

## ***Quantitative wearable sensors for objective assessment of PD***

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## **Abstract**

There is a rapidly growing interest in the quantitative assessment of Parkinson's disease-associated signs and disability using wearable technology. Both persons with Parkinson's disease and their clinicians see advantages in such developments. Specifically, quantitative assessments using wearable technology may allow for continuous, unobtrusive, objective and ecologically valid data collection. Also, this approach may improve patient-doctor interaction, influence therapeutic decisions and ultimately ameliorate patients' global health status. In addition, such measures have the potential to be used as outcome parameters in clinical trials, allowing for frequent assessments, e.g., in the home setting. This review discusses promising wearable technology, addresses which parameters should be prioritized in such assessment strategies, and reports about studies that have already investigated daily life issues in Parkinson's disease using this new technology.

## Introduction

Clinical visits provide only a brief snapshot of the condition that persons with Parkinson's disease (PD) present in that particular situation. However, PD is notorious for its fluctuations, which may occur both within and across days. Moreover, performance during the clinical visit does not always reflect how patients perform at home. A well-known example is freezing of gait, which is often difficult to elicit in the examination room, even in patients who are severely debilitated by frequent freezing episodes at home<sup>1</sup>. Other events are by definition absent during routine clinical visits, such as nighttime disability caused by axial akinesia<sup>2</sup>. Measuring such disease-related outcomes objectively (fairly, without bias or external influence), continuously (without interruption), unobtrusively (not involving direct elicitation of data from the user) and with high ecological validity (approximating the real-world that is being examined, for example at the patients' homes), could boost the efficiency and clinical relevance of those visits, and improve patient management. This clinical wish appears to be coming within reach with the advent of new, wearable technology that can quantitatively collect, analyze and deliver data to both the patient and doctor. The relevance and accessibility of these data acquired from wearable technology is improving thanks to the development of sophisticated software and web-based applications (e.g.<sup>3</sup>). Objective recordings from wearable sensors may better help to capture meaningful data than information from surveys, paper and diaries that is retrospectively assessed<sup>4</sup> and prone to recall- and other sources of bias. In addition, consistency of symptom ratings may differ considerably between patient and doctor. Indeed, trained observers' and patients' ratings have surprisingly low agreement<sup>5,6</sup>.

From a scientific and methodological perspective, there is also great interest in such assessment strategies. For example, in some negative clinical trials, small effects may have been missed because the clinically based outcomes were unable to detect them (discussed in<sup>7,8</sup>). Use of wearable technique in future clinical trials might offer a way to detect such subtle changes more readily through a high responsiveness to change. This could potentially be important, e.g. when evaluating potential disease-modifying agents, because even small effects offer a proof of concept that the intervention at least achieved some biological effects. An additional advantage for clinical trials is the ability of wearable devices to measure outcomes at multiple time points, enhancing the statistical power.

Overall, continuous assessments of disease-associated signs and disabilities of persons with PD, e.g. in the home environment, are urgently required as they probably have high ecological validity. The technique is still in its infancy, and many aspects, including validity, reliability and data security issues must be considered before such assessment strategies can be applied routinely. From our point of view the following symptoms and signs are particularly relevant in this respect:

#### Motor disabilities

- Axial disability (gait and transfer deficits, freezing of gait, balance deficits, and falls)

- Distal bradykinesia

- Dyskinesias

- Tremor

- Dysarthria

- Sedentary lifestyle and physical inactivity

#### Non-motor disabilities

- Sleep disturbances

- Autonomic dysfunctions

Table 1 reviews wearable assessment tools that have already been used to detect some of these signs and symptoms, with a particular focus on studies that assessed responsiveness of therapy, and on techniques that were tested in an everyday environment. A discussion about device-assisted detection strategies cannot be comprehensive (and there are indeed examples of emerging – also not body-worn – objective measures of disability in people with PD<sup>9</sup>), but based on some illustrative examples, we aim to give readers a feel for the current status and potential applications of this new and potentially important wearable technology.

### ***Motor disabilities***

#### ***Axial signs***

Axial signs such as postural instability and gait deficits, including freezing of gait (FOG), have long been considered as late symptoms of PD. However, using new assessment strategies

and algorithms, it is becoming clear that at least some gait and balance parameters can be altered in early or even preclinical stages of PD<sup>10-12</sup>.

### Gait and transfer deficits

PD is characterised by a hypokinetic gait, with slow and shuffling steps, as well as an asymmetrically reduced arm swing<sup>13</sup>. This hypokinetic gait usually improves with dopaminergic medication<sup>14</sup>, deep brain stimulation (DBS)<sup>15</sup> and with a variety of physical therapy interventions, including high-amplitude movements<sup>16</sup>, dancing<sup>17</sup> and Nordic Walking<sup>18, 19</sup>. It would be helpful for clinicians to be reliably informed about the progression of gait disability and the therapeutic effects of applied interventions. However, gait assessment during a typical clinical visit is mostly only qualitative, subjective and brief.

During recent years, wearable technical solutions have markedly enhanced the quality of gait assessment. For example, a small device with acceleration and angular velocity sensors worn on the shank has been used to assess stride length over a 24-h period<sup>20</sup>. The investigators found a 100% agreement between the stride length measurement assessed with the wearable sensors, and video observation. Others have used pressure-sensitive foot insoles as sensors, and developed a different outcome, namely a coefficient representing the variability and inaccuracy in phase generation<sup>21, 22</sup>. Their results showed that gait variability was larger in persons with PD than in controls. This is relevant because gait variability can be used as marker to help predict the risk of future falls<sup>23-25</sup>.

Collection of disease-relevant gait data may even be possible using a single wearable sensor. For example, stride-to-stride variability in PD patients can be assessed using the acceleration signal of the vertical axis derived from a sensor which is worn at the lower back<sup>26</sup>.

Moreover, the authors found that automated frequency-based measures solely from the vertical acceleration signals differentiated PD patients from controls, and also distinguished between PD patients in their ON and OFF state with acceptable accuracy<sup>26</sup>. Interestingly, this difference was also visible when the participants walked around the medical center, suggesting that frequency-based analysis approaches could provide ecologically valid estimates of stride-to-stride variability even under everyday circumstances<sup>26</sup>. Acceptable accuracy for the detection of ON/OFF phases has also been demonstrated for the parameter

stride length, assessed with an unobtrusive inertial measurement unit worn at the left shank<sup>27</sup>.

Data derived from angular velocity transducers attached to the lower back indicate that turning when walking is slower, and that trunk movements are slower in untreated early-to-moderate PD patients, compared to controls<sup>28</sup>. Reduced arm swing and arm swing asymmetry are also hallmarks of PD. A recent study<sup>29</sup> found a reduced peak arm swing velocity on the more affected side of untreated early-to-moderate PD patients compared to controls using a gyroscope attached to the dorsum of each wrist. Similar results were found by use of accelerometers attached to the forearms<sup>30</sup>.

### Freezing of gait

FOG is a disabling phenomenon characterized by brief episodes during which patients are unable to generate effective forward stepping movements. It is one of the most important factors that constrain quality of life in PD<sup>31</sup>. Moreover, FOG now appears to be one of the most important causes of falls<sup>32, 33</sup>. FOG is a treatable condition. For example, OFF-period FOG responds relatively well to medication, but in rare cases L-dopa can worsen FOG<sup>34</sup>. Also, non-medical interventions such as cueing strategies<sup>35</sup> and robot-assisted gait training<sup>36</sup> can reduce FOG frequency and severity.

All these aspects argue for an evaluation of FOG. However, it can be extremely difficult to elicit FOG episodes when examining affected PD patients in the hospital<sup>1</sup>, because examinations are typically performed under “ideal” circumstances (wide open corridors, even terrain, well-lit environment) that are unlikely to elicit FOG, and the sheer knowledge of being observed can suppress the sign. This underscores the need for continuous assessments, preferably in the home environment of the patient.

What techniques are currently available to detect FOG? A broadly studied approach aims to assess FOG by evaluating the spatiotemporal kinematic parameters of gait<sup>37, 38</sup>. For example, one lab-based study examined people with PD who had to avoid suddenly appearing obstacles while walking on a moving treadmill, a paradigm known to elicit FOG<sup>39</sup>. Gait kinematics were assessed using motion analysis, based on feedback of goniometers. With a frequency-based approach that has previously been shown to detect FOG in PD accurately<sup>40</sup>, even very subtle FOG episodes could be detected with acceptable sensitivity and high

specificity, compared to judgement by two movement disorders specialists in a video analysis<sup>39</sup>. The detection of such subtle FOG is potentially relevant because they might serve as a marker for more severe FOG, making the transformation of this technology into ambulatory assessment highly demanding.

The first attempts to detect FOG online during ecologically valid real life-conditions with wearable devices are promising. In a recent study, 237 FOG events were detected with a sensitivity of 73% and a specificity of 82%, compared to judgement by professional physiotherapists in a post-hoc video analysis<sup>41</sup>. These devices can potentially be used even for online cueing of actual FOG events<sup>42</sup>.

### Balance deficits

Balance impairment in PD greatly affects quality of life. The response to medical therapy is complex, as some elements of postural control may improve, others are resistant to treatment, and still others may in fact worsen<sup>43, 44</sup>. Balance deficits may also improve with specific physical therapy interventions, such as strength and balance training<sup>45</sup> or, with a lower level of evidence, tai chi<sup>46</sup>. A notorious problem that hampers further development of better treatment strategies is the lack of reliable and sensitive clinical outcome measures, including the subjective scoring of the test outcome (judging the number and quality of the compensatory stepping reactions)<sup>47</sup>. It would therefore be helpful to have an unobtrusive quantitative “mobile” assessment of balance control, in order to detect deficits as early as possible, and to monitor progression.

Wearable technology is now available to detect even subtle balance deficits. Most approaches aim to measure sway of the trunk or the body’s centre of gravity, as a derivative of balance control, assuming that less sway equates with better balance performance (note that this is not necessarily true, as some have argued that under certain circumstances, large sway excursions are actually useful, for example to “probe” the environment<sup>48, 49</sup>; Moreover, in PD patients dyskinesia has been shown to relevantly influence balance parameters<sup>50</sup>). For example, a linear accelerometer attached to the lower back can be used to detect mild postural sway abnormalities in early-stage, untreated PD patients during quiet stance, and the results are comparable with those of a more expensive, lab-based static posturography assessment (forceplates)<sup>51</sup>.

It is also possible to detect postural sway with wearable sensors while subjects are moving about freely, e.g. while walking. For example, a combination of two angular sensors, again attached to the lower back, has been used to measure trunk sway in the pitch (anterior-posterior) and roll (medio-lateral) plane, while subjects performed a variety of everyday gait and balance tasks<sup>52</sup>. The results showed that persons with PD have larger anterior-posterior and medial-lateral angular velocity deviations at the trunk when performing stance tasks, compared to controls. When this device is rotated 90 degrees, one of the sensors now measures rotations in the yaw plane (vertical axis), and this is highly relevant because this permits assessment of axial turning during walking (now recognized as the most common precipitant of FOG). The same device was recently used to determine balance differences in PD patients before and after biofeedback training, suggesting that this kind of training has beneficial effects on trunk stability<sup>53</sup>.

Anticipatory postural adjustments represent another interesting balance parameter associated with an increased risk of freezing and falling. In order to allow for stepping movements, anticipatory weight shifts are necessary to “free up” the swing leg. Lab-based assessments had demonstrated that these anticipatory postural adjustments are reduced in persons with PD<sup>54, 55</sup>. Using a sensor at the lower back, it was found that anticipatory postural adjustments towards the stance leg (as measured from the peak trunk acceleration) were smaller in untreated PD patients compared to control individuals<sup>56</sup>, also indicating that wearable technology is able to detect changes of this parameter.

#### Combined assessments

Combinations of axial movements such as transfers, gait, turning and balance reflect a more true-to-life condition. The Timed up and Go (TUG) test is a widely used clinical paradigm to test such combinations. However, the usefulness of this test is limited by the fact that only the total time to perform all these different and complex movements is measured. A number of studies evaluating subcomponents of the TUG (e.g. sit-to-stand and stand-to-sit transfer<sup>57</sup>) by using wearable sensors have recently been published. One study found that, when comparing early PD patients with controls, total TUG time was similar between the groups



but cadence, angular velocity of arm swing, turning duration and time to perform turn-to-sits differed significantly<sup>58</sup>.

Such objective gait assessments may now become readily available to a wide audience through the use of commercially available smart-phones with built-in accelerometers. Such devices can be used to quantify performance on the TUG, and in fact equally good as a device that was specifically developed for movement analysis<sup>59</sup>. We expect that smart-phones will soon develop into pervasive, low-cost tools for continuous quantitative assessment of movement and mobility.

### Fall events

Falls are usually defined as “events where subjects inadvertently come to rest on a lower level”<sup>60</sup>. There is an enormous interest to monitor falls because of the associated morbidity (injuries, loss of independence) and even mortality<sup>61</sup>. Fall frequency should therefore be one of the most relevant outcome parameters in future disease progression studies and clinical trials. Particularly the latter application is becoming increasingly important, in light of exciting new evidence for therapeutic interventions that may reduce falls, including cholinesterase inhibitors<sup>62</sup> and strength and balance training<sup>45, 63</sup>.

Falls are sporadic, episodic events, so prolonged monitoring is necessary to capture these rare incidents in individuals with low risk of falling. Importantly, being able to record the actually occurring fall would theoretically open up avenues for “on line” fall prevention, for example by attaching an inflatable device that would be activated to cushion the impact of the fall once its onset was recorded. The first experience with falls detection during everyday life is becoming available, for example by use of a single sensor with accelerometers worn at the lower back<sup>64</sup>. Moreover, it is possible to determine a fall by extracting data from the tri-axial accelerometer of smart-phones which is evaluated with several threshold-based algorithms and position data<sup>65</sup>.

### ***Distal bradykinesia***

Bradykinesia describes slowness in the execution of a movement, and is a cardinal motor symptom of PD that generally responds well to dopaminergic medication and DBS, with distal bradykinesia showing the best response<sup>66</sup>. Thus, assessment of this feature can be used as a reflection of the effectiveness of medical treatment. Moreover, it would be helpful

to have an objective measure for bradykinesia, alongside (or perhaps even instead of) the semiquantitative and subjective assessment that is now used in clinical practice. For this purpose, assessment of distal bradykinesia with wearable sensors could help to improve the monitoring of medical treatment, aiming to achieve better control with reduction of OFF phases and fluctuations.

Aspects of distal bradykinesia have already been measured with wearable devices<sup>67</sup>. Moreover, recent results indicate that ecologically valid detection of bradykinesia during the day is feasible. Griffiths and colleagues<sup>68</sup> measured bradykinesia in people with PD and controls during a 10-day period at home using a wrist-worn device, coupled with sophisticated software to analyse the recorded signals, and found clear differences between the groups, as well as a high correlation to the UPDRS-III score, and improvement in scores in response to changes in medication. Similar results were obtained with a motion capture device worn on one finger and the wrist when PD patients were asked to perform bradykinesia items of the UPDRS at home<sup>69</sup>.

### ***Dyskinesias***

Dyskinesias are a disabling adverse effect of long-term l-dopa treatment. These occur in approximately 50% of PD patients after a mean of five years of l-dopa treatment, and include peak-dose and diphasic dyskinesias, and dystonia<sup>70, 71</sup>. New treatment options are becoming available<sup>72</sup>, but evaluation during a clinical visit is prone to bias because dyskinesias are typically influenced by emotional changes. Moreover, single assessments during a clinical visit offer insufficient insight into the nature and severity of dyskinesias that occur in daily life. This makes it particularly relevant to measure dyskinesias continuously and quantitatively in the home setting.

Assessment of dyskinesias using wearable technique appears to be a promising approach. Accuracies of 84% and higher for the correct classification of dyskinesias were reported using multiple body-worn sensors<sup>73-75</sup>. Even a single device worn at the shoulder<sup>76</sup> showed good agreement with simultaneously performed rating scores that were made by experienced neurologists. Results of a recent study using a single wrist-worn sensor suggest that dyskinesia could be quantified also in a home setting<sup>68</sup>, however this needs further evaluation. It should also be noted that studies using wearable technique did not

differentiate between dyskinesia subtypes, such as ON, OFF and diphasic dyskinesias, and did not report about occurrence or absence of therapy-associated dystonias. However, we cannot exclude that clever analytical algorithms may in future be able to separate the more dystonic type of dyskinesias (as in diphasic dyskinesias) from the more choreatic peak-dose dyskinesias. This would certainly be a great help to clinicians, because making this distinction based on history taking can be very difficult.

### ***Tremor***

Although tremor is not seen as one of the main quality of life-constraining signs of PD<sup>31</sup>, evaluation of tremor remains relevant as it is easily recognized by the social environment, and because it can be very incapacitating for individual patients. Moreover, quantification of tremor can provide accurate information about the efficacy of medical therapy as tremor responds relatively well to dopaminergic medication. Such a quantitative evaluation cannot easily be performed during the typically short-lived patient – doctor consultations, but requires an objective continuous quantitative assessment, e.g. with wearable sensors.

The first results using either the Wii remote<sup>77</sup>, or tri-axial accelerometers placed at four different positions on the body<sup>78</sup> showed an acceptable accuracy in detecting the severity of tremor. Feasibility of tremor detection in PD has been demonstrated by use of small sensors located at the wrist<sup>79</sup>, forearm<sup>67</sup> and lower back<sup>80</sup>, as well as – in a home setting – a finger-worn motion sensor combined with a wrist-worn command module<sup>69</sup>. A downside of all published studies is that none reported whether the applied systems were able to differentiate between distinct subforms of tremor (e.g. resting tremor versus action tremor) under everyday conditions.

### ***Dysarthria***

An estimated 70%–90% of people with PD develop speech or voice disorders, specifically hypokinetic dysarthria<sup>81</sup>. Depending on their specific symptom profile, dopaminergic medication and DBS can alter specific parameters of speech in individual patients. For example, specific DBS settings that offer major motor improvements may lead to dysarthric side effects. Being able to objectively assess and analyse speech and voice would be a great advantage for both patients and clinicians, for example to track the treatment response. To date, researchers have mainly collected quantitative speech data using head-mounted or

desktop microphones, combined with solid-state digital recording devices<sup>81</sup> or computer-integrated software<sup>82</sup>. However, it is conceivable that wearable technique such as smart-phone-based sensors with adequate analysis software can deliver objective speech information as well.

### ***Sedentary lifestyle and physical inactivity***

Mobility and physical activity are among the most important factors capable of maintaining good quality of life<sup>83</sup>. In people with PD and elderly without parkinsonism, regular physical activity potentially has preventive effects, e.g. regarding occurrence of cardiovascular events, diabetes mellitus, dementia, depression and sleep disturbances<sup>84</sup>, flexibility, balance and muscle strength<sup>45, 85</sup> and falls<sup>86</sup>. Currently we have the unsatisfying situation that neither the patient nor the doctor has an objective feedback about these parameters.

Wearable sensors can give an estimate of mobility and physical activity by defining, e.g. number and intensity of certain activities such as walking and performing transfers in a defined time period. Pilot validation studies suggest that wearable sensors can be used as simple and objective tools to assess mobility in the patient's own environment. Walking periods and number of steps were appropriately detected by a single sensor at the lower back<sup>87</sup>, as were activities such as walking, cycling, standing, sitting, and lying<sup>88, 89</sup>. However, accuracy of such activity sensors for long-term monitoring of walking distances seems still to be limited<sup>90</sup>. Interestingly, by use of a wrist-worn sensor in a home setting, it was recently shown that people with PD have lower physical activity levels than controls<sup>91</sup>.

### ***Non-motor disabilities***

#### ***Sleep disturbances***

Almost two thirds of persons with PD suffer from complex sleep disturbances that severely affect their quality of life<sup>92</sup>. Insomnia is most common, followed by rapid REM sleep behaviour disorder (RBD), excessive daytime sleepiness, and restless legs syndrome<sup>93</sup>. Currently, assessment of sleep is only possible with questionnaires or time- and resource-consuming polysomnography which cannot be provided to the whole PD community. Thus, quantitative and more easy-to-use assessment tools are needed.

The first results using wearable technique such as tri-axis accelerometers are promising. In a laboratory-based study with healthy individuals and patients with obstructive sleep apnea syndrome, body posture scores of a single accelerometer worn at the lower back, and the polysomnography position reached an intraclass correlation of 0.84<sup>94</sup>. In people with PD, movement patterns during sleep have been shown to be accessible with a single sensor at home<sup>91</sup>.

### ***Autonomic dysfunction***

People with PD often suffer from autonomic dysfunction. Orthostatic hypotension, impaired heart rate variability, sexual and gastrointestinal dysfunction, sialorrhea and sweating are among them<sup>95</sup>. They have an enormous impact on quality of life of affected patients, and are extremely difficult to assess, in particular in a clinical setting. Although autonomic dysfunction is generally difficult to treat, at least some of the symptoms are treatable, e.g. with increased physical activity<sup>95,96</sup>.

Wearable sensors may be an elegant option to offer an ecologically valid continuous and quantitative assessment of autonomic symptoms. As shown with a 24 hours ambulatory ECG and a sensor worn at the wrist for 7 days in the home environment to measure circadian regulation of heart rate variability and resting activity, PD patients had lower activity levels when out of bed and higher activity levels when in bed, compared to controls<sup>91</sup>. Moreover, PD patients had a lower total frequency component and a reduced low frequency/high frequency ratio of the heart rate variability<sup>91</sup>. This suggests that the circadian rhythm of the autonomic nervous system is altered in PD, and that continuous assessment of physical activity and heart rate variability using wearable technique are promising outcome variables for the evaluation of the autonomic system.

### **Conclusion**

It is increasingly possible to assess PD-related signs with wearable technical devices which are relatively unobtrusive, cheap and which offer objective recordings over prolonged periods under ecologically valid circumstances. However, the currently available techniques have not yet found their way into routine clinical assessment. We expect this to change

drastically in the near future, in light of a rapidly growing interest among PD patients, clinicians and methodologists, aiming to pragmatically collect objective and ecologically relevant data to evaluate therapeutic effects and to rate disease severity. Wearable technical devices can provide potentially relevant, factual, accurate and continuous health data that are less open to subjective interpretation. Ultimately such techniques will help to overcome the drawbacks that are inherent to single or multiple “snapshot” assessments in current clinical practice and clinically oriented research.

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