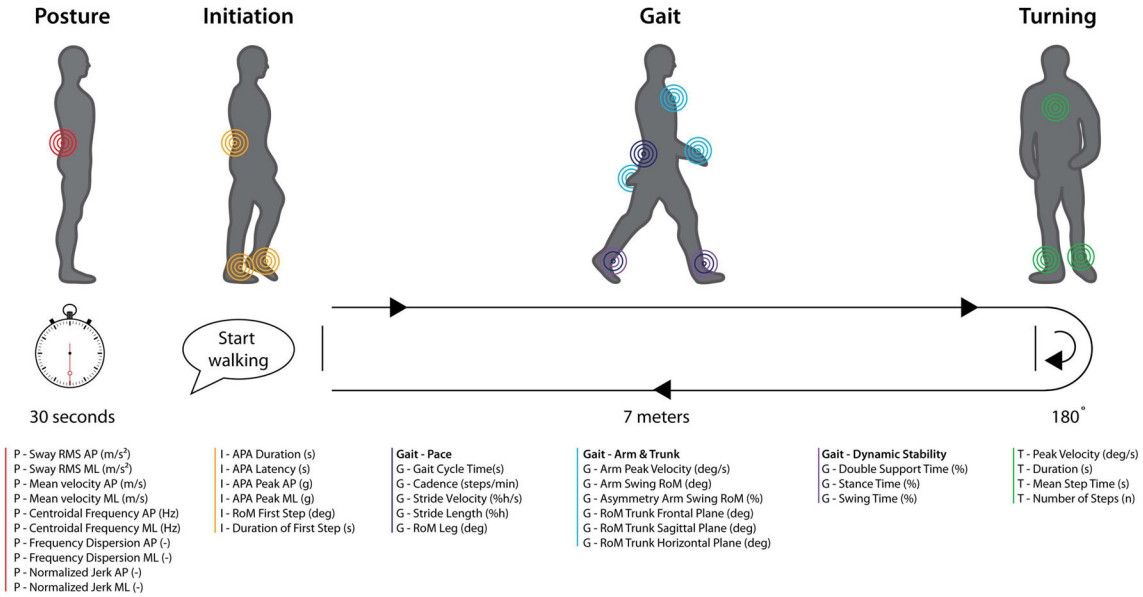

Figure 1.

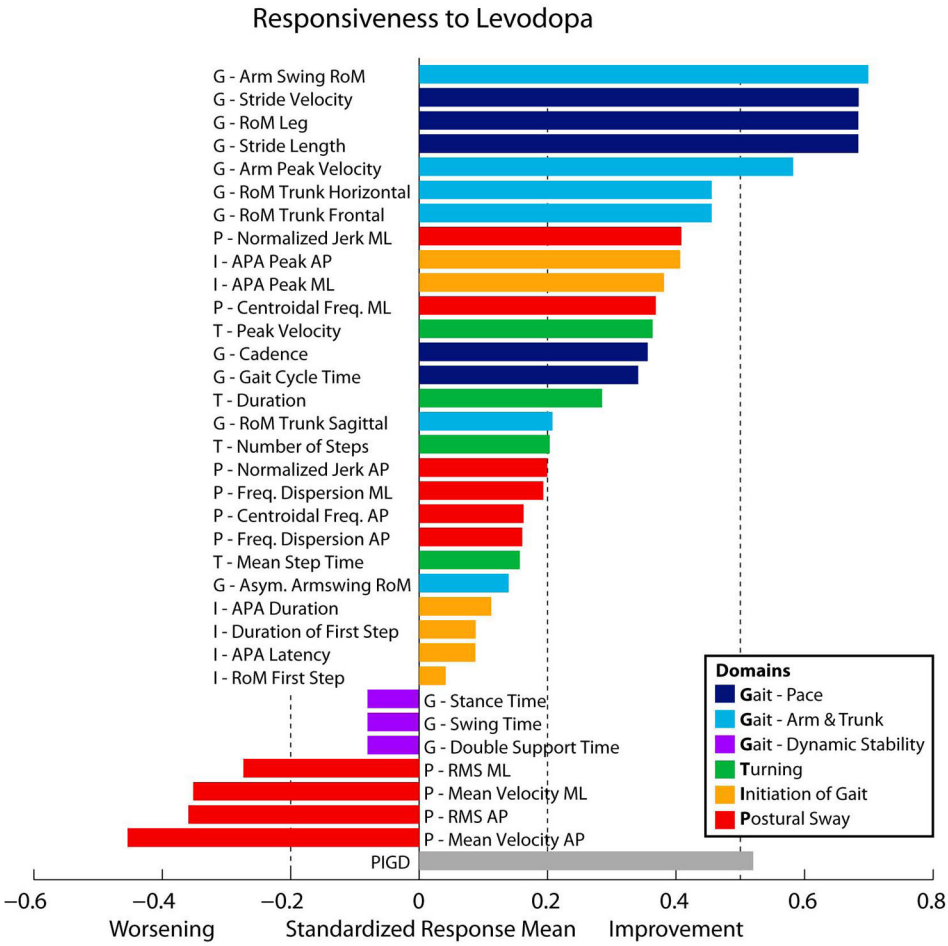

Figure 2.

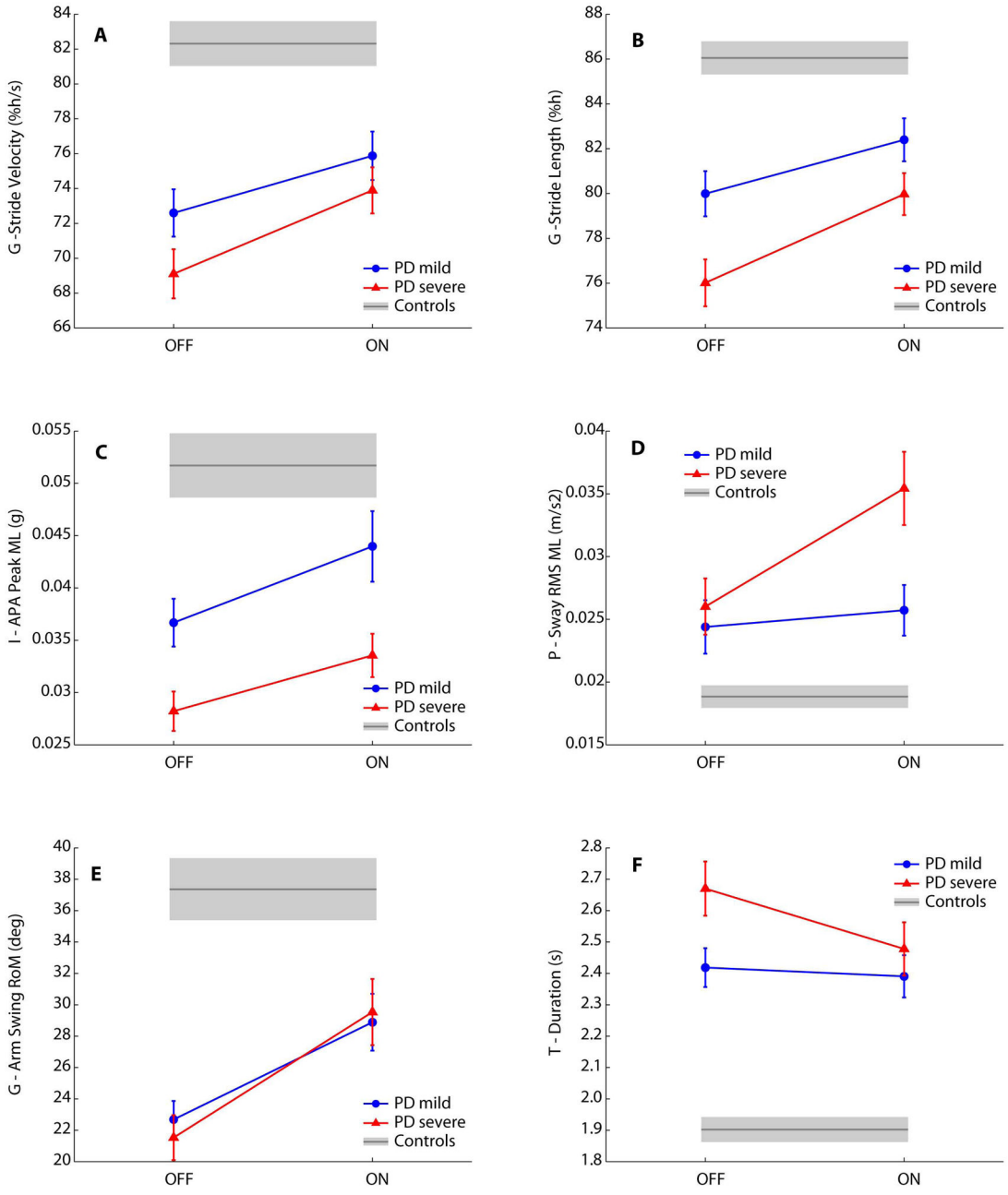

Figure 3.

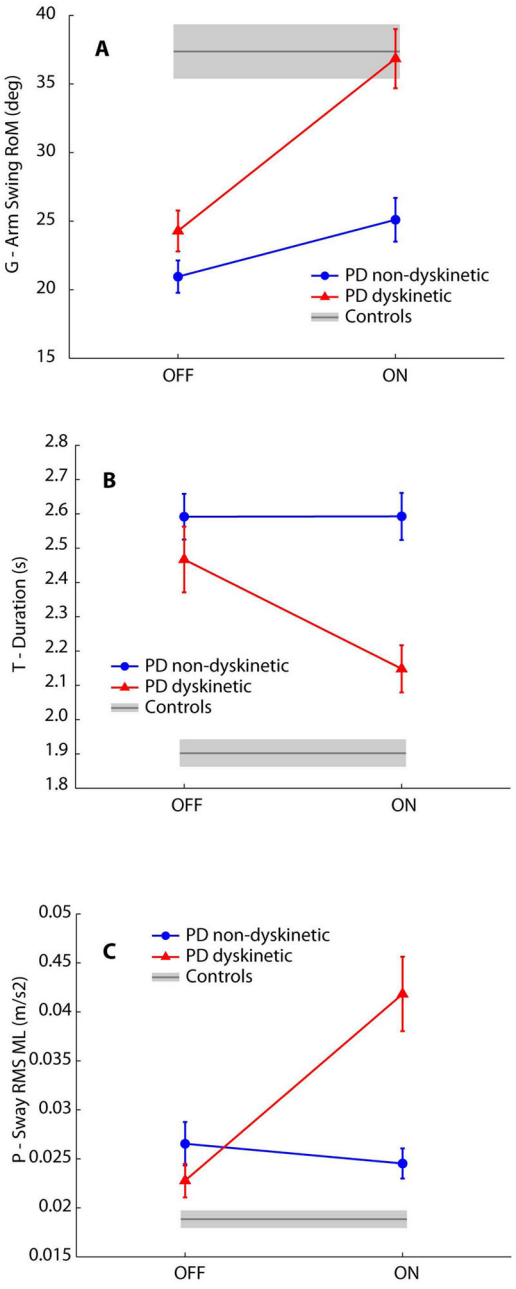

Figure 4.

Mov Disord. Author manuscript; available in PMC 2016 February 16.

Table 1

Participant Characteristics

	PD			Controls
	mild (Hoehn & Yahr II)	**severe (Hoehn & Yahr III-IV)**	**total**	
n	52	52	104	64
Age (years)	66.7 ± 5.5 (54–76)	66.3 ± 6.6 (56–80)	66.5 ± 6.1 (54–80)	65.4 ± 6.0 (53–77)
Height (m)	1.73 ± 0.10	1.72 ± 0.08	1.73 ± 0.09	1.68 ± 0.09
Weight (kg)	82.0 ± 14.5	80.1 ± 14.4	81.0 ± 14.4	75.1 ± 15.9
Male (%)	76.9	65.4	71.2	34.4
Disease Duration (years)	7.2 ± 3.9 (1–16)	10.4 ± 6.8 (2–29)	8.8 ± 5.8 (1–29)	
Hoehn & Yahr				
OFF	2.0 ± 0.0 (2–2)	3.1 ± 0.3 (3–4)	2.5 ± 0.6 (2–4)	
ON	2.1 ± 0.3 (2–3)	2.6 ± 0.6 (2–4)	2.4 ± 0.6 (2–4)	
Motor UPDRS				
OFF	32.8 ± 10.5 (10–58)	38.8 ± 11.9 (12–63)	35.8 ± 11.6 (10–63)	
ON	27.7 ± 12.2 (7–57)	31.8 ± 11.5 (7–56)	29.8 ± 11.9 (7–57)	
PIGD				
OFF	3.6 ± 1.7 (0–8)	5.8 ± 2.3 (1–11)	4.7 ± 2.3 (0–11)	
ON	3.2 ± 2.1 (0–7)	4.4 ± 2.3 (0–12)	3.8 ± 2.3 (0–12)	
Dyskinesia OFF/ON (n)	0/15	0/25	0/40	
ON	5.8 ± 4.3 (1–12)	6.7 ± 4.7 (1–18)	6.5 ± 4.3 (1–18)	
PDQ-39 Mobility	13.4 ± 12.3 (0–45)	26.3 ± 17.2 (0–62.5)	20.1 ± 16.1 (0–62.5)	
ABC Scale	85.9 ± 14.3 (42.5–100)	75.2 ± 15.9 (44.4–100)	80.4 ± 15.9 (42.5–100)	95.9 ± 5.9 (70.3–100)
Falls	n=49	n=50	n=99	n=46
0	73.5% (36)	54% (27)	63.6% (63)	82.6% (38)
1	20.4% (10)	14% (7)	17.2% (17)	13.0% (6)
≥2	6.1% (3)	32% (16)	19.2% (19)	4.4% (2)
Levodopa Equivalent Daily Dose (mg/day)	718.9 ± 389.0 (200–2100)	2240.7 ± 5666.5 (75–37560)	1480.1 ± 4068.6 (75–37560)	
Amantadine (n)	15% (8)	19% (10)	17% (18)	
Agonist (n)	54% (28)	54% (28)	54% (56)	

	PD			Controls
	mild (Hoehn & Yahr II)	severe (Hoehn & Yahr III-IV)	total	
Anticholinergics (n)	2% (1)	10% (5)	6% (6)	
MAO-B inhibitor (n)	12% (6)	17% (9)	14% (15)	

mean ± std (range)

Appendix 1

Nomenclature

Instrumented Measure	Unit	Definition
Gait - Pace		Pace during straight ahead walking
Gait Cycle Time	s	Duration of a complete gait cycle
Cadence	steps/min	Stepping rate
Stride Velocity	%h/s	Average gait speed normalized for height
Stride Length	%h	Distance between two consecutive heel strikes normalized for height
RoM Leg	deg	Range of motion of the leg (calculated from the integrated sagittal angular velocity, approximation of step length). Average of the left and right sides.
Gait - Arm & Trunk Movement		Arm and trunk movement during straight ahead walking
Arm Peak Velocity	deg/s	Peak (95%) angular velocity of most affected arm.
Arm Swing RoM	deg	Range of motion of most affected arm during arm-swing.
Asymmetry Arm Swing RoM	%	Average asymmetry of the left and right arm swing range of motion
RoM Trunk Frontal Plane	deg	Average range of motion of trunk in frontal plane
RoM Trunk Sagittal Plane	deg	Average range of motion of trunk in sagittal plane
RoM Trunk Horizontal Plane	deg	Average range of motion of trunk in horizontal plane
Gait - Dynamic Stability		Dynamic stability during straight ahead walking
Double Support Time	% of gait cycle	Percentage of a gait cycle that both feet are on the ground
Stance Time	% of gait cycle	Average percentage of a gait cycle that either foot is on the ground
Swing Time	% of gait cycle	Average percentage of a gait cycle that either foot is off the ground
Turning		180 degree turn
Peak Velocity	deg/s	Peak (95%) angular velocity of trunk during turning
Duration	s	Duration of a 180 degree turn
Mean Step Time	s	Average duration of step during 180 degree turn
Number of Steps	n	Total number of steps during 180 degree turn
Initiation of Gait		Anticipatory postural adjustments (APA) made when attempting to voluntarily initiate the first step to begin walking
APA Duration	s	Time from APA onset to end
APA Latency	s	Time from APA onset to first heel strike (from APA onset to peak angular velocity of the stepping leg, approximation of the first step velocity)
APA Peak AP	g	Peak trunk acceleration forward from baseline
APA Peak ML	g	Peak acceleration toward the stance foot of the lateral trunk acceleration
RoM First Step	deg	Range of motion of the leg (calculated from the integrated sagittal angular velocity, approximation of first step length)

Instrumented Measure	Unit	Definition
Duration of First Step	s	Time from toe-off to first heel strike
Postural Sway		Standing quietly for 30 seconds.
Sway RMS AP	m/s^2	Root mean square of acceleration time series in anteroposterior direction
Sway RMS ML	m/s^2	Root mean square of acceleration time series in mediolateral direction
Mean velocity AP	m/s	Mean velocity of center of pressure in anteroposterior direction
Mean velocity ML	m/s	Mean velocity of center of pressure in mediolateral direction
Centroidal Frequency AP	Hz	Centroidal frequency in anteroposterior direction; variability of the acceleration traces power ranging from 0 to 1
Centroidal Frequency ML	Hz	Centroidal frequency in mediolateral direction; variability of the acceleration traces power ranging from 0 to 1
Frequency Dispersion AP	-	Anteroposterior frequency dispersion; dimensionless measure of variability of the frequency content of the power spectral density (0 for a pure sinusoid, it increases with spectral bandwidth to 1)
Frequency Dispersion ML	-	Mediolateral frequency dispersion; dimensionless measure of variability of the frequency content of the power spectral density (0 for a pure sinusoid, it increases with spectral bandwidth to 1)
Normalized Jerk AP	-	Smoothness of sway, time derivative of anteroposterior acceleration normalized to range of anteroposterior acceleration excursion and duration
Normalized Jerk ML	-	Smoothness of sway, time derivative of mediolateral acceleration normalized to range of mediolateral acceleration excursion and duration

deg = degree; g = acceleration of gravity; %h = percent of subject's height; Hz = Herz; n = number; m/s^2 = acceleration; s = seconds; - = dimensionless

Appendix 2

Postural Control and Gait Characteristics

	PD mild OFF	PD mild ON	PD severe OFF	PD severe ON	Control	L-dopa (ON ~ OFF)	Severity (Mild ~ Severe)	Interaction (L-dopa x Severity)	PD OFF ~ Control	PD ON ~ Control
	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	p-value	p-value	p-value	p-value	p-value
Gait - Pace										
Gait Cycle Time (s)	1.11 ± 0.09	1.10 ± 0.09	1.11 ± 0.11	1.08 ± 0.09	1.06 ± 0.09	**0.001**	0.600	0.216	**0.001**	**0.024**
Cadence (steps/min)	108.73 ± 8.29	110.04 ± 9.03	109.29 ± 9.97	111.67 ± 8.96	114.38 ± 9.43	**0.001**	0.536	0.291	**<0.001**	**0.019**
Stride Velocity (%h/s)	72.87 ± 9.49	75.88 ± 9.83	69.11 ± 9.99	73.90 ± 9.35	82.32 ± 10.03	**<0.001**	0.141	0.202	**<0.001**	**<0.001**
Stride Length (%h)	80.33 ± 7.27	82.40 ± 6.80	75.86 ± 7.32	79.97 ± 6.55	86.05 ± 5.79	**<0.001**	**0.017**	0.096	**<0.001**	**<0.001**
RoM Leg (deg)	75.83 ± 6.94	77.75 ± 6.72	71.94 ± 6.84	75.23 ± 6.48	80.81 ± 5.04	**<0.001**	**0.024**	0.272	**<0.001**	**<0.001**
Gait – Arm & Trunk Movement										
Arm Peak Velocity (deg/s)	115.00 ± 37.21	137.66 ± 58.36	112.88 ± 36.93	142.56 ± 56.90	168.43 ± 45.95	**<0.001**	0.881	0.424	**<0.001**	**0.001**
Arm Swing RoM (deg)	22.86 ± 8.28	28.88 ± 12.82	21.53 ± 10.14	29.53 ± 14.91	37.36 ± 15.43	**<0.001**	0.906	0.377	**<0.001**	**0.001**
Asymmetry Arm Swing RoM (%)	64.46 ± 62.54	60.55 ± 50.28	67.23 ± 50.67	56.69 ± 48.69	36.83 ± 40.04	0.165	0.929	0.575	**0.027**	0.060
RoM Trunk Frontal Plane (deg)	4.21 ± 1.35	4.84 ± 1.54	4.41 ± 1.88	5.02 ± 2.33	4.86 ± 1.62	**<0.001**	0.564	0.888	**0.036**	0.822
RoM Trunk Sagittal Plane (deg)	4.34 ± 1.20	4.29 ± 1.13	4.13 ± 1.42	4.57 ± 1.48	4.32 ± 1.10	**0.038**	0.791	0.038	0.686	0.569
RoM Trunk Horizontal Plane (deg)	4.21 ± 1.35	4.84 ± 1.54	4.41 ± 1.88	5.02 ± 2.33	4.86 ± 1.62	**<0.001**	0.564	0.888	**0.036**	0.822
Gait - Dynamic Stability										
Double Support Time (% of gait cycle)	22.41 ± 4.13	23.02 ± 4.25	22.64 ± 4.68	22.75 ± 4.63	22.58 ± 4.15	0.425	0.946	0.604	0.936	0.659
Stance Time (% of gait cycle)	61.21 ± 2.06	61.51 ± 2.12	61.32 ± 2.34	61.38 ± 2.31	61.29 ± 2.08	0.425	0.946	0.604	0.936	0.659
Swing Time (% of gait cycle)	38.79 ± 2.06	38.49 ± 2.12	38.68 ± 2.34	38.62 ± 2.31	38.71 ± 2.08	0.425	0.946	0.604	0.936	0.659
Turning										
Peak Velocity (deg/s)	149.75 ± 26.15	155.73 ± 30.54	138.71 ± 30.36	150.16 ± 32.26	183.15 ± 32.49	**<0.001**	0.124	0.196	**<0.001**	**<0.001**
Duration (s)	2.42 ± 0.43	2.39 ± 0.48	2.67 ± 0.61	2.48 ± 0.60	1.90 ± 0.31	**0.005**	0.095	**0.032**	**<0.001**	**<0.001**
Mean Step Time (s)	0.59 ± 0.07	0.60 ± 0.07	0.60 ± 0.08	0.57 ± 0.06	0.59 ± 0.07	0.114	0.677	**0.031**	0.380	0.898
Number of Steps (n)	4.44 ± 0.96	4.44 ± 0.97	4.96 ± 1.17	4.60 ± 1.11	3.58 ± 0.81	0.041	0.081	0.071	**<0.001**	**<0.001**
Initiation of Gait										

	PD mild OFF	PD mild ON	PD severe OFF	PD severe ON	Control	L-dopa (ON ~ OFF)	Severity (Mild ~ Severe)	Interaction (L-dopa x Severity)	PD OFF ~ Control	PD ON ~ Control
	mean ± std	mean ± std	mean ± std	mean ± std	mean ± std	p-value	p-value	p-value	p-value	p-value
APA Duration (s)	0.40 ± 0.15	0.38 ± 0.09	0.38 ± 0.10	0.37 ± 0.10	0.36 ± 0.10	0.284	0.326	0.588	0.208	0.523
APA Latency (s)	0.55 ± 0.14	0.56 ± 0.33	0.57 ± 0.20	0.56 ± 0.21	0.57 ± 0.48	0.402	0.289	0.437	0.794	0.799
APA Peak AP (g)	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.05 ± 0.03	**<0.001**	0.224	0.226	**0.001**	0.362
APA Peak ML (g)	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.02	**<0.001**	**0.002**	0.570	**<0.001**	**<0.001**
RoM First Step (deg)	35.02 ± 6.43	35.38 ± 8.69	32.40 ± 7.99	32.77 ± 8.81	40.96 ± 7.69	0.694	0.223	0.864	**<0.001**	**<0.001**
Duration of First Step (s)	0.42 ± 0.08	0.43 ± 0.34	0.43 ± 0.19	0.43 ± 0.20	0.45 ± 0.49	0.400	0.146	0.570	0.667	0.739
Postural Sway										
Sway RMS AP (m/s^2)	0.066 ± 0.026	0.079 ± 0.035	0.073 ± 0.030	0.090 ± 0.056	0.056 ± 0.018	**0.001**	0.187	0.536	**0.001**	**<0.001**
Sway RMS ML (m/s^2)	0.024 ± 0.014	0.027 ± 0.016	0.026 ± 0.015	0.035 ± 0.020	0.019 ± 0.007	**0.008**	**0.037**	**0.046**	**0.003**	**<0.001**
Mean velocity AP (m/s)	0.128 ± 0.059	0.164 ± 0.083	0.143 ± 0.071	0.188 ± 0.108	0.113 ± 0.059	**<0.001**	0.139	0.628	**0.029**	**<0.001**
Mean velocity ML (m/s)	0.036 ± 0.021	0.044 ± 0.030	0.041 ± 0.030	0.065 ± 0.055	0.028 ± 0.015	**<0.001**	**0.036**	0.058	**0.004**	**<0.001**
Centroidal Frequency AP (Hz)	0.655 ± 0.311	0.622 ± 0.239	0.624 ± 0.337	0.550 ± 0.170	0.588 ± 0.112	0.105	0.243	0.530	0.236	0.912
Centroidal Frequency ML (Hz)	1.408 ± 0.500	1.282 ± 0.488	1.283 ± 0.498	1.061 ± 0.368	1.130 ± 0.268	**<0.001**	**0.026**	0.385	**0.002**	0.526
Frequency Dispersion AP (-)	0.825 ± 0.046	0.815 ± 0.036	0.832 ± 0.058	0.824 ± 0.054	0.811 ± 0.036	0.110	0.329	0.840	**0.019**	0.193
Frequency Dispersion ML (-)	0.680 ± 0.124	0.700 ± 0.112	0.701 ± 0.115	0.726 ± 0.087	0.717 ± 0.071	0.055	0.209	0.824	0.121	0.804
Normalized Jerk AP (-)	1.374 ± 0.793	1.203 ± 0.419	1.223 ± 0.634	1.108 ± 0.392	1.153 ± 0.229	**0.048**	0.171	0.676	0.126	0.977
Normalized Jerk ML (-)	3.008 ± 1.449	2.517 ± 1.162	2.852 ± 1.361	2.246 ± 1.051	2.351 ± 0.665	**<0.001**	0.288	0.744	**0.003**	0.859

p-values <0.05 are given in boldface