Technology-based assessment of motor and nonmotor phenomena in Parkinson disease

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Introduction: The increasing development and availability of portable and wearable technologies is rapidly expanding the field of technology-based objective measures (TOMs) in neurological disorders, including Parkinson disease (PD). Substantial challenges remain in the recognition of disease phenomena relevant to patients and clinicians, as well as in the identification of the most appropriate devices to carry out these measurements.

Areas covered: The authors systematically reviewed PubMed for studies employing technology as outcome measures in the assessment of PD-associated motor and nonmotor abnormalities.

Expert commentary: TOMs minimize intra- and inter-rater variability in clinical assessments of motor and nonmotor phenomena in PD, improving the accuracy of clinical endpoints. Critical unmet needs for the integration of TOMs into clinical and research practice are the identification and validation of relevant endpoints for individual patients, the capture of motor and nonmotor activities from an ecologically valid environment, the integration of various sensor data into an open-access, common-language platforms, and the definition of a regulatory pathway for approval of TOMs. The current lack of multidomain, multisensor, smart technologies to measure in real time a wide scope of relevant changes remain a significant limitation for the integration of technology into the assessment of PD motor and nonmotor functional disability.

1. Introduction

Parkinson disease (PD) is a multisystem neurodegenerative disorder resulting in a complex pattern of disability due to the impairment of both motor (i.e., tremor, bradykinesia, rigidity) and nonmotor (i.e., cognition, sleep, autonomic) functional systems [1]. PD-associated clinical features are usually quantified by clinicians using validated clinical scales, such as the Movement Disorder Society Unified Parkinson’s disease Rating Scale (MDS-UPDRS) [2], and the Non-Motor Symptoms Scale for Parkinson’s disease (NMSS) [3]. These instruments, however, are prone to limitations such as subjectivity, inter-rater variability, and limited accuracy in capturing small variations between and within patients.

Technology advancements have expanded the application of a new generation of technology-based objective measures (TOMs) to detect and monitor a functional range critical for the comprehensive characterization and long-term monitoring of patients with PD [4,5]. TOMs may capture multiple motor activities, such as frequency and amplitude of movements, severity of tremor and dyskinesia, and extent of gait and postural impairment [6-8]. In addition, TOMs may characterize nonmotor phenomena that cannot be captured by conventional clinical scales, such as sleep architecture, respiratory rate, beat-to-beat blood pressure changes, heart rhythm variability (HRV), and electroencephalographic (EEG) activity [9,10].

By reducing the standard deviation of clinical endpoints and minimizing intra- and inter-rater variability in clinical assessments, TOMs have the potential to improve the quality of diagnostic definitions [11]. Multiple challenges, however, limit the integration of TOMs into the clinical and research practice, including standardization of extracted parameters, cost of technology, patient compliance [12], and risk of producing outcome measures that have little practical meaning to end-users [13,14]. In order to be purposeful, any measures of function need to represent variables that are important to patients and can be amenable to interventions by clinicians and researchers [15].

We sought to systematically review studies that employed technology for the evaluation of motor and nonmotor phenomena in PD, appraising the extent of current integration of TOMs into the assessment of functional disability.

1.1. Body

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16].
1.1.1. Search methods
We searched PubMed for human studies published in English between January 1980 and June 2018 using a combination of free text and MeSH (Medical Subject Headings) for the following terms (Table e-1, online): Parkinson, smartphone, sensor, palm, computer, accelerometer, tablet, digital, electronic, microphone, gyroscope, actigraphy, gait analysis, voice analysis, pedometry, smartwatch, barometer, wearables, applications, apps, Wi-Fi, internet, Bluetooth, battery, touchscreen, camera, oximeter, facial recognition, tilt table, CANTAB, electroencephalogram, electrocardiogram, electromyogram, electronic diary, and UPSIT. No restrictions were applied to gender, age, ethnicity, disease duration, or disease severity.

1.1.2. Inclusion and exclusion criteria
We included original studies employing TOMs as primary, secondary, or exploratory outcomes for the qualitative or quantitative assessment of symptoms, severity, and functional disability associated with PD. We excluded case reports, review articles, and studies using imaging, genetic, or corporal fluids (e.g., blood, cerebrospinal fluid) sampling technologies.

1.1.3. Selection of studies
Abstracts were independently reviewed for eligibility criteria by two investigators (A.S. and S.S.). Disagreements were anticipated to be settled by consensus among the authors. Duplicated studies were identified and excluded. The reference lists of selected articles were additionally screened for pertinent studies not included in the original search strategy.

1.1.4. Data extraction and assessment of risk of bias
The following data were extracted from eligible studies using a standardized form: (a) year of publication; (b) study design; (c) study population; (d) inclusion and exclusion criteria; (e) primary and secondary outcome measures; (f) results; and (g) study limitations. Given the heterogeneity of study designs, we followed the Cochrane handbook recommendations and assessed the risk of bias of individual studies utilizing the National Heart, Lung, and Blood Institute tools (NHLBI) [17], as per the Cochrane handbook recommendations [18]. These tools are tailored to study types (i.e., cross-sectional, case-control, interventional) and include a qualitative, internal validity checklist (‘Yes,’ ‘No,’ and ‘Nonapplicable’) for domains such as methodological pertinence, potential sources of bias, confounding, and adequacy of results for quality classification as ‘good,’ ‘fair,’ or ‘poor.’ In general, a ‘good’ rating applies to studies with low risk of bias whose results are deemed valid; ‘fair’ to studies susceptible to some biases but deemed insufficient to invalidate their results; and ‘poor’ to studies with significant risk of bias.

1.1.5. Data analysis
Included studies were categorized per functional domain investigated (motor vs. nonmotor) and sorted per year of publication and technology employed. Results were summarized in tables and discussed in the text.

1.2. Results
The search strategy resulted in the identification of 2941 studies published between 1980 and 2018. A total of 2817 studies did not meet all inclusion criteria or were considered duplicates (Figure 1). Thus, we included 124 studies (106 cross-sectional, 11 case-control, and 7 prospective cohorts) which underwent data extraction and individual appraisal of the quality of evidence and risk of bias (Tables e-2 and e-3, online).

There were 61 studies (59 cross-sectional and 2 case-control) employing TOMs for the assessment of qualitative measures of motor phenomena such as gait and postural instability (n = 33 studies), bradykinesia (n = 13 studies), tremor (n = 8 studies), and rigidity (n = 7 studies), and 63 studies (48 cross-sectional, 7 prospective cohort, and 8 case control) employing TOMs for the assessment of nonmotor phenomena such as sleep disorders (n = 23 studies), cognitive impairment (n = 18 studies), dysautonomia (n = 12 studies), visual deficits (n = 3 studies), and voice analysis (n = 7 studies) (Figure 2). The overall number of published studies integrating TOMs into the assessment of PD-associated motor (gait, postural stability, bradykinesia, rigidity, tremor) and nonmotor (sleep, cognitive function, autonomic function, speech) deficits have steadily increased over the years (Figure 3).

1.2.1. Gait and posture stability
Kinematic systems [19–43] and wearable sensors [44–50] were employed in the assessment of temporal (reaction time, gait cycle duration), spatial (step length, step height), and biomechanical (ankle torque, vertical landing force) variables of gait, and in the evaluation of gait strategies (i.e., number of steps, single versus multiple step response) during treadmill-based assessments or instrumented walking tests, such as the timed-up-and-go [29,38,44,46]. Balance and postural instability were assessed using force platforms [27,28,32,37,51–55] and wearable sensors [44–48] (Figure 3) to measure the trajectory of the center of pressure (COP) and center of mass (COM) displacement [22,23,28,32,53], as well as the trunk acceleration [53] during backwards pull [27,32,48,52], double task tests [51], and postural sway with eyes open and eyes closed [23] (Figure 4).

Significant differences were observed in PD patients versus healthy controls in spatial and temporal gait variables [30,32,40,47,55], as well as in the postural response to external perturbations [32]. Gait parameters were also used to assess the progression of PD-associated gait and postural instability [22,24,25,27,28,37,45,47,52,53] and to assess the response to pharmacological [29] and nonpharmaceutical [20] therapies (Table 1).

Kinematic and EMG measurements were employed to assess turning and freezing of gait (FOG), evaluating both spatial and temporal gait parameters [30,50,56], as well as the pattern of axial muscle activation during turns [33]. Freezers showed greater variability in stride length, stride time, and cadence compared to nonfreezers [30,50,56] along with reduced thoracic adaptation to hip movements during gait and turns [31,33,34], increased number of steps, prolonged turning time [57], and decreased range of motion in the ankle and hip joints immediately before FOG episodes [35].
1.2.2. Bradykinesia and rigidity

Wearable sensors [58–60], infrared cameras [19,21,26,61,62], tablet-based measurements [63,64], Diadochokinesimeter (65), dexterity pegboard [65], and light emitting diode (LED) photosensitive system [66] were used to evaluate amplitude, smoothness, and peak velocity of movements during standardized motor tasks such as finger tapping [21,61,63], pronation-supination [67], reach-to-grasp [19,26,62], wrist extension [59], goal directed movements [60], handwriting [64], and facial expression [66,68,69]. Muscle rigidity was evaluated using a dynamometer [54,70].

There were similar reaction times and movement lengths in PD patients vs. healthy controls, but lower maximum speed and, consequently, longer execution time in PD [19,39]. TOMs accurately captured changes in transport time, wrist velocity, and arm acceleration during reach-to-grasp motor tasks [26,62]. Tablet-based measurements objectively quantified amplitude, velocity [64], and motor blocks during handwriting [63]. Wearable sensors were used to assess the effect of dopaminergic medications on speed and amplitude of movements, showing a more pronounced effect on the former [71]. Finally, optokinetic analyses were employed to assess orofacial movements, such as vertical jaw movements during speech [66] and hypomimia [68,69], showing sufficient accuracy in objectively capturing differences between PD patients and healthy controls (Table 2).

A study evaluated PD-associated trunk rigidity using a dynamometer to measure resistive torques during passive trunk flexion and extension [54]. The internal validity of this approach was confirmed by different authors reporting a direct correlation between dynamometer-based rigidity assessment and health-related quality of life in PD [70]. Unlike this study, however, most studies did not evaluate the extent to which changes measured by specific TOMs correlated with relevant changes as perceived by patients.

1.2.3. Tremor

Accelerometer- [72–75], gyroscope- [76,77], EMG- [72–74,78], kinematic- [72], and tablet-based [78] measurements were used to capture key phenomenological characteristics of tremor, namely frequency, amplitude, and variability under different testing conditions. TOMs effectively differentiated between Parkinsonian, essential [76–78], and functional (psychogenic) tremors [79], and provided objective measurements of tremor severity in real-life condition using both wearable devices [74] and smartphone applications [75,80].
TOMs were also employed in the detection of subclinical tremor [73] and the analysis of the different tremor components during resting, movement initiation, and decelerating phase of movement [72]. Innovative machine-learning algorithms have been recently developed to evaluate the variability of tremor in the time-domain during resting and motor activities [76,77] (Table 2).

1.2.4. Speech

Multidimensional voice software programs for acoustic analysis (i.e., Praat, a freeware developed by the University of Amsterdam) have been employed for the quantitative assessment of amplitude, prosody, speed, grammar, and fluency of speech during sustained-vowels phonation, alternating and sequential motion rates, and normal reading [81]. TOMs proved useful in sensitively capturing differences in speech between PD patients and healthy controls, including maximal phonation time, phonation quotient, percent jitter, percent shimmer, and noise-to-harmonic ratio [81–83], suggesting their employment in the diagnostic assessment of PD [84], monitoring of PD-associated functional disability [85], and prognostic assessment of functionally relevant outcomes such as cognitive decline [86]. An automated speech assessment has been proposed as part of a battery of test, including also posture analysis, gait assessment, finger tapping, and response time, to monitor PD symptoms at the home environment using commercially available smartphone applications [87] (Table 3).

1.2.5. Sleep

Sleep studies employed polysomnography (PSG) and actigraphy to evaluate the quality of sleep in PD [88–92], or to diagnose PD-associated conditions such as sleep apnea [92,93], REM sleep behavior disorders [92–99], sleep attacks [100–102], periodic limb movements [103], and nocturia [104]. The effect of pharmacological and nonpharmacological treatments on nocturnal sleep quality was also investigated using PSG [100,105–107].

Fragmented sleep architecture and reduced quality of sleep were found both in mild and advanced PD [108], with strong correlation between sleep efficiency, as measured by the PSG, and clinical measures of sleep quality, such as the Epworth sleepiness scale (EPPS), the PD sleep scale (PSS), and the Pittsburgh Sleep Quality Index (PSQI) [109]. Additional studies evaluated the effect of pharmacological and nonpharmacological treatments on PD-associated quality of sleep, reporting an objective improvement in the architecture of sleep with advanced
therapeutic options such as levodopa/carbidopa intestinal gel infusion (LCIG) [106] and subthalamic nucleus deep brain stimulation [107]. (Table 4).

1.2.6. Cognitive function
Electroencephalographic (EEG) spectral analysis was used to evaluate cognitive function in PD [110–114], demonstrating a correlation between slow EEG rhythm in the temporo-occipital regions and poor performance on visuospatial tests [113,115], as well as a correlation between increased risk of dementia and slow EEG activity in the posterior regions during REM sleep, and in the temporal regions during wakefulness [112,115–118]. Promising yet preliminary results were reported by studies investigating the application of evoked potential-based measures in the differential diagnosis of PD [119,120] and in the assessment of PD-associated cognitive dysfunction [116–118,121–127], visual impairment [127–129], and behavioral disorders [130] (Table 3).

1.2.7. Autonomic function
Cardiovascular and sweating autonomic testing, as well as HRV and 24-hour ambulatory blood pressure monitoring have been employed in the assessment of sympathetic [131,132] parasympathetic [132,133], and cholinergic autonomic function [10]. Significant differences were observed between PD and healthy controls suggesting a role for autonomic testing in the diagnostic classification of PD [134], characterization of patients at risk of poor functional outcome [135] or higher risk of dementia [136], and in distinguishing PD from atypical Parkinsonian syndromes [137,138]. Recent studies also suggested that failure at the autonomic function testing might predict disease progression and survival in PD [139], as well as assist in the identification of patients expected to respond differentially to a range of treatments [140] (Table 5).

2. Conclusion
This systematic review showed that an increasing number of studies employed TOMs for the assessment of PD-associated motor and nonmotor phenomena over the last two decades (Figure 5). A range of technologies were used to evaluate motor endpoints such as gait, balance, bradykinesia, tremor, rigidity, and speech, as well as nonmotor endpoints such as sleep, cognition, and autonomic function. TOMs demonstrated the potential of capturing motor and nonmotor phenomena with greater accuracy and reduced intra- and inter-rater variability than clinical scales and self-administered questionnaires. However, only a few studies correlated TOMs with patient-centered clinical scales, quality of life questionnaires, or handicap index. In addition, minimal clinically important differences have been estimated for a limited number of TOMs.

A possible limitation of our study consists of a searching strategy limited to published studies. We did not conduct searches in multiple databases, as well as Grey Literature or ongoing trials (e.g., clinicaltrials.gov). Thus, our conclusions do not take into consideration currently ongoing research endeavors.
3. Expert commentary

While substantially improving the accuracy of both motor and nonmotor clinical endpoints in PD, ultimately resulting in improved diagnostics and monitoring of functional disability [11], the integration of TOMs into randomized controlled trials and routine clinical practice remains limited by several unresolved issues [141]. An important roadblock is the lack of a clear regulatory pathway from the FDA and the EMA for the routine employment of TOMs in both clinical and research settings. Less than 3% of ongoing clinical trials of neurodegenerative disorders have employed TOMs as an outcome measure. However, a survey from medical directors from pharmaceutical companies indicated that the majority of them are considering using TOMs in future clinical trials within the next five years [141]. Also, a smartwatch for the monitoring of epileptic seizures was recently approved by regulatory agencies based on data demonstrating their accuracy and usefulness in clinical practice [142,143]. This preliminary experience encourages similar studies in the field of movement disorders.

The ideal outcome measure would be objective, exhibit minimal intra- and inter-operator variability, continuously capture relevant data in the patient’s home environment, and sensitively capture small but meaningful changes over a prolonged period of time. Available TOMs meet some of these criteria but fail others, such as capturing motor and nonmotor activities from an ecologically valid environment. Currently, most of the gait and balance measures rely on tests assessing the patient’s functional capacity (e.g., timed-up-and-go) rather than functional activity (e.g., continuous recording of natural unrestricted gait). In addition, the resolution of biomechanical sensors remains restricted to the anatomical area on which the sensors are applied, possibly yielding low quantitative agreement with the broader range of motor disability, quality of life, and other measurable patient-relevant endpoints [11,144].

The assessment of nonmotor symptoms poses even more significant challenges due to the frequent use of cumbersome technologies such as PSG, EEG, or tilt table, which highlight the need for a tradeoff between the comprehensiveness of the assessment and their ecological validity. Simplified sleep mea-
| Study                | Design         | Population | Selection Criteria                                                                 | Aim                                                                 | Technology                                      | Results                                                                 | Quality |
|---------------------|----------------|------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------|
| Schlachetzki 2017   | Cross-sectional| 190 PD     | Inc: PD, H&Y < 4; Exc: movement limitations for conditions other than PD           | Measure gait characteristics in PD                                  | Wearable sensor (accelerometer and gyroscope)                                 | Gait parameters differed between HC and PD at moderate disease stage and/or higher levels of motor impairment | Good    |
| Son 2017            | Cross-sectional| 20 PD      | Inc: PD, H&Y < 4; Exc: movement limitations                                         | Investigate turning in PD with 3D analysis during timed up and go   | Motion analysis                                                                | Step length and foot clearance height, and timed up and go test during turning phase may be helpful turning measures in across multiple PD severities | Good    |
| Conradsson 2017     | Cross-sectional| 19 PD      | Inc: PD, age ≥ 60, MMSE ≥ 24, H&Y 2–3; Exc: movement limitations, visual impairment | Determine if dopaminergic medication improves preplanned and unplanned walking turns in PD | Kinematic analysis                                                             | Turning impairments remained even after dopaminergic medication          | Good    |
| Pham 2017           | Cross-sectional| 24 PD      | Inc: PD, severe self-reported freezing; Exc: dementia, depression                   | Assess a model for detection of FOG in PD                          | FOG detector with kinematic analysis                                          | FOG events can be detected with a automated single sensor located at the ankle or hip | Good    |
| Pasloustra, 2015    | Cross-sectional| 139 PD     | Inc: PD with pull test score 0–2; Exc: N/R                                         | Assess postural instability in PD                                   | Wearable sensor Accelerometer                                                  | PD foot motion estimates postural instability                           | Good    |
| Svehlik 2009        | Cross-sectional| 20 PD      | Inc: PD, PD meds, other medical conditions affecting gait; dementia                | Evaluate time-distance, stride length, and ankle range of motion during gait in PD | Motion analysis Force plate                                                    | PD patients have slower and shorter stride length and reduced ankle range of motion | Good    |
| Kim 2009            | Cross-sectional| 7 PD       | Inc: PD; Exc: N/R                                                                  | Evaluate postural responses of patients with PD during perturbation | Force plate Kinematic analysis                                                | PD showed worse ankle feedback gain during perturbation                 | Good    |
| Cho 2009            | Cross-sectional| 10 PD      | Inc: PD; Exc: N/R                                                                  | Examine walking dynamics in PD                                      | Motion analysis                                                                 | PD has greater gait impairment with decreased foot control and arm swing dynamics | Good    |
| McVey 2009          | Cross-sectional| 10 PD      | Inc: PD; Exc: N/R                                                                  | Estimate postural instability in PD                                 | Force plate Kinematic analysis                                                | Early PD has greater postural instability vs. HC                         | Good    |
| Alice 2007          | Cross-sectional| 10 PD      | Inc: PD, history of FOG; Exc: medical conditions affecting gait other than PD     | Describe strides characteristics prior to freezing vs. voluntary and ongoing gait | Kinematic analysis                                                             | PD had decrease in ankle and hip joint range of motion prior to freezing, with preserved movement shape | Good    |
| Hong 2007           | Cross-sectional| 12 PD      | Inc: PD, mild turning problems; Exc: N/R                                            | Determine if PD retain turning ability after rotating platform walking | Kinematic analysis                                                             | PD retained turning ability after rotating platform walking task         | Good    |
| Ferrarin 2005       | Cross-sectional| 10 PD      | Inc: PD, bilateral STN DBS, severe motor fluctuations, response to L-dopa; Exc: dementia, depression, abnormal cerebral MRI, other illnesses | Assess the effects of L-dopa and STN DBS separately and combined on gait in PD | Kinematic analysis                                                             | PD meds and bilateral STN DBS additively and synergistically improve gait parameters such as speed, stride length, and ROM of knee and ankle joints | Good    |
| Stolze 2001         | Cross-sectional| 9 PD       | Inc: Bilateral STN stimulation; Exc: N/R                                           | Examine the impact of STN-DBS on gait in PD                         | Kinematic analysis                                                             | STN-DBS increases gait velocity and stride length                        | Good    |
| Parisi 2015         | Cross-sectional| 34 PD      | Inc: N/R; Exc: N/R                                                                 | Correlate wearable sensor data with UPDRS                          | Wearable sensor                                                                | Wearable sensor accurately predicted UPDRS scores                        | Fair    |

(Continued)
| Study            | Design     | Population | Selection Criteria                                      | Aim                                                                 | Technology          | Results                                                                 | Quality |
|------------------|------------|------------|--------------------------------------------------------|----------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------|---------|
| Chomiak 2015     | Case-control | 24 PD w&w/o freezing | Inc: PD, walking unassisted                               | Evaluate if stepping-in-place with a concurrent mental task can be used for evaluating cognitive–motor deficits in PD | Kinematic analysis | Step height was significantly worse in PD during concurrent subtraction and stepping-in-place tasking | Fair    |
| Dillmann 2014    | Cross-sectional | 40 PD 25 HC | Inc: akinetic-rigid PD                                   | Analyze movements of the upper and lower limbs in PD                  | Kinematic analysis  | PD demonstrated greater intersegmental coordination                     | Fair    |
| Barbe 2014       | Case-control | 34 PD w&w/o freezing | Inc: PD, akinetic-rigid, right handed, age 40–80          | Assess spatial and temporal gait variability between FOG episodes in freezers vs. nonfreezers | Kinematic analysis | Freezers have a higher spatial gait variability between freezing episodes | Fair    |
| Moore 2013       | Cross-sectional | 25 PD | Inc: PD, self-reported freezing, MMSE ≥24                 | Evaluate sensor placement for accuracy in detecting FOG in PD         | Accelerometer       | A simpler single lumbar sensor had comparable accuracy to a 7 sensor system for detecting FOG | Fair    |
| Zampieri 2011    | Cross-sectional | 6 PD 8 HC | Inc: N/R                                                  | Evaluate stride length, stride velocity, cadence, peak arm swing velocity, and turning velocity during Timed Up and Go | Wearable sensor    | PD exhibited faster gait in laboratory than at home, although with shorter gait and steps in both conditions vs. HC | Fair    |
| Merello 2010     | Cross-sectional | 20 PD 17 HC | Inc: PD Normal MRI H&Y in OFF = 3                         | Evaluate COM, COP, step length, and speed changes during festination in PD | Kinematic analysis | Patients with festination attempt to align COP to COM                   | Fair    |
| Salarian 2010    | Cross-sectional | 12 PD 12 HC | Inc: H&Y 1 to 2.5, no history of PD drugs                 | Evaluate cadence, turning duration, and arm-swing angular velocity during Time Up and Go | Wearable sensor    | PD demonstrated slower cadence and arm swing angular velocity and longer turning time duration | Fair    |
| Ganesan 2010     | Cross-sectional | 20 PD 20 HC | Inc: H&Y = 2, stable PD meds, normal pull test, right dominance | Evaluate subclinical balance impairment in PD with normal pull test | Force plate         | PD patients had subclinical direction-specific balance impairment        | Fair    |
| Johnsen 2010     | Cross-sectional | 22 PD | Inc: PD, STN DBS                                        | Evaluate the effect of anatomical position of STN DBS on gait in PD | Kinematic analysis | Step velocity, step length, and balance had greater improvement with dorsal STN DBS compared to ventral STN DBS in PD. | Fair    |

(Continued)
| Study         | Design    | Population | Selection Criteria | Aim | Technology | Results                                                                 | Quality |
|---------------|-----------|------------|--------------------|-----|------------|-------------------------------------------------------------------------|---------|
| Cantiniaux 2010 | Cross-sectional | 11 PD 11 HC | Inc: PD, bilateral STN DBS Exc: other walking or speech disorders | Assess the effects of L-dopa and STN DBS on gait and speech patterns in PD vs. HC | Kinematic analysis, Speech analysis | Walking and speech velocity were correlated, but STN DBS and L-dopa improved walking velocity while having no effect on speech velocity | Fair     |
| Mancini 2009  | Cross-sectional | 11 PD 12 HC | Inc: PD, no history of PD meds Exc: other neurologic disorders or gait impairments | Evaluate anticipatory postural adjustments and characterize step initiation deficits in PD | Force plate, Accelerometer | Untreated PD exhibited smaller peak trunk acceleration vs. HC | Fair     |
| Hong 2009     | Cross-sectional | 11 PD 12 HC | Inc: PD Exc: N/R | Determine objective differences in turning in PD vs. HC during a turning task | Kinematic analysis, EMG | PD differed from HC in axial control but had similar lower limb muscle patterns during turning task | Fair     |
| Stack 2008    | Cross-sectional | 28 PD 12 HC | Inc: PD, walk w/o assistance Exc: Neurological comorbidities | Analyze differences in turning in PD vs. HC during a turning task | Motion analysis | PD differed on step count, time, and quality of turn versus HC | Fair     |
| Huxham 2008   | Cross-sectional | 10 PD 10 HC | Inc: PD Exc: N/R | Analyze head and trunk rotation of PD vs. HC during walking turns | Kinematic analysis | PD demonstrated greater rotation of head and trunk versus HC | Fair     |
| Carpinella 2007 | Cross-sectional | 6 PD       | Inc: PD, UPDRS part III score 12–20 Exc: N/R | Quantitatively describe locomotor symptoms in mild PD | Kinematic analysis, Force plate | Early stage of PD had mild alterations of steady-state linear walking and in transitional conditions during direction changes | Fair     |
| Ferrarin 2002 | Cross-sectional | 4 PD 4 HC | Inc: PD, STN DBS Exc: N/R | Assess gait changes with STN DBS in PD vs. HC | Kinematic analysis, Force plate | STN DBS improves gait patterns in PD but reduces ankle power production during stimulation | Fair     |
| Van Emmerik 1999 | Cross-sectional | 27 PD 11 HC | Inc: recent PD diagnosis Exc: PD meds | Evaluate coordination and stability during walking in PD | Kinematic analysis | Analysis of changes in velocity during walking can identify coordination deficits and trunk rigidity | Fair     |
| Doan 2010     | Cross-sectional | 10 PD 8 HC | Inc: PD Exc: N/R | Evaluate standing and reaching in a challenging environmental context | Force plate | PD delayed trunk flexion and peak end-point velocity | Poor     |
| Bleuse 2008   | Cross-sectional | 10 PD 10 HC | Inc: PD Exc: N/R | Describe postural instability in PD vs. HC during limb movement | Force plate | PD had postural instability prior to limb movement | Poor     |

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&h/o, with and without; N/R, nonreported; min, minutes; REM, Rapid eye movement; DBS, Deep brain stimulation; STN, Subthalamic nucleus; COM, center of mass; COP, center of pressure; H&Y, Hoehn & Yahr; MMSE, Mini-Mental State Examination; ROM, range of motion.
| Study         | Design     | Population | Selection Criteria                                                                 | Aim                                                                 | Technology                          | Results                                                                 | Quality |
|--------------|------------|------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------|---------|
| Rabelo 2017  | Cross-sectional | 15 PD     | Inc: Older patients with PD                                                        | Propose and evaluate an objective method for the assessment of       | Gyroscope, accelerometer, magnetometer, and EMG                       | Methods detected objective bradykinesia differences between PD and HC  | Good    |
|              |            | 12 HC      | Exc: Dementia, upper limb movement limitations                                      | bradykinesia                                                          |                                     |                                                                        |         |
| Jeon 2017    | Cross-sectional | 85 PD     | Inc: PD with hand tremor                                                           | Assess automatic scoring system for PD                                | Wearable sensor, Gyroscope, Accelerometer                           | Predicted UPDRS tremor scores with high accuracy                       | Good    |
|              |            |            | Exc: leg tremor and dyskinesia                                                     | tremor                                                                |                                     |                                                                        |         |
| Bologna 2016 | Cross-sectional | 18 PD     | Inc: PD                                                                            | Assess deficits in facial emotional processing and recognition in PD   | Optokineti system                                                      | Altered emotional processing in PD                                     | Good    |
|              |            | 16 HC      | Exc: dementia, neuropsychiatric disorders, facial movements or trauma              |                                                                      |                                     |                                                                        |         |
| Ricciardi, 2015 | Cross-sectional | 40 PD     | Inc: PD                                                                            | Correlate reduced expressiveness and altered emotion processing in PD | Optokineti system                                                      | Reduced facial expressiveness correlates with impaired emotional       | Good    |
|              |            | 17 HC      | Exc: cognitive deficits, depression                                                 |                                                                      |                                     | recognition.                                                           |         |
| Muller 2010  | Cross-sectional | 27 PD     | Inc: PD patients                                                                   | Evaluate pronation and supination of forearm in PD vs. HC            | Diadochokinesimeter                                                   | PD patients showed reduced maximum velocity, interval and amplitude    | Good    |
|              |            | 27 HC      | Exc: motor fluctuations                                                            |                                                                      |                                     |                                                                        |         |
| Rand 2010    | Cross-sectional | 12 PD     | Inc: PD                                                                            | Assess wrist and trunk kinematic parameters in PD vs. HC             | Kinematic systems                                                     | PD considerably lengthened transport time, especially during the      | Good    |
|              |            | 12 HC      | Exc: other neurological disease                                                    |                                                                      |                                     | aperture closure period, and decreased peak velocity of wrist         |         |
|              |            |            |                                                                                        |                                                                      |                                     | and trunk movement                                                    |         |
| Espay 2009   | Cross-sectional | 23 PD     | Inc: PD                                                                            | Categorize the spectrum of movements in PD in terms of speed and     | Wearable motion sensor                                               | Amplitude and speed impairments may be associated with different      | Good    |
|              |            | 16 HC      | Exc: severe tremor, DBS, cognitive impairment, UMN/LMN signs, atypical parkinsonism| amplitude                                                             |                                     | functional aspects in PD                                              |         |
| Mak 2007     | Cross-sectional | 21 PD     | Inc: PD, H&Y 2 or 3, stable PD medication                                          | Develop an objective measure to quantify trunk rigidity in PD         | Force plate                                                          | Method differentiated trunk rigidity in PD versus HC. There were      | Good    |
|              |            | 21 HC      | Exc: N/R                                                                           |                                                                      |                                     | increases in work done and resistive peak torques upon motor tasks   |         |
| Castiello 2000 | Cross-sectional | 14 PD     | Inc: PD patient; Right dominance                                                     | Evaluate reach-to-grasp movement in PD patients during ON and OFF     | Motion analysis                                                       | Dopaminergic medication reduced bradykinesia and fine-tuning kinematic| Good    |
|              |            | 14 HC      | Exc: Motor complications due to therapy                                              | states                                                                 |                                     | movement during reach-to-grasp task                                   |         |
| Lin 2018     | Cross-sectional | 15 ET     | Inc: ET or PD                                                                      | Quantify tremor spatially and temporally in PD                        | Tablet-based                                                          | Tablet measures of tremor correlates well with current clinical        | Fair    |
|              |            | 15 PD      | Exc: N/R                                                                           |                                                                      |                                     | assessments                                                           |         |
| Summa 2017   | Cross-sectional | 7 PD      | Inc: PD, H&Y 1 – 2.5                                                               | Analyze the kinematic and dynamic characteristics of goal-directed   | Kinematic analysis                                                   | Prono-supination task is consistent to quantify bradykinesia with     | Fair    |
|              |            | 7 HC       | Exc: movement limitations for conditions other than PD                              | movements                                                             |                                     | gyroscopes. Peak power seems appropriate for bradykinesia symptom     |         |
|              |            |            |                                                                                        |                                                                      |                                     | evaluation.                                                           |         |
| Heremans 2016 | Cross-sectional | 30 PD     | Inc: PD, H&Y 1 – 3                                                                 | Assess writing quality in PD with and without FOG                     | Tablet-based                                                          | Patients with FOG showed decreased writing amplitudes and increased   | Fair    |
|              |            | 15 HC      | Exc: depression, neurological comorbidities                                          |                                                                      |                                     | variability compared to HC and PD w/o FOG                             |         |
| Fraiwan 2016 | Cross-sectional | 21 PD     | Inc: PD                                                                            | Detect and quantify hand tremor in PD                                 | Accelerometer                                                        | Detected hand tremor and diagnosed PD with high accuracy              | Fair    |
|              |            | 21 HC      | Exc: N/R                                                                           |                                                                      |                                     |                                                                        |         |
| Study                  | Design          | Population | Selection Criteria                                                                 | Aim                                                                 | Technology               | Results                                                                 | Quality |
|-----------------------|-----------------|------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------|------------------------------------------------------------------------|---------|
| Van Gilst 2015        | Case-control    | 36 PD      | Inc: PD; Exc: psychiatric diagnosis, DBS, other neurological disease, hypnotics    | Evaluate the influence of sleep on motor functioning in PD           | PSG dexterity pegboard  | Sleep benefit is not paralleled by an actual improvement in motor functioning | Fair    |
| Thanawattano 2015     | Cross-sectional | 22 ET      | Inc: ET or PD; Exc: N/R                                                             | Assess tremor in time domain ('temporal fluctuation')               | Wearable sensor gyroscope | Temporal fluctuation distinguishes tremor in PD and ET                | Fair    |
| Thanawattano 2015     | Cross-sectional | 30 PD      | Inc: PD or ET; Exc: N/R                                                             | Quantify tremor fluctuation during resting and kinetic tasks in PD   | Gyroscope                | Tremor fluctuation can distinguish PD from ET tremor                  | Fair    |
| Kotschet 2014         | Cross-sectional | 68 PD      | Inc: levodopa responsive PD; Exc: N/R                                              | Evaluate relationship between episodes of sleep immobility to bradykinesia, dyskinesia and daytime sleepiness | Accelerometer            | Immobility is a marker of daytime sleep in PD                          | Fair    |
| Cano-de-la-Cuerda, 2014 | Cross-sectional | 36 PD      | Inc: PD with good walking ability; Exc: Dementia, depression                        | Evaluate finger-tapping in PD                                      | Kinematic systems        | Wearable sensor detected decreased amplitude of finger-tapping in PD  | Fair    |
| Jobbágy 2004          | Cross-sectional | 10 PD      | Inc: N/R; Exc: N/R                                                                 | Assess a qualitative pattern-matching technique for detecting events in movement recordings | Motion analysis          | Reaction time and movement length were similar in PD and HC, but PD reached lower maximum speeds longer execution times than HC. | Fair    |
| Fimbel 2003           | Cross-sectional | 18 PD      | Inc: PD, atypical parkinsonism, right handed; Exc: neurological comorbidities       | Measure frequency changes during tapping                            | EMG                      | Absolute change in tremor frequency and marked intraindividual variability with tapping in psychogenic tremor | Fair    |
| Zeuner 2003           | Cross-sectional | 12 PD      | Inc: N/R; Exc: N/R                                                                 | Examine the impact of levodopa on the voluntary movements in PD      | Kinematic systems        | PD patients increase reach velocity and decrease movement time after taking levodopa  | Fair    |
| Kelly 2002            | Cross-sectional | 9 PD       | Inc: N/R; Exc: N/R                                                                 | Evaluate distance between the vertical projections of the COM and the COP to reflect postural control during gait initiation | Kinematic systems        | PD patients allow less COM-COP distance than HC                        | Fair    |
| Martin 2002           | Cross-sectional | 12 PD      | Inc: PD; H&Y 1 to 3; Exc: acute illnesses, OH                                     | Evaluate kinetic tremor (reach a target) in tremor-dominant PD      | Accelerometer EMG Kinematic systems | Accelerometer detected greater frequency of kinetic tremor before the onset of the movement in PD Levodopa increase velocity in self-paced tasks | Fair    |
| Johnson 1994          | Cross-sectional | 13 PD      | Inc: H&Y 1 to 3, hand rest tremor; Exc: N/R                                       | Evaluate the acute change in motor performance after Levodopa       | Kinematic systems        | Motion analysis detected differences between ON and OFF motor states during a syllable repetition task | Fair    |
| Svensson 1993         | Cross-sectional | 9 PD       | Inc: PD; Exc: Poor dental status                                                   | Examine tremor features in PD                                      | Tablet-based             | Digitizing tablet can be used to record sudden discontinuations during planar movements in PD | Poor    |
| Vaillancourt 2000     | Cross-sectional | 12 HC      | Inc: no clinical signs of tremor; Exc: N/R                                        | PD tremor was more regular vs. physiological tremor in HC            | Accelerometer EMG        | PD tremor was more regular vs. physiological tremor in HC              | Poor    |

PD, Parkinson's disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, nonreported; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EMG, Electromyography; UMN, upper motor neuron; LMN, lower motor neuron; COM, center of mass; COP, center of pressure; H&Y, Hoehn & Yahr; FOG, freezing of gait
### Table 3. Eligible studies assessing cognitive function and speech.

| Study            | Design       | Population | Selection Criteria | Aim | Technology | Results | Quality |
|------------------|--------------|------------|--------------------|-----|------------|---------|---------|
| Godino-Llorente 2017 | Cross-sectional | 50 PD     | Inc: PD, Exc: other neurological disorders | Assess speech biomarkers to evaluate PD | Speech analysis | Articulatory biomarkers accurately identify PD | Good |
| Vaicikynas 2017    | Cross-sectional | 64 PD     | Inc: PD, Exc: N/R  | Assess sustained phonation for diagnosis of PD | Speech analysis | Acoustic analysis can accurately detect PD | Good |
| Markser 2015       | Case-control | 30 PD w/o cognitive impairment | Inc: DBS indication, Exc: N/R | EEG metrics after DBS | EEG | STN-DBS has a negative effect on the patients grand total EEG scores | Good |
| Arora 2015         | Cohort       | 10 PD 10 HC | Inc: PD, Exc: N/R | Assess if symptom recordings can differentiate PD vs. HC | Tablet-based Speech analysis Gyroscope Accelerometer | PD symptoms can be feasibly measured via smartphone | Good |
| Nojszewsk 2009     | Cross-sectional | 46 PD 14 HC | Inc: PD, Exc: severe illness, deafness | Neuropsychological test relation determination to AEP | AEP | AEP of different latencies are helpful in the assessment of cognitive changes associated with PD. | Good |
| Tanaka 2018        | Cross-sectional | 137 PD       | Inc: PD with ambulatory and OH data, Exc: acute illnesses | Assess relationship between nocturnal BP and dementia in PD | 24-hour ambulatory BP and heart rate | Nocturnal BP rise and OH correlated with dementia | Fair |
| Gauvin 2017        | Cross-sectional | 18 PD 16 HC | Inc: PD, Exc: other neurological disorders | Assessed verbal monitoring in PD | Speech analysis | PD has different verbal monitoring patterns and greater impairment vs. HC | Fair |
| Latrelle 2016      | Prospective cohort | 68 PD 44 HC | Inc: PD, Exc: dementia, stroke, epilepsy | Prediction of PDD by PSG | PSG | PD patients who developed PDD had higher slowing ratio in temporal, parietal, and occipital regions during REM sleep | Fair |
| Rektorova 2016     | Cohort       | 44 PD       | Inc: PD, Exc: depression | Assessed relationship between speech impairment and cognitive decline | Speech analysis | Impairment of speech prosody predicted rapid cognitive decline | Fair |
| Zimmermann 2015    | Cross-sectional | 48 PD       | Inc: PD, Exc: dementia, stroke, epilepsy, low-quality EEG | Test EEG slowing relation to cognitive performance | EEG | Global EEG slowing is a marker for overall cognitive impairment and specific domains | Fair |
| Latrelle 2015      | Prospective cohort | 68 PD w/o cognitive impairment 47 HC | Inc: PD, Exc: dementia, stroke, epilepsy | Test PSG prediction of dementia | PSG | Sleep spindle alterations related to dementia development | Fair |
| Fischer 2010       | Cross-sectional | 10 PD 9 HC  | Inc: English native speakers, Exc: dementia, depression, serious illness, speech impairment | Examine voice onset measures in PD | Voice analysis | PD medication had an effect on voice onset time change | Fair |
| Fonseca 2009       | Cross-sectional | 32 PD 26 HC | Inc: PD, Exc: antipsychotics, benzodiazepines | Evaluate relation between quantitative EEG and cognitive disturbance | EEG | EEG abnormalities were associated with mild cognitive impairment or dementia in PD versus HC | Fair |
| Matsui 2007        | Cross-sectional | 40 PD w/o dementia | Inc: H&Y 3 or 4 | Examine P300 differences between PDD and PD | EEG | P300 latency was markedly delayed in PDD patients | Fair |
| Bunton 2005        | Cross-sectional | 7 PD 6 HC | Inc: PD, Exc: atypical parkinsonism | Determine patterns of lung volume use in PD during an extemporaneous speaking task | Microphone, magnetometer | Speakers with PD began speaking at lower lung volumes and had an increased variability in starting lung volumes across the speech sample versus HC | Fair |
| Katsarou 2004      | Cross-sectional | 45 PD 40 HC | Inc: PD, MMSE > 25, Exc: dementia | Compare P300 between PD patients and HC | EEG | Nondemented PD patients had a prolonged P300 latency versus HC | Fair |
| Antal 2000         | Cross-sectional | 20 PD 20 ET 20 HC | Inc: PD or ET, Exc: retinopathy, glaucoma, DM, alcoholism | Compare components of VEP in patients with PD and ET | VEP | No significant overall group difference | Fair |
| Study          | Design          | Population | Selection Criteria                                                                 | Aim                                         | Technology       | Results                                                                 | Quality |
|---------------|-----------------|------------|-------------------------------------------------------------------------------------|---------------------------------------------|------------------|--------------------------------------------------------------------------|---------|
| Hawkes 1997   | Cross-sectional | 37 PD      | Inc: PD, MMSE > 26, Exc: head trauma, DM, alcoholism                                | Evaluate olfactory function in PD           | UPSIT, Olfactory  | Over 70% of PD were abnormal. The evoked potentials were significantly  | Fair    |
|               |                 | 47 HC      |                                                                                     |                                             | evoked potentials | delayed but comparable to HC. Simultaneous VEP and visual event related  |         |
|               |                 |            |                                                                                     |                                             | VEP              | potentials recordings are helpful to distinguish younger PD patients from |         |
|               |                 |            |                                                                                     |                                             | EEG              | HC                                                                      |         |
| Sagliocco 1997| Cross-sectional | 17 PD      | Inc: PD, MMSE ≥ 23, visual acuity ≥ 20/40, Exc: unable to cooperate                | Compare simultaneously recorded VEP and event related potentials in PD | VEP              | P3 amplitude may be more sensitive than neuropsychological measures for  | Fair    |
|               |                 | 17 HC      |                                                                                     |                                             | EEG              | subtle brain dysfunction in early PD                                     |         |
| Green 1996    | Cross-sectional | 20 PD      | Inc: PD, Exc: depression                                                            | Understand P3-associated variability in PD  | EEG              |                                                                          | Fair    |
|               |                 | 20 HC      |                                                                                     |                                             |                  |                                                                          |         |
| Pekkonen 1995 | Cross-sectional | 13 PD      | Inc: severe illness, deafness                                                        | Determine stimulus change impairment in PD  | EEG              |                                                                          | Fair    |
|               |                 | 11 HC      |                                                                                     |                                             |                  |                                                                          |         |
| Okuda 1995    | Case-control    | 32 PD      | Inc: visual acuity > 0.7, Exc: ophthalmological disease                             | Measure differences in VEP in PD, PDD, and HC | VEP              |                                                                          | Fair    |
|               |                 | 22 HC      |                                                                                     |                                             |                  |                                                                          |         |
| Kim 1995      | Cross-sectional | 16 PD      | Inc: PD, MMSE > 24, Exc: antipsychotics, brain image lesion                        | Use P300 as index of cognitive function in PD | EEG              |                                                                          | Fair    |
|               |                 | 15 HC      |                                                                                     |                                             |                  |                                                                          |         |
| Peppe 1995    | Cross-sectional | 18 PD      | Inc: de novo PD, Exc: DM, retinopathy                                              | Determine VEP characteristics in de novo PD | VEP              |                                                                          | Fair    |
|               |                 | 8 HC       |                                                                                     |                                             |                  |                                                                          |         |
| Bodis-Wollner | Cross-sectional | 50 PD      | Inc: PD, Exc: dementia, thalamotomy, depression                                     | Determine event related potentials characteristics in PD | EEG              |                                                                          | Fair    |
| 1995          |                 |            |                                                                                     |                                             |                  |                                                                          |         |
| Vierregge 1994| Cross-sectional | 14 PD      | Inc: right handed, Exc: depression, dementia, deafness                              | Assess selective auditory attention with processing negativity in PD | EEG              |                                                                          | Fair    |
|               |                 | 16 HC      |                                                                                     |                                             |                  |                                                                          |         |
| Filipovic 2001| Cross-sectional | 16 PD w&w/o depression                                                                 | Inc: PD, Exc: severe tremor, focal brain lesions | Determine readiness potential patterns that distinguish w&w/o depression | EEG              |                                                                          | Poor    |
| Buttner 1996  | Cross-sectional | 39 PD      | Inc: PD, Exc: dementia, retinopathy, Daltonism                                       | Assess chromatic VEP in PD patient          | VEP              |                                                                          | Poor    |
|               |                 | 43 HC      |                                                                                     |                                             |                  |                                                                          |         |

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, nonreported; min, minutes; PDD, Parkinson’s disease dementia; PSG, Polysomnography; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EEG, electroencephalography; VEP, Visual evoked potentials; AEP, Auditory evoked potentials; DM, Diabetes mellitus; HTN, Hypertension; & Yahr; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; ERP, event related potential; UPSIT, Smell Identification Test
### Table 4. Eligible studies assessing sleep.

| Study               | Design               | Population | Selection Criteria                                                                 | Aim                                                                 | Technology | Results                                                                 | Quality |
|---------------------|----------------------|------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------|-------------------------------------------------------------------------|---------|
| Loo 2008            | Prospective Case-control | 200 PD    | Inc: newly diagnosed PD, MMSE > 24                                                | Correlate RLS and PD                                                | PSG        | Weak association between RLS and PD                                     | Good    |
|                     |                      | 200 HC     | Exc: N/R                                                                            |                                                                      |            |                                                                         |         |
| Zibetti 2017        | Prospective Cohort   | 11 PD      | Inc: Levodopa carbidopa intestinal gel                                            | Evaluate the impact of gel infusion on sleep parameters              | PSG        | PSG showed less fragmented sleep pattern in PD patients treated with Levodopa carbidopa intestinal gel | Fair    |
| Schroeder 2016      | Case-control         | 50 PD      | In: early and mid-duration PD                                                       | Explore REM density in PD across disease duration                    | PSG        | REM density is reduced in patients with mid-duration PD and correlates with subjective scores on sleep impairment | Fair    |
|                     |                      | 31 HC      | Exc: Dementia                                                                       |                                                                      |            |                                                                         |         |
| Alatriste-Booth 2015| Cross-sectional      | 120 PD     | In: PD                                                                              | Sleep disorders prevalence in PD                                    | PSG        | Sleep apnea-hypopnea syndrome and RBD were the most frequent sleep disorders. | Fair    |
| Valli 2015          | Prospective cohort   | 15 PD      | Inc: PSG recording                                                                  | Test differences in dream content of PD patients w&w/o RBD          | PSG        | No differences in dream content of PD patients w/w/o RBD.              | Fair    |
|                     |                      | w&w/o RBD  | Exc: Dementia, hallucinations                                                        |                                                                      |            |                                                                         |         |
| Louter 2014         | Case-control         | 45 PD      | In: PD                                                                              | Actigraphy as a diagnostic tool for RBD in PD patients              | Actigraphy | PD patients w/RBD have more bouts scored as 'wake' using actigraphy, compared to patients w/o RBD. | Fair    |
|                     |                      | w&w/o RBD  | Exc: <10 min of REM sleep in PSG                                                    |                                                                      |            |                                                                         |         |
| Vaughan 2013        | Cross-sectional      | 60 PD      | In: PD                                                                              | Clinical factors related to nocturia and sleep disruption            | PSG        | More episodes of nocturia associated with less total sleep time and efficiency | Fair    |
|                     |                      |            | Exc: dementia, DBS, serious comorbidities                                           |                                                                      |            |                                                                         |         |
| Naismith 2010       | Cross-sectional      | 22 PD      | In: PD                                                                              | Evaluate actigraphy for RBD reported by PD patients                 | Actigraphy | PD patients w/RBD have higher number of wake bouts than PD patients w/o RBD | Fair    |
|                     |                      | w&w/o RBD  | Exc: N/R                                                                            |                                                                      |            |                                                                         |         |
| Shpirer 2006        | Prospective cohort   | 46 PD      | In: PD                                                                              | Compare sleep characteristics of PD versus HC                        | PSG        | PD had lower sleep efficiency, longer Stage 2 sleep and shorter REM sleep | Fair    |
| Dhawan 2006         | Cross-sectional      | 59 PD      | In: PD, H&Y 3 to 5                                                                 | Compare sleep problems in untreated PD compared to advanced PD and HC | PSG        | Advanced PD demonstrated PSG patterns of periodic limb movement of sleep, obstructive sleep apnea, and RBD | Fair    |
|                     |                      | 131 HC     | Exc: N/R                                                                            |                                                                      |            |                                                                         |         |
| Diederich 2005      | Case-control         | 49 PD      | In: PD                                                                              | Nocturnal respiration impact on sleep continuity and architecture   | PSG        | In nonobese PD patients, sleep apnea syndrome is not a major cause for sleep fragmentation | Fair    |
|                     |                      | 49 HC      | Exc: N/R                                                                            |                                                                      |            |                                                                         |         |
| Gagnon 2004         | Cross-sectional      | 15 PD      | In: PD, H&Y 1 to 3                                                                 | Compare EEG of PD w&w/o RBD                                        | EEG        | EEG slowing reported during wakefulness in nondemented PD is strongly correlated to RBD | Fair    |
|                     |                      |            | Exc: atypical parkinsonism, antidepressants, serious illness                       |                                                                      |            |                                                                         |         |
|                     |                      |            | Inc: PD undergoing DBS                                                             |                                                                      |            |                                                                         |         |
| Cicolin 2004        | Cross-sectional      | 5 PD       | In: PD                                                                              | Evaluate sleep architecture modifications after STN DBS             | PSG        | STN DBS increases total sleep time and reduces wakefulness after sleep onset | Fair    |
|                     |                      |            | Exc: N/R                                                                            |                                                                      |            |                                                                         |         |
| Moller 2002         | Cross-sectional      | 6 PD       | In: unusually fast or sudden onset of sleep, combined dopamine agonist + levodopa  | Investigate nighttime sleep quality and degree of daytime sleepiness in PD patients with sleep attacks | PSG        | Unusually fast or sudden onset of sleep in PD patients is a phenomenon of daytime sleepiness | Fair    |
|                     |                      |            | Exc: N/R                                                                            |                                                                      |            |                                                                         |         |
| Gagnon 2002         | Cross-sectional      | 33 PD      | In: H&Y 1–3, use of dopamine agonists                                               | Determine the frequency of RBD among patients with PD               | PSG        | A third of patients with PD meet RBD criteria based on PSG, but only half of these cases would have been detected by history taking. | Fair    |
|                     |                      | 16 HC      | Exc: atypical signs for PD diagnosis                                                |                                                                      |            |                                                                         |         |
| Young 2002          | Cross-sectional      | 18 PD      | In: PD, Epworth scale ≥8                                                           | Determine the effect of mild versus severe PD on sleep parameters   | PSG        | There was no significant difference in objective sleep parameters between the two groups. | Fair    |
|                     |                      |            | Exc: H&Y 3                                                                          |                                                                      |            |                                                                         |         |
| Study          | Design     | Population | Selection Criteria                                                                 | Aim                                                                 | Technology | Results                                                                 | Quality |
|---------------|------------|------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------|------------------------------------------------------------------------|---------|
| Comella 1993  | Cross-sectional | 10 PD      | Inc: L-dopa + dopamine agonist for ≥6 months                                       | Compare PSG in PD with and without hallucinations                    | PSG        | The hallucinator group had a lower sleep efficiency, a reduced total REM sleep time, and a reduced REM percentage | Fair    |
|               |            |            | Exc: dementia, depression, serious illness                                          |                                                                      |            |                                                                        |         |
| Perez-Lloret 2009 | Cross-sectional | 71 PD 21 HC | Inc: PD, MMSE >24                                                                  | Correlate sleep logs compared to PD Sleep Scale                      | Actigraphy | Retrospective sleep quality evaluation by the PDSS and day-to-day evaluation by sleep log coincided | Poor    |
| Norlinah 2009 | Cross-sectional | 51 PD      | Inc: PD                                                                             | Determine the prevalence of sleep disorders in PD                    | PSG        | The prevalence of PSG-quantified sleep disturbances is high. Sleep fragmentation is the most common | Poor    |
|               |            |            | Exc: active psychiatric condition, benzodiazepine, sedative or excessive alcohol use |                                                                      |            |                                                                        |         |
| Moller 2009   | Case-control | 14 PD w&w/o sleep attack | Inc: PD, sudden sleep onset                                                         | Characterize and analyze sleep attack patterns on EEG               | EEG        | Sleep attacks are characterized by NREM stage 1 and 2 sleep in daytime EEG | Poor    |
| Diederich 2009 | Cross-sectional | 62 PD      | Inc: PD, sleep complaints                                                          | Examine the influence of diurnal dopaminergic medication on sleep   | PSG        | No impact of diurnal dopaminergic medication on nocturnal slow-wave sleep in PD patients | Poor    |
| Uemura 2009   | Cross-sectional | 79 PD 79 HC | Inc: PD                                                                             | Examine the relation between the PD sleep scale and PSG             | PSG        | PD sleep scale had significant correlation with PSG-measured sleep efficiency. | Poor    |
| Roth 2003     | Case-control | 16 PD w&w/o sleep episodes | Inc: H&Y 1–3, use of dopamine agonists                                               | Determine the association of dopamine agonists, daytime sleepiness, and sleep episodes | PSG        | Sleep episodes are related with excessive daytime sleepiness and unrelated to nocturnal sleep or use of any specific dopamine agonist | Poor    |

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&w/o, with and without; N/R, nonreported; PSG, Polysomnography; REM, Rapid eye movement; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EEG, electroencephalography; RBD, REM-sleep behavior disorder; H&Y, Hoehn & Yahr; MMSE, Mini-Mental State Examination
| Study                 | Design        | Population | Selection Criteria                                                                 | Aim                                                                 | Technology                  | Results                                                                 | Quality |
|----------------------|---------------|------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------|-------------------------------------------------------------------------|---------|
| Pavy-LeTraon 2018    | Cross-sectional | 62 MSA-P   | Inc: PD or MSA-P, Exc: N/R                                                         | Differentiate MSA from PD                                             | Cardiovascular and sweating autonomic testing | Cardiovascular and sweating tests are useful for differentiating MSA-P and PD | Good    |
|                      |               | 96 PD      | Inc: PD or probable MSA with OH, Exc: other illnesses that affect autonomic function | 24 h ambulatory blood pressure compared to head-up tilting for diagnosing OH in PD and MSA |                             | 24 h ambulatory BP and heart rate                                       |         |
| Vichayanrat 2017     | Cross-sectional | 23 MSA     | Inc: PD or probable MSA with OH, Exc: other illnesses that affect autonomic function | Assess 24 h ambulatory blood pressure compared to head-up tilting for diagnosing OH in PD and MSA | Cardiovascular autonomic testing                  | Dysautonomia affected patients with STN DBS and LCIG equally          | Good    |
|                      |               | 18 PD      | 33 PD w/o AF                                                                         | Assess dysautonomia in PD with STN DBS or LCIG                         |                             |                                                                          |         |
|                      |               | w/autonomic failure                  | 30 PD w/STN-DBS, 30 PD w/LCIG                                                      |                                                                           |                             |                                                                          |         |
| Merola 2017          | Cross-sectional | 30 PD      | Inc: PD, Exc: N/R                                                                     | Assess dysautonomia in PD with STN DBS or LCIG                         | Cardiovascular autonomic testing                  | Earlier autonomic dysfunction onset correlates with rapid progression and shorter survival | Good    |
|                      |               | w/STN-DBS | 30 PD w/LCIG                                                                         |                                                                           |                             |                                                                          |         |
| De Pablo-Fernandez 2017 | Cross-sectional | 100 PD    | Inc: PD from autopsy, Exc: atypical Parkinsonisms and other illnesses                | Correlate onset of autonomic dysfunction with progression and survival | Autonomic function testing (urinary/ED, GI, cardiovascular, and sweating) |                                                                          | Fair    |
| Baschieri 2015       | Cross-sectional | 34 MSA-P   | Inc: PD or MSA-P, Exc: other illnesses that affect autonomic function                | Differentiate MSA from PD                                             | Cardiovascular autonomic testing                  |                                                                          | Fair    |
| Haapaniemi 2001      | Cross-sectional | 54 PD      | Inc: treatment-naive PD, Exc: autonomic dysfunction                                  | Examine autonomic cardiovascular regulation in untreated PD            | 24-hour ECG monitoring                           | Patients with mild hypokinesia had higher heart frequency than patients with more severe hypokinesia. | Fair    |
|                      |               | 47 HC      |                                                                                      |                                                                           |                             |                                                                          |         |
| Tanaka 2000          | Cross-sectional | 29 PD      | Inc: PD, Exc: atypical parkinsonism, depression                                       | Compare the P3 and N1 amplitude between demented, nondemented PD, and HC | ECG                          | There was an increased P3 amplitude and ECG power in nondemented PD patients versus controls | Fair    |
|                      |               | 11 HC      |                                                                                      |                                                                           |                             |                                                                          |         |
| Oka 1997             | Cross-sectional | 30 PD      | Inc: PD, H&Y 1–4, Exc: atypical parkinsonism, anti Parkinsonian drugs other than L-dopa/carbidopa | Evaluation of QTc interval in patients with PD versus HC               | ECG                          | QTc intervals in PD significantly longer than in HC. Unrelated to administration of levodopa | Fair    |
|                      |               | 30 HC      |                                                                                      |                                                                           |                             |                                                                          |         |
| Oka 2003             | Cross-sectional | 20 PD      | Inc: N/R, Exc: N/R                                                                    | Evaluation of R-R interval and BP during Valsava maneuver and deep inspiration | ECG, continuous BP monitoring | Baroreflex sensitivity in PD is smaller than in HC                      | Poor    |
|                      |               | 50 HC      |                                                                                      |                                                                           |                             |                                                                          |         |
| Mastrocola 1999      | Cross-sectional | 13 PD      | Inc: PD, Exc: DM, HTN, drugs affecting autonomic tone                                 | Evaluate autonomic dysfunction in PD                                  | 24-h ECG monitoring                           | Significant difference in ECG parameters between PD and HC, reflecting a reduction in autonomic function. | Poor    |

PD, Parkinson’s disease; HC, Healthy control; Inc, Inclusion; Exc, Exclusion; w&/w/o, with and without; N/R, nonreported; min, minutes; PDD, Parkinson’s disease dementia; DBS, Deep brain stimulation; STN, Subthalamic nucleus; EEG, electroencephalography; ECG, Electrocardiography; DM, Diabetes mellitus; HTN, Hypertension; LCIG, levodopa-carbidopa infusion gel; MSA and MSA-P, Multiple System Atropia – Parkinsonism; OH, orthostatic hypotension; BP, blood pressure; H&Y, Hoehn and Yahr
surements collected from an actigraphy may be preferred over the more accurate but less ecologically representative PSG [145]. A similar context applies to the evaluation of autonomic function. In a recent publication [146], we proposed that a 24h-ambulatory blood pressure monitoring might be effectively employed as a screening test for cardiovascular autonomic neuropathy, a disabling comorbidity in PD with relevant socio-economic impact [147]. Autonomic dysfunction remains underrecognized and undertreated in PD [148] in part because its ascertainment relies on cardiovascular autonomic testing available only in a few specialized laboratories. In conclusion, these findings highlight the urgent need for developing relatively simple and unobtrusive systems to monitor motor and nonmotor endpoints in the home and community settings rather than during in-hospital evaluations.

A significant limitation consists of the lack of a multisensor, open-access, common-language platform combining the results of different sensors into a multidimensional TOM expressing a global measure of PD-associated functional disability. Although this unmet need has been reiterated by the Movement Disorders Society (MDS) in various international meetings and position papers [149], diagnostic and monitoring systems developed by different manufacturers continue to remain incompatible with one another. As a result, it is difficult or impossible to combine data gathered by different TOMs. This point represents one of the most critical areas of need, identified by the MDS Task Force for the Integration of Technology in PD as requiring further development. Only few studies have employed a smartphone application that integrates the capture of voice, posture, gait, finger tapping, and response time in the patient home environment, with high patient participation as well as sensitivity and specificity in the collected outcome measures [87].

4. Five-year view

Continuous improvements in technology are creating increasing opportunities for TOMs to improve self-management options and overall healthcare outcomes in PD. Thus, their integration into research and practice is expected to grow in the next five years. Critical challenges consist of validation of measures with patient-centered relevant endpoints, standardization of procedures, and approval by regulatory authorities.

Key issues
- Clinical scales for the assessment of Parkinson disease (PD) symptoms are prone to limitations such as subjectivity, inter-rater variability, and limited accuracy in capturing small variations within and between patients. A new generation of technology-based objective measures (TOMs) may provide a more accurate characterization of motor and nonmotor phenomena associated with PD.
- We searched PubMed for human studies employing TOMs as primary, secondary, or exploratory outcomes for the qualitative or quantitative evaluation of PD-associated motor and nonmotor symptoms. There were 61 studies assessing motor phenomena such as gait and postural instability (n = 33 studies), bradykinesia (n = 13 studies), tremor (n = 8 studies), and rigidity (n = 7 studies), and 63 studies assessing nonmotor phenomena such as sleep disorders (n = 23 studies), cognitive impairment (n = 18 studies), dysautonomia (n = 12 studies), sensory deficits (n = 3 studies), and voice analysis (n = 7 studies).
- Although TOMs have the potential to significantly improve the accuracy of both motor and nonmotor clinical endpoints, their integration into randomized controlled trials and routine clinical practice remains limited by several unresolved issues, including validation of patient-centered outcomes, standardization of measurements, and approval by regulatory authorities.
- While TOMs have not yet been shown to be superior to the clinical evaluation, their integration into research and practice is expected to substantially increase in the next five years and translate into enhanced care, better self-management options for PD patients, and overall improved healthcare outcomes. A survey from 12 medical directors from pharmaceutical companies indicated that 83% of them are considering using TOMs in future clinical trials within the next five years.
Declaration of interest
A Merola is supported by the NIH (KL2 TR001426), has received speaker honoraria from CSL Behring and Cygnus Therapeutics, and has received grant support from Lundbeck. A Fasano has received grants/research support from MJ Fox Foundation, University of Toronto, McLaughlin Centre; has received honoraria or consultation fees from AbbVie, Boston Scientific, Chiesi Farmaceutici, Ipsen, Medtronic, Novartis, TEVA Canada, UCB Pharma; and has participated in sponsored advisory boards for AbbVie, Boston Scientific, and Ipsen. AJ Espay is supported by the NIH, has received grant support from CleveMed/Great Lakes Neurotechnologies, Davis Phinney Foundation, and MJ Fox Foundation; was an investigator in Chelsea-sponsored studies, has acted as a scientific advisor to Lundbeck, and is marketer for Droxidopa but has no financial interest in either company. They have received personal compensation as a consultant/advisory board member for Solvay, Abbott, Chelsea Therapeutics, TEVA, Impax, Merz, Lundbeck, and Eli Lilly; has received honoraria from TEVA, UCB, the AAN, and the Movement Disorder Society; and publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer. The authors have no further conflicts of interest to declare.

Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding
This paper was not funded.

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