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Potential of APDM Mobility Lab for the monitoring of the progression of Parkinson's disease

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Summary

APDM's Mobility Lab system provides portable, validated, reliable, objective measures of balance and gait that are sensitive to PD. In this review, we describe the potential of objective measures collected with the Mobility Lab system for tracking longitudinal progression of PD. Balance and gait are among the most important motor impairments influencing quality of life for people with PD. Mobility Lab uses body-worn, Opal sensors on the legs, trunk and arms during prescribed tasks, such as the instrumented Get Up and Go test or quiet stance, to quickly quantify the quality of balance and gait in the clinical environment. The same Opal sensors can be sent home with patients to continuously monitor the quality of their daily activities. Objective measures have the potential to monitor progression of mobility impairments in PD throughout its course to improve patient care and accelerate clinical trials.

Keywords

Mobility; Parkinson's disease; inertial sensors; objective measures; Mobility Lab

The aim of this review commentary is to summarize the potential for balance and gait measures from Mobility Lab by APDM to track severity of Parkinson's disease. We first describe the clinical importance and challenge of assessing the severity of Parkinson's disease (PD) and its progression in an objective and reliable way. This introduction leads to the potential of wearable sensors to objectively characterize balance and gait impairments in PD.

Assessing Parkinson's disease stage and its rate of progression: the challenge

Parkinson disease is common among older people, affecting more than 1 in every 100 people over the age of 75 years [1–3]. On a worldwide basis, it is thought that approximately 10 million older people have PD. With a large proportion of the population aging, by the year 2020 more than 40 million people in the world will have this progressive, neurological condition [2]. Patients with PD report that balance disorders are the most important cause of reduced quality of life (PD Alliance.org). Balance disorders are the hallmark of PD and can severely compromise an individual's ability to perform important motor skills such as walking, turning around, and transferring in and out of bed [4].

All signs of movement disorders in PD, summarized in Table 1, can affect balance control. For example, tremor adds high frequencies to postural sway [5]; rigidity results in flexed posture and impaired ankle torque for posture and gait; bradykinesia results in slow gait speed, slow turning velocity, and slow postural responses; akinesia and freezing prolong step initiation; and dyskinesia may increase postural sway [6].

One challenge in measuring progression of PD is that its most promising medication, levodopa, improves tremor, bradykinesia and rigidity, but can impair some aspects of balance and result in dyskinesia that further impairs balance and gait. Levodopa is a dopamine precursor and several decades after its introduction, it remains the “gold standard” medical treatment for PD [7, 8]. In the early stage of the disease, the therapeutic effect of levodopa is very good and improves motor function, such as bradykinesia of gait. However, levodopa does not improve all types of balance control and may increase postural sway and impair postural responses [6, 9]. In addition, with disease progression and long-term therapy, subjects with PD start to experience motor fluctuations. Their motor condition may fluctuate between the OFF state (as a result of insufficient levodopa levels) and the ON state (in which levodopa levels are sufficient for the patient to respond as a non-parkinsonian person). In addition, subjects with PD in the ON state may develop motor complications, such as abrupt involuntary movements, known as dyskinesias, in response to peak levels of levodopa. Over the long-term, these fluctuations of motor symptoms may contribute to severe disability among subjects with PD.

Like levodopa, deep brain stimulation (DBS) of the subthalamic nucleus (STN) and internal globus pallidus (GPi) may provide an effective treatment for the alleviation of some motor signs [10, 11]. However, research studies on the effects of DBS on specific gait and balance are still controversial and DBS may even lead to an aggravation of freezing of gait and imbalance [12–17]. Two recent reviews [10, 11] specifically point out that while both STN and GPi-DBS improve some gait parameters and quiet standing postural control in subjects with PD, but have no effect, or may even aggravate, dynamic postural control, in particular with STN-DBS.

Therefore, measuring motor symptoms, treatment-related complications, and progression in PD is complex and challenging. The complexity is associated with the significant between- and within-patient variability in the manifestation of symptoms as well as with the emergence of motor fluctuations as a result of chronic treatment. Monitoring motor signs in PD, and specifically gait and balance impairments, is particularly challenging because gait and balance impairments respond poorly to most interventions, progress and add new impairments (e.g., freezing of gait) with disease progression, and consist of many different subsystems that vary in their response to intervention.

Limitations of clinical measures of balance and gait

Currently, clinical measures of progression of PD rely primarily on expert-delivered rating scales of PD signs and patient judgment of severity of symptoms. In a clinical setting today, the state of the art is to monitor progression of PD with clinical rating scales, such as Part III of the Unified Parkinson’s disease Rating Scale (UPDRS). [18–21]. Balance and gait are

measured with the Postural Instability and Gait Disability (PIGD) subscore (including posture, gait, sit-to-stand and the pull test) with scores from 0 (normal) to 16 (severe or unable to stand or walk) [18]. Quality of life is measured with the PD Quality of Life questionnaire (PDQ-39) [22], which is based on judgments of clinicians and perception of people with PD. The MDS-UPDRS (a revision of the UPDRS sponsored by the Movement Disorders society published in 2008) is a multidimensional scale, most widely used to clinically assess PD motor impairments and disability [23]. It is made-up of four parts, covering behaviors and mood (Part I), ADL (Part II), motor performance (Part III), and complications of therapy (Part IV).

During the evaluation of symptoms and treatments, both clinician- and patient-oriented outcomes offer complementary information [24]. In addition, paper diaries target self-assessments in the subjects' home environment. Subjects record the time they spend in 'off' (a motor state in which PD symptoms reappear as a result of insufficient levels of medication), in 'On' (in which medication levels are sufficient for good motor symptoms control) and in 'On with dyskinesia' (the appearance of hyper-kinetic movements related to excessive levels of medication).

However, the use of rating scales is not practical for long-term, repeated and remote follow-up of parkinsonian symptoms since they are relatively time-consuming, require a clinical visit, depend on considerable clinical expertise and some of their items have poor inter-clinician reliability [25, 26]. Furthermore, the clinical visit may not accurately represent the patients' activities in their home environment and may influence outcomes [27]. For example, the 'white coat effect' often results in better balance and gait when observed during a short test in the clinic than experienced in daily life. Home diaries capture symptom fluctuations better than clinical measures, but diaries are notoriously unreliable [28]. Since the use of clinical scales provides only a snapshot of symptom severity during the clinical visit, repeated measurements are useful in revealing the full extent of the subjects' condition and avoiding bias while measuring the effects of treatment [29]. Therefore, there is a need to add objective, observer-independent measures of PD motor impairments that can be measured during normal daily activities, as well as during prescribed tasks in the clinic.

Portable, objective measures and their potential

The most popular approach to objective assessments of PD symptoms, outside a specialized gait laboratory, involves the use of wearable, inertial sensor technology [30]. There are a number of objective assessment tools, several commercial products and many more developed for laboratories, reported in the literature that aim to provide objective assessments of PD-related symptoms including bradykinesia, therapy-induced dyskinesias, akinesia, posture and gait deficits among others [31–35]. Among the companies that have commercialized body-worn, inertial sensors, some are focused on systems that are simple and reliable for the clinical market, for example, see Table II.

The APDM Mobility Lab system (<http://www.apdm.com/mobility/>) uses synchronized, wearable inertial sensors to specifically monitor quality of gait and balance using a wide range of measures from the upper and lower body. Mobility Lab has been designed as a

portable gait and balance laboratory for clinicians and clinical researchers. Mobility Lab allows streamlined gait and balance assessment by making it easy to collect, store, analyze, and interpret balance and gait data from a large set of prescribed tasks. Mobility Lab™ is composed of: 1) a set 1–6 wireless, body-worn Opal™ inertial sensors, each with a docking station, 2) an Access Point for wireless data transmission and synchronization of the independent sensors, 3) user-friendly software to guide the user and subject(s) through the testing protocols, and 4) automated analysis and reporting of the recorded data. Figure 1 shows the location of the Opal sensors on the body and the small size of the Opal sensors that include 3-axis accelerometers and gyroscopes and a magnetometer, with a 12-hour battery and data storage for up to a month of daily use.

Depending on the measures and test, one to six Opals are attached to the body with straps, one posterior on the lower back (at the level of L5) for balance and postural transitions measures, two on the feet for gait measures, two on the arms, and one on the sternum. Figure 2 shows examples of metrics related to arm range of motion and turning during gait. These two measures have been shown to be particularly sensitive to PD [36], even in early stages [37], and levodopa replacement [6, 38] with important consequences. Reduced arm swing is one of the first noticed clinical signs in PD and changing direction while walking often causes instability and freezing of gait in PD.

Mobility Lab is easy to use, light and portable. With Mobility Lab, the user can choose which set of clinical tests to perform, such as the instrumented Timed-up and Go, Two-minute Walk, and Postural Sway tests [39], and receive the objective measures immediately after each test is performed. The clinimetric properties of Mobility Lab measures have been validated with gold-standard laboratory metrics and tested in diverse populations [37, 39–44].

For example, a subset of postural sway measures have been found sensitive to untreated, mild-to-moderate PD (13 untreated PD and 12 healthy controls) and those measures have been validated against the force plate gold standard and their test-retest reliability has been assessed in 17 subjects with PD as well as 17 healthy controls [42, 45]. Time-domain measures of postural sway (eg; sway dispersion, sway jerkiness, and sway area) showed the best test-retest reliability (with and Intraclass correlation coefficient, ICC, ranging from 0.55 to 0.84 in PD and from 0.60 to 0.89 in CTR). In addition, the time-domain measures were significantly correlated with the clinical postural stability (PIGD) score from the Motor UPDRS (r ranged from 0.50 to 0.63, $0.01 < p < 0.05$).

Clinimetrics were also evaluated for the instrumented Timed-up and Go, in the same population of untreated PD. [37, 43] Temporal measures of gait showed an excellent reliability ($ICC > 0.90$) and spatial measures (stride-length and stride-velocity) showed somewhat lower, but yet good, reliability ($ICC > 0.75$). Reliability of the estimated duration of turns and turn-to-sit transitions was also very high.

More recently, Dewey et al., [46] used the Mobility Lab system in a large cohort of 135 early-to-moderate subjects with PD. The cohort included both de novo subjects (never treated with Levodopa) as well as subjects in a moderate stage of the disease (tested ON

their antiparkinson medication). Their findings identified two sets of clinically meaningful measures of gait (from the instrumented Timed-up and go) and balance (from the instrumented postural sway test); one that can identify the presence of disease and a second set which can estimate disease severity. Interestingly, when grouping the subjects with PD in 5 subgroups based on PIGD subscore, the number of variables that were able to discriminate subjects with PD from healthy subjects was higher for gait than postural sway measures, but both worsened as the disease advanced. Interestingly, Fig. 3 shows that the separation between PD and healthy subjects gait and balance measures was largest for subjects with mild-moderate disease.

However, the work from Dewey [46] did not take into account the medication status. In fact, our recent findings[6] show how levodopa is a double-edged sword for balance and gait in a cohort of 104 subjects with PD. The largest improvements with levodopa were found for arm swing and pace-related gait measure, see Figure 4. Gait dynamic stability was unaffected by PD and not responsive to levodopa. In addition, 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 [6].

We also used APDM's instrumented Time-up and Go and postural sway tests to measure changes in balance and gait across 18 months in a small cohort of 13 untreated subjects with PD [37, 45]. Specifically, we showed that arm swing velocity, turn duration, trunk rotation and cadence were the most sensitive and specific measures to discriminate untreated PD [37]. We found that turning duration and arm speed progressively deteriorated over 18 months (Figure 5, unpublished data), whereas many other measures, such as gait speed and the clinical PIGD did not show change over that time period.

In addition, measures of postural sway, such as medio-lateral sway dispersion and sway velocity were also sensitive to disease progression [47]. In those subjects that remain untreated (N=5), it is possible to clearly see sway dispersion and sway velocity worsening at the 12 months compared to baseline, while in those subjects who started levodopa treatment (N=8) after the baseline session, an improvement is seen in the same measures.

We recently used Mobility Lab to collect pilot data before and after GPi DBS in 12 subjects with PD. We were able to quickly measure postural sway and gait in the clinic, while the subjects were attending their clinical appointments, in the ON state before surgery and in best state 60–90 days after surgery (ON DBS and levodopa). Sway dispersion significantly improved after surgery ($p=0.005$), while stride velocity showed a slight but not significant increase ($p=0.2$). These results, although preliminary, are promising and show the potential to improve outcomes with DBS, as it can provide a quick objective and quantitative assessment of gait and balance that clinicians could use to follow subjects with PD and optimize programming.

In summary, these findings show the potential for the Mobility Lab system to monitor disease progression in PD. However, single-event mobility measures in the clinic might not accurately reflect functional mobility during daily life. Clinical testing involves attention on balance and gait performance not typical during daily life activities. Clinical prescribed tasks

also cannot assess within-day, day-to-day, or other clinically relevant windows of change, such as medication-induced motor fluctuations or fatigue. The assessment of mobility during activities of daily living has the potential to objectively quantify mobility function outside the clinic similar to how a Holter heart rate monitor evaluates cardiac function over days and weeks. Although, previously, continuous monitoring was limited to use of accelerometers to measure the quantity of activity, now it is possible, with the latest generation of sensors, to continuously monitor quality of activity during daily life. We recently collected data with 3 Opals sensors on the shoes and belt continuously for seven days in 13 subjects with PD and 9 healthy controls of similar age. [48] New algorithms to detect walking and turning periods were first validated by comparing with video data of foot motion carried by subjects on their belts [49]. Specifically, we measured each change in direction while walking with an algorithm that, first detects periods of walking of 10 seconds or longer and then search for potential turns. The horizontal rotational rate of the lumbar sensor has been used to detect turning events during gait periods [48]. The turning characteristics were averaged across the week and the coefficient of variation was calculated for the following measures: 1) number of turns per hour, 2) turn angle amplitude, 3) turn duration, 4) turn peak velocity, 5) number of steps to complete a turn. In addition, activity rate was also calculated as the percent of time when subjects were walking, compared to the total monitoring time per day.

Subjects with PD showed impaired quality of turning compared to healthy control subjects, specifically a reduced turning velocity and increased number of steps to complete a turn (Figure 7, A and B). Measures of quality of turning were related to disease severity, as quantified with the UDPRS Motor Part III (Figure 7C). In contrast, no differences were seen in the overall activity (number of steps per day or percent of the day walking) during the seven days between PD and control subjects.

Expert commentary

Gait and balance objective measures may eventually become effective movement disorder biomarkers in tracking Parkinson's disease progression, especially when their pathophysiological correlates are better understood (see review by Horak and Mancini, [50]). Gait and balance are affected by all Parkinsonian motor signs and continue to progress even when bradykinesia, tremor and rigidity do not. Although often difficult to detect clinically, balance and gait are impaired very early in the disease and continue to progress, despite the best medical management. However, no single measure of balance or gait can reflect severity of Parkinsonism as different measures may progress at different rates and are differentially sensitive to change with levodopa medications, DBS surgery, or exercise interventions. Reliable and validated measures for PD to identify individuals at risk for falls, monitor response to therapy and track PD progression throughout its course would dramatically improve care in subjects with PD and accelerate research into both PD cause and therapeutics. Furthermore, clinical trials of neuroprotective interventions for PD currently lack accurate, quantitative measures for longitudinal tracking of posture and gait that are sensitive to change, even in early stages of the disease.

Five-year view

A limitation of assessment of mobility in the clinic is that it does not adequately reflect typical mobility function during daily life. Also, single, sparsely-spaced measures cannot assess within-day, day-to-day or other clinically relevant windows of change such as medication-induced motor fluctuations or fatigue. Currently, a solution to overcome this issue is activity monitors. Activity monitors can be worn for several days, and reflect the quantity but not the quality of mobility or the patterns of activity that emerge from continuous monitoring. Activity monitors measure total daily movements as reflected by accelerations and/or the percent of the day a subject is standing, walking or sitting/lying. Common measures include total activity duration, total number of steps taken, and the time spent in each activity. However, activity measures do not characterize specific gait impairments (shuffling, freezing, etc), features of postural control (excessive postural sway, small stepping responses), or the qualitative patterns of daily fluctuations.

Recently, new studies [48, 51–53] have focused on fluctuations of motor signs in PD that can be measured at home using wearable, light-weight inertial sensors placed in different part of the body. Novel measures calculated from both accelerometers and gyroscopes enables a detailed analysis of gait bouts and turning over a week of continuous recording, as well as analysis of patterns of accumulated activity. We believe that in the next five years, commercial systems will become available to allow continuous monitoring of quality of walking and turning to improve care of people with PD.

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Key issues

- Objective monitoring of balance and gait in Parkinson's disease is important to adequately assess disease stage and response to treatment and intervention.
- Specific balance and gait measures may progress differently through the course of the disease and are affected differently by interventions.
- Mobility Lab offers a wireless, easy-to-use alternative for clinicians to objectively assess gait and balance in PD
- Mobility Lab offers validated, objective measures of balance and gait that may be helpful in tracking disease progression
- Different objective measures of balance and gait are sensitive to untreated to moderate PD, levodopa replacement and DBS.
- Turning, arm swing during gait and sway dispersion may be reflecting changes in disease severity measured 18m apart.
- Measures of turning during walking might be more helpful compared to straight-ahead spatio-temporal gait measures in monitoring PD progression.
- To track disease progression more than measures collected in a one-time visit might be necessary, to characterize motor fluctuations and variability during the whole day
- Continuous monitoring of mobility at home, with wearable sensors, has the potential of being the more appropriate way to monitor PD progression, but more work in this area needs to be carried out.

A. Location of Opal sensors

B. Example of sensor attached to the wrist

C. Size of Opal sensors

Figure 1.
Sensors on body/photo of Opal

Figure 2.

Example of measures calculated with Mobility Lab. A) Range of motion, velocity, and symmetry of arm swing during gait. B) Turning during gait includes measures of turning angle, turning duration, velocity, and number of steps to complete a turn.

Figure 3.

Gait and Balance measures that differentiate subjects with PD and control subjects at different stages of disease severity (quantified by the PIGD subscore). Figure adapted from Dewey et al., [46]

Figure 4.
Effect of levodopa on gait and balance measures, measured by the standardize response mean (Adapted from Curtze et al, [6]).

Figure 5.

Change in group mean ($\pm$ SEM) balance and gait measures over time in 12 subjects with early PD (denovo) and 12 age-matched control subjects over 18 months. Upper panel: turning duration and arm swing during gait, measured during the instrumented Timed-up and go over 18 months. Lower panel: medio-lateral sway dispersion and sway velocity during 2 minutes of quiet stance over 12 months.

Figure 6.

Effect of DBS in GPi on balance (A. Medio-lateral sway dispersion) and gait (B. Stride velocity) in 12 patients with PD. Means ($\pm$ SEM) are represented in the best state before surgery (ON levodopa medication) and in the best state after surgery (ON levodopa and ON DBS) 60–90 days after DBS surgery. Significant ($p < .01$) improvement of balance by reducing sway dispersion but no improvement in gait is shown.

Figure 7.

Quality of turns measured across 7 days of continuous monitoring in 12 subjects with PD and 15 control subjects (Adapted from Mancini et al [48]). A) and B) box plots compare medians and interquartile range of quality of turning measures between the PD and control groups; C) Relationship between disease severity and quality of turns in the group with PD.

Table 1

Signs of movement disorders in people with Parkinson's disease impact their balance control [50].

Symptom	Description	Impact on Balance
<i>Tremor</i>	Resting tremor (5–7 Hz)	High frequencies of sway
<i>Rigidity</i>	Hypertonicity in agonist and antagonist muscles	Flexed posture; Weak torque to control CoM
<i>Bradykinesia</i>	Reduced movement speed and amplitude	Slow forces to control CoM
<i>Akinesia</i>	Difficulty in initiating movements like gait	Poor postural control for gait initiation
<i>Freezing episodes</i>	Motor blocks, sudden inability to walk	Impaired postural stepping for equilibrium
<i>Impaired postural control</i>	Difficulty maintaining stance balance or in response to perturbations, difficulty transferring	Falls without recovery of equilibrium during stance, perturbations and transfers
<i>Dyskinesia</i>	Wiggling, twitching involuntary movements	Fast turns and large sway area

Table 2

Systems available on the market that use one or more combinations of inertial sensors. Only systems that provide a report for clinicians are listed below. Abbreviations, IMU: Inertial Measurement Unit (3-D Accelerometer, 3-D Gyroscope, 3-D Magnetometer)

Product/Company	Sensors	Measures
<i>Mobility Lab APDM</i>	One-to six IMUs (feet, waist, wrists, sternum)	Spatio-temporal measures of gait, arm swing and trunk angles during gait, turning characteristics, sit-to-stand, and balance during quiet stance (modified clinical test of sensory interaction and balance).
<i>Move Test McRoberts</i>	One IMU on the waist	Spatio-temporal measures of gait, sit-to-stand, and balance during quiet stance. - No measures of upper trunk, arm swing during gait.
<i>Kinesia Greater Lakes Technology</i>	One-to two wireless inertial sensors (accelerometers and gyroscopes)	Tremor, bradykinesia, dyskinesia - No measures of spatio-temporal gait, arm swing during gait, or balance during quiet stance.
<i>BalanSens, LEGSys Biosensics</i>	One (balance) to five wireless inertial sensors (accelerometers and gyroscopes)	Balance during quiet stance, spatio-temporal gait parameters, knee and hip joint angles. - No measures of upper trunk or arm swing during gait, or turning.
<i>Gait Analysis Package Gait Up</i>	Two wireless IMUs on feet	Spatio-temporal measures of gait and turning. - No measures of upper trunk, arm swing during gait, or balance during quiet stance.