Effect of Levodopa and Environmental Setting on Gait and Turning Digital Markers Related to Falls in People with Parkinson's Disease

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ABSTRACT: **Background:** It is unknown whether medication status (*off* and *on* levodopa) or laboratory versus home settings plays a role in discriminating fallers and non-fallers in people with Parkinson's disease (PD).
Objectives: To investigate which specific digital gait and turning measures, obtained with body-worn sensors, best discriminated fallers from non-fallers with PD in the clinic and during daily life.
Methods: We recruited 34 subjects with PD (17 fallers and 17 non-fallers based on the past 6 month's falls). Subjects wore three inertial sensors attached to both feet and the lumbar region in the laboratory for a 3-minute walking task (both *off* and *on* levodopa) and during daily life activities for a week. We derived 24 digital (18 gait and 6 turn) measures from the 3-minute walk and from daily life.
Results: In clinic, none of the gait and turning measures collected during *on* levodopa state were significantly different between fallers and non-fallers. In contrast, digital measures collected in the *off* levodopa state were significantly different between groups, (average turn velocity, average number of steps to complete a turn, and variability of gait speed, $P < 0.03$). During daily life, the variability of average turn velocity ($P = 0.023$) was significantly different in fallers than non-fallers. Last, the average number of steps to complete a turn was significantly correlated with the patient-reported outcomes.
Conclusions: Digital measures of turning, but not gait, were different in fallers compared to non-fallers with PD, in the laboratory when *off* medication and during a daily life.

Falls represent a significant problem for people with Parkinson's disease (PD) leading to reduced quality of life,[1] hospitalization,[2,3] fractures (Paul et al.[2] and Thurman, Stevens, and Rao 2006),[4] and increased mortality.[5] Further, ~60% of people with PD fall at least once a year and 39% fall recurrently.[6] Because of these serious consequences, proper fall management has become a priority in PD, and fall prevention requires identification of patients at higher risk for falling.

Because most falls occur while walking and turning,[7–9] understanding gait and turning impairments when patients are both in the *off* and *on* levodopa state is very important. Specifically, it is unclear whether the likelihood of falling is affected by levodopa state. For example, it has been proposed that falls occur in the *on* levodopa state when patients are more active and walk faster with impaired balance control and sometimes, dyskinesia,[10,11] whereas others have proposed that falls mostly occur in the *off* levodopa state because of bradykinesia, rigidity, and impaired motor performance.[12] Characterizing the relationship between gait quality and falls in the *off* and *on* levodopa states may help clinicians considering whether a certain medication state would be better to assess fall risk during a clinic visit.[13]

In addition to understanding the effects of medication state on fall risk, understanding the effects of environmental setting while

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evaluating fall risk is important. Specifically, although a clinic/ laboratory gait assessments in *off* and *on* levodopa state provide information about gait ability under a supervised controlled condition, these assessments may not reflect functional gait performance during daily life.[14–16] It has been shown that gait impairments worsen during daily life in people with PD where multitasking, cluttered environments, and varied challenging conditions are very common.[15,17,18]

Recently, the use of wearable sensor technologies has made it possible to quantify gait in the clinic and during real-life using the same algorithms.[15–19] Although various gait measures obtained with wearable inertial sensors have been shown to discriminate between fallers and non-fallers in PD (either *off* or *on* or daily living conditions),[12,20–25] it remains unclear which of these measures are most meaningful under particular medication and test environment conditions. Hence, the aim of this pilot study was to compare the discriminative ability of a wide range of gait and turning parameters in separating fallers from non-fallers in relation to their levodopa state and environmental settings.

Methods

Participants

Thirty-four people with idiopathic PD participated in the study. Inclusion criteria for PD were a diagnosis of idiopathic PD from

a movement disorders neurologist with the United Kingdom PD Society Brain Bank criteria, Hoehn and Yahr scores of II–IV, and complaints about gait and balance. Exclusion criteria included the inability to follow protocol instructions, other factors affecting gait such as musculoskeletal disorders, uncorrected vision or vestibular problems, or inability to stand or walk in the home without an assistive device. The experimental protocol was approved by the institutional review board of the Oregon Health & Science University (eIRB 15578). All the participants provided informed written consent (Figs. 1 and 2).

Laboratory Data Collection

In the laboratory, participants were asked to wear three inertial sensors (Opals by APDM Wearable Technologies-a Clario company, Portland, OR); one sensor on top of each foot and one over the lower lumbar area with an elastic belt. Each Opal sensor includes a tri-axial accelerometer, gyroscope, and magnetometer with a sampling rate of 128 Hz. The Opal is lightweight (22 g), has a battery life of 12 hours, and includes 8 GB of storage, that can record over 30 days of data. Participants completed in both the *off* and *on* levodopa states: a 3-min walking task at their natural pace while wearing the Opal sensors and the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[26] III motor signs. The *off* levodopa state was defined as a state after at least 12-hours of anti-parkinsonian medication overnight. The *on* levodopa state was assessed on the same day after the *off* state testing and 1 hr after a regular dose of levodopa. In addition, self-
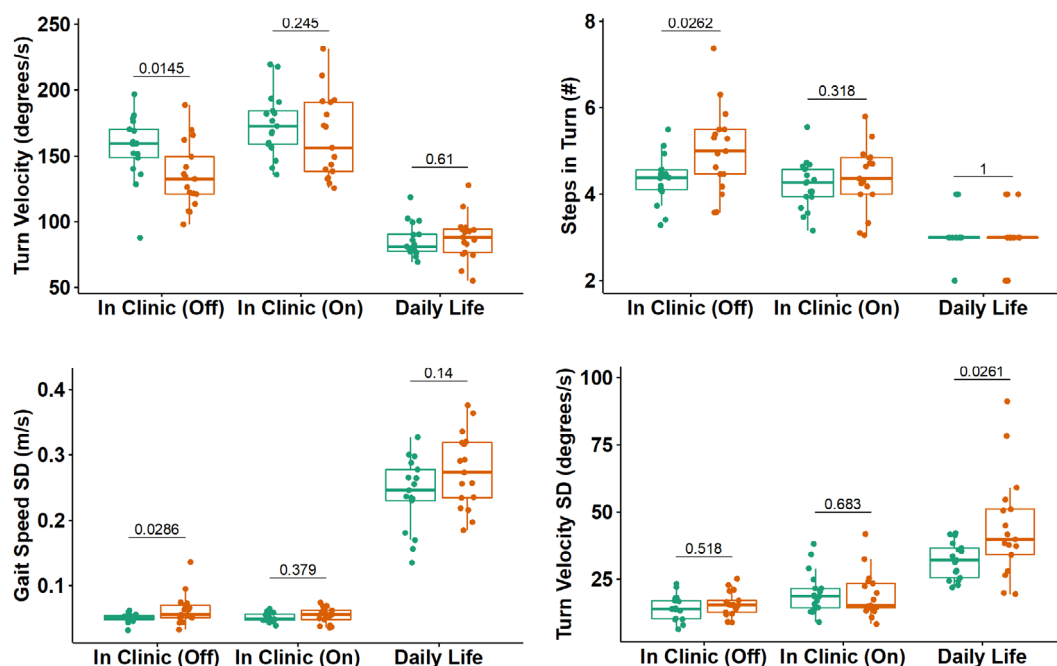
FIG. 1. Boxplot of gait and turning measures discriminating fallers from non-fallers in clinic (*on* and *off* levodopa state) and during daily life. Non-fallers are represented by the color green and the color red represents fallers.
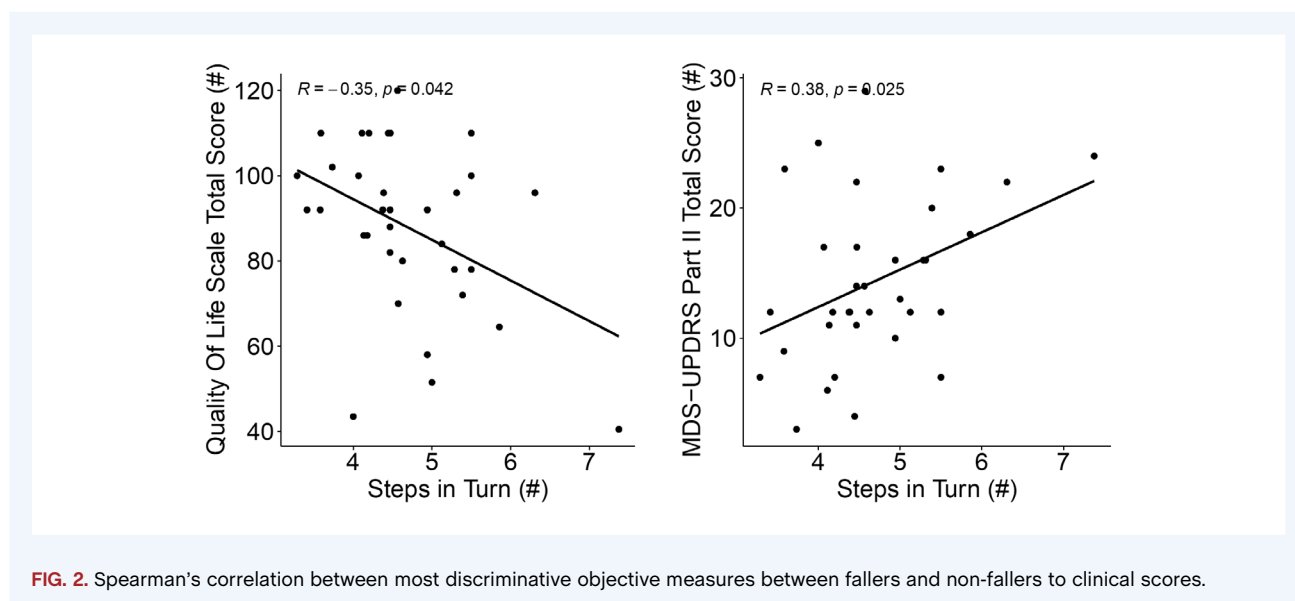
FIG. 2. Spearman's correlation between most discriminative objective measures between fallers and non-fallers to clinical scores.

reported fall history based on the prior 6 months was collected and participants were classified as fallers (at least one fall) or non-fallers based on fall history before the study visit. Overall cognition was assessed with the Montreal Cognitive Assessment (MoCA)[27] Finally, patient-reported scales, including the MDS-UPDRS, part II, the quality-of-life space questionnaires,[28] and the Parkinson's Disease Questionnaire-39 (PDQ-39)[29] were collected for each participant.

Daily Life Gait Data Collection

Participants were asked to wear two Opal-instrumented socks by APDM Wearable Technologies-a Clario Company and an Opal sensor over the lower lumbar area (at top of pelvis with an elastic belt that clipped together) for a week of continuous monitoring for at least 8 hr/d. The details of the instrumented socks were previously described in Shah et al.[17] Briefly, instrumented socks incorporated the same inertial sensors on top of the foot as the Opal, with the battery separated from the sensor and positioned just above the lateral malleolus. Participants removed the sensors at night to recharge the batteries. Data were stored in the internal memory of the Opals. Participants mailed back the sensors using a pre-paid mailing box after completion of a week of data collection. Raw data were uploaded to a secure cloud-based database on Amazon Web Server on return of the devices, processed on the same server and calculated gait metrics were then downloaded to a local computer for further analysis.

Digital Gait and Turning Measures in Clinic

We used the commercial gait analysis algorithms included in Mobility Lab, Version 2 (APDM Wearable Technologies-a Clario Company)[30] to extract spatial and temporal measures of gait and 180° turning, which have been validated previously.[31,32]

Digital Gait and Turning Measures During Daily Life

The algorithms used to calculate the measures of gait and turning were the same for the laboratory and daily life data and were detailed previously.[33] In summary, the daily life algorithm first searches for possible bouts of walking, using a time-domain approach to inertial sensor data from the feet and for turns, based on yaw-rotational orientation of the pelvis. Second, individual steps are combined into potential bouts of walking, as long as the duration from one step to the next step is no longer than 2.5 s. Finally, each possible bout that contains at least three steps and is at least 3 s in duration is processed with the commercial gait analysis algorithms included in Mobility Lab V2 for prescribed gait tests (APDM).[30] For the gait measures reported in this paper, we calculated a mean and variability across all strides over a week of recording and included only the periods of straight walking, and excluded walking during turns. For turning measures, we used a previously published algorithm to detect and characterize each turn.[34] Briefly, a turn was defined as a trunk rotation around the vertical plane with a minimum of 40°/s, and a start and end of the turn was defined with a threshold of 15°/s. Only turns with durations between 0.5 and 10 s, and turn angles of 40° or more were considered.

In total, for both laboratory and during daily life data, we considered 24 gait and turning measures (including mean and standard deviation). The complete list of measures and definitions are presented in Table S1.

Statistical Analysis

Because of small sample size, Mann–Whitney U test was used to compare the differences between faller and non-faller groups. Spearman's correlation was used to assess the relation between most discriminative mobility measures discriminating fallers from

non-fallers and severity of PD (such as UDPRS part II, and III, Life Space total score). All statistical analysis was performed using R Version 1.1.456 software. Because of the exploratory nature of this analysis, the statistical significance was set to $P < 0.05$.

Results

Group Characteristics and Adherence

From a total of 34 people with PD, 17 were fallers and 17 were non-fallers based on history of falls. Table 1 compares the demographic characteristics between fallers and non-fallers. There were no significant differences between the groups for demographic characteristics and activity measures from daily life (Table 1).

Digital Gait and Turning Measures Separating Fallers from Non-Fallers in the *Off* And *On* State (in Clinic)

Digital measures, from the 3-min walk test, that best separated the faller group from the non-faller group were: average turn velocity ($P = 0.014$), average number of steps to complete a 180° turn ($P = 0.026$), and variability of gait speed ($P = 0.028$) collected in the *off* levodopa state (See Fig.1 and Table 2) *on* levodopa state.

Digital Gait and Turning Measures Separating Fallers from Non-Fallers During Daily Life

One measure of variability, specifically, the variability of average turn velocity ($P = 0.044$), was statistically significant between fallers and non-fallers during daily life, with fallers showing more variability. (See Fig.1 and Table 2).

Associations with Patient Reported Outcome Measures

Both patient-reported outcomes, MDS-UPDRS part II total score ($r = 0.38$; $P = 0.02$) and Life Space total score ($r = −0.35$; $P = 0.04$) were significantly correlated with the average number of steps to complete a 180° turn during *off* levodopa state. (See Fig. 2).

TABLE 1 *Participant demographic information for non-faller and faller groups*

	Non-fallers (n = 17)	**Fallers (n = 17)**	**P**
Age (yr)	66.82 (6.61)	68.69 (11.10)	0.29
Disease duration (yr)	7.29 (5.6)	9.24 (4.58)	0.14
H & Y *on* (n)	2 (0)	2.18 (0.53)	0.164
H & Y *off* (n)	2.06 (0.24)	2.29 (0.59)	0.153
MDS-UPDRS part III total score *on* (n)	29.47 (8.49)	32.65 (9.92)	0.36
MDS-UPDRS part III total score *off* (n)	43.88 (11.3)	46.18 (10.02)	0.39
MDS-UPDRS part III PIGD score *on* (n)	2.59 (1.42)	3.53 (2.62)	0.34
MDS-UPDRS part III PIGD score *off* (n)	3.53 (1.66)	5.35 (3.28)	0.09
MoCA total score (n)	26.94 (2.38)	26.88 (2.93)	0.81
LEDD total score (mg/day)	1541.94 (2342.53)	1128.1 (533.18)	0.36
PDQ-39 total score (%)	13.91 (7.3)	23.3 (14.82)	0.13
PDQ-39 mobility score (%)	11.91 (12.14)	21.76 (18.68)	0.11
MDS-UPDRS dyskinesia *on* (n)	0.35 (0.49)	0.53 (0.51)	0.31
Activity measures from daily life			
Bouts/hr (n)	7.82 (3.05)	7.65 (4.16)	0.70
Strides/hr (n)	149.87 (60.95)	161.07 (94.82)	0.85
Turns/hr (n)	20.19 (9.33)	21.34 (15.71)	0.97

Abbreviations: H & Y, Hoehn and Yahr scale; MDS-UPDRS Part III, Movement Disorders Society-Unified Parkinson's Disease Rating Scale, motor sub-score; MoCA, Montreal Cognitive Assessment; LEDD, levodopa equivalent daily dose; PDQ-39, Parkinson's Disease Questionnaire-39.

TABLE 2 *Digital gait and turning measures between fallers and non-fallers in clinic (off, on* levodopa *states) and during daily life*

Metric	Off			On			Daily life		
	Non-fallers (n = 17)	Fallers (n = 17)	P	Non-fallers (n = 17)	Fallers (n = 17)	P	Non-fallers (N = 17)	Fallers (n = 17)	P
Turn velocity (°/s)	**156.21 (24.73)**	**135.26 (25)**	**0.01**	173.79 (23.8)	164.29 (31.73)	0.25	85.92 (12.91)	87.64 (16.95)	0.61
Steps in turn (n)	**4.34 (0.56)**	**5.02 (0.98)**	**0.03**	4.2 (0.57)	4.38 (0.74)	0.32	3.06 (0.56)	3.06 (0.56)	1.00
Gait speed SD (m/s)	**0.05 (0.01)**	**0.06 (0.02)**	**0.03**	0.05 (0.01)	0.05 (0.01)	0.38	0.24 (0.05)	0.28 (0.06)	0.14
Stride length SD (m)	0.04 (0.01)	0.06 (0.03)	0.05	0.05 (0.01)	0.04 (0.01)	0.89	0.22 (0.05)	0.27 (0.08)	0.07
Turn duration (s)	2.36 (0.36)	2.63 (0.44)	0.09	2.2 (0.25)	2.38 (0.33)	0.15	2.24 (0.23)	2.17 (0.31)	0.38
Stride time SD (s)	0.03 (0.01)	0.03 (0.01)	0.09	0.02 (0)	0.02 (0.01)	0.45	0.19 (0.05)	0.16 (0.03)	0.06
Elevation at mid swing (cm)	2.19 (0.41)	2.02 (0.48)	0.12	2.12 (0.45)	1.99 (0.49)	0.21	2.79 (0.91)	2.75 (0.6)	0.87
Foot strike angle SD (°)	1.57 (0.3)	1.83 (0.67)	0.13	1.7 (0.56)	1.78 (0.71)	0.84	6.64 (2.06)	7.59 (2.08)	0.25
Double support (%)	21.23 (4.41)	21.99 (3.38)	0.19	19.79 (2.92)	20.66 (2.87)	0.50	23.8 (4.66)	22.61 (3.11)	0.31
Stride time (s)	1.04 (0.06)	1.06 (0.06)	0.20	1.01 (0.05)	1.04 (0.07)	0.17	1.15 (0.12)	1.11 (0.07)	0.54
Cadence (steps/min)	116.28 (6.61)	113.28 (6.08)	0.21	119.13 (6.14)	115.92 (7.54)	0.16	105.19 (9.78)	108.32 (7.11)	0.54
Swing (%)	39.37 (2.19)	39.04 (1.68)	0.23	40.1 (1.43)	39.67 (1.43)	0.45	37.7 (2.21)	38.34 (1.49)	0.19
Toe *off* angle (°)	32.31 (6.01)	31.42 (4.7)	0.41	34.29 (4.05)	33.72 (4.76)	0.95	26.37 (6.52)	27.56 (5.72)	1.00
Steps in turn SD (n)	0.81 (0.24)	0.86 (0.23)	0.43	0.76 (0.25)	0.88 (0.25)	0.16	1.86 (0.25)	1.98 (0.28)	0.31
Cadence SD (steps/min)	2.86 (0.92)	3.4 (2.08)	0.52	2.56 (0.42)	2.74 (0.79)	0.84	6.79 (1.54)	6.36 (1.58)	0.27
Turn velocity SD (°/s)	14.38 (4.66)	15.71 (4.53)	0.52	20.06 (7.76)	19.11 (8.47)	0.68	**31.91 (6.87)**	**44.23 (19.08)**	**0.03**
Turn duration SD (s)	0.32 (0.08)	0.36 (0.11)	0.55	0.3 (0.08)	0.33 (0.11)	0.31	0.93 (0.12)	0.98 (0.22)	0.89
Foot strike angle (°)	11.8 (4.61)	12.77 (5.98)	0.66	14.52 (2.6)	15.85 (4.08)	0.22	17.22 (4.77)	17.14 (6.75)	0.84
Swing SD (%)	0.92 (0.28)	1.09 (0.72)	0.73	0.95 (0.38)	1 (0.57)	0.86	3.33 (0.92)	3.53 (0.98)	0.81
Stride length (m)	1.09 (0.21)	1.12 (0.23)	0.79	1.2 (0.11)	1.25 (0.22)	0.39	1.08 (0.21)	1.16 (0.26)	0.23
Double support SD (%)	1.44 (0.38)	1.58 (1.01)	0.89	1.43 (0.52)	1.46 (0.58)	0.73	6.02 (2.28)	7.03 (2.96)	0.54
Gait speed (m/s)	1.06 (0.21)	1.05 (0.21)	0.92	1.19 (0.1)	1.21 (0.22)	0.62	0.94 (0.23)	1.05 (0.24)	0.25
Toe *off* angle SD (°)	1.47 (0.42)	1.52 (0.55)	0.92	1.39 (0.34)	1.29 (0.26)	0.41	4.64 (1.16)	4.96 (1.16)	0.66
Elevation at mid swing SD (cm)	0.29 (0.07)	0.34 (0.2)	0.97	0.3 (0.07)	0.31 (0.1)	0.95	1.98 (0.78)	2.09 (0.77)	0.76

$P<0.05$

Discussion

Our findings demonstrated that levodopa medication state and environment both affect the discriminative ability of gait and turning measures to separate fallers from non-fallers. Specifically, measures representing the turning quality in fallers seem the most sensitive to discriminate PD fallers from non-fallers in both the *off* levodopa state and during daily life. In addition, the number to steps to complete a turn was related to patient-reported quality of life consistent with capturing meaningful, functional mobility characteristics of the fallers.

In Clinic

Slower turning measures (slower turn velocity and more steps to complete 180° turns) best discriminated PD fallers from non-fallers while in the *off* levodopa state. These results are consistent with impairments of turning in PD largely reported in the literature.[35–42] Further, turning characteristics are even more sensitive to early, untreated PD than are characteristics of straight-ahead, linear gait in a clinical Timed Up and Go Test.[43] Because turning is found to be associated with falls in older adults,[44,45] more steps and slower turn velocity to complete a turn in PD may reflect a very cautious turning strategy to assist in balance control.[46,47] To the authors' knowledge, this is the first preliminary evidence showing the potential of digital turning measures during *off* state as marker of falls in PD.

In addition to slow turning characteristics, higher gait speed variability was observed in fallers compared to non-fallers with PD. Although larger variability in multiple gait measures, such as stride-time variability, were shown to be associated with fall risk in PD,[12,48–50] in our small study stride-time variability showed a $P < .06$ in daily life and $P < .09$ in the *off* state to discriminate between fallers from non-fallers.

Overall, we found that *off* state (vs. *on* levodopa state) is more informative in detecting fallers. Our findings are in line with the findings of Hoskovcová et al.,[24] Foreman et al.,[51] and Valkovic et al.[13]

During Daily Life

Turning in individuals with PD is characterized by longer turning duration, more steps to complete turns, slower peak and average velocity, and smaller turn angles compared to age-matched, healthy controls in daily life.[17,34,44,52,53] In our study, we found variability of turning velocity during daily activities best discriminated fallers from non-fallers. In fact, higher variability in various gait and turning measures was observed previously in patients with PD compared to healthy control participants during free living conditions,[18,52,54] and has been shown to be related to fall risk in PD.[55]

Activity measures (ie, number of gait bouts, steps and turns per hour) were similar between fallers and non-fallers during daily life. This result is consistent with the result of Weiss et al.[55] where the authors found that the number of steps during 3-day recordings were similar between fallers and non-fallers.

We found that measures representing slow turning in the *off* levodopa state showed a significant correlation with patient-reported outcomes (representing what patients care about) suggesting concurrent (clinical) validity or meaningfulness of the measures. Future studies need to determine the test–retest reliability and sensitivity of the top measures to disease progression to investigate if these measure can be useful for digital endpoints for clinical trials.

There are several limitations of the current study. First, despite the findings suggesting the advantage of *off* medication testing, these results should be interpreted with caution because of the small sample size. The burden of assessing participants both *off* and *on* medication was high; therefore, we have a limited sample size. Second, all participants were first tested in *off* and then tested in *on* medication states on the same day, and there was no randomization in testing order based on medication state. Third, in our laboratory, patients only were tested for 180° turns, whereas in daily life we did not have that restriction so it is difficult to directly compare turning measures. Finally, we performed all analyses by taking the average and standard deviation of each measure across all strides over a week. However, in reality, gait speed and other measures are different for gait bouts of different lengths.[17–19] Hence, future research with larger samples, testing in multiple days and randomizing medication states, and looking into the gait and turning measures from a similar bout size in clinic and during daily life are needed to more strongly validate the use of *off* medication and daily life testing.

Conclusion

Objective measures of turning, specifically slower turning (represented by slower average turn velocity and higher number of steps to complete a turn) during a 3-min walk when *off* levodopa and increased variability of average turn velocity during daily life, were most sensitive to discriminate PD fallers from non-fallers and number of steps to turn 180° during *off* levodopa state was related to patient-reported quality of life.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique;

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Disclosures

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1 Gait measures and their definitions.