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# Digital biomarkers in movement disorders

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# Digital biomarkers in movement disorders

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# Editorial: Digital biomarkers in movement disorders

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Editorial on the Research Topic
Digital biomarkers in movement disordersitor

## Introduction

There is a substantial gap in the assessment of movement disorders in the clinic, and clinical trials, with the current gold standard involving clinical rating scales performed by expert clinicians. This not only limits access but these rater-dependent measures are time-consuming, lack sensitivity to disease progression, have ceiling effects in advanced disease, and floor effects in the early stages (1). In addition, for therapeutic and disease-modifying clinical trial readiness in movement disorders, there are increasing calls for sensitive and rater-independent, multi-modal biomarkers, including quantitative digital motor biomarkers to quantify the motor examination, identify the earliest signs of disease manifestation, and obtain a fine-grained monitoring of disease progression (2–5). Such measures could be deployed remotely (6, 7), increasing access, particularly in underserved regions, and reducing the sample size, with consequent reduction of time and costs. Such measures are particularly important in rare or combined movement disorders, where sample sizes are small, and the presence of overlapping features and phenomenology make clinical assessment especially challenging. To overcome such obstacles, objective measures of motor performance using digital technology are currently being studied, and such measures are now being included in early-adopting clinical trials (8).

## Patients' perspectives and use feasibility

Firstly, patient perspectives on the use of digital technology are of vital importance to ensure data clinically relevant and important to patients is collected, and as buy-in from patients is essential for effective deployment (9, 10). To this end, Paccoud et al. performed a large-scale patient survey regarding the willingness of people with Parkinson's disease (PD) to adopt and engage with digital devices. They found a high level of willingness to use digital technology and acceptance of data sharing. This study further emphasizes the importance of having a patient-centered focus for

deploying digital technology and highlighting differences in preferences across the age range. Further, Evers et al. sought to identify the perspectives of patients and healthcare providers (physiotherapists, nurses, and neurologists) regarding personalized monitoring of PD symptoms. They also conducted focus groups of these groups, and interviews with neurologists, comparing currently used monitoring tools to wearable sensors. Barriers included wanting to avoid focusing on symptoms of PD, and lack of an easy-to-use tool. Importantly, they identified a mismatch between priorities in patients and those of providers (which varied considerably by specialty), highlighting that personalized, patient-centered strategies will be important in the future.

In tandem with digital assessment of motor symptoms and movement analysis, digital patient-reported outcome measures, including digital diaries to assess motor fluctuations and disease progression in people with movement disorders such as PD, are important as clinical and research tools (11). Asai et al. compared an electronic diary to a standard paper diary assessing motor fluctuations. Electronic diaries were faster and showed a greater degree of correlation with patient-reported measures of disease severity, suggesting that electronic diaries may be more accurate than paper diaries in reflecting motor fluctuations in PD.

Wearable sensors, including those for continuous monitoring of mobility in daily life, are a burgeoning field in the assessment of movement disorders (12–14), with considerable interest in PD (15). Antonini et al. describe the results of two multi-site clinical studies assessing the performance and wearability of a system called PDmonitor. The system includes five inertial measurement unit (IMU) sensors to attach to both wrists and ankles and across the waist. They assessed meaningful aspects of wearable sensor use, including acceptable wearability of the device. Measurements assessing bradykinesia, gait, tremor, freezing of gait, dyskinesias, and on/off states correlated with clinical evaluations, suggesting the feasibility of assessing PD motor symptoms. Acceptability of the technology was good, as well as compliance. Interestingly, the study indicated that the monitoring device worn on the waist seemed to be more inconvenient compared to devices worn on other body parts.

Telemonitoring systems can be used to continuously monitor patients with movement disorders (16) over long periods, and for potential eligibility assessment of therapies (17). Konitsiotis et al. performed a telemonitoring study in 17 people with PD using a mobile app and five wearable sensors to measure everyday activities and digital reported outcomes over a 2-year time period. Telemonitoring positively impacted motor symptom control and enhanced patient satisfaction, which could improve adherence to treatment plans.

## Gait assessment in the laboratory and in daily life

Gait analysis is a common research tool for the assessment of gait disorders, including PD (18). A marker-based infrared camera setup represents the gold standard for gait analysis. However, this approach can only be performed in a specialized gait laboratory, and hence, video-based assessment has evolved over time (19). Yin et al. used a markerless integrated camera system, including an RGB and depth camera, to perform 3D gait analysis. They compared early-stage PD patients to controls and used machine-learning approaches. Several typical features distinguished early-stage PD from controls, an integrated analysis accurately identified PD, and machine-learning algorithms predicted clinical scores.

Shah et al. compared people with PD with falls and those without falls, using three inertial sensors. They created models to predict future fall risk, with the most consistent predictive features being gait variability, particularly variability of the toe-out angle of the foot, as well as turning domains, including pitch angle during mid-swing and peak turn velocity.

## Combination of multiple digital technology systems

Furthermore, digital technology systems (3, 20) can also be used in combination. Debelle et al. used multi-component digital technologies to collect mobility and medication data and to assess feasibility. They assessed people with PD over 7 days with a single IMU applied to the lower back to assess digital mobility outcomes, a smartphone to contextualize data, a smartwatch to assess self-reported medication adherence, and a diary to track motor complications, as well as a usability questionnaire. They suggested the feasibility of their approach, with the IMU and smartphone being usable, although there were issues with the smartwatch, both technical and related to tremor, or not feeling reminder vibrations, as well as a lack of familiarity with the system, indicating potential limitations.

As an attempt to operationalize digital health approaches (21), Alberts et al. sought to apply digital technologies together as the Waiting Room of the Future for PD, which could be deployed into the clinic and integrated into the electronic health record. Their PD-Optimize paradigm involves digital assessments completed on an iPad of motor function (manual dexterity and walking speed, a digital adaptation of the 10 m walking test) and cognitive aspects (visual memory and processing speed), combined with patient-reported outcomes. They describe the development and integration of their platform into clinical practice. Insights from the clinical use of PD-Optimize led to the development of a virtual reality platform to evaluate instrumental activities of daily living in PD patients.

## Atypical Parkinsonism and other movement disorders

Digital technology has also been applied to atypical Parkinsonism, with comparison to PD, and as potential markers of disease progression (22, 23). Dale et al.reviewed the use of multiple modalities assessing gait and balance (force plates, 3D motion capture, and inertial sensors) and exercise interventions in progressive supranuclear palsy (PSP). They describe cross-sectional studies using wearable sensors comparing PSP to PD and longitudinal studies assessing PSP, and their limitations. They suggest potential practical applications, including abnormal anticipatory posture and the use of wearable sensors for longitudinal assessment, which may be useful for clinical trials.

Robertson-Dick et al. performed a first study of gait analysis in fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS has a wide clinical spectrum including tremor, ataxia and Parkinsonism. Digital measures have sought to identify features of prodromal disease in FXTAS (24). The authors used digital gait markers to compare patients with FXTAS, PD, and essential tremor (ET) using six IMUs under various gait conditions, and an instrument Timed Up and Go, in addition to cognitive assessments. Metrics differentiated PD from FXTAS and ET but none distinguished FXTAS from ET, and suggested that future study may aid in accurate and timely diagnoses.

Posturography using force plates is a long-established method to assess static and dynamic balance in vestibular disorders (25) and movement disorders (26–30). Bao et al. used static and dynamic posturography and compared PD and multiple system atrophy (MSA) of the Parkinsonism (MSA-P) and cerebellar (MSA-C) types. While static posture was similar between groups, all dynamic posturography parameters differentiated MSA from PD, with worse postural control in the medial-lateral direction. MSA patients had a greater degree of worsening with the eyes closed condition.

The simple use of spiral drawing is a useful assessment for clinically distinguishing different movement disorders (31), with increasing research interest in digital automated analysis (32) and particularly for the severity assessment of tremor disorders (33), such as ET (34). Toffoli et al. compared patients with PD to controls using a smart ink pen and utilizing machine learning for classification. PD patients had reduced fluency, with smoothness, correlating with clinical scores, and lower, more variable applied force, with accurate classification of PD compared to controls.

Musician's dystonia is a debilitating occupational dystonia, which has received little research assessing motor physiology (35, 36). Sata et al. take an uncommon case study of musician's dystonia involving the lower extremities of a drummer, and used electromyography of lower extremity muscles to assess bass drum pedaling and performed muscle synergy analysis using non-negative matrix factorization. This revealed shared muscle synergies in data with and without dystonic movement. Spatially, there was dystonia-specific muscle synergy, hypothesized to be related to compensatory movement, while temporally there was earlier over activation in timing, considered related to the dystonic movements.

## Conclusion

We are at the threshold of the accepted use of digital biomarkers to assess movement and motor disorders in isolation or as a combined platform and their integration into clinical practice (37). In addition to a growing literature on sensor-based assessment, there is also the potential for automated video analysis using computer vision (38, 39). Such approaches could aid in early diagnosis (including in prodromal stages), promote more accurate and earlier differential diagnosis, and track patient symptoms over time. These advantages hold the potential for more accurate clinical assessment, which benefits clinical care and research, and may lower sample sizes, time, and eventually costs of clinical trials.

## Author contributions

CS: Writing – review & editing, Conceptualization, Writing – original draft. FP: Conceptualization, Writing – review & editing. MM: Writing – review & editing, Conceptualization. CA: Conceptualization, Writing – review & editing.

## Conflict of interest

CS has provided scientific advisory for SwanBio/Spur Therapeutics and his institution has received research funding from Sanofi-Genzyme for a study of video oculography in late-onset GM2 gangliosidosis. He has received financial support from SwanBio/Spur Therapeutics, Encora Therapeutics, Sanofi-Genzyme, Biogen, and Biohaven for the conduct of clinical trials. He has received honoraria from the International Parkinson and Movement Disorders Society, the American Academy of Neurology/Continuum and Oakstone CME for the production of educational material. He has received grant support from the National Institutes of Health K23 NS118045. CA has received speaker honoraria from Abbvie, Bial, Zambon, Lusofarmaco, Ralpharma. FP joined Janssen Pharmaceutical Companies of Johnson and Johnson in October 2022. MM is supported by the National Institutes of Health, R01 HD100383, R01 HD107074, R01 AG077380, R01 HD110389, U01 NS113851, and the Michael J Fox Foundation for Research, MJFF-024177, and MJFF-024692.

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## References

1. Narayanaswami P. The spectrum of functional rating scales in neurology clinical trials. *Neurotherapeutics*. (2017) 14:161–75. doi: 10.1007/s13311-016-0488-5

2. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's disease: challenges and opportunities. *Mov Disord*. (2016) 31:1272–82. doi: 10.1002/mds.26642

3. Adams JL, Lizarraga KJ, Waddell EM, Myers TL, Jensen-Roberts S, Modica JS, et al. Digital technology in movement disorders: updates, applications, and challenges. *Curr Neurol Neurosci Rep*. (2021) 21:16. doi: 10.1007/s11910-021-01101-6

4. Ilg W, Milne S, Schmitz-Hübsch T, Alcock L, Beichert L, Bertini E, et al. Quantitative gait and balance outcomes for ataxia trials: consensus recommendations

by the ataxia global initiative working group on digital-motor biomarkers. *Cerebellum.* (2024) 23:1566–92. doi: 10.1007/s12311-023-01625-2

5. Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. *Handb Clin Neurol.* (2017) 144:209–25. doi: 10.1016/B978-0-12-801893-4.00018-3

6. Liu Y, Zhang G, Tarolli CG, Hristov R, Jensen-Roberts S, Waddell EM, et al. Monitoring gait at home with radio waves in Parkinson's disease: a marker of severity, progression, and medication response. *Sci Transl Med.* (2022) 14:eadc9669. doi: 10.1126/scitranslmed.adc9669

7. van den Bergh R, Evers LJW, de Vries NM, de Lima ALS, Bloem BR, Valenti G, et al. Usability and utility of a remote monitoring system to support physiotherapy for people with Parkinson's disease. *Front Neurol.* (2023) 14:1251395. doi: 10.3389/fneur.2023.1251395

8. Gordon MF, Grachev ID, Mazeh I, Dolan Y, Reilmann R, Loupe PS, et al. Quantification of motor function in huntington disease patients using wearable sensor devices. *Digit Biomark.* (2019) 3:103–15. doi: 10.1159/000502136

9. Riggare S, Stamford J, Hägglund M. A long way to go: patient perspectives on digital health for Parkinson's disease. *J Parkinsons Dis.* (2021) 11:S5–s10. doi: 10.3233/JPD-202408

10. Graeber J, Warmerdam E, Aufenberg S, Bull C, Davies K, Dixon J, et al. Technology acceptance of digital devices for home use: qualitative results of a mixed methods study. *Digit Health.* (2023) 9:20552076231181239. doi: 10.1177/20552076231181239

11. Vizcarra JA, Sánchez-Ferro Á, Maetzler W, Marsili L, Zavala L, Lang AE, et al. The Parkinson's disease e-diary: developing a clinical and research tool for the digital age. *Mov Disord.* (2019) 34:676–81. doi: 10.1002/mds.27673

12. McGurrin P, McNames J, Haubenberger D, Hallett M. Continuous monitoring of essential tremor: standards and challenges. *Mov Disord Clin Pract.* (2022) 9:1094–8. doi: 10.1002/mdc3.13558

13. Mohammadi-Ghazi R, Nguyen H, Mishra RK, Enriquez A, Najafi B, Stephen CD, et al. Objective assessment of upper-extremity motor functions in spinocerebellar ataxia using wearable sensors. *Sensors*. (2022) 22:7993. doi: 10.3390/s22207993

14. Tortelli R, Rodrigues FB, Wild EJ. The use of wearable/portable digital sensors in Huntington's disease: a systematic review. *Parkinsonism Relat Disord.* (2021) 83:93–104. doi: 10.1016/j.parkreldis.2021.01.006

15. Warmerdam E, Hausdorff JM, Atrsaei A, Zhou Y, Mirelman A, Aminian K, et al. Long-term unsupervised mobility assessment in movement disorders. *Lancet Neurol.* (2020) 19:462–70. doi: 10.1016/S1474-4422(19)30397-7

16. Salaorni F, Bonardi G, Schena F, Tinazzi M, Gandolfi M. Wearable devices for gait and posture monitoring via telemedicine in people with movement disorders and multiple sclerosis: a systematic review. *Expert Rev Med Devices.* (2024) 21:121–40. doi: 10.1080/17434440.2023.2298342

17. Niruban A, Dostal V, Mutimer A, Tsamis K, Kontaxis S, Kostikis N, et al. Assessing eligibility for apomorphine therapy in Parkinson's disease: the telemonitoring potential. *Mov Disord Clin Pract.* (2025). doi: 10.1002/mdc3.14345

18. di Biase L, Di Santo A, Caminiti ML, De Liso A, Shah SA, Ricci L, et al. Gait analysis in Parkinson's disease: an overview of the most accurate markers for diagnosis and symptoms monitoring. *Sensors*. (2020) 20:3529. doi: 10.3390/s20123529

19. Bonato P, Feipel V, Corniani G, Arin-Bal G, Leardini A. Position paper on how technology for human motion analysis and relevant clinical applications have evolved over the past decades: striking a balance between accuracy and convenience. *Gait Posture.* (2024) 113:191–203. doi: 10.1016/j.gaitpost.2024.06.007

20. Silva de. Lima AL, Hahn T, Evers LJW, de Vries NM, Cohen E, Afek M, et al. Feasibility of large-scale deployment of multiple wearable sensors in Parkinson's disease. *PLoS ONE.* (2017) 12:e0189161. doi: 10.1371/journal.pone.0189161

21. Maetzler W, Rochester L, Bhidayasiri R, Espay AJ, Sánchez-Ferro A, van Uem JMT. Modernizing daily function assessment in Parkinson's disease using capacity, perception, and performance measures. *Mov Disord.* (2021) 36:76–82. doi: 10.1002/mds.28377

22. Abate F, Russo M, Ricciardi C, Tepedino MF, Romano M, Erro R, et al. Wearable sensors for assessing disease severity and progression in progressive supranuclear palsy. *Parkinsonism Relat Disord.* (2023) 109:105345. doi: 10.1016/j.parkreldis.2023.105345

23. Sidoroff V, Raccagni C, Kaindlstorfer C, Eschlboeck S, Fanciulli A, Granata R, et al. Characterization of gait variability in multiple system atrophy and Parkinson's disease. *J Neurol.* (2021) 268:1770–9. doi: 10.1007/s00415-020-10355-y

24. O'Keefe JA, Bang D, Robertson EE, Biskis A, Ouyang B, Liu Y, et al. Prodromal markers of upper limb deficits in FMR1 premutation carriers and quantitative outcome measures for future clinical trials in fragile X-associated tremor/ataxia syndrome. *Mov Disord Clin Pract.* (2020) 7:810–9. doi: 10.1002/mdc3.13045

25. Nashner LM, Peters JF. Dynamic posturography in the diagnosis and management of dizziness and balance disorders. *Neurol Clin May.* (1990) 8:331–49. doi: 10.1016/S0733-8619(18)30359-1

26. Nonnekes J, Aerts MB, Abdo WF, Bloem BR. Medio-lateral balance impairment differentiates between Parkinson's disease and atypical parkinsonism. *J Parkinsons Dis.* (2014) 4:567–9. doi: 10.3233/JPD-140436

27. Reyes A, Salomonczyk D, Teo WP, et al. Computerised dynamic posturography in premanifest and manifest individuals with Huntington's disease. *Sci Rep.* (2018) 8:14615. doi: 10.1038/s41598-018-32924-y

28. Rossi-Izquierdo M, Franco-Gutiérrez V, San-Román-Rodríguez E, Patiño-Castiñeira B, Alberte-Woodward M, Guijarro-Del-Amo M, et al. What could posturography tell us about balance in essential tremor? *Gait Posture.* (2022) 96:338–42. doi: 10.1016/j.gaitpost.2022.06.013

29. Müller J, Ebersbach G, Wissel J, Brenneis C, Badry L, Poewe W. Disturbances of dynamic balance in phasic cervical dystonia. *J Neurol Neurosurg Psychiatry.* (1999) 67:807–10. doi: 10.1136/jnnp.67.6.807

30. Onursal Kilinç Ö, Ayvat E, Ayvat F, relationship between trunk position sense and postural control in ataxic individuals. *Gait Posture.* (2019) 68:258–63. doi: 10.1016/j.gaitpost.2018.12.007

31. Alty J, Cosgrove J, Thorpe D, Kempster P. How to use pen and paper tasks to aid tremor diagnosis in the clinic. *Pract Neurol.* (2017) 17:456–63. doi: 10.1136/practneurol-2017-001719

32. Memedi M, Sadikov A, Groznik V, Žabkar J, MoŽina M, Bergquist F, et al. Automatic spiral analysis for objective assessment of motor symptoms in Parkinson's disease. *Sensors.* (2015) 15:23727–44. doi: 10.3390/s150923727

33. Longardner K, Shen Q, Tang B, Wright BA, Kundu P, Nahab FB. An algorithm for automated measurement of kinetic tremor magnitude using digital spiral drawings. *Digit Biomark.* (2024) 8:140–8. doi: 10.1159/000539529

34. Legrand AP, Rivals I, Richard A, Apartis E, Roze E, Vidailhet M, et al. New insight in spiral drawing analysis methods - application to action tremor quantification. *Clin Neurophysiol.* (2017) 128:1823–34. doi: 10.1016/j.clinph.2017.07.002

35. Furuya S, Tominaga K, Miyazaki F, Altenmüller E. Losing dexterity: patterns of impaired coordination of finger movements in musician's dystonia. *Sci Rep.* (2015) 5:13360. doi: 10.1038/srep13360

36. Oku T, Furuya S. Neuromuscular incoordination in musician's dystonia. *Parkinsonism Relat Disord.* (2019) 65:97–104. doi: 10.1016/j.parkreldis.2019.05.011

37. Luis-Martínez R, Monje MHG, Antonini A, Sánchez-Ferro Á, Mestre TA. Technology-enabled care: integrating multidisciplinary care in Parkinson's disease through digital technology. *Front Neurol.* (2020) 11:575975. doi: 10.3389/fneur.2020.575975

38. Friedrich MU, Relton S, Wong D, Alty J. Computer vision in clinical neurology: a review. *JAMA Neurol.* (2025). doi: 10.1001/jamaneurol.2024.5326

39. Stenum J, Hsu MM, Pantelyat AY, Roemmich RT. Clinical gait analysis using video-based pose estimation: multiple perspectives, clinical populations, and measuring change. *PLoS Digit Health Mar.* (2024) 3:e0000467. doi: 10.1371/journal.pdig.0000467

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# Dynamic postural balance indices can help discriminate between patients with multiple system atrophy and Parkinson's disease

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**Background:** Patients with Parkinson's disease (PD) and those with multiple system atrophy (MSA) show similar symptoms but have different clinical treatments. It will be helpful to discriminate between these two kinds of patients at an early or middle stage. The purpose of this study is to highlight the differences in posturographic characterization between patients with PD and those with MSA during quiet standing and perturbed standing.

**Methods:** A total of clinically diagnosed 42 patients with PD and 32 patients with MSA participated in the experiment. Patients were asked to first stand on a static balance force platform and then on a dynamic balance (medial-lateral rocker) force platform to measure the center of pressure (COP) trajectory during an eyes-open (EO) state. The posturographic parameters were obtained under the two standing conditions for statistical analysis.

**Results:** Four posturographic variables were calculated and analyzed, namely, the standard deviation of COP position (SD), sway path of COP position (SP), an elliptical area covering the 95% COP position trajectory (EA), sway path of COP position (SP), and integral area of the power spectral density at 0–0.5 Hz frequency band (PSD). Except for variable EA, the other three variables are all in the medial-lateral (ML) direction. In the static balance experiment, there were no significant differences between the four variables between patients with PD and those with MSA. However, in the dynamic balance experiment, the obtained four variables all presented significant differences between patients with PD and those with MSA.

**Conclusion:** The dynamic posturographic variables with significant differences between patients with PD and those with MSA imply that patients with MSA have worse postural control ability in the medial-lateral (ML) direction compared to patients with PD. The obtained dynamic indices may help supplemental clinical evaluation to discriminate between patients with MSA and those with PD.

KEYWORDS

**Parkinson's disease (PD), multiple system atrophy (MSA), balance control, center of pressure (COP), posturography**

## Introduction

Patients with Parkinson's disease (PD) and those with multiple system atrophy (MSA) have many overlapping symptoms clinically, such as tremors, rigidity, bradykinesia, and posture instability, and they all have relatively large spontaneous sways when standing (1, 2). Movement disorders can be exceedingly difficult between differential diagnoses of neurodegenerative diseases, such as patients with PD and patients with MSA, who are very easily misdiagnosed (3). Accurate diagnosis is very important for correct treatment. Patients with PD are normally diagnosed by senior movement disorder specialists based on the Movement Disorder Society (MDS) diagnostic criteria for PD, which was drafted by Postuma et al. (4). MSA was diagnosed based on a novel set of diagnostic criteria from MDS, which was drafted by Wenning et al. (5). The new MSA diagnostic criteria aim at improving diagnostic accuracy, particularly in early disease stages.

Postural instability (PI) is one of the cardinal signs in the clinical diagnostic criteria of Parkinson's disease. Clinical differentiation of MSA typically relied on postural instability (PI) within 3 years of motor onset by neurologists (6). However, the differential diagnosis of neurodegenerative movement disorders can be exceedingly difficult (1). For the diagnosis of MSA, pathologically confirmed dementia with Lewy bodies (DLB) is the most common misdiagnosis, followed by progressive supranuclear palsy (PSP) and PD (7). According to Koga's report, only 62% of MSA patients' clinical diagnosis was confirmed at autopsy (7). Miki et al. researched and presented a clinicopathological study involving 203 people, of whom 78.8% were correctly diagnosed with MSA by pathological confirmation (8). In another study of surveys that confirmed MSA by autopsy, the correct diagnosis was 81.2% (9). On the contrary, the diagnosis of Parkinson's disease continues to be challenging, with misdiagnosis rates as high as 20–30% in the early stages (10). Such diagnostic inaccuracy is largely due to the failure to recognize atypical parkinsonian disorders (APDs) (10). The presence and severity of PI among patients with Parkinson's are commonly evaluated by the number of clinical tests. The most widely used tests for PI are the TUG test, the Tandem Gait test, and the pull test (11, 12). The pull test has been incorporated into the MDS-UPDRS scales (13). Tandem gait and TUG tests were used to distinguish APDs from PD (14). Though PI could not be detected in early PD patients without symptoms through these clinical tests, subclinical posture instability could be evaluated by objective assessments (15).

An objective method for the evaluation of posture stability in the clinic is to observe the patient's standing posture through posturography (16). Some subclinical PI symptoms have been shown through objective assessment of posturography in patients without any visible symptoms of PI (17). Panyakaew et al. compared the static standing PI of patients between the PD group and MSA group under eye open (EO) and eye closed (EC) conditions by analyzing the posturographic parameters (13). In the state of EC, the elliptical area covering the trajectory of the COP position in patients with MSA was larger than that in patients with PD. However, in the state of EO, there was no salient distinction. When comparing patients with PD, visual conditions have more impact on the standing posture of patients with MSA (18). But the studies comparing spontaneous sway between patients with PD and those with MSA under visual deprivation conditions have less practical meaning. In clinical practice, the standing posture of patients is normally evaluated with one eye open (EO). When patients with PD are in a state of EO, dynamic balance experiments can effectively distinguish the postural differences between patients with PD and healthy controls, which are often difficult to distinguish under the static balance condition (19). Dynamic balance experiments can also help to evaluate the motor adaptability of patients with PD (20). When a patient is standing on a dynamic force platform, the body is forced to follow the swing plane to perform a swing movement. In this disturbing environment, the standing person needs to increase their postural control to maintain body balance (21). The severity of postural sway in MSA should be shown to be worse than that of PD due to a more widespread degeneration in MSA (22). It is thus hypothesized that patients with PD and those with MSA may exhibit distinct PI features in the state of EO under dynamic standing.

The direction of PI among patients with PD and those with MSA has also been studied. Kamieniarz et al. found that the PI of patients with PD is mainly reflected in the anterior-posterior (AP) direction (2). In clinical trials, patients with MSA showed PI in the medial-lateral (ML) direction, while patients with PD did not present such features (23). Specifically, patients with MSA often have a broad stance width (24), which indicates that patients with MSA have more instability in the ML direction. Thus, it is better to use the tandem gait test for the detection of MSA (25). Patients with PD preserved their balance in the medial-lateral direction, so that many patients with PD are still able to ride their bicycles, even in the face of severe walking difficulties (26). Researchers found that patients with MSA showed a lack of coordination ability and postural defects in the ML direction in a cycling experiment (27). The previous studies demonstrated that the analysis of the posturographic characterization of patients with MSA should be focused on the ML direction, and the dynamic swing should also be in the ML direction in order to enhance the interference in the dynamic balance experiment.

The purpose of this study was to compare the differences in posturographic characterization between patients with PD patients and those with MSA under static and dynamic balance conditions at the state of EO. The obtained distinct posturographic features may help screen out patients with MSA from patients with PD during the stage of onset.

# Methods

## Participants

A total of 74 patients participated in the experiment. They were recruited from the outpatient clinics of the neurological department at Runjin Hospital in Shanghai between December 2019 and November 2020. Of them, 42 were patients with PD, and 32 were probable patients with MSA. The average age of patients with PD was 68.2 ± 7.1 years; the average age of patients with MSA was 64.8 ± 10.1 years. All patients performed assessments on the Hoehn &Yahr (H&Y) scale and the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Other examinations, such as the Berg Balance Scale (BBS) assessment, the Minimum Mental State Examination (MMSE), and the Gait and Falls Questionnaire (GFQ), were also recorded. Patients were excluded once they met one of the following conditions: H&Y stages 4–5, a history of severe neurological and psychiatric disorders, patients with significant cognitive impairment (MMSE < 24) or unable to complete the questionnaire independently, severe medical conditions preventing the patient from completing the experiment, there existing implantable materials such as intracranial stents, pacemakers, coronary stents, and cochlear implants; pregnant or lactating women. All subjects were asked not to take sedatives. All subjects were assessed at least 8 h after the last dose of anti-parkinsonian medications used to reduce the impact of dopaminergic medications (28). PD was diagnosed by senior movement disorder specialists based on the Movement Disorder Society (MDS) diagnostic criteria for PD (4). In the course of PD assessment, secondary causes (drug-induced, inflammatory, toxin-induced, and vascular parkinsonism), parkinsonism with other neurodegenerative diseases (progressive supranuclear palsy, multiple system atrophy, cortical basal ganglia degeneration, Wilson's disease, etc.), and other neurological diseases, such as stroke, were excluded. MSA was diagnosed based on the diagnostic criteria for MSA, which were drafted by Gilman et al. in 2008 (6). Probable patients with MSA who participated in the experiment were categorized as MSA-P with predominant parkinsonism but no cerebellar features or as MSA-C with predominant cerebellar signs but mild or no parkinsonism (29). The baseline clinical characteristics of all subjects were recorded by two doctors with more than 10 years of clinical experience. This study was conducted in accordance with the guidelines of the Helsinki Declaration of the World Medical Association (2000) and was approved and supervised by the Ethics Committee of Shanghai Ruijin Hospital (approval No. LWEC2019017). After receiving a detailed description of the experiment, all participants signed informed consent forms. The patients' demographic information is listed in Table 1.

## Device

The patients participating in the experiment needed to stand on a platform, 60 cm × 40 cm in size. The platform is a self-developed dynamic COP measuring system comprised of an AMTI (model bp400600, Advanced Mechanical Technology Inc., MA, USA) force board, a data collector, a rocker controller, and a host computer. A detailed description of the system is provided by Chen et al. and Chang et al. (30, 31). The frequency of data acquisition is set at 500 Hz. The system can work in either a stationary or dynamic state. One state is that the platform is stationary in the horizontal plane, in which the *x*-axis is in the ML direction and the *y*-axis is in the AP direction. Another state is that the platform rotates around the *y*-axis at a small angle (within ±4°) and swings periodically along the ML direction with a frequency of 1 Hz. A schematic diagram of the dynamic force platform is shown in Figure 1.

## Experimental procedures

All of the patients participated in the static balance experiment and the dynamic balance experiment. In the static balance experiment, the patient stood barefoot naturally and with shoulder width apart, hands drooping naturally. The range of the distance between heels was 20 ± 3 cm, and the range of the angles of the feet with respect to the AP axis was 20 ± 2°. The patient gazed at a fixed eye-level mark 3 m in front. In the dynamic balance experiment, the patient's standing posture was the same as that of the static balance experiment. After the patient stood on the platform for 20 s, the platform started to swing in the ML direction. In both experiments, before recording, the patient was asked to stand for 30 s to confirm that the COP signals were maintained at a relatively stable level. The recording period was set to 70 s for each state, with the first 5 s allocated for the fade-in, the next 60 s for the formal test, and the last 5 s for the fade-out. To maintain the reliability of the collected data, each patient's test was repeated three times, and the average value was taken during the calculation of posturographic parameters. The interval between each patient's tests was 5 min, during which time the patient left the platform for relaxation. In the experiment, if the patient had difficulty maintaining balance, the experiment was terminated.

## Analysis of the COP parameters

Before the statistical analysis, the COP signal obtained by the force platform was processed by fourth-order Butterworth low-pass filtering, and the cutoff frequency was set to 10 Hz. The filtered signal was calculated by the self-developed MATLAB algorithms. In the balance test, the coordinate origin of the

TABLE 1 Demographic data of the PD and MSA groups.

| Variable | PD ($N = 42$) (mean ± std) | MSA ($N = 32$) (mean ± std) | MSA-C ($N = 16$) (mean ± std) | MSA-P ($N = 16$) (mean ± std) |
|---|---|---|---|---|
| Age | 68.2 ± 7.1 | 64.8 ± 10.1 | 65.5 ± 10.69 | 64.1 ± 8.1 |
| Disease duration (Y) | 4 ± 3.28 | 3.3 ± 2.76 | 3.4 ± 2.86 | 3.2 ± 2.5 |
| Sex (% Femail) | 22(52%) | 14(44%) | 7(44%) | 7(44%) |
| Body weight (kg) | 63.2 ± 13.6 | 67.3 ± 12.8 | 65 ± 11.2 | 69.6 ± 13.8 |
| Height (cm) | 164 ± 7.29 | 166 ± 9.4 | 165 ± 10.4 | 167 ± 8.4 |
| Body mass index | 23.5 ± 2.9 | 24.26 ± 2.58 | 23.9 ± 1.58 | 24.62 ± 3.58 |
| H&Y score | 2.02 ± 0.57 | 2.6 ± 0.57 | 2.7 ± 0.77 | 2.5 ± 0.37 |
| MDS-UPDRS score (total) | 55.6 ± 21.9 | 76.65 ± 24.2 | 78.2 ± 22.2 | 75.1 ± 26.2 |
| Berg Balance Scale | 51.95 ± 4.1 | 41.23 ± 10.7 | 40.1 ± 11.7 | 42.36 ± 11.7 |
| MMSE | 27 ± 1.95 | 25.88 ± 2.14 | 25.2 ± 1.1 | 26.56 ± 2.1 |
| GFQ | 20 ± 11.8 | 22 ± 8.19 | 22.5 ± 6.2 | 21.45 ± 9.1 |

BBS, Berg Balance Scale; H&Y, Hoehn-Yahr Scale; MDS-UPDRS, MDS-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; MSA, multiple system atrophy; GFQ, Gait and Falls Questionnaire.

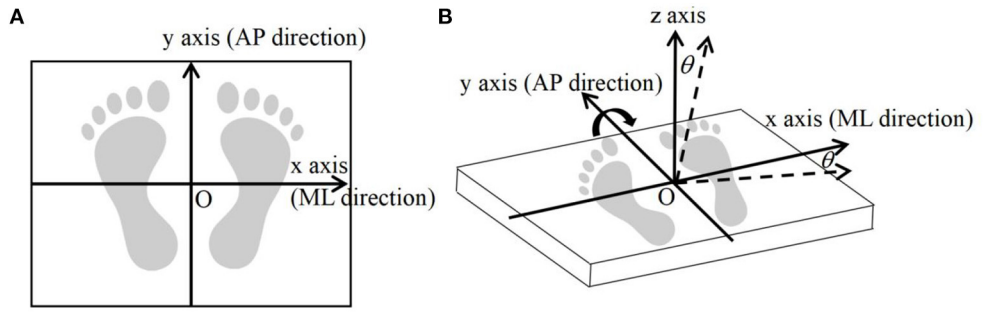


FIGURE 1
Schematic diagram of the dynamic force platform. **(A)** The patient stands still and upright on the stationary force platform with bare feet, with the *y*-axis in the AP direction and the *x*-axis in the ML direction. **(B)** The patient stands upright and barefoot on the dynamic force platform. The platform swings periodically around the *y*-axis. The patient needs to maintain body balance during the swinging process. The *z*-axis is the vertical direction when the patient stands. $\theta$ is the instantaneous swing angle of the platform. ML, medial-lateral; AP, anterior-posterior.

COP signal was the central position of the force plate. Since the starting point of each collected COP signal was different for each test, the average coordinate values of COP displacement (in the $x$ and $y$ directions) were taken as the offset values and were removed by the program algorithm before the actual calculation. In the dynamic balance test, the force platform swings periodically around the $y$-axis with an instantaneous swing angle $\theta$ (Figure 1). The $x$ and $y$ coordinates of the COP position under dynamic balance can be calculated in real-time through a coordinate transformation matrix, obtaining the instantaneous swing angle $\theta$ by counting the control pulses (31).

After obtaining the position coordinates of the COP under static balance and dynamic balance, the relevant posturographic parameters were calculated. There are many parameters related to posturographic characterization (32). In this study, four spatiotemporal variables were chosen: (1) the standard deviation (SD) of COP displacement, (2) the elliptical area covering the 95% confidence of COP position trajectory (EA) (33), (3) the sway path of COP position, and a frequency domain variable, (4) power spectral density (PSD) at 0–0.5 Hz frequency band (34). Table 2 lists the specific expressions of the four parameters. The calculation formulas for those variables were provided in the Supplementary material. Although the posturographic parameters were calculated in both the AP and ML directions, the results showed that only the parameters in the ML direction presented significant differences between the MSA and PD groups. Therefore, except for *EA*, the other three parameters listed in Table 2 are in the ML direction by default.

TABLE 2 Variables used in the analysis of the COP displacement.

| Variable | Description |
|---|---|
| *SD* | Standard deviation of COP position in ML direction |
| *EA* | Ellipse Area covering the 95% confidence of COP position |
| *SP* | Sway Path of COP position in ML direction |
| *PSD* | Integral area of power spectral density at 0–0.5Hz frequency band in ML direction |

COP, the center of pressure; ML, medial-lateral.

## Statistical analysis

After obtaining the COP signal from the tester, the statistical analysis was carried out using the IBM SPSS Statistics 25.0 software. The Shapiro–Wilk statistic was used to test the normality of the distribution of all variables. Because the data do not strictly follow a normal distribution, differences among the MSA group and PD groups were evaluated using the Mann–Whitney test for *post hoc* pair-wise tests for variables. To compare between the MSA-C, MSA-P, and PD groups, Kruskal–Wallis rank sum test was performed with Mann–Whitney tests for *post hoc* pair-wise comparisons. The significance level was set to 0.05. The correlations between the variables and the patient's clinical scale (H&Y) were calculated with Spearman's rank test. To determine the sample size, a power analysis was performed based on the previously published studies between MSA and PD. A sample size of at least 15 subjects per group was identified to detect an effect size of 0.5 with a power of 0.8 (35). A sample size of at least 15 subjects per group was needed.

# Results

We present the results of the statistical analysis of the four posturographic parameters. Subscripts *_st* and *_dy* are used to represent the conditions of static balance and dynamic balance, respectively. Table 3 lists the statistical results of the parameters obtained from the MSA patient group and the PD patient group in both the static and dynamic balance experiments. There were no significant differences between the PD and MSA groups with the four posturographic parameters in the static balance experiment. However, in the dynamic balance experiment, there were significant differences in these same parameters between the MSA group and the PD group. The variable *PSD_dy* ($p$-value = 0.006, effect size $d$ value = 0.52) displays the largest difference.

Table 4 lists the statistical results between the MSA-C, MSA-P, and PD groups in both the static and dynamic experiments. Again, there were no significant differences between the PD, MSA-C, and MSA-P groups with all four static parameters. However, these four same parameters in dynamic balance all showed significant differences between the PD group and the MSA-C group, and two variables (*SD_dy* and *EA_dy*) present significant differences between the PD and the MSA-P groups.

TABLE 3 Statistical results of posturographic variables between PD and MSA groups.

| State of EO | PD ($N = 42$) | MSA ($N = 32$) | MSA vs. PD |
|---|---|---|---|
| Variable | Mean ± std | Mean ± std | P-value |
| Static | | | |
| *SD_st* | 0.007 ± 0.0082 | 0.0069 ± 0.0048 | 0.398 |
| *EA_st* ($cm^2$) | 5.37 ± 12.25 | 9.1 ± 25.43 | 0.071 |
| *SP_st* (cm) | 131.48 ± 139 | 151 ± 95.7 | 0.703 |
| *PSD_st* | 0.599 ± 1.24 | 0.217 ± 0.142 | 0.263 |
| Dynamic | | | |
| *SD_dy* | 0.026 ± 0.0089 | 0.037 ± 0.014 | 0.001** |
| *EA_dy* ($cm^2$) | 52.1 ± 27.1 | 83.3 ± 57.13 | 0.002** |
| *SP_dy* (cm) | 656.28 ± 215 | 835.13 ± 315.7 | 0.001** |
| *PSD_dy* | 6.93 ± 5.47 | 12.96 ± 1.67 | 0.001** |

*Indicates p-value < 0.05, **Indicates p value < 0.01. PD, Parkinson's disease; MSA, multiple system atrophy; st, static; dy, dynamic.

Figure 2A shows the typical elliptical area (*EA_st*) of a sample PD patient and a sample MSA patient with EO in the static balance experiment. The value of the blue elliptical area (the patient with PD) is similar to the value of the red elliptical area (the patient with MSA). Figure 2B depicts the elliptical area (*EA_dy*) of the same patient with PD and the same patient with MSA in the dynamic balance experiment. The *EA_dy* value of the patient with PD (46.13 $cm^2$) was significantly smaller than that of the patient with MSA (92.91 $cm^2$).

Figure 3 shows processed sample data of a patient with PD and a patient with MSA in the form of power spectral density of COP changes with the frequency of COP. The variable PSD is displayed in the figure as the integral area of the corresponding curve up to the 0.5 Hz frequency band. In Figure 3A of the static balance experiment, there is little difference in the integral area under the PSD curve (*PSD_st*) between the PD sample and the MSA sample. However, in Figure 3B of the dynamic balance experiment, a salient difference can be seen in the variable *PSD_dy* between the PD sample and the MSA sample.

Table 5 lists Spearman's rank correlation (rho) between the subject's posturographic variable and H&Y scale score. It can be seen that the dynamic balance variable sway path (*SP_dy*) in the MSA group is most relevant (rho = −0.484).

# Discussion and conclusion

In this study, the differences in postural balance between Parkinson's disease and MSA were studied. The posturographic characterization of PD and MSA groups under both the static

TABLE 4 Statistical results of posturographic variables MSA-C, MSA-P, and PD groups.

| State of EO | PD ($N = 42$) | MSA-C ($N = 16$) | MSA-P ($N = 16$) | PD vs MSA-C | PD vs MSA-P | MSA-C vs MSA-P |
|---|---|---|---|---|---|---|
| Variable | Mean ± std | Mean ± std | Mean ± std | P-value | P-value | P-value |
| Static | | | | | | |
| *SD_st* | 0.007 ± 0.0082 | 0.007 ± 0.002 | 0.0067 ± 0.008 | 0.554 | 0.128 | 0.254 |
| *EA_st* ($cm^2$) | 5.37 ± 12.2 | 12.9 ± 4.78 | 5.29 ± 70 | 0.144 | 0.156 | 0.696 |
| *SP_st* (cm) | 131.48 ± 139 | 162.68 ± 44 | 139.9 ± 155 | 0.59 | 0.486 | 0.752 |
| *PSD_st* | 0.599 ± 1.24 | 0.17 ± 0.18 | 0.26 ± 0.67 | 0.135 | 0.16 | 0.8 |
| Dynamic | | | | | | |
| *SD_dy* | 0.026 ± 0.0089 | 0.039 ± 0.013 | 0.035 ± 0.016 | 0.001** | 0.035* | 0.235 |
| *EA_dy* ($cm^2$) | 52.1 ± 27.1 | 89.8 ± 72.8 | 76.8 ± 36.7 | 0.008** | 0.028* | 0.669 |
| *SP_dy* (cm) | 656.28 ± 215 | 944 ± 315 | 726 ± 284 | 0.001** | 0.159 | 0.094 |
| *PSD_dy* | 6.93 ± 5.47 | 16.06 ± 10 | 9.87 ± 8 | 0.001** | 0.044* | 0.08 |

*Indicates p-value<0.025, **Indicates p-value<0.01. PD, Parkinson's disease; MSA, multiple system atrophy; N, number; st, static; dy, dynamic.

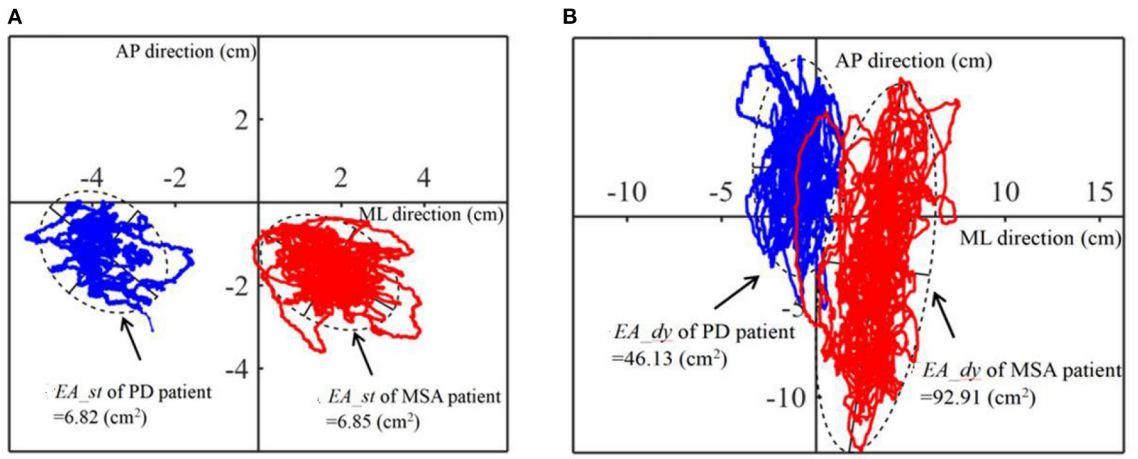


FIGURE 2
Schematic diagram of parameter *EA* of one PD patient and one MSA patient. **(A)** Static balance experiment. **(B)** Dynamic balance experiment. PD, Parkinson's disease; MSA, multiple system atrophy; COP, the center of pressure; ML, medial-lateral; AP, anterior-posterior.

balance and the dynamic balance conditions at the state of EO was represented by three spatiotemporal parameters, namely, *SD*, *SP*, and *PEA*, and one frequency domain variable, namely, *PSD*. The four parameters in the static balance experiment show no significant differences between the PD and the MSA groups at the state of EO. However, significant differences in the four parameters between the PD and the MSA groups were presented in the dynamic balance experiments.

The posturographic variables, such as standard deviation (*SD*), sway path (*SP*), and elliptical area (*EA*), are all spatiotemporal measures of the COP trajectory. A previous study reported that in the EC state, the elliptical area of the COP displacement trajectory with patients with MSA under static standing was statistically larger than that with patients with PD. The different results under EO and EC conditions indicated that the effect of vision block on postural instability in patients with MSA is greater than that in patients with PD (18). The larger elliptical area covering the COP position trajectory usually indicates that the body has a poorer ability for postural control (36). The current results showed no significant differences between the MSA group and the PD group under the static balance condition, which implies that such spatiotemporal variables are normally inadequate to differentiate the postural control abilities between patients with MSA and those with PD during quiet standing in the EO state. In the dynamic balance experiment, the patients needed to respond to the coordination with the swinging platform along the ML direction. The experimental results show that the spatiotemporal

variables of patients with MSA are statistically significantly larger than those of the PD group. Since patients with MSA usually have a broad-based stance and more instability in the ML direction, it is more difficult for patients with MSA to adjust and coordinate balance in the ML direction under interference, thus resulting in larger spatiotemporal variables. Other clinical studies also reported that the feature of ML balance impairment from various atypical parkinsonians like MSA can be revealed from simple observation tests (23). But in the early stages of the patient's illness, some subclinical posture instability could be difficult to evaluate without objective assessments (17). This study may provide an objective measure to assist these observation tests.

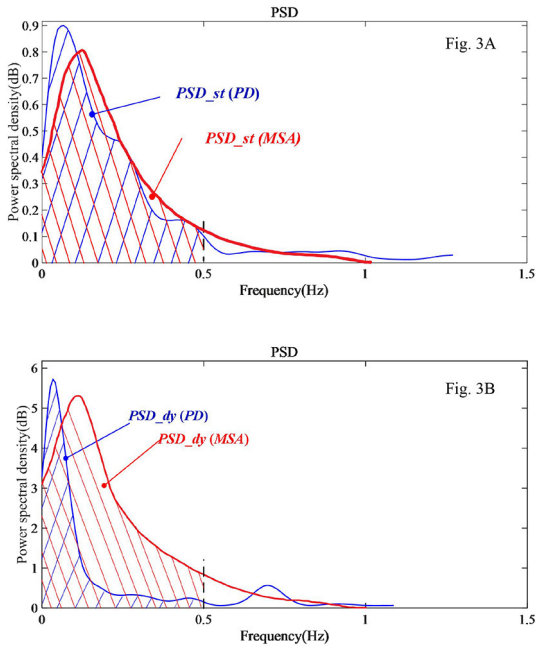


FIGURE 3
PSD analysis diagram of a sample PD and a sample MSA patients' COP signal in the EO state. **(A)** Static balance experiment. **(B)** Dynamic balance experiment.

The power spectra of the COP time series provided more information about the structure of the COP signal. The power spectral density of the COP signals is mainly concentrated below the 0.5 Hz frequency range, which is represented by the variable *PSD*. In our study, the results show that the value of *PSD_dy* for the MSA group was statistically higher than that of the PD group in the dynamic balance experiment, whereas no statistical differences in *PSD_st* were seen between those two groups in the static balance experiment. It can be deduced that COP oscillations were more exacerbated in MSA than PD groups in the dynamic standing along the ML direction. This is possibly caused by a more widespread degeneration in MSA than in PD groups. The frequency below 0.5 Hz can reflect an oscillation that was part of the descending drive to the motor neuron pool (37, 38). A larger oscillation in the lower frequency band indicates increased activity within the relevant postural subsystem, either due to pathology or compensatory efforts. When the sway amplitude in the ML direction exceeds a threshold range, the intermittent control mechanism will be triggered (39). It has been reported that COP oscillations below 0.5 Hz were exacerbated in an early and moderate PD relative to the healthy group in the state of EO (40). Since all the participants were in an early or moderate stage of the disease, balance impairments in the ML direction were not obvious and could not be discriminated against during static standing. The coordinative disorder was amplified when standing on the dynamic platform, resulting in a significant difference in the variable between the two groups of patients.

TABLE 5 Spearman's rank correlation (rho) between subjects' posturographic variables and H&Y scale score.

| State of EO | PD ($N = 42$) | | MSA ($N = 32$) | | MSA-C ($N = 16$) | | MSA-P ($N = 16$) | |
|---|---|---|---|---|---|---|---|---|
| Variable | Rho | P-value | Rho | P-value | Rho | P-value | Rho | P-value |
| Static | | | | | | | | |
| *SD_st* | −0.088 | 0.611 | 0.14 | 0.462 | 0.373 | 0.189 | 0.122 | 0.654 |
| *EA_st* ($cm^2$) | −0.077 | 0.646 | −0.154 | 0.417 | 0.656 | 0.011* | −0.017 | 0.95 |
| *SP_st* (cm) | −0.007 | 0.966 | 0.219 | 0.571 | 0.372 | 0.19 | −0.063 | 0.816 |
| *PSD_Power_st* | 0.174 | 0.318 | 0.192 | 0.621 | 0.194 | 0.1 | 0.094 | 0.2 |
| Dynamic | | | | | | | | |
| *SD_dy* | 0.112 | 0.48 | 0.405 | 0.026* | 0.302 | 0.295 | 0.011 | 0.968 |
| *EA_dy* ($cm^2$) | 0.171 | 0.278 | 0.327 | 0.077 | 0.089 | 0.763 | −0.075 | 0.783 |
| *SP_dy* (cm) | 0.119 | 0.453 | 0.484 | 0.007** | 0.195 | 0.504 | 0.093 | 0.731 |
| *PSD _dy* | 0.04 | 0.8 | 0.472 | 0.008** | 0.337 | 0.239 | 0.137 | 0.613 |

*Indicates p-value<0.05, **Indicates p-value<0.01. PD, Parkinson's disease; MSA, multiple system atrophy; EO, eyes-open, COP, the center of pressure; st, static; dy, dynamic.

Furthermore, the four parameters were compared between MSA-C and MSA-P patients. The four COP parameters of MSA-C patients were statistically larger than those of MSA-P patients in the dynamic balance experiment. Generally, the cerebellum is severely damaged in MSA-C patients, which can result in a worse postural control ability compared with MSA-P patients. The variable *PSD_dy* shows the largest difference between MSA-C and MSA-P, with a significant difference ($p$-value = 0.016). This is also consistent with the previous study by Li et al., who found that MSA-C can be effectively distinguished from MSA-P by relying on PSD (41). The staging of the functional disability associated with Parkinson's disease is commonly evaluated through H&Y scales (42). The H&Y scales have been validated not only in PD but also in MSA for the assessment of severity and disability. In our study, the participants in the experiment are in the early or middle stages, and the corresponding H&Y scale is 1–3 levels. Spearman's rank correlation was performed between the four posturographic variables and H&Y scales for both the PD and MSA groups. *SP_dy* (rho = 0.484, $p$-value = 0.007) was found to be the most relevant variable in the MSA group. This parameter may be used as a marker for studying the degree of disability in MSA.

We studied the quantitative posturographic parameters of body balance in a PD group and an MSA group under the conditions of static balance and dynamic balance. The postural balance indices with significant differences in the dynamic balance condition reflected that the postural control ability of patients with MSA is poorer in the ML direction compared to patients with PD. Those indices can be used to help distinguish between patients with MSA and patients with PD.

## Data availability statement

The data presented in the study are deposited in the Figshare website repository, accessible with the following link, https://doi.org/10.6084/m9.figshare.19633638.v6.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Ruijin Hospital (Approval Number LWEC2019017). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

KC and JL got the original ideas and designed the study. WB and PL performed the experiments. WB, PL, YY, and KC ran the statistics. WB and KC drafted the manuscript. KC and JL supervised the study. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1089439/full#supplementary-material

## References

1. Krismer F, Wenning GK. Multiple system atrophy: insights into a rare and debilitating movement disorder. *Nat Rev Neurol.* (2017) 13:232–43. doi: 10.1038/nrneurol.2017.26

2. Kamieniarz A, Michalska J, Brachman A, Pawłowski M, Słomka KJ, Juras G. A posturographic procedure assessing balance disorders in Parkinson's disease: a systematic review. *Clin Interv Aging.* (2018) 13:2301–16. doi: 10.2147/CIA.S180894

3. Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, et al. SIC Task Force appraisal of clinical diagnostic criteria for parkinsonian disorders. *Mov Disord.* (2003) 18:467–86. doi: 10.1002/mds.10459

4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* (2015) 30:1591–9. doi: 10.1002/mds.26424

5. Wenning GK, Stankovic I, Vignatelli L, Fanciulli A, Calandra-Buonaura G, Seppi K, et al. The movement disorder society criteria for the diagnosis of multiple system atrophy. *Mov Disord.* (2022) 37:1131–48. doi: 10.1002/mds.29005

6. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology.* (2008) 71:670–6. doi: 10.1212/01.wnl.0000324625.00404.15

7. Koga S, Aoki N, Uitti RJ, van Gerpen JA, Cheshire WP, Josephs KA, et al. When DLB, PD, and PSP masquerade as MSA: an autopsy study of 134 patients. *Neurology.* (2015) 85:404–12. doi: 10.1212/WNL.0000000000001807

8. Miki Y, Foti SC, Asi YT, Tsushima E, Quinn N, Ling H, et al. Improving diagnostic accuracy of multiple system atrophy: a clinicopathological study. *Brain.* (2019) 9:2813–27. doi: 10.1093/brain/awz189

9. Miki Y, Tsushima E, Foti SC, Strand KM, Asi YT, Yamamoto AK, et al. Identification of multiple system atrophy mimicking Parkinson's disease or progressive supranuclear palsy. *Brain.* (2021) 144:1138–51. doi: 10.1093/brain/awab017

10. Poewe W, Wenning G. The differential diagnosis of Parkinson's disease. *Eur J Neurol.* (2002) 9:23–30. doi: 10.1046/j.1468-1331.9.s3.3.x

11. Raccagni C, Nonnekes J, Bloem BR, Peball M, Boehme C, Seppi K, et al. Gait and postural disorders in parkinsonism: a clinical approach. *J Neurol.* (2019) 267:3169–76. doi: 10.1007/s00415-019-09382-1

12. Wenning GK, Ben-Shlomo Y, Hughes A, Daniel SE, Lees A, Quinn NP. What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? *J Neurol Neurosurg Psychiatry.* (2000) 68:434–40. doi: 10.1136/jnnp.68.4.434

13. Martínez-Martín P, Gil-Nagel A, Gracia LM, Gómez JB, Martínez-Sarriés J, Bermejo F. Unified Parkinson's Disease Rating Scale Characterisitics and Structure. *Mov Disord.* (1994) 9:76–83. doi: 10.1002/mds.870090112

14. Borm CDJM, Krismer F, Wenning GK, Seppi K, Poewe W, Pellecchia MT, et al. Axial motor clues to identify atypical parkinsonism: A multicentre European cohort study. *Parkinsonism Relat Disord.* (2018) 56:33–40. doi: 10.1016/j.parkreldis.2018.06.015

15. Panyakaew P, Anan C, Bhidayasiri R. Visual deprivation elicits subclinical postural inflexibilities in early Parkinson's disease. *J Neurol Sci.* (2015) 349:214–9. doi: 10.1016/j.jns.2015.01.022

16. Hufschmidt A, Dichgans J, Mauritz KH, Hufschmidt M. Some methods and parameters of body sway quantification and their neurological applications. *Arch Phys Med Rehabil.* (1980) 228:135–50. doi: 10.1007/BF00365601

17. Chastan N, Debono B, Maltête D, Weber J. Discordance between measured postural instability and absence of clinical symptoms in Parkinson's disease patients in the early stages of the disease. *Mov Disord.* (2008) 23:366–72. doi: 10.1002/mds.21840

18. Panyakaew P, Anan C, Bhidayasiri R. Posturographic abnormalities in ambulatory atypical parkinsonian disorders: Differentiating characteristics. *Parkinsonism Relat Disord.* (2019) 66:94–9. doi: 10.1016/j.parkreldis.2019.07.016

19. Mancini M, Rocchi L, Horak FB, Chiari L. Effects of Parkinson's disease and levodopa on functional limits of stability. *Clin Biomech (Bristol, Avon).* (2008) 23:450–8. doi: 10.1016/j.clinbiomech.2007.11.007

20. Asakawa T, Fang H, Sugiyama K, Nozaki T, Kobayashi S, Hong Z. Human behavioral assessments in current research of Parkinson's disease. *Neurosci Biobehav Rev.* (2016) 68:741–72. doi: 10.1016/j.neubiorev.2016.06.036

21. Zhou Z, Wu C, Hu Z, Chai Y, Chen K, Asakawa T. Effects of white Gaussian noise on dynamic balance in healthy young adults. *Sci Rep.* (2021) 11:5455. doi: 10.1038/s41598-021-84706-8

22. Visser JE, Bloem BR. Role of the basal ganglia in balance control. *Neural Plast.* (2005) 12:161–74. doi: 10.1155/NP.2005.161

23. Nonnekes J, Aerts MB, Abdo WF, Bloem BR. Medio-lateral balance impairment differentiates between Parkinson's disease and atypical parkinsonism. *J Parkinsons Dis.* (2014) 4:567–9. doi: 10.3233/JPD-140436

24. Bloem B, Bhatia K. Gait and balance in basal ganglia disorders. *Clin Disord Balance, Posture Gait (2nd).* (2004) 2004:173–206. doi: 10.1201/b13189

25. Abdo WF, Borm GF, Munneke M, Verbeek MM, Esselink RAJ, Bloem BR. Ten steps to identify atypical parkinsonism. *J Neurol Neurosurg Psychiatry.* (2006) 77:1367–9. doi: 10.1136/jnnp.2006.091322

26. Snijders AH, van Kesteren M, Bloem BR. Cycling is less affected than walking in freezers of gait. *J Neurol Neurosurg Psychiatry.* (2011) 83:575–6. doi: 10.1136/jnnp-2011-300375

27. Aerts M, Abdo WF, Bloem BR. The "bicycle sign" for atypical parkinsonism. *Lancet.* (2011) 377:125–6. doi: 10.1016/S0140-6736(11)60018-4

28. Hattori N, Kitabayashi H, Kanda T, Nomura T, Toyama K, Mori A. A Pooled Analysis From Phase 2b and 3 Studies in Japan of Istradefylline in Parkinson's Disease. *Mov Disord.* (2020) 35:1481–7. doi: 10.1002/mds.28095

29. Low PA, Reich SG, Jankovic J, Shults CW, Stern MB, Novak P, et al. Natural history of multiple system atrophy in the USA: a prospective cohort study. *Lancet Neruol.* (2015) 14:710–9. doi: 10.1016/S1474-4422(15)00058-7

30. Chen H, Hu Z, Chai Y, Tao E, Chen K, Asakawa T. Galvanic vestibular stimulation with low intensity improves dynamic balance. *Transl Neurosci.* (2021) 12:512–21. doi: 10.1515/tnsci-2020-0197

31. Chang Z, Chen K, Liu R. Development of a dynamic force platform for human's balance testing. In: *Proceedings of the Seventh Asia International Symposium on Mechatronics.* (2020). Berlin, Germany: Springer.

32. Baratto L, Morasso PG, Re C, Spada G. A new look at posturographic analysis in the clinical context: sway-density vs other parameterization techniques. *Motor Control.* (2002) 6:246–70. doi: 10.1123/mcj.6.3.246

33. Schubert P, Kirchner M. Ellipse area calculations and their applicability in posturography. *Gait Posture.* (2014) 39:518–22. doi: 10.1016/j.gaitpost.2013.09.001

34. Yamamoto T, Suzuki Y, Nomura K, Nomura T, Tanahashi T, Fukada K, et al. A classification of postural sway patterns during upright stance in healthy adults and patients with Parkinson's disease. *J Adv Comput Intell Intell Inf.* (2011) 15:997–1007. doi: 10.20965/jaciii.2011.p0997

35. Na BS, Ha J, Park J-H, Ahn JH, Kim M, Kim JS, et al. Comparison of gait parameters between drug-naïve patients diagnosed with multiple system atrophy with predominant parkinsonism and Parkinson's disease. *Parkinsonism Relat Disord.* (2019) 60:87–91. doi: 10.1016/j.parkreldis.2018.09.018

36. Frenklach A, Louie S, Koop MM, Bronte-Stewart H. Excessive postural sway and the risk of falls at different stages of Parkinson's disease. *Mov Disord.* (2009) 24:377–85. doi: 10.1002/mds.22358

37. Kanekar N, Lee Y-J, Aruin AS. Frequency analysis approach to study balance control in individuals with multiple sclerosis. *J Neurosci Methods.* (2014) 222:91–6. doi: 10.1016/j.jneumeth.2013.10.020

38. Bizid R, Jully JL, Gonzalez G, François Y, Dupui P, Paillard T. Effects of fatigue induced by neuromuscular electrical stimulation on postural control. *J Sci Med Sport.* (2009) 12:60–6. doi: 10.1016/j.jsams.2007.10.006

39. Bottaro A, Yasutake Y, Nomura T, Casadio M, Morasso P. Bounded stability of the quiet standing posture: An intermittent control model. *Human Mov Sci.* (2008) 27:473–95. doi: 10.1016/j.humov.2007.11.005

40. Kamieniarz A, Michalska J, Marszałek W, Stania M, Słomka KJ, Gorzkowska A, et al. Detection of postural control in early Parkinson's disease: Clinical testing vs modulation of center of pressure. *PLoS ONE.* (2021) 16:e0245353. doi: 10.1371/journal.pone.0245353

41. Li X, Wang Y, Wang Z, Xu Y, Zheng W. 3-Hz postural tremor in multiple system atrophy cerebellar type (MSA-C)-a static posturography study. *Neurol Sci.* (2018) 39:71–7. doi: 10.1007/s10072-017-3130-3

42. Margaret M, Melvin D. Parkinsonism:onset, progression, and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427

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# Spiral drawing analysis with a smart ink pen to identify Parkinson's disease fine motor deficits

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**Introduction:** Since the uptake of digitizers, quantitative spiral drawing assessment allowed gaining insight into motor impairments related to Parkinson's disease. However, the reduced naturalness of the gesture and the poor user-friendliness of the data acquisition hamper the adoption of such technologies in the clinical practice. To overcome such limitations, we present a novel smart ink pen for spiral drawing assessment, intending to better characterize Parkinson's disease motor symptoms. The device, used on paper as a normal pen, is enriched with motion and force sensors.

**Methods:** Forty-five indicators were computed from spirals acquired from 29 Parkinsonian patients and 29 age-matched controls. We investigated between-group differences and correlations with clinical scores. We applied machine learning classification models to test the indicators ability to discriminate between groups, with a focus on model interpretability.

**Results:** Compared to control, patients' drawings were characterized by reduced fluency and lower but more variable applied force, while tremor occurrence was reflected in kinematic spectral peaks selectively concentrated in the 4–7 Hz band. The indicators revealed aspects of the disease not captured by simple trace inspection, nor by the clinical scales, which, indeed, correlate moderately. The classification achieved 94.38% accuracy, with indicators related to fluency and power distribution emerging as the most important.

**Conclusion:** Indicators were able to significantly identify Parkinson's disease motor symptoms. Our findings support the introduction of the smart ink pen as a time-efficient tool to juxtapose the clinical assessment with quantitative information, without changing the way the classical examination is performed.

KEYWORDS

**smart ink pen, spiral analysis, Parkinson's disease, movement disorders, eHealth**

## 1. Introduction

Handwriting analysis is considered a promising biomarker for PD assessment, as impairments in the gesture can occur before the onset of typical symptoms (1). For this reason, handwriting tasks performed on paper have been introduced, as they are simple and fast to perform (2). Archimedes' spiral can be a useful task in the clinical PD evaluation, since its shape can elicit tremor in upper limbs (2, 3). However, the evaluation concerns only the produced traces, without focusing on the underlying movements.

Since the uptake of digitizers able to capture the coordinates of the pen on the screen and the exerted pressure, a huge effort had been put into quantitative spiral analysis (4), resulting in a series of statistical and classification studies. Statistical studies aim at finding spiral-derived features characterizing the PD population and report a reduced velocity and applied pressure in the advanced stage of the disease (5), a decreased fluency during OFF state (6), and an impaired spatiotemporal drawing execution (7). Other work quantified the effect of medication in alleviating bradykinesia and tremor amplitude (8). Moderate correlations were found between UPDRS III and its sub-scores, and indicators measuring spatial irregularity (9), velocity variability (10), and pressure (5). Classification studies, starting from spiral-derived features, exploit machine learning (ML) algorithms to train models aiming at distinguishing PD patients from healthy controls (11–13). The best results, obtained from 62 PD patients and 15 controls, reached classification accuracies above 95% (14–16).

Although the examined literature highlights the potential of quantitative spiral assessment for the objective characterization of motor symptoms, some limitations hamper its adoption. These limits include the undermined naturalness of writing performed on the small and frictionless surface of a digitizer, leading to an altered execution (17). Most studies tried to restore the natural feeling using a sheet of paper over the device surface, but inaccuracies in pen lifts can arise due to the different pressure required by the two media (18). Moreover, the use of digitizers during clinical practice may not be straightforward and time-efficient, often requiring technical support of an operator.

To overcome such limits, this work aims at computing indicators from spirals drawn using an innovative smart ink pen (19–22) to: i) discriminate between PD patients and age-matched healthy controls using both statistical and ML methods; ii) assess the correlation with PD clinical scales. The pen is sensorized with an inertial measurement unit and a force sensor, and is designed to write on paper, allowing the quantitative assessment of handwriting tasks while preserving the gesture naturalness. The device works like a normal pen and could be employed in the clinical routine without requiring technical support or increasing the time spent for the visit.

# 2. Method

## 2.1. Smart ink pen

The smart ink pen (19) looks like a normal ink pen (height 147 mm, maximum diameter 14.65 mm weight 48 g), but it is enriched with a load cell connected to the pen tip—to record the force exerted on the writing surface—and with tri-axial accelerometers and gyroscopes—to detect motion and tremor. It includes a memory and a communication unit to store and transmit data through Bluetooth Low Energy. The sampling frequency is set to 50 Hz.

## 2.2. Participants

PD patients were enrolled by IRCCS Istituti Clinici Scientifici (ICS) Maugeri (Milan, Italy). Patients' inclusion criteria were:

- Age $\geq$ 18 years;
- PD diagnosis;
- Mini Mental State Examination (MMSE) $\geq$ 24;
- Absence of disorders impairing handwriting, other than PD.

Politecnico di Milano (Milan, Italy) recruited the age-matched control group, whose inclusion criteria were:

- Age $\geq$ 18 years;
- MMSE $\geq$ 24;
- No musculoskeletal, neurological, or cardiovascular disorders impairing handwriting.

Age, gender, handedness and MMSE were collected from both groups. Patients were evaluated through the UPDRS (23) and the Hoehn and Yahr (H&Y) scale (24). From the UPDRS, the Jankovic (25), Schiess (26) and Kang (27) scores for PD motor symptoms classification were derived. High scores correspond to a tremor dominant patient, low scores to an akinetic-rigid (26, 27), or affected by postural instability patient (25), while medium scores to a mixed (26, 27) or indeterminate (25) one. Participants signed an informed consent prior to participation in the study. The protocol was approved by the Ethical Boards of ICS Maugeri (2457 CE) and Politecnico di Milano (n. 10/2018), for the respective recruited group.

## 2.3. Acquisition protocol

Subjects were asked to trace a spiral with the smart ink pen, following a template printed on a sheet of paper, possibly avoiding lifting the pen. The operator asked the subject to perform the spiral drawing (maximum diameter 6 cm, five loops separated by 1.2 cm) starting from the center and following the template line. Subjects were sitting on a standard chair, in front of a desk (height 72 cm) and instructed to assume an ergonomic posture, the feet resting on the floor. Patients performed the tasks under the ON medication state and, given the asymmetry of PD symptoms especially in the early stage, both hands were tested. Controls performed the task only with the dominant hand. All subjects performed the test twice.

## 2.4. Data analysis

Data analysis was performed in Matlab® R2021b for the indicator extraction and the statistical analysis, while ML algorithms were implemented in Python® 3.8.10.

### 2.4.1. Indicator extraction

This phase included the pre-processing of the raw signals, followed by the extraction of 45 relevant indicators, divided into 7 domains. The drawing product was not considered in the analysis. Kinematic signals were band-pass filtered (2–12 Hz) with a zero-phase, 4th-order Butterworth filter. The following subscripts will appear in the names of the indicators extracted from kinematics, to clarify which signal was used for the computation: "*_A*" for acceleration; "*_G*" for angular velocity; "*_G_filt*" for angular velocity filtered around the spectral peak, "_T" for tremor contribution [extracted from the acceleration through empirical mode decomposition (28)].

- *Kinematics.* Indicators in this domain reflect the spatiotemporal behavior of the drawing gesture. The time (*Execution_Time*) and the number of strokes (*Strokes_Num*) required to complete the drawing were computed. The average and the variation coefficient of the difference between consecutive extrema in angular velocity (*ConsPeakDiff_G_Avg* and *ConsPeakDiff_G_CV*) were extracted (29).
- *Force.* The force generated while drawing is a key feature of the disease (4, 30). The average and variation coefficient of the exerted force were extracted (*F_Avg and F_CV*). To measure force variability in terms of amplitude, we considered the overshoot (*F_OVS*) (12), which is the difference between maximum and median value, and the difference in consecutive peaks (*ConsPeakDiff_F_Avg* and *ConsPeakDiff_F_CV*) (29). We included the number of changes in force in the time unit (*NC_F*), which quantifies the oscillations in the force profile (12).
- *Smoothness.* These indicators are related to the fluency in the drawing execution, which is relevant in characterizing PD (30). The number of extrema in kinematic signals (*NC_A*, *NC_G*) was retained (12). The presence of high frequency movements was investigated through the Spectral Arc Length (*SPARC_G*) (31); this indicator was computed considering different thresholds (*10*, *20*, *30*, *40*, *45*, and *50*) referring to the percentage of the peak value considered for noise removal. The logarithmic dimensionless squared jerk was computed for acceleration (*LDLJ_A*) and angular velocity (*LDLJ_G*) (32).
- *Tilt.* The domain refers to the inclination angle of the pen and was quantified by its average (*Tilt_Avg*), variance (*Tilt_Var*), and coefficient of variation (*Tilt_CV*).
- *Frequency.* This domain comprises indicators that describe the frequency content of the kinematics. We computed the Power Spectral Density (PSD) estimates through Welch's method (window length = 500 samples; overlap = 50%; frequency resolution = 0.1 Hz). Given the PSD, the relative power was computed for both acceleration and angular velocity (*RPW_A* and *RPW_G*) in different frequency bands (0–2 Hz; 2–4 Hz; 4–7 Hz, and 8–12 Hz). For angular velocity, the maximum relative power in an interval around the peak was computed (*RPW_G_filt_max*). The mean harmonic power (*MHP_T*) (33) was implemented to measure the presence of high frequency components.
- *Amplitude.* These indicators measure the amplitude of kinematic signals in time and frequency. The root mean square of the acceleration (*RMS_A*) and angular velocity (*RMS_G*) was computed on 10-s segments of the signals. After filtering the angular velocity in an interval centered around the spectral peak, the RMS was applied on 1-s windows of the resulting signal and averaged for the extraction of the maximum value (*RMS_G_filt_max*) (34). The signal-to-noise ratio (*SNR_T*) was calculated as the ratio between the tremor signal filtered around the peak frequency, and the remaining noise. To assess how evident is the peak in the PSDs, we computed the relative outlier level (*Out_Lev_Rel_A* and *Out_Lev_Rel_G*) as the distance between the PSD peak and the PSD mean. The product between the relative outlier level and the PSD peak value produced the amplitude per outlier level (*AmpXOut_Lev_A* and *AmpXOut_Lev_G*) (35).
- *Regularity.* The domain measures tremor regularity. The occurrence of repetitive patterns in the tremor signal was quantified through the Approximate Entropy (*ApEn_T*) (36). Tremor predictability was also measured by Recurrence Rate (*RR_T*) and Determinism (*DET_T*) (37). The Tremor Stability Index, applied in Luft et al. (38) in postural activities, was adapted to the spiral drawing condition (*TSI_T*) to measure the frequency variability in tremor cycles. The angular velocity change rate was computed over 1-s windows and the maximum value was retained (*G_Rate_max*).

See Supplementary Table I for the summary of the indicators computed in the study.

### 2.4.2. Statistical analysis

The statistical analysis was conducted with the two-fold aim of: i) finding the most suitable indicators for distinguishing the drawings executed with the dominant hand by patients and controls; ii) assessing which indicators correlate with clinical scales for the PD population. The mean of the indicators obtained in the two tests was considered in the analysis, to capture information not based on a single sample. For the first aim, after testing indicators normality with the Lilliefors test, the Unpaired *t*-test and the Mann-Whitney test were applied to normal and non-normal indicators, respectively. For the second aim, following previous studies (5, 9), correlation was assessed through Spearman's Rank Correlation Coefficient (RHO. $|RHO| \leq 0.3$ weak; $0.3 < |RHO| < 0.7$ moderate, $|RHO| \geq 0.7$ strong) between the extracted indicators and a series of UPDRS-derived scores, the H&Y scale score, and the Jankovic, Schiess and Kang scores. The UPDRS-derived scores included the UPDRS II tremor item (nr.16); the total UPDRS III score; the UPDRS III resting tremor item (nr.20); the hands score, obtained as the sum of the following UPDRS III items: action or postural tremor of hands (nr.21), rigidity (nr.22), finger taps (nr.23), hand movements (nr.24) and rapid alternating movements of hands (nr.25).

The sample size was chosen according to (5), where significant correlations between indicators and clinical scales ranged from 0.356 to 0.650. We considered the mean value of these 2 correlation results (0.503), leading to a sample size of 29 (confidence level: 95%, power: 80%).

### 2.4.3. Machine learning

As we were interested in identifying the most relevant indicators in the between-group discrimination, ML methods were employed. Classification models were trained to differentiate between patients and controls and model explainability techniques applied, to gain insight about the model reasoning.

Different models were tested. The logistic regression, acting as a reference, and three models based on decision trees: random forest, LightGBM (39) and Catboost (40). For each model, two subsets of indicators were evaluated: subset 1-all 45 indicators; subset 2-statistically different indicators in the between-group comparison. Given the reduced dimensionality of the available dataset, all trials were conducted employing the Leave-One-Out Cross Validation approach. The classifier performance was evaluated through Accuracy, f1 score, Recall and Precision. To gain a better understanding about the indicators importance and trend in the classification task, the Shapley Additive Explanation (SHAP) technique (41, 42) was applied on the model achieving the best performance. This allowed revealing the

TABLE 1 Statistically significant results of the between-group comparison.

| Domain | Indicator | PD | Control | *p*-value |
|---|---|---|---|---|
| Kinematics | *Strokes_Num* [#] | 1.5 (1.75) | 3 (2.63) | 0.005* |
| Force | *ConsPeakDiff_F_Avg* [arbitrary] | 8.07 (5.17) | 11.28 (6.56) | 0.014* |
| | *NC_F* [#/s] | 3.74 ± 0.68 | 3.09 ± 0.63 | 0.0004*** |
| Smoothness | *NC_A* [#/s] | 5.82 (0.51) | 5.76 (0.32) | 0.029** |
| | *SPARC_G_10* [a.u.] | −42.75 (41.99) | −23.65 (18.49) | 0.0009*** |
| | *SPARC_G_20* [a.u.] | −25.64 (44.72) | −12.62 (18.54) | 0.005** |
| | *SPARC_G_30* [a.u.] | −15.79 (33.39) | −7.31 (7.70) | 0.006** |
| | *SPARC_G_40* [a.u.] | −6.83 (18.82) | −3.85 (5.31) | 0.011* |
| | *SPARC_G_45* [a.u.] | −5.35 (13.96) | −3.84 (4.70) | 0.019* |
| | *SPARC_G_50* [a.u.] | −3.71 (11.85) | −3.00 (3.62) | 0.005** |
| | *LDLJ_A* [a.u.] | −6.69 ± 0.99 | −5.31 ± 1.15 | <10E-05*** |
| | *LDLJ_G* [a.u.] | −12.32 ± 2.37 | −9.26 ± 2.40 | <10E-05*** |
| Frequency | *RPW_A_0-2* [a.u.] | 0.52 ± 0.13 | 0.68 ± 0.14 | <10E-04*** |
| | *RPW_A_2-4* [a.u.] | 0.16 ± 0.05 | 0.13 ± 0.04 | 0.013* |
| | *RPW_A_4-7* [a.u.] | 0.16 ± 0.05 | 0.10 ± 0.05 | <10E-04*** |
| | *RPW_A_8-12* [a.u.] | 0.15 ± 0.04 | 0.10 ± 0.05 | <10E-04*** |
| | *RPW_G_2-4* [a.u.] | 0.18 (0.09) | 0.38 (0.38) | <10E-05*** |
| | *RPW_G_4-7* [a.u.] | 0.51 ± 0.16 | 0.36 ± 0.10 | <10E-04*** |
| | *RPW_G_8-12* [a.u.] | 0.21 (0.16) | 0.17 (0.13) | 0.045* |
| Amplitude | *Out_Lev_Rel_G* [a.u.] | 4.03 (1.42) | 3.02 (0.74) | 0.002** |
| | *AmpXOut_Lev_A* [a.u.] | 0.0063 (0.0081) | 0.0013 (0.0032) | 0.0006*** |
| | *AmpXOut_Lev_G* [a.u.] | 0.056 (0.094) | 0.015 (0.014) | 0.0002*** |
| Regularity | *RR_T* [a.u.] | 0.28 (0.37) | 0.69 (0.45) | 0.0002*** |
| | *DET_T* [a.u.] | 0.64 (0.32) | 0.94 (0.27) | 0.0004*** |
| | *TSI_T* [Hz] | 4.84 ± 1.37 | 6.00 ± 1.76 | 0.007** |

Indicators (measurement unit in square brackets, a.u. stands for dimensionless) trend in the 2 groups is reported: mean ± standard deviation for normal distribution, median (interquartile range) for nonnormal distribution. The *p*-value (* < 0.05, ** < 0.01, and *** < 0.001) is reported in last column.

most sensitive indicators in the classification, thus increasing the model interpretability.

# 3. Results

## 3.1. Participants

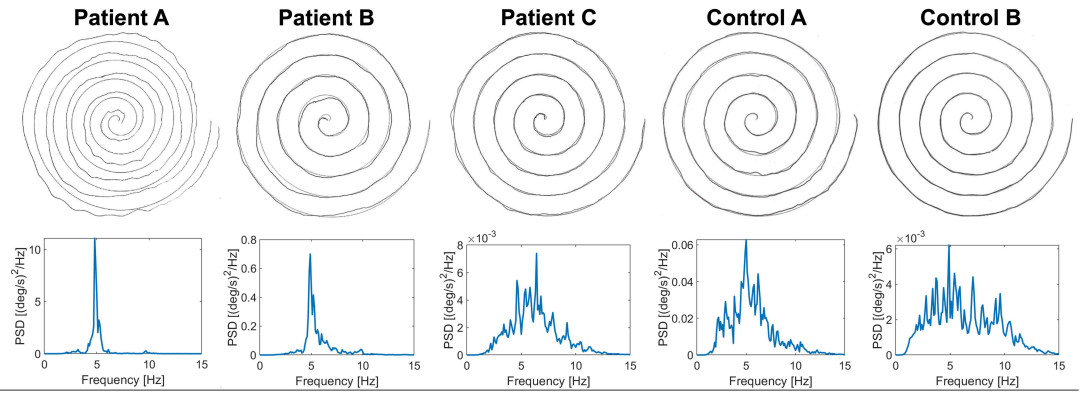
Thirty participants per group were recruited. However, one patient and one control subject were excluded from the analysis as their traces were characterized by an excessive number of pen lifts (>20). Therefore, the analysis regarded the spirals drawn by 29 PD patients (gender: 14 M; handedness: 29 R; age: 72.52 ± 7.37 yo; MMSE: 27.77 ± 1.64; UPDRS III: 19.17 ± 7.67; years since onset: 7.34 ± 4.94) and 29 controls (gender: 11 M; handedness: 29 R; age: 72.28 ± 8.30 yo; MMSE: 28.21 ± 1.57). The statistical analysis did not reveal between-group differences in either age ($p = 0.91$) or MMSE score ($p = 0.31$). The demographic and clinical characteristics for all participants are reported in Supplementary Table II.

## 3.2. Statistical analysis

Table 1 summarizes the statistically significant results of the between-group comparison. The complete results are available in Supplementary Table III.

In the *Smoothness* domain, the reduced *SPARC* and *LDLJ* indicators for the PD group, together with an increased *NC_A*, reflected a less fluent drawing execution. This finding is in agreement with the dysgraphia manifestation associated to the disease (4, 30). As for *Frequency*, the occurrence of tremor in PD spirals was highlighted by a different power distribution in the PSD for both acceleration and angular velocity signals: patients were characterized by a higher relative power in the band associated with PD tremor (4–7 Hz), while lower proportions were observed in the lowest frequency bands (0–2 H z for acceleration, 2–4 Hz for angular velocity) (43, 44). In line with (35), indicators related to spectral peak deviation in the PSD (*Out_Lev_Rel_G*, *AmpXOut_Lev_A* and *AmpXOut_Lev_G*) revealed significantly more evident peaks in the 2–12 Hz band for the PD group.

The importance of such domains is further explained by the examples in Figure 1. Patient A's spiral trace is affected by tremor and




| Indicators | | | | | |
|---|---|---|---|---|---|
| *AmpXOut_Lev_G* [a.u.] | 1.39 | 0.23 | 0.04 | 0.02 | 0.01 |
| *TSI_T* [a.u.] | 5.00 | 2.54 | 2.90 | 4.64 | 6.58 |
| *RPW_G_2-4* [a.u.] | 0.04 | 0.06 | 0.20 | 0.21 | 0.38 |
| *RPW_G_4-7* [a.u.] | 0.91 | 0.76 | 0.48 | 0.57 | 0.36 |
| *SPARC_G_50* [a.u.] | -20.97 | -25.91 | -3.01 | -1.13 | -1.13 |
| *LDLJ_A* [a.u.] | -6.70 | -6.76 | -7.67 | -7.66 | -5.84 |
| *RPW_A_8-12* [a.u.] | 0.18 | 0.17 | 0.16 | 0.16 | 0.06 |
| *LDLJ_G* [a.u.] | -11.73 | -11.65 | -14.51 | -13.51 | -13.96 |
| *NC_F* [#/s] | 5.22 | 3.73 | 4.58 | 2.13 | 2.26 |
| *SPARC_G_10* [a.u.] | -33.48 | -77.65 | -18.72 | -2.50 | -2.55 |
| **Clinical Scores** | | | | | |
| UPDRS III | 17 | 28 | 16 | N.A. | N.A. |
| H&Y | 1.5 | 3 | 1.5 | N.A. | N.A. |
| Jankovic | 0.7 | 0.9 | 0.0 | N.A. | N.A. |
| Schiess | 0.5 | 0.9 | 0.0 | N.A. | N.A. |
| Kang | 0.4 | 0.8 | 0.0 | N.A. | N.A. |
| UPDRS II – tremor | 1 | 2 | 0 | N.A. | N.A. |
| UPDRS III – resting tremor | 1 | 3 | 0 | N.A. | N.A. |
| UPDRS III - hands | 5 | 10 | 12 | N.A. | N.A. |

FIGURE 1
Spiral traces, angular velocity PSD, relevant indicators, and clinical scores for three patients (A–C) and two control subjects (A, B).

the occurrence of the symptom is well captured by the quantitative analysis. Indeed, the PSD of angular velocity is heavily concentrated around the peak, a fact that is represented by high values of *RPW_G_4-7* and *AmpXOut_Lev_G*. The reduced fluency during the execution is well captured by the *SPARC* indicators. Despite looking quite different with respect to Patient A spiral, Patient B spiral shows a similar behavior in terms of PSD and indicators. The less visible tremor in the trace generates lower values for *RPW_G_4-7* and *AmpXOut_Lev_G*, which are however above the central tendency of the PD group. Patient C presents the best-executed spiral among the three. However, *LDLJ_A* and *LDLJ_G* highlight a lack of smoothness in the drawing also in this case. Tremor is not evident from the trace, but its occurrence is detected by the analysis: the broader spectrum in the angular velocity with respect to patients A and B is translated into a lower *RPW_G_4-7*, yet approximately half of the total power.

Table 2 reports the correlations that resulted statistically significant. High values in Jankovic, Schiess and Kang scores, and in UPDRS III resting tremor score were associated with an increased *RPW_G_4-7* and *NC_A*. A reduced fluency in the drawing gesture was correlated with the overall impact of the disease: lower *SPARC* corresponded to high scores in H&Y (dominant hand) and UPDRS III (non-dominant hand).

Although the significant correlation results, the correspondence between clinical scales and indicators was not always respected. For instance, considering Figure 1, patient B clinical scores are in line with indicators: the high UPDRS scores of tremor and resting tremor are reflected into increased *RPW_G_4-7* and *AmpXOut_Lev_G*. On the other hand, Patient A is reported with mild tremor and mild hand impairment, and Jankvoic-Schiess-Kang scores assign the patient to the postural instability/akinetic-rigid category. However, both trace and indicators show the occurrence of tremor (*RPW_G_4-7* and *AmpXOut_Lev_G*) and lack of smoothness in the drawing (*SPARC*).

## 3.3. Machine learning

Concerning ML classification with subset 1 (all indicators), the following performances were obtained: i) Logistic Regression, accuracy 84.48%, f1 score 84.21%, recall 82.76%, precision 85.71%; ii) Random Forest, accuracy 77.59%, f1 score 78.69%, recall 82.76%, precision 75.00%; iii) LightGBM, accuracy 89.65%, f1 score 90.00%, recall 93.10%, precision 87.10%; iv) Catboost, accuracy 87.93%, f1 score 87.72%, recall 86.21%, precision 89.28%. As for subset 2 (statistically significant indicators): i) Logistic Regression, accuracy

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TABLE 2 Correlation analysis results.

| | Dominant | | | Non-dominant | | |
|---|---|---|---|---|---|---|
| Clinical score | Indicator | RHO | *p*-value | Indicator | RHO | *p*-value |
| H&Y | *SPARC_20* [a.u.] | −0.40 | 0.033 | *RPW_A_2-4* [a.u.] | 0.41 | 0.030 |
| | *SPARC_30* [a.u.] | −0.37 | 0.049 | | | |
| Jankovic | *NC_A* [#/s] | 0.56 | 0.002 | *RPW_G_4-7* [a.u.] | 0.45 | 0.017 |
| | *RPW_G_4-7* [a.u.] | 0.40 | 0.034 | | | |
| | *ConsPeakDiff_G_Avg* [deg/s] | 0.43 | 0.018 | | | |
| Schiess | *NC_A* [#/s] | 0.47 | 0.010 | *RPW_G_4-7* [a.u.] | 0.43 | 0.024 |
| | *RPW_G_4-7*[a.u.] | 0.39 | 0.037 | | | |
| Kang | *NC_A* [#/s] | 0.49 | 0.008 | *RPW_G_4-7* [a.u.] | 0.44 | 0.020 |
| | *RPW_G_4-7* [a.u.] | 0.37 | 0.045 | | | |
| | *ConsPeakDiff_G_Avg* [deg/s] | 0.41 | 0.029 | | | |
| UPDRS II tremor | *RPW_G_4-7* [a.u.] | 0.40 | 0.029 | *RPW_G_4-7* [a.u.] | 0.42 | 0.026 |
| UPDRS III | *RPW_A_2-4* [a.u.] | 0.37 | 0.049 | *SPARC_30* [a.u.] | −0.39 | 0.043 |
| | | | | *SPARC_40* [a.u.] | −0.44 | 0.018 |
| | | | | *SPARC_45* [a.u.] | −0.45 | 0.015 |
| | | | | *SPARC_50* [a.u.] | −0.41 | 0.031 |
| | | | | *RPW_A_2-4* [a.u.] | 0.50 | 0.006 |
| UPDRS III–resting tremor | *NC_A* [#/s] | 0.43 | 0.020 | RPW_G_4-7 [a.u.] | 0.50 | 0.007 |
| | *RPW_G_4-7*[a.u.] | 0.43 | 0.019 | *AmpXOut_Lev_G* [a.u.] | 0.38 | 0.048 |
| | *RPW_G_8-12* [a.u.] | −0.37 | 0.048 | | | |
| | *ConsPeakDiff_G_Avg* [deg/s] | 0.37 | 0.046 | | | |
| UPDRS III–hands | *F_CV* [a.u.] | 0.41 | 0.027 | *SPARC_40* [a.u.] | −0.43 | 0.022 |
| | | | | *SPARC_45* [a.u.] | −0.45 | 0.015 |
| | | | | *SPARC_50* [a.u.] | −0.42 | 0.028 |
| | | | | *MHP_T* [Log((mm/s$^2$)$^2$/Hz)] | 0.40 | 0.033 |

For each clinical score, significantly correlated indicators are reported for the 2 hands with measurement unit, Spearman's RHO and *p*-value.

77.59%, f1 score 79.97%, recall 79.31%, precision 76.67%; ii) Random Forest, accuracy 79.31%, f1 score 79.99%, recall 82.76%, precision 77.42%; iii) LightGBM, accuracy 86.21%, f1 score 86.21%, recall 86.21%, precision 86.21%; iv) Catboost, accuracy 94.83%, f1 score 95.08%, recall 100%, precision 90.63%. The classification performances are summarized in Supplementary Table IV. Overall, the best performances were obtained by the Catboost model on subset 2, which allowed correctly classifying all PD patients, with only 3 misclassified controls (Figure 2A). The results of the SHAP analysis, performed on the Catboost model trained with subset 2, provided further insight about the way the different indicators impacted subjects' classification (Figure 2B). The plot presents the first ten indicators (according to SHAP results), in decreasing order of importance for the classifier decision. For each indicator, each point represents a subject and conveys two pieces of information: the SHAP value and the indicator value. The SHAP value is encoded by the horizontal position of the point: the more positive the SHAP value, the more the indicator pushes the classification of the subject toward the PD group, while negative values push it in the direction of the control group. The color represents the indicator value (red high, blue low).

This reveals, for example, that *AmpXOut_Lev_G* steered the most the classification of a subject toward the PD group (strongly positive SHAP values). Additionally, high (red) *AmpXOut_Lev_G* values are found only for positive SHAP values; this suggests that a clearly detectable peak in the angular velocity PSD leads the classification toward the PD group. A less variable tremor frequency (low *TSI_T*) pushed the prediction toward the PD group, as blue points are all located in the right portion of the graph. The power distribution represented another critical aspect for the differentiation: low *RPW_G_2-4* and high *RPW_G_4-7* pushed the classification toward the PD group, as they were associated with positive SHAP values. Low *SPARC_G_50, LDLJ_A, LDLJ_G* and *SPARC_G_10*, indicating the lack of fluency, were associated with a classification in the patient group (blue points only for positive SHAP value). High *NC_F* pushed the prediction toward the PD group, since red points are mainly concentrated in the right part of the plot.

The SHAP analysis allowed the investigation of the model reasoning, including gaining insight into the misclassifications. In

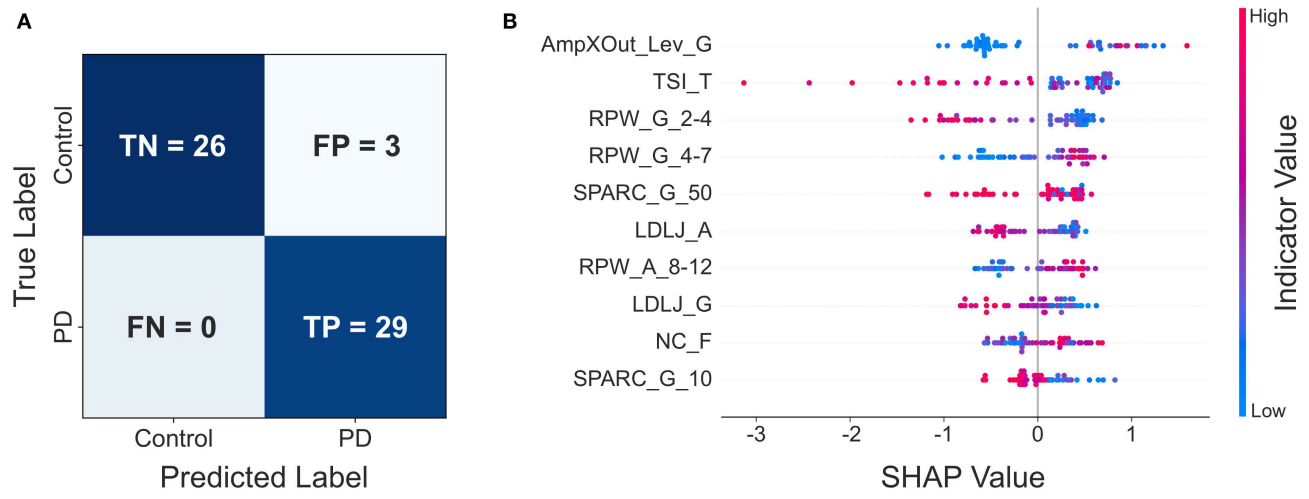


FIGURE 2
**(A)** Confusion matrix of the Catboost classifier trained with subset 2; **(B)** resulting SHAP plot.

Figure 1, Control A was one of the misclassified subjects (false positive) by the best model, while Control B was correctly assigned to the healthy group (true negative). Looking at Patient C (true positive) and Control A (false positive) traces and spectra, they both look similar. This similarity may explain why Control A was misclassified as PD. Indeed, looking at the *Frequency* indicators of Control A, *RPW_G_2-4* and *RPW_A_8_12* values are almost the same of Patient C, while *RPW_G_4-7* is even higher in Control A. Similarities are found in jerk-based indicators, highlighting a similar fluency. The *AmpXOut_Lev_G* value, although lower than in Patient C, highlights the presence of a more evident spectral peak with respect to the control group central tendency of 0.015. The *TSI_T* indicator reflects a stable tremor frequency, comparable to the one of the PD population. Altogether, these trends may be responsible for pushing the classification of Control A toward the PD group. Considering Control B, who was correctly assigned to the Control group, the trace is characterized by a good accuracy. The greater dispersion of its PSD over the entire frequency band, indicating the absence of relevant tremor components, is translated into comparable values of *RPW_G_2-4* and *RPW_G_4-7*, as well as in a reduced *AmpXOut_Lev_G* value. The highly variable tremor frequency (*TSI_T*), and the increased fluency of the acceleration signal (*LDLJ_A*) also underlie the correct classification.

## 4. Discussion

This work aimed at analyzing the spiral drawing execution of 29 PD patients and 29 age-matched controls, acquired with an innovative smart ink pen, to find the most suitable indicators in identifying and characterizing some disease motor symptoms.

A total of 45 indicators, divided into 7 domains, were extracted from the signals recorded by the pen inertial and force sensors, without information related to the spiral coordinates. Nevertheless, the outcome of the performed analysis was extremely good.

Significant between-group differences emerged in 25 indicators, with *Frequency* and *Smoothness* being the most relevant domains in the characterization of the disease. This is coherent with the spiral task, which is typically employed in pen-and-paper settings to elicit upper limb tremor and abnormal movement in neurological patients (2). Also the *Force* domain revealed trends in line with the literature, with patients applying a reduced and more variable force on the writing surface (45). The correlation analysis demonstrated that *Frequency* and *Smoothness* indicators are related with the patients' clinical scores. Great angular velocity power concentration in the 4–7 Hz tremor band and increased number of inversions in acceleration were correctly associated with high clinical scores assessing the occurrence of tremor (UPDRS II tremor, UPDRS III resting tremor, Jankovic, Schiess and Kang scores). The execution fluency decreased with increasing disease severity according to UPDRS III and H&Y scores. The correlation results were comparable with previous studies (5, 9) and, although significant, ranged from weak to moderate. We believe this does not indicate the indicators inaccuracy in quantifying the patients' symptoms, but rather reflects the well-known limitations of the clinical scales, including the low granularity of the assigned scores and the lack of separate scores for left and right side. Our hypothesis is supported by the identification of cases of mismatch between the clinical scores and the pen indicators, which were able to detect relevant alterations not visible from the spiral trace, nor from the clinical score. For instance, in Patient A, tremor and lack of fluency were detected in traces where their occurrence was not evident by visual inspection. These findings show how the use of the smart ink pen to perform clinical writing tests could be beneficial to complement the picture that emerges from the clinical examination with additional information related to the patient's conditions.

Considering classification, the performances of the Catboost model trained on subset 2 (only statistically significant indicators from the between-group analysis) were comparable to the best results found in the literature (14–16). But our focus was mostly on model explainability, a critical aspect in the path to the adoption of ML in healthcare: the understanding of the model decision-making is fundamental for clinicians (46). Yet, this aspect is poorly explored in the literature (14, 15), or provides results that are difficult to interpret (16). In our work, the SHAP analysis allowed identifying the most relevant indicators for the classification and gaining insight

into the model misclassifications. Indeed, highly ranked indicators in the SHAP analysis exhibiting values similar to the PD group were responsible for the false positive cases.

Some limitations of the study can be pointed out. The sample size should be increased to further confirm the current results. In the recruitment, patients were clinically assessed by a single experienced rater; future work should study test-retest reliability of pen indicators compared to inter-rater agreement during clinical assessment. In future research, it would be interesting to study the differences between dominant and nondominant hands in both populations, as the between-group difference considered the dominant hand only. The conducted analysis should also be evaluated in patients at early stages of the disease—when patients' complaints cannot be clinically confirmed—or in preclinical stages, e.g., in PD genetic forms.

This work showed that the indicators extracted from the smart ink pen provide relevant information for the identification of PD motor symptoms. Such results support the use of the smart ink pen for PD spiral analysis in the clinical practice. Since the device looks like a normal ink pen and is used on simple paper, its introduction in the clinical examination would not change the way the spiral test is already performed, neither extend the duration of the visit. This point is crucial for adoption: given the increasingly limited time and resources in the healthcare systems, the smart ink pen represents a simple and time-efficient technology that transparently adapts to the clinical practice, supporting the graphomotor-based assessment with the identification of subtle but relevant patterns. Simplicity and transparent monitoring are two key requirements also for the remote health context. For this reason, the proposed device reveals important potential applications also in the remote patient assessment, with adequate frequency outside the clinical setting. The use of the device in both scenarios would allow improving and optimizing the treatment choice and result in improved patient's outcomes.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Politecnico di Milano Ethical Committee (opinion n. 10/2018) and ICS Maugeri Ethical Committee (2547 CE). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

ST: data analysis, manuscript writing, and manuscript final editing. FL: study design, data analysis, manuscript writing, and manuscript final editing. MP: study design, data acquisition, and manuscript revision. MG, BD, and LL: data acquisition and manuscript revision. MD: study design and manuscript revision. SF: acquisition of funding, study design, manuscript writing, and manuscript revision. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1093690/full#supplementary-material

## References

1. Parkinson J. An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci.* (2002) 14:223–36; discussion 222. doi: 10.1176/jnp.14.2.223

2. Alty J, Cosgrove J, Thorpe D, Kempster P. How to use pen and paper tasks to aid tremor diagnosis in the clinic. *Pract Neurol.* (2017) 17:456–63. doi: 10.1136/practneurol-2017-001719

3. Wang S, Bain PG, Aziz TZ, Liu X. The direction of oscillation in spiral drawings can be used to differentiate distal and proximal arm tremor. *Neurosci Lett.* (2005) 384:188–92. doi: 10.1016/j.neulet.2005.04.084

4. Thomas M, Lenka A, Kumar Pal P. Handwriting analysis in Parkinson's disease: current status and future directions. *Mov Disord Clin Pract.* (2017) 4:806–818. doi: 10.1002/mdc3.12552

5. Zham P, Kumar DK, Dabnichki P, Arjunan SP, Raghav S. Distinguishing different stages of Parkinson's disease using composite index of speed and pen-pressure of sketching a spiral. *Front Neurol.* (2017) 8:435. doi: 10.3389/fneur.2017.00435

6. Danna J, Velay JL, Eusebio A, Véron-Delor L, Witjas T, Azulay JP, et al. Digitalized spiral drawing in Parkinson's disease: a tool for evaluating beyond

the written trace. *Hum Mov Sci.* (2019) 65:80–8. doi: 10.1016/j.humov.2018.08.003

7. San Luciano M, Wang C, Ortega RA, Yu Q, Boschung S, Soto-Valencia J, et al. Digitized spiral drawing: apossible biomarker for early Parkinson's disease. *PLoS ONE.* (2016) 11:e0162799. doi: 10.1371/journal.pone.0162799

8. Smits EJ, Tolonen AJ, Cluitmans L, van Gils M, Zietsma RC, Borgemeester RWK, et al. Graphical tasks to measure upper limb function in patients with Parkinson's disease: validity and response to dopaminergic medication. *IEEE J Biomed Health Inform.* (2017) 21:283–9. doi: 10.1109/JBHI.2015.2503802

9. Saunders-Pullman R, Derby C, Stanley K, Floyd Al, Bressman S, Lipton RB, et al. Validity of spiral analysis in Early Parkinson's disease. *Mov Disord.* (2008) 23:531–7. doi: 10.1002/mds.21874

10. Liu X, Carroll CB, Wang SY, Zajicek J, Bain PG. Quantifying drug-induced dyskinesias in the arms using digitised spiral-drawing tasks. *J Neurosci Methods.* (2005) 144:47–52. doi: 10.1016/j.jneumeth.2004.10.005

11. Drotár P, Mekyska J, Smékal Z, Rektorová I, Masarová L, Faundez-Zanuy M. Prediction potential of different handwriting tasks for diagnosis of Parkinson's. In: *The 4th IEEE International Conference on E-Health and Bioengineering - EHB 2013 Grigore T Popa University of Medicine and Pharmacy*. Romania: IEEE. (2013). p. 6–9.

12. Drotár P, Mekyska J, Rektorová I, Masarová L, Smékal Z, Faundez-Zanuy M. Evaluation of handwriting kinematics and pressure for differential diagnosis of Parkinson's disease. In: 4th IEEE International Conference on E-Health and Bioengineering - EHB 2013 Grigore T Popa University of Medicine and Pharmacy. Ia§i: IEEE (2013).

13. Zham P, Arjunan SP, Raghav S, Kumar DK. Efficacy of guided spiral drawing in the classification of Parkinson's disease. *IEEE J Biomed Health Inform.* (2018) 22:1648–52. doi: 10.1109/JBHI.2017.2762008

14. Gil-Martín M, Montero JM, San-Segundo R. Parkinson's disease detection from drawing movements using convolutional neural networks. *Electronics.* (2019) 8:907. doi: 10.3390/electronics8080907

15. Kurt I, Ulukaya S, Erdem O. Classification of Parkinson's disease using dynamic time warping. *Telecommun Forum.* (2019) 90:27–30. doi: 10.1109/TELFOR48224.2019.8971180

16. Chandra J, Muthupalaniappan S, Shang Z, Deng R, Lin R, Tolkova I, et al. Screening of Parkinson's disease using geometric features extracted from spiral drawings. *Brain Sci.* (2021) 11:1–17. doi: 10.3390/brainsci11101297

17. Gerth S, Dolk T, Klassert A, Fliesser M, Fischer MH, Nottbusch G, et al. Adapting to the surface: a comparison of handwriting measures when writing on a tablet computer and on paper. *Hum Mov Sci.* (2016) 48:62–73. doi: 10.1016/j.humov.2016.04.006

18. Heckeroth J, Kupferschmid E, Dziedzic T, Kalantzis N, Cakovská BG, Fernandes C, et al. Features of digitally captured signatures vs. pen and paper signatures: similar or completely different? *Forensic Sci Int.* (2021) 318:110587. doi: 10.1016/j.forsciint.2020.110587

19. Lunardini F, Febbo D di, Malavolti M, Cid M, Serra M, Piccini L, et al. A smart ink pen for the ecological assessment of age-related changes in writing and tremor features. *IEEE Trans Instrum Meas.* (2021) 70:3045838. doi: 10.1109/TIM.2020.3045838

20. Febbo D di, Lunardini F, Malavolti M, Pedrocchi A, Borghese NA, Ferrante S. IoT ink pen for ecological monitoring of daily life handwriting. In: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS.* Montreal, QC: IEEE (2020). p. 5749–52.

21. di Febbo D, Lunardini F, Malavolti M, Pedrocchi A, Borghese NA, Ferrante S. IoT ink pen for the ecological study of age-related changes in handwriting. *Annu Int Conf IEEE Eng Med Biol Soc.* (2020) 2020:5749–52. doi: 10.1109/EMBC44109.2020.9175999

22. Toffoli S, Lunardini F, Parati M, Gallotta M, Maria B de, Anna ED, et al. A smart ink pen for spiral drawing analysis in patients with Parkinson's disease. *Annu Int Conf IEEE Eng Med Biol Soc.* (2021) 2021:6475–8 doi: 10.1109/EMBC46164.2021.9629681

23. Fahn S, Elton R. Unified Parkinson's disease rating scale. *Recent Dev Parkinsons Dis.* (1987) 2:153–63.

24. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427

25. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golble L, et al. Variable expressions of Parkinson's disease: a base-line analysis of the DATATOP cohort. *Neurology.* (1990) 40:1529–34. doi: 10.1212/WNL.40.10.1529

26. Schiess MC, Zheng H, Soukup VM, Bonnen JG, Nauta HJW. Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. *Parkinsonism Relat Disord.* (2000) 6:69–76. doi: 10.1016/S1353-8020(99)00051-6

27. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. *Mov Disord.* (2005) 20:1133–42. doi: 10.1002/mds.20513

28. Zhang JZ, Price BT, Adams RD, Burbank K, Knaga TJ. Detection of involuntary human hand motions using empirical mode decomposition and hilbert-huang transform. In: *Midwest Symposium on Circuits and Systems*, Knoxville, TN: IEEE. (2008). p. 157–60.

29. Memedi M, Sadikov A, Groznik V, Žabkar J, Možina M, Bergquist F, et al. Automatic spiral analysis for objective assessment of motor symptoms in Parkinson's disease. *Sensors (Basel).* (2015) 15:23727–44. doi: 10.3390/s150923727

30. Letanneux A, Danna J, Velay JL, Viallet F, Pinto S. From micrographia to Parkinson's disease dysgraphia. *Mov Disord.* (2014) 29:1467–75. doi: 10.1002/mds.25990

31. Balasubramanian S, Melendez-Calderon A, Roby-Brami A, Burdet E. On the analysis of movement smoothness. *J Neuroeng Rehabil.* (2015) 12:1–11. doi: 10.1186/s12984-015-0090-9

32. Melendez-Calderon A, Shirota C, Balasubramanian S. Estimating movement smoothness from inertial measurement units. *Front Bioeng Biotechnol.* (2021) 8:558771. doi: 10.3389/fbioe.2020.558771

33. Muthuraman M, Hossen A, Heute U, Deuschl G, Raethjen J. A new diagnostic test to distinguish tremulous Parkinson's disease from advanced essential tremor. *Mov Disord.* (2011) 26:1548–52. doi: 10.1002/mds.23672

34. Tolonen A, Cluitmans L, Smits E, van Gils M, Maurits N, Zietsma R. Distinguishing Parkinson's disease from other syndromes causing tremor using automatic analysis of writing and drawing tasks. In: *2015 IEEE 15th International Conference on Bioinformatics and Bioengineering, BIBE 2015.* Belgrade: IEEE (2015). p. 5–8.

35. Sadikov A, Zabkar J, Možina M, Groznik V, Georgiev D, Bratko I, et al. *A Decision Support System for Tremor Detection* (2015). Available online at: www.ailab.si/parkinsoncheck

36. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci USA.* (1991) 88:2297–301. doi: 10.1073/pnas.88.6.2297

37. Meigal AY, Rissanen SM, Tarvainen MP, Georgiadis SD, Karjalainen PA, Airaksinen O, et al. Linear and nonlinear tremor acceleration characteristics in patients with Parkinson's disease. *Physiol Meas.* (2012) 33:395–412. doi: 10.1088/0967-3334/33/3/395

38. Luft F, Sharifi S, Mugge W, Schouten AC, Bour LJ, van Rootselaar AF, et al. A power spectral density-based method to detect tremor and tremor intermittency in movement disorders. *Sensors (Switzerland).* (2019) 19:4301. doi: 10.3390/s19194301

39. Ke G, Meng Q, Finley T, Wang T, Chen W, Ma W, et al. Light GBM: a highly efficient gradient boosting decision tree. In: von Luxburg U, Guyon I, Bengio S, Wallach H, Fergus R, editors. *1st Conference on Neural Information Processing Systems*. Long Beach, CA: Curran Associates Inc (2017). p. 3145–55.

40. Prokhorenkova L, Gusev G, Vorobev A, Dorogush AV, Gulin A. Catboost: unbiased boosting with categorical features. In: Bengio S, Wallach H, Larochelle H, Grauman K, Cesa-Bianchi N, Garnett R, editors. *Advances in Neural Information Processing Systems*, Vol. 31. Montreal, QC (2018). p. 6638–48.

41. Lundberg SM, Lee SI. A unified approach to interpreting model predictions. In: *Advances in Neural Information Processing Systems.* (2017). p. 4766–75.

42. Lundberg SM, Erion G, Chen H, DeGrave A, Prutkin JM, Nair B, et al. From local explanations to global understanding with explainable AI for trees. In: *31st Conference on Neural Information Processing Systems*. Long Beach, CA: Curran Associates Inc (2020). p. 56–67. doi: 10.1038/s42256-019-0138

43. Duval C. Rest and postural tremors in patients with Parkinson's disease. *Brain Res Bull.* (2006) 70:44–8. doi: 10.1016/j.brainresbull.2005.11.010

44. Heida T, Wentink EC, Marani E. Power spectral density analysis of physiological, rest and action tremor in Parkinson's disease patients treated with deep brain stimulation. *J Neuroeng Rehabil.* (2013) 10:1–11. doi: 10.1186/1743-0003-10-70

45. Rosenblum S, Samuel M, Zlotnik S, Erikh I, Schlesinger I. Handwriting as an objective tool for Parkinson's disease diagnosis. *J Neurol.* (2013) 260:2357–2361. doi: 10.1007/s00415-013-6996-x

46. Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. *BMC Med.* (2019) 17:1–9. doi: 10.1186/s12916-019-1426-2

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# Gait and turning characteristics from daily life increase ability to predict future falls in people with Parkinson's disease

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**Objectives:** To investigate if digital measures of gait (walking and turning) collected passively over a week of daily activities in people with Parkinson's disease (PD) increases the discriminative ability to predict future falls compared to fall history alone.

**Methods:** We recruited 34 individuals with PD (17 with history of falls and 17 non-fallers), age: 68 ± 6 years, MDS-UPDRS III ON: 31 ± 9. Participants were classified as fallers (at least one fall) or non-fallers based on self-reported falls in past 6 months. Eighty digital measures of gait were derived from 3 inertial sensors (Opal® V2 System) placed on the feet and lower back for a week of passive gait monitoring. Logistic regression employing a "best subsets selection strategy" was used to find combinations of measures that discriminated future fallers from non-fallers, and the Area Under Curve (AUC). Participants were followed *via* email every 2 weeks over the year after the study for self-reported falls.

**Results:** Twenty-five subjects reported falls in the follow-up year. Quantity of gait and turning measures (e.g., number of gait bouts and turns per hour) were similar in future fallers and non-fallers. The AUC to discriminate future fallers from non-fallers using fall history alone was 0.77 (95% CI: [0.50–1.00]). In contrast, the highest AUC for gait and turning digital measures with 4 combinations was 0.94 [0.84–1.00]. From the top 10 models (all AUCs>0.90) via the best subsets strategy, the most consistently selected measures were variability of toe-out angle of the foot (9 out of 10), pitch angle of the foot during mid-swing (8 out of 10), and peak turn velocity (7 out of 10).

**Conclusions:** These findings highlight the importance of considering precise digital measures, captured *via* sensors strategically placed on the feet and low back, to quantify several different aspects of gait (walking and turning) during daily life to improve the classification of future fallers in PD.

KEYWORDS

**Parkinson's disease, daily life, gait, future falls, turning, inertial sensors**

# Introduction

Falls are prevalent in people with Parkinson's Disease (PD), occurring in 60.5% of patients per year (1). Moreover, fall history is a prominent risk factor for recurring falls in PD, with 39% of patients experiencing recurring falls (1). In addition, people with PD who experience impairments in gait and turning difficulties are significantly more likely to fall at home compared to those with tremor as the primary symptoms (2).

Given the heightened risk of falls in people with PD, it is important to consider which aspects of gait and turning difficulties contribute to fall events. Traditionally, clinical assessments such as the Unified Parkinson's Disease Rating Scale (UPDRS) are used to assess disease severity, gait and turning difficulties (3, 4). Additionally, fall history, as recorded by diary or other self-reports are implemented to monitor falls. Such outcomes, among others, have been shown to be predictors of recurring falls in people with PD (1).

A critical shortcoming of these assessments is the inability to objectively measure gait and turning abnormalities in the patient's everyday environment where falls occur. Furthermore, brief clinical or laboratory assessments of gait and turning (e.g., straight-ahead gait and turning) may not accurately reflect functional mobility of patients in their everyday lives, or capture inherent day-to-day variations in movement patterns that may be indicative of functional capacity (5). Therefore, daily life monitoring of gait and turning could help assess the risk of falling in people with PD, and provide insight into patient behavior outside of traditional testing facilities.

Wearable sensors and advanced algorithms allow researchers to capture objective mobility measures both in the clinic and at home (6–10) that may improve our understanding of fall risk in people with PD. It has been shown that environments and tasks associated with daily living can amplify gait and turning impairments in people with PD (7–9). Given the ubiquity of falls and fall recurrence in PD, researchers have worked to identify digital biomarkers, captured during daily life walking and turning, that can assist with identifying fall risk and optimize clinical trial conduct. Several gait and turning metrics obtained from wearable sensors in laboratory settings and during daily life have been shown to discriminate between fallers and non-fallers in PD (11–15). However, it is still unclear which measures, among the high volume of gait and turning measures calculated from inertial sensors, most accurately discriminate fallers from non-fallers with PD during daily life.

The aim of this study was to investigate if digital measures from different components of gait and turning collected from a week of daily activities increased discriminative ability to predict future falls compared to fall history alone. We hypothesize that variability and turn metrics will best discriminate fallers from non-fallers during daily life, and will show an increased discriminative ability to predict future fallers compared to falls history alone. The main contribution of this study is to show the importance of considering precise digital measures, captured via sensors strategically placed on the feet and low back, to quantify several different aspects of gait (walking and turning) during daily life to improve the classification of future fallers in PD.

# Methods

## Participants

Thirty-four people with idiopathic PD participated in the study. Inclusion criteria were a diagnosis of idiopathic Parkinson's disease from movement disorders specialist with the United Kingdom Parkinson's disease Society Brain Bank criteria, Hoehn & Yahr scale of II-IV, and complaints about gait and balance. Exclusion criteria were the inability to follow protocol instructions, and other factors affecting gait and balance such as musculoskeletal disorders, uncorrected vision or vestibular problems, or inability to stand or walk in the home without an assistive device. The experimental protocol was approved by the Institutional Review Board of the Oregon Health & Science University (eIRB #15578). All the participants provided informed written consent. The same participants have been used in our previous research work comparing gait and turning measures in two levodopa states in the clinic (On vs. Off), and daily life settings (16).

## Clinical assessment

Clinical characteristics (including demographic, motor and cognitive status, and patient-reported outcomes) were assessed with a comprehensive battery of validated tests. Specifically, we collected age, sex, height, weight, disease duration, medications, and the Movement Disorders Society (MDS-revised) Unified Parkinson's disease Rating Scale (MDS-UPDRS) (3); the Hoehn and Yahr Rating Scale; the New Freezing of Gait Questionnaire (NFoGQ) (17); the Parkinson's Disease Questionnaire-39 (PDQ-39); and the Montreal Cognitive Assessment (MoCA) (18).

## Falls data collection

Self-reported fall history based on the previous 6 months was collected and participants were classified as fallers (at least one fall) or non-fallers based on falls history prior to the study visit. For future falls, following a week of continuous monitoring of gait. participants were asked complete a 12-month, fall-monitoring period immediately after the 1 week of daily life gait data collection. Participants received bimonthly emails to indicate if they experienced a fall or near fall during the previous 2 weeks. If participants failed to respond, a research assistant called them to ascertain if they had fallen in the previous 2 weeks. A fall was defined as "an event that results in coming to rest unintentionally on the ground or other lower level". Future-fallers were classified as participants with $>1$ fall in the 12-month period after daily life gait data collection. If a fall(s) occurred, we collected number of falls and nature of injury.

## Daily life data collection

Participants were asked to wear 2 Opal-instrumented socks, one on each foot, and an Opal sensor over the lower lumbar area with

an elastic belt (APDM Wearable Technologies-a Clario Company, Portland, OR, USA) for a week of continuous monitoring of at least 8 hours/day during daily activities including both on and off states. The details of the instrumented socks were previously described in Shah et al. (9). Briefly, instrumented socks incorporated the same inertial sensors on top of the foot as used in the Opal, with the battery separated from the sensor and positioned just above the lateral malleolus. Each Opal sensor includes tri-axial accelerometer, gyroscope, and magnetometer and was configured to sample at a rate of 128 Hz. The Opal is lightweight (22 g), has a battery life of 12 h, and includes 8 GB of storage, which can record over 30 days of data.

Participants were asked to remove the sensors at night and plugged in to recharge the batteries. During the daily activities, data were continuously collected and stored in the internal memory of the Opals. Participants were asked to mail back the sensors using a pre-paid mailing box after completion of a week of data collection. Once we receive the devices, the raw data were uploaded to a secure cloud-based database on Amazon Web Server (AWS), processed on the same server and calculated gait metrics were then downloaded to a local computer for further analysis.

## Digital gait and turning measures during daily life

The algorithms used to calculate the measures of gait and turning were the same for the laboratory and daily life data as were detailed previously (19). In summary, the daily life algorithm first searches for possible bouts of walking from inertial sensor data from the feet using a time-domain approach. Second, individual steps are combined into potential bouts of walking if the duration from one step to the next step is less than 2.5 seconds. Finally, each possible bout that contains at least 3 seconds in duration and at least 3 steps is processed with the commercial gait analysis algorithms included in Mobility Lab V2 for prescribed gait tests (APDM Wearable Technologies, A Clario company) (20). For the gait measures reported in this paper, we calculated a mean and variability across all strides over the week of recording and included only the periods of straight walking. Straight walking were periods of walking in which the heading angle of the foot during stance changed by no more than 20 degrees during a single stride and that did not contain detected turns as determined from the lumbar sensor (21). For turning measures, we used a previously published algorithm to detect and characterize each turn (21). Specifically, all the turns with an amplitude larger than 40 degrees were detected as a turn and we did not restrict any particular range of turns but considered all. In total, we derived 52 measures and grouped into four domains (Lower Body, Lower Trunk, Turning, and Variability) similar to described in Shah et al. (22).

## Statistical analysis

The normality of data was examined by the Shapiro-Wilk test. For the demographics measures that were non-normally distributed, the Mann- Whitney U test was used to compare fallers and non-fallers. Otherwise, independent samples *t*-test (or Chi-squared test) was used to examine possible group differences.

To investigate which combination of digital gait and turning measures discriminate fallers from non-fallers group, we used logistic regression employing a best subset selection (23). The best subset selection strategy selects the best model from all possible subsets according to goodness-of-fit criteria. To assess the goodness-of-fit, we used the Bayesian Information Criteria (BIC) (23). We selected the top 15 models based on BIC for two, three, and finally for four digital outcome measures of mobility ($15^*3 = 45$ models total). Finally, we computed the Area Under the ROC Curve (AUC) using "ROC" function (empirical ROC) in R (24, 25) and ranked the top 10 models based on the AUC. All statistical analysis was performed using R Version 1.1.456 software.

## Power analysis

We recently showed that variability of the number of steps during turning was a sensitive metric in predicting falls in the 6 months after the week of continuous monitoring in a group of healthy elderly fallers (26). Out of 35 healthy elderly participants (sample of convenience), 7 fell at least once in the 6 months after the week of continuous monitoring. To determine the number of subjects needed in this study, we compared the variability of the number of steps needed to complete a turn by subjects who experienced one or more falls to variability in the subjects that did not fall. Given the fallers group mean variability of 0.59 (SD 0.04) and the non-fallers group mean of 0.54 (SD 0.03), for alpha = 0.05 and a power of 95%, we are adequately powered to separate fallers and non-fallers with a sample size of 12 subjects per group.

# Results

## Group characteristics and adherence

From a total of 34 people with PD, 17 were fallers and 17 were non-fallers based on self-reported fall history. Table 1 compares the demographic characteristics between non-fallers and fallers. The demographic and other digital measures mostly followed the normal distribution and we did not find any multimodal distribution. There were no significant differences between the groups for demographic characteristics, smart socks compliance and activity measures from daily life. After 1-year follow up from the data collection, out of 34 people, 25 people were fallers and 9 people were non-fallers (see Supplementary Table S1 for number of past falls and future falls for each subject).

## Digital gait and turning measures separating fallers from non-fallers during daily life

The AUC to discriminate future fallers from non-fallers using fall history alone was 0.77 (95% CI: [0.50–1.00]). In contrast, the highest AUC for gait and turning digital measures with 4 combinations was 0.94 [0.84–1.00]. From the top 10 models (all

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

| | Non-fallers ($N = 17$) | Fallers ($N = 17$) | $p$ |
|---|---|---|---|
| Age (yrs) | 66.82 (6.61) | 68.69 (11.10) | 0.29 |
| Disease Duration (yrs) | 7.29 (5.6) | 9.24 (4.58) | 0.14 |
| H and Y ON (#) | 2 (0) | 2.18 (0.53) | 0.164 |
| H and Y OFF (#) | 2.06 (0.24) | 2.29 (0.59) | 0.153 |
| MDS-UPDRS Part III total score ON (#) | 29.47 (8.49) | 32.65 (9.92) | 0.36 |
| MDS-UPDRS Part III total score OFF (#) | 43.88 (11.3) | 46.18 (10.02) | 0.39 |
| MDS-UPDRS Part III PIGD score ON (#) | 2.59 (1.42) | 3.53 (2.62) | 0.34 |
| MDS-UPDRS Part III PIGD score OFF (#) | 3.53 (1.66) | 5.35 (3.28) | 0.09 |
| MoCA total score (#) | 26.94 (2.38) | 26.88 (2.93) | 0.81 |
| LEDD total score (mg/day) | 1,541.94 (2,342.53) | 1,128.1 (533.18) | 0.36 |
| PDQ39 total score (%) | 13.91 (7.3) | 23.3 (14.82) | 0.13 |
| PDQ39 Mobility score (%) | 11.91 (12.14) | 21.76 (18.68) | 0.11 |
| MDS-UPDRS Dyskinesia ON (#) | 0.35 (0.49) | 0.53 (0.51) | 0.31 |
| NFOGQ past month (#) | 0.47 (0.51) | 0.76 (0.44) | 0.08 |
| Activity measures from daily life | | | |
| Number of days | 6.76 (0.56) | 6.41 (1.28) | 0.31 |
| Total hours of recording | 64.57 (8.64) | 62.07 (16.02) | 0.58 |
| Bouts/hours (#) | 7.82 (3.05) | 7.65 (4.16) | 0.70 |
| Strides/hours (#) | 149.87 (60.95) | 161.07 (94.82) | 0.85 |
| Turns/hours (#) | 20.19 (9.33) | 21.34 (15.71) | 0.97 |

H and Y, Hoehn and Yahr scale; MDS-UPDRS Part III, Movement Disorders Society-Unified Parkinson's Disease Rating Scale, motor sub-score; MoCA, Montreal Cognitive Assessment; LEDD, levodopa equivalent daily dose; PDQ39, Parkinson's Disease Questionnaire-39; NFOGQ Past Month, First question of NFOGQ for freezing in last month.

AUCs > 0.90) *via* the best subsets strategy, the most consistently selected gait measures were variability of toe-out angle of foot (9x), pitch angle of the foot during mid-swing (8x), and the maximum average turn velocity (7x) (see Table 2). Figures 1, 2 show the ROC curves and AUC values for the top 4 fall prediction models selected *via* best subsets of gait metrics strategy and using falls history alone.

Considering the definition of the recurrent fallers ($n = 20$ fallers and 14 non-fallers), the most consistently selected gait measures were the pitch angle of the foot during mid-swing (8x), stride time variability (8x), and foot-strike angle variability (7x) (see Supplementary Table S2).

## Discussion

This study offers preliminary evidence that different aspects of gait and turning during daily life (specifically, gait, turning, and variability domains) are important to predict future fallers. Further, digital measures from different components of gait showed more discriminative ability to predict future fallers from non-fallers compared to falls history, alone.

The top ten models incorporating digital gait and turning measures in this study were able to separate fallers from non-fallers with an AUC over 0.90 compared to fall history alone, which yielded an AUC of 0.77. Gait variability was the most consistent domain selected, with toe out angle variability being the most common variability measure selected, followed by stride time variability. These findings are consistent with previous research showing association between gait variability and fall risk in people with PD (27–29).

Digital measures of gait and turning have been shown to have a good predictive value for a fall risk. For an example, Van Schooten et al. reported an AUC of 0.82 when assessing predictive value of accelerometry based measures of gait for detecting falls in 169 older adults (30). In 26 patients with multiple sclerosis, toe-off angle in daily living has been identified as a significant predictor of falls in patients with multiple sclerosis, with an AUC of 0.86 (31). Additionally, an AUC of 0.93 was reported using clinical and functional characteristics in a multivariate model of fall prediction in 49 patients with PD (22), while fall classification accuracies of between 70–80% have been reported using machine learning models with gait metrics as principal predictors in 251 patients with PD (13). In this study, gait and turning domains were most consistently selected by best subset selection following the variability domain. Specifically, pitch angle (dorsiflexion) of the foot during mid-swing and peak turn velocity were most prevalent. Pitch angle of the foot is a particularly pertinent measure for fall risk as it reflects the amount of toe clearance achieved by the participant during mid swing, and thus may contribute to trips or stumbles while walking. Additionally, daily life turning characteristics in people with PD have been shown to be significantly impaired compared to age-matched controls

TABLE 2 Combination of digital gait measures that best discriminated future fallers from non-fallers in PD during daily life.

| Digital measures of gait and turning | | | | | | | | AUC |
|---|---|---|---|---|---|---|---|---|
| 1st | | 2nd | | 3rd | | 4th | | |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Turn velocity maximum | | Cadence variability | | 0.94 (0.84–1) |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Turn velocity Maximum | | Stride time variability | | 0.93 (0.82–1) |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Double support variability | | Stride time variability | | 0.93 (0.83–0.99) |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Turn velocity maximum | | Stance time variability | | 0.93 (0.82–1) |
| Pitch angle of the foot during mid-swing | | Turn angle | | Turn velocity maximum | | Stride time variability | | 0.93 (0.82–1) |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Turn velocity maximum | | – | | 0.92 (0.81–1) |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Double support variability | | Stance time variability | | 0.92 (0.81–0.99) |
| Pitch angle of the foot at toe-off | | Toe-out angle variability | | Turn velocity maximum | | Cadence variability | | 0.91 (0.79–1) |
| Pitch angle of the foot maximum at toe-off | | Toe-out angle variability | | Turn velocity maximum | | Stride time variability | | 0.91 (0.78–1) |
| Pitch angle of the foot during mid-swing | | Toe-out angle variability | | Trunk transverse range of motion | | Stride time variability | | 0.91 (0.78–0.99) |

Lower body. Variability. Turning. Lower trunk.

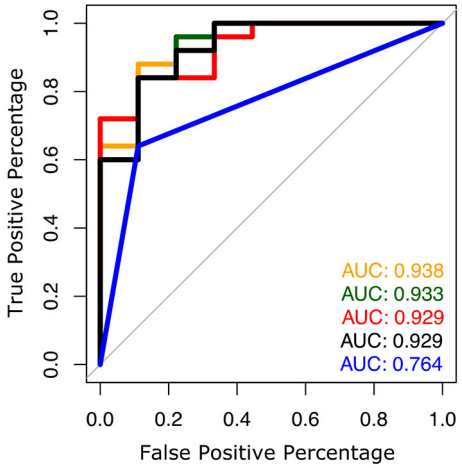


FIGURE 1
ROC plots to predict future falls based on falls history alone (blue line) and various combinations of gait measures (top 4 from Table 2).

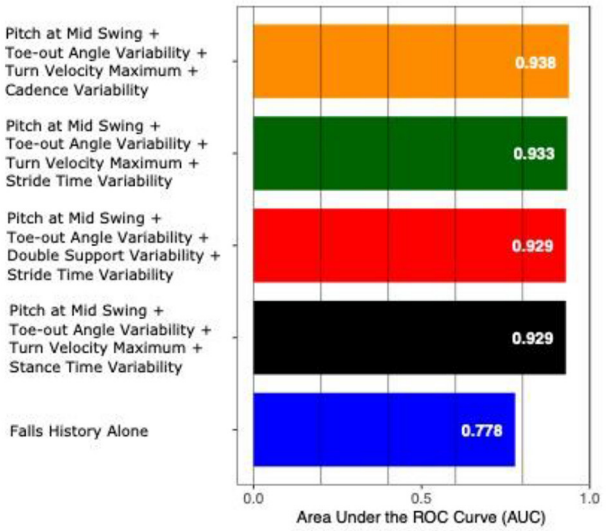


FIGURE 2
AUC values to predict future falls based on falls history alone and various combinations of gait measures (top 4 from Table 2).

(9, 21, 32–34), and turning is associated with falls in older adults (35, 36).

Findings from several recent studies highlight gait, variability, and turning domains in daily life as particularly relevant to understanding PD disease severity and fall prediction during daily living. del Din et al. showed that daily-living gait and variability measures, collected with a wearable sensor, were significantly different in individuals with PD compared to controls (7), and thereafter showed that similar domains were significantly different between fallers with PD compared to non-fallers with PD (11). Galperin et al. used a wearable sensor for 7 days of daily-living monitoring of individuals with PD and a history of falls (37). Their findings showed that daily-living gait and variability measures accounted for 62% of explained variance in the MDS-UPDRS- part III scores of fallers with PD, followed by laboratory measures (30%) and participant demographics/characteristics (7%) (37). More recently, Shah et al. demonstrated that gait, turning, and variability measures, captured with wearable sensors during 1 week of continuous home monitoring, were most significant in distinguishing patients with PD from healthy controls (19). Our results suggest that turning might be more important in identifying the patients who are at risk of their first fall, while gait variability might be more important in identifying the recurrent fallers.

These findings provide support for the collection of digital gait, variability, and turning markers to objectively assess fall risk of people with PD during daily life. Notably, three body worn sensors were required to capture gait, turning, and variability domains during daily life monitoring. The use of instrumented socks to capture mobility of each foot represents a novel approach that may be useful for home monitoring during clinical trials, as they are less obtrusive for continuous monitoring compared to sensors strapped to the foot. Moreover, implementing three body worn

sensors allows for more accurate measurement of gait, variability, and turning domains compared to a single lumbar sensor, which neglects to capture foot angle and variability of foot placement.

There are several limitations of the current study. First, we recommend caution in interpreting the results as the individual models from this small size study are not yet validated in a separate cohort. Hence the performance of the models may be optimistic. Second, future studies with larger cohorts are needed to validate these preliminary findings. Third, we performed the analysis by taking the mean of each measure for all the strides over a week for each subject and thus gave equal weight to each stride. But in reality, gait speed and other measures vary for gait bouts of different lengths (7, 38–40). Hence, future work will focus on how gait bout length affects the discriminatory power of the proposed fall models. Forth, the follow-up period may also affect the ability of fall history to predict future falls. Finally, test-retest reliability and sensitivity of the top measures related to disease progression and falls should be investigated to explore the utility of these digital endpoints for clinical trials.

## Conclusion

Inertial sensors worn on the feet and lumbar level for 7 days provided measures of gait pace, variability and turning that increased the ability to predict future falls in people with PD, beyond predictions from fall history alone.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

This study involved human participants; the protocol was reviewed and approved by the Institutional Review Board of Oregon Health & Science University (eRIB #15578). All participants provided written informed consent to participate in this study.

## Author contributions

VS: conception, organization, execution of research project, design, execution, review and critique of statistical analysis, writing of the first draft, and review and critique of manuscript preparation. AJ: writing of the first draft and review and critique of manuscript preparation. JM, JN, ME-G, and KS: review and critique of the statistical analysis and manuscript preparation. PC-K: organization and execution of research project, review and critique of statistical analysis, and review and critique of manuscript preparation. GH: organization and execution of research project and review and critique of manuscript preparation. MM and FH: conception and organization of research project, design, review and critique of statistical analysis, and review and critique of manuscript preparation. ME-G and JM: conception. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

OHSU and VS, JM, ME-G, and FH have a significant financial interest in APDM Wearable Technologies, a Clario company, that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU. KS and AJ are employees of APDM Wearable Technologies, a Clario company.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1096401/full#supplementary-material

## References

1. Allen NE, Schwarzel AK, Canning CG. Recurrent falls in Parkinson's disease: a systematic review. *Parkinsons Dis.* (2013) 2013:906274. doi: 10.1155/2013/906274

2. Pelicioni PHS, Menant JC, Latt MD, Lord SR. Falls in parkinson's disease subtypes: Risk factors, locations and circumstances. *Int J Environ Res Public Health.* (2019) 16:2216. doi: 10.3390/ijerph16122216

3. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disor.* (2008) 23:2129–70. doi: 10.1002/mds.22340

4. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Movement Disor.* (2013) 28:1544–51. doi: 10.1002/mds.25684

5. Weiss A, Herman T, Giladi N, Hausdorff JM. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. *PLoS ONE.* (2014) 9:e96675. doi: 10.1371/journal.pone.0096675

6. Corrà MF, Atrsaei A, Sardoreira A, Hansen C, Aminian K, Correia M, et al. Comparison of laboratory and daily-life gait speed assessment during on and off states in parkinson's disease. *Sensors.* (2021) 21:3974. doi: 10.3390/s21123974

7. Del Din S, Godfrey A, Galna B, Lord S, Rochester L. Free-living gait characteristics in ageing and Parkinson's disease: Impact of environment and ambulatory bout length. *J NeuroEng Rehabilit.* (2016) 13:1–12. doi: 10.1186/s12984-016-0154-5

8. Hillel I, Gazit E, Nieuwboer A, Avanzino L, Rochester L, Cereatti A, et al. Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gaps between gait performance in the lab and during 24 / 7 monitoring. *Eur Rev Aging Phys Activity.* (2019) 16:1–12. doi: 10.1186/s11556-019-0214-5

9. Shah VV, McNames J, Mancini M, Carlson-Kuhta P, Spain RI, Nutt JG, et al. Laboratory versus daily life gait characteristics in patients with multiple sclerosis, Parkinson's disease, and matched controls. *J NeuroEng Rehabilit.* (2021) 17:1–12. doi: 10.1186/s12984-020-00781-4

10. Warmerdam E, Hausdorff JM, Atrsaei A, Zhou Y, Mirelman A, Aminian K, et al. Long-term unsupervised mobility assessment in movement disorders. *Lancet Neurol.* (2020) 19:462–70. doi: 10.1016/S1474-4422(19)30397-7

11. Del Din S, Galna B, Godfrey A, Bekkers EM, Pelosin E, Nieuwhof F, et al. Analysis of free-living gait in older adults with and without Parkinson's disease and with and without a history of falls: identifying generic and disease-specific characteristics. *J Gerontol Series A Biol Sci Med Sci.* (2019) 74:500–506. doi: 10.1093/gerona/glx254

12. Delval A, Betrouni N, Tard C, Devos D, Dujardin K, Defebvre L, et al. Do kinematic gait parameters help to discriminate between fallers and non-fallers with Parkinson's disease? *Clin Neurophysiol.* (2021) 132:536–41. doi: 10.1016/j.clinph.2020.11.027

13. Gao C, Sun H, Wang T, Tang M, Bohnen NI, Müller MLTM, et al. Model-based and model-free machine learning techniques for diagnostic prediction and classification of clinical outcomes in Parkinson's disease. *Scientific Reports.* (2018) 8:7129. doi: 10.1038/s41598-018-24783-4

14. Hoskovcová M, Dusek P, Sieger T, Brozová H, Zárubová K, Bezdicek O, et al. Predicting falls in Parkinson disease: What is the value of instrumented testing in off medication state? *PLoS ONE.* (2015) 10:e0139849. doi: 10.1371/journal.pone.0139849

15. Rehman RZ, Zhou Y, Del Din S, Alcock L, Hansen C, Guan Y, et al. Gait analysis with wearables can accurately classify fallers from non-fallers: A step toward better management of neurological disorders. *Sensors.* (2020) 20:1–17. doi: 10.3390/s20236992

16. Shah VV, McNames J, Carlson-Kuhta P, Nutt JG, El-Gohary M, Sowalsky K, et al. Effect of Levodopa and Environmental Setting on Gait and Turning Digital Markers Related to Falls in People with Parkinson's Disease. *Movement Disorders Clin Pract.* (2022). doi: 10.1002/mdc3.13601

17. Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Ehab G, Thomaes T, et al. Reliability of the new freezing of gait questionnaire : Agreement between patients with Parkinson' s disease and their carers. *Gait Posture.* (2009) 30:459–63. doi: 10.1016/j.gaitpost.2009.07.108

18. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x

19. Shah VV, McNames J, Mancini M, Carlson-Kuhta P, Spain RI, Nutt JG, et al. Quantity and quality of gait and turning in people with multiple sclerosis, Parkinson's disease and matched controls during daily living. *J Neurol.* (2020) 267:1188–96. doi: 10.1007/s00415-020-09696-5

20. Mancini M, King L, Salarian A, Holmstrom L, McNames J, Horak FB. Mobility Lab to Assess Balance and Gait with Synchronized Body-worn Sensors. *J Bioeng Biomed Sci.* (2013) 7:1–5. doi: 10.4172/2155-9538.S1-007

21. Shah VV, Curtze C, Mancini M, Carlson-Kuhta P, Nutt JG, Gomez CM, et al. Inertial sensor algorithms to characterize turning in neurological patients with turn hesitations. *IEEE Trans Biomed Eng.* (2021) 68:2615–2625. doi: 10.1109/TBME.2020.3037820

22. Custodio N, Lira D, Herrera-Perez E, Montesinos R, Castro-Suarez S, Cuenca-Alfaro J, et al. Predictive model for falling in Parkinson disease patients. *Eneurologicalsci.* (2016) 5:20–4. doi: 10.1016/j.ensci.2016.11.003

23. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning.* (2009). Available online at: https://hastie.su.domains/ElemStatLearn/

24. Fawcett T. An introduction to ROC analysis. *Pattern Recognit Lett.* (2006) 27:861–74. doi: 10.1016/j.patrec.2005.10.010

25. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinform.* (2011) 12:1–8. doi: 10.1186/1471-2105-12-77

26. Mancini M, Schlueter H, El-Gohary M, Mattek N, Duncan C, Kaye J, et al. Continuous monitoring of turning mobility and its association to falls and cognitive function: a pilot study. *J Gerontol A.* (2016) 71:1102–8. doi: 10.1093/gerona/glw019

27. Callisaya ML, Blizzard L, Schmidt MD, Martin KL, Mcginley JL, Sanders LM, et al. Gait, gait variability and the risk of multiple incident falls in older people: A population-based study. *Age Ageing.* (2011) 40:481–7. doi: 10.1093/ageing/afr055

28. Hausdorff JM. Gait variability: methods, modeling and meaning. *J Neuroeng Rehabil.* (2005) 6:1–6. doi: 10.1186/1743-0003-2-19

29. Hausdorff JM. Gait dynamics in Parkinson's disease: Common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos.* (2009) 19:1–14. doi: 10.1063/1.3147408

30. Van Schooten KS, Pijnappels M, Rispens SM, Elders PJ, Lips P, van Dieën JH. Ambulatory fall-risk assessment: amount and quality of daily-life gait predict falls in older adults. *J Gerontol A.* (2015) 70:608–15. doi: 10.1093/gerona/glu225

31. Arpan I, Shah VV, McNames J, Harker G, Carlson-Kuhta P, Spain R, et al. Fall prediction based on instrumented measures of gait and turning in daily life in people with multiple sclerosis. *Sensors.* (2022) 22:5940. doi: 10.3390/s22165940

32. El-Gohary M, Pearson S, McNames J, Mancini M, Horak F, Mellone S, et al. Continuous monitoring of turning in patients with movement disability. *Sensors (Switzerland).* (2014) 14:356–69. doi: 10.3390/s140100356

33. Haertner L, Elshehabi M, Zaunbrecher L, Pham MH, Maetzler C, Uem JMT, et al. Effect of fear of falling on turning performance in Parkinson' s disease in the lab and at home study cohort demographics and clinical. *Front Aging Neurosci.* (2018) 10:1–8. doi: 10.3389/fnagi.2018.00078

34. Mancini M, Weiss A, Herman T, Hausdorff JM. Turn around freezing: Community-living turning behavior in people with Parkinson's disease. *Front Neurol.* (2018) 9:1–9. doi: 10.3389/fneur.2018.00018

35. Leach JM, Mellone S, Palumbo P, Bandinelli S, Chiari L. Natural turn measures predict recurrent falls in community-dwelling older adults: A longitudinal cohort study. *Sci Rep.* (2018) 8:1–9. doi: 10.1038/s41598-018-22492-6

36. Mancini M, El-Gohary M, Pearson S, Mcnames J, Schlueter H, Nutt JG, et al. Continuous monitoring of turning in Parkinson's disease: Rehabilitation potential. *NeuroRehabilitation.* (2015) 37:3–10. doi: 10.3233/NRE-151236

37. Galperin I, Hillel I, Del Din S, Bekkers EM, Nieuwboer A, Abbruzzese G, et al. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. *Parkinsonism Relat Disor.* (2019) 62:85–90. doi: 10.1016/j.parkreldis.2019.01.022

38. Rispens SM, van Schooten KS, Pijnappels M, Daffertshofer A, Beek PJ, van Dieen JH. Do extreme values of daily-life gait characteristics provide more information about fall risk than median values? *JMIR Res Protoc.* (2015) 4:e3931. doi: 10.2196/resprot.3931

39. Rehman RZU, Guan Y, Shi JQ, Alcock L, Yarnall AJ, Rochester L, et al. Investigating the impact of environment and data aggregation by walking bout duration on parkinson's disease classification using machine learning. *Front Aging Neurosci.* (2022) 14:808518. doi: 10.3389/fnagi.2022.808518

40. Shah VV, McNames J, Harker G, Mancini M, Carlson-Kuhta P, Nutt JG, et al. Effect of bout length on gait measures in people with and without Parkinson's disease during daily life. *Sensors.* (2020) 20:5769. doi: 10.3390/s20205769

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# Feasibility and usability of a digital health technology system to monitor mobility and assess medication adherence in mild-to-moderate Parkinson's disease

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**Introduction:** Parkinson's disease (PD) is a neurodegenerative disorder which requires complex medication regimens to mitigate motor symptoms. The use of digital health technology systems (DHTSs) to collect mobility and medication data provides an opportunity to objectively quantify the effect of medication on motor performance during day-to-day activities. This insight could inform clinical decision-making, personalise care, and aid self-management. This study investigates the feasibility and usability of a multi-component DHTS to remotely assess self-reported medication adherence and monitor mobility in people with Parkinson's (PwP).

**Methods:** Thirty participants with PD [Hoehn and Yahr stage I ($n$ = 1) and II ($n$ = 29)] were recruited for this cross-sectional study. Participants were required to wear, and where appropriate, interact with a DHTS (smartwatch, inertial measurement unit, and smartphone) for seven consecutive days to assess medication adherence and monitor digital mobility outcomes and contextual factors. Participants reported their daily motor complications [motor fluctuations and dyskinesias (i.e., involuntary movements)] in a diary. Following the monitoring period, participants completed a questionnaire to gauge the usability of the DHTS. Feasibility was assessed through the percentage of data collected, and usability through analysis of qualitative questionnaire feedback.

**Results:** Adherence to each device exceeded 70% and ranged from 73 to 97%. Overall, the DHTS was well tolerated with 17/30 participants giving a score > 75% [average score for these participants = 89%, from 0 (worst) to 100 (best)] for its usability. Usability of the DHTS was significantly associated with age ($\rho = -0.560$, BCa 95% CI [−0.791, −0.207]). This study identified means to improve usability of the DHTS by addressing technical and design issues of the smartwatch. Feasibility,

usability and acceptability were identified as key themes from PwP qualitative feedback on the DHTS.

**Conclusion:** This study highlighted the feasibility and usability of our integrated DHTS to remotely assess medication adherence and monitor mobility in people with mild-to-moderate Parkinson's disease. Further work is necessary to determine whether this DHTS can be implemented for clinical decision-making to optimise management of PwP.

KEYWORDS

**Parkinson's disease, medication adherence, smartwatch, wearable technology, remote monitoring, mobility, inertial measurement units, motor complications**

## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by cardinal motor symptoms which impact quality of life and independence in individuals with PD; therefore, careful clinical management is of primary importance. Adherence to prescribed medication dosage and timing is vital for effective management of motor symptoms. One of the most effective strategies for managing these symptoms is dopaminergic therapy such as levodopa (1, 2). As PD progresses, increased (3) and/or more frequent (4) doses of levodopa are necessary to ease motor symptoms, but motor complications such as dyskinesias (involuntary movements) and/or motor fluctuations can develop (5). During "ON" periods, symptoms and functional impairment improve following medication intake, whereas "OFF" periods correspond to a worsening of symptoms as the dose wears off (1).

Due to complex medication regimens, adherence is often suboptimal, resulting in poor response to medication, reduced quality of life and increased symptom fluctuation severity (6). It has been shown that over a third of people with PD (PwP; 36.3%, $n = 45$) taking three or more doses of medication daily report poor adherence (6). Modification of complex medication regimens often follows short, infrequent appointments with a clinician, which have been especially affected by the COVID-19 pandemic (7, 8). In addition, patient-clinician interactions are influenced by patient recall and performance bias, and clinicians observe PwP at different stages ("ON," "OFF" periods) of their medication regimen. Consequently, clinicians often lack adequate insight of daily and habitual motor fluctuations to appropriately adapt medication regimens. This highlights the need for remote and real-world monitoring of mobility and motor symptoms in response to medication in PwP. By objectively modelling and predicting how mobility and motor symptoms change throughout the day in response to medication, clinicians may be able to optimise medication regimens and reduce motor fluctuations in PwP.

Digital health technology systems (DHTSs) have the "potential to transform healthcare research" (9) and present a means for remote monitoring of mobility and assessment of medication adherence and in PwP. Specifically, body-worn sensors [e.g., inertial measurement units (IMUs)] can monitor digital mobility outcomes (DMOs) in an unobtrusive manner, allowing for objective quantification of mobility in PwP (10), such as gait speed (11–13). Other connected devices (e.g., smartphones) provide a valuable indication of contextual factors that affect DMOs (14), such as the likelihood that the individual is indoors or outdoors. Digital health technology (DHT) also presents an avenue to improve individuals' medication adherence in PD, by providing notifications to remind them of their medication intake times (15, 16). A widely used DHT device is the Personal KineticGraph (PKG®, Global Kinetics Corp, Australia). The PKG continuously monitors and stores motor symptom data and can send medication reminders (17). However, it does not provide real-time feedback to users, quantify gait components, or register the specific medication taken, therefore limiting its use for comprehensive remote monitoring of PD. Therefore, the first step to enhance customisation and adaptation of medication regimens in PwP, is for research to focus efforts on utilising DHT to comprehensively monitor PwP in their daily life and explore how motor complications and mobility respond to medication. Reducing the burden of complex medication regimens on PwP will improve their quality of life and offer improved management of motor symptoms.

To achieve this, the present study investigates whether a new DHTS integrating a smartwatch, smartphone and IMU can be utilised to monitor mobility and assess medication adherence in PwP. Specifically, the IMU allows for continuous monitoring of DMOs; the smartwatch reminds individuals of their medication intake times and records self-reported intakes through interaction with the digital screen; and the smartphone sends notifications to the smartwatch and records contextual data. Additionally, a diary is filled by participants on a daily basis to record motor complications (i.e., ON and OFF fluctuations and dyskinesia). As highlighted by the World Health Organisation (WHO) (18), feasibility and usability of a DHTS should be amongst the first assessments conducted for the development of new digital health interventions. Indeed, individuals' needs and ability to use DHTS vary with demographic and clinical status, but usability of DHTS is rarely explored (19).

Therefore, as a first step to model how mobility and motor symptoms respond to medication, the present paper aims to investigate: (i) the feasibility and (ii) the usability of the aforementioned DHTS and of a diary to remotely monitor mobility, assess daily medication adherence and track motor complications in PwP. We first hypothesised that the DHTS and motor complications diary will be feasible for PwP, and second, as PD

is a progressive disease, that usability of the DHTS's components will decline as participants age and PD progresses. Finally, we provide recommendations and identify potential ways to improve the DHTS for future studies.

# Materials and methods

This section has been prepared following the EVIDENCE (EValuatIng connecteD sENsor teChnologiEs) guidelines for the evaluation of a DHTS in Utility and Usability studies (20).

## Participants and protocol

Participants with PD were recruited as part of the Medical Research Council (MRC) Confidence in Concept (CiC) funded study "Translating digital healthcare to enhance clinical management: evaluating the effect of medication on mobility in people with Parkinson's Disease" (ISRCTN Number: 13156149, https://www.isrctn.com/ISRCTN13156149). This study is also a sub-study of the Mobilise-D—Clinical Validation Study (REC reference: 20/PR/0792) (21).

Due to the paucity of research exploring concurrent real-world mobility and medication adherence in PwP using DHTS, there was insufficient data to inform a reliable power calculation. For this feasibility study, a sample size of 30 was defined according to Consensus-based Standards for the selection of health Measurement Instruments guidelines for measurement properties (22). Ethical approval was obtained from the London—Westminster Research Ethics Committee (REC reference: 21/PR/0469) and the study was conducted in accordance with the declaration of Helsinki (23).

## Eligibility criteria

Eligibility criteria are the same as previously published for the Mobilise-D project (21) and are displayed in Table 1. In the later stages of the disease (Hoehn and Yahr stages IV and V), loss of independence can decrease the ability to perform activities of daily living, this induces difficulties to remotely monitor mobility with IMUs. Additionally, prevalent cognitive impairments associated with disease progression may alter the capacity to utilise the DHTS. Therefore, only people in the early stages of the disease were recruited for this study (inclusion criteria: Hoehn and Yahr stages I to III).

TABLE 1 Inclusion and exclusion criteria for participant recruitment.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Adults aged 18 or over | Occurrence of any of the following within 3 months prior to informed consent: myocardial infarction, hospitalisation for unstable angina, stroke, coronary artery bypass graft, percutaneous coronary intervention, implantation of a cardiac resynchronization therapy device, active treatment for cancer or other malignant disease, uncontrolled congestive heart disease (NYHA class >3), acute psychosis or major psychiatric disorders or continued substance abuse |
| Ability to consent and comply with any study specific procedures | |
| Able to read and write in English | |
| Patients with the clinical diagnosis of PD according to the recent criteria of the Movement Disorder Society (24) | |
| Hoehn and Yahr stage I–III | History consistent with Dementia with Lewy Bodies, atypical parkinsonian syndromes (including multiple system atrophy or progressive supranuclear palsy, diagnosed according to accepted criteria) |
| On stable Parkinson's disease medication doses (i.e., taking the same medications for 4 weeks or more). | |
| Able to walk 4 m independently with or without walking aids | Repeated strokes or stepwise progression of symptoms, leading to a diagnosis of "vascular parkinsonism" |
| Willingness to wear an IMU, a smartwatch and use a smartphone | Drug-induced parkinsonism |

## Study protocol

### Recruitment and screening

Participants were recruited between June 2021 and March 2022 from local movement disorder clinics and from the "Mobilise-D—Clinical Validation Study" at the Newcastle University (UK) site. Potential participants attended an eligibility screening appointment during which the ability to consent was assessed, informed consent was obtained, and eligibility criteria were reviewed.

### Study assessments

A flowchart of the study protocol is displayed in Figure 1.

Within 14 days of screening, participants attended a single visit assessment at the Clinical Ageing Research Unit of Newcastle University in which their demographic and clinical characteristics were assessed. Clinical characteristics were measured using validated tools and questionnaires (25–33).

At the end of this visit, participants were equipped with the DHTS and a demonstration of the smartwatch use was made. Detailed written instructions for the day-to-day use of the devices were provided to participants which included the contact details of the research team.

### Seven-day continuous remote monitoring

The monitoring period started the day after the screening visit, with self-reported medication adherence, mobility and motor complications being monitored over seven consecutive days.

### IMU to monitor DMOs

To monitor their DMOs, participants wore an IMU [Axivity, AX6, including triaxial accelerometers and gyroscopes, dimensions 23 × 32.5 × 8.9 mm, mass 11 g, frequency 100 Hz, accelerometer range ±8 g, gyroscope range ±2,000 ° degrees per second (dps)] on their lower back (fifth lumbar vertebra) throughout the monitoring

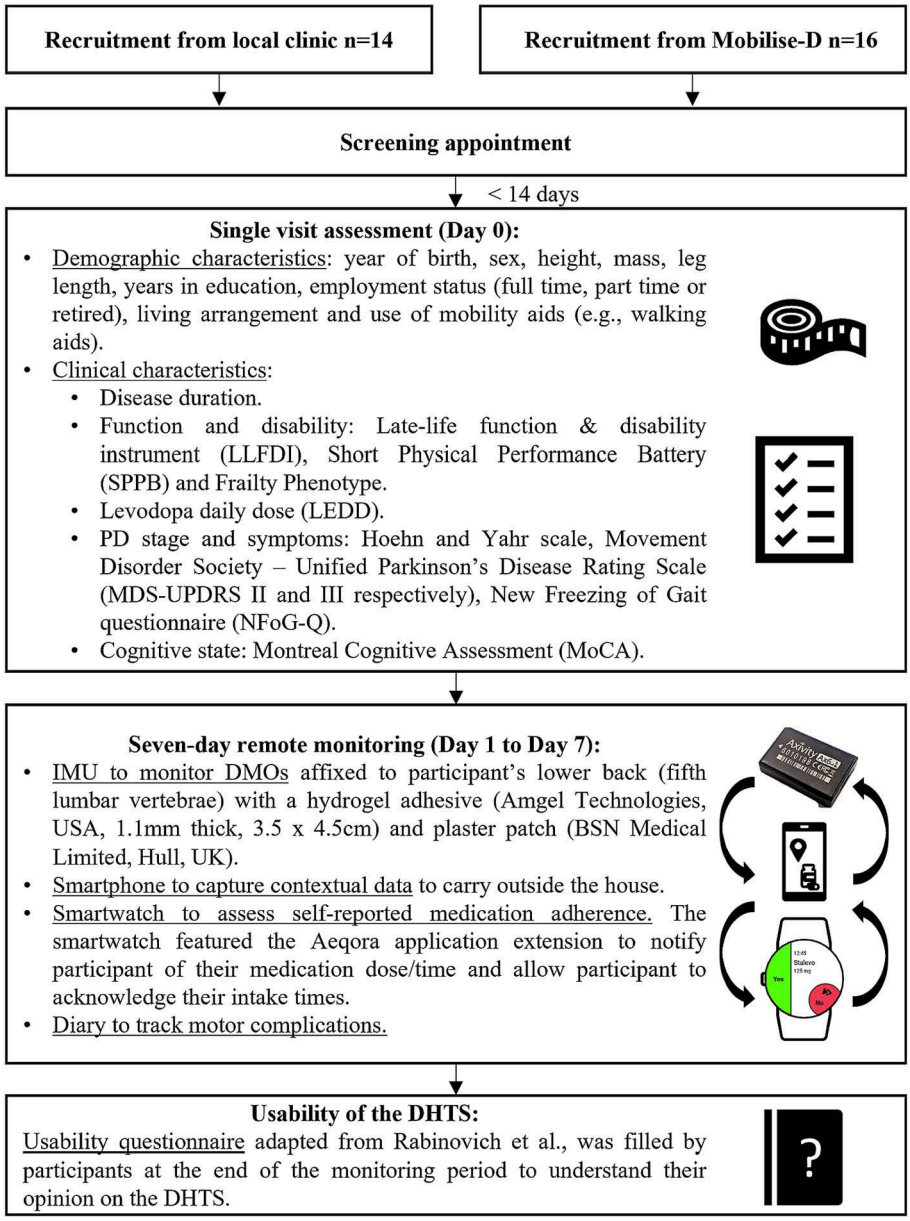


FIGURE 1
Flowchart of the study protocol.

period, and were asked to continue their daily activities as usual and not to change their routine.

## Smartphone to contextualise DMOs

During the monitoring period, participants were also asked to carry a smartphone (Samsung Galaxy S9, S10 or S21, Samsung Group, Suwon-si, South Korea) when leaving their home. The Aeqora mobile application (Department of Computer Science, The University of Sheffield, UK) was pre-installed onto the smartphone to (a) send medication notifications to the smartwatch, and (b) collect contextual information such as weather conditions, geolocation, and the number of steps participants took outside of their home, per day (34). Geolocation data will be used in the future to discern DMOs obtained from indoor and outdoor environments using a deep learning model approach (35).

## Smartwatch to assess self-reported medication intake

Participants' prescribed medication intake times were sent, *via* the smartphone, to a smartwatch (Ticwatch Pro, Mobvoi) through the custom-made Aeqora application extension, and the smartwatch vibrated to notify participants to take their medication at the programmed intake times. Participants interacted with the smartwatch to acknowledge and log their medication intake times, clicking either "Yes" or "No" on the screen when prompted.

Participants were able to input any additional medication intake [Per Required Need (PRN)].

### Diary to track motor complications

To track motor complications (ON and OFF fluctuations, dyskinesia), participants filled in a paper-based medication diary each day; indicating their "OFF-status" (when participants felt their medication was not working) with an "O" and dyskinesia with a "D." The diary recorded data over 16-h per day, from 06:00 to 22:00 from Day 1 to Day 7. A copy of the medication diary is provided as Supplementary material 1.

### Questionnaire to evaluate the usability of the DHTS

At the end of the monitoring period, to evaluate usability of the DHTS, participants completed an adapted version of Rabinovich et al.'s (36) usability questionnaire. The questionnaire used a 5-point ordinal scale, 5 being the most favourable and 1 the least favourable scores, with answers of "no opinion" scored as 3. Participants also provided an overall score for the DHTS, from 0 (worst score) to 100 (best score). Open text questions were added to the questionnaire to allow participants to provide feedback on individual devices and on the DHTS. Specifically, participants were asked to "give any other comments on the DHTS and its devices," and to describe, where appropriate, the "problems" they had with, and the "features [they] liked" about the DHTS and individual devices. A copy of the usability questionnaire is provided in the Supplementary material 2.

At the end of the 7-day assessment, participants returned all the devices, the usability questionnaire and the motor complications diary through the post using pre-paid tracked envelopes.

## Data processing and analysis

### Data processing

To gain comprehensive insight into the usability of the DHTS we utilised a mixed methods approach (19). Statistical analysis was carried out using SPSSv28 (IBM, NY). Histograms and boxplots were visually inspected to assess the distribution of the data. Outliers (values that are 1.5 × interquartile range lower or greater than first or third quartiles, respectively) were kept in the analysis. Where appropriate, mean and standard deviation or median and range of the demographic and clinical characteristics were reported.

Qualitative analysis of free text questionnaire responses was carried out by two researchers (EP and HD) who together assessed all participants' responses and developed key themes and subthemes. Individually, the researchers then grouped all responses into these themes and subthemes and finally met to review the groupings and form a consensus.

Data was downloaded from the IMU onto a computer and segmented into seven days and analysed in MATLAB (R2018a, Mathworks, California, United States). Walking bouts (i.e., periods of walking with a minimum threshold of three steps) were identified and gait speed and number of steps per day were calculated from the raw IMU data using validated algorithms in MATLAB (13, 37).

Data logged on the smartwatch and smartphone was uploaded to the secure eScience platform (38) and processed using validated algorithms for the contextual data (34), and manually for self-reported medication intake. Raw data from the smartwatch was exported to .xlsx files and included the following items for each day: medication type, time, dose and participants' input ("Yes" or "No"). The number of hours spent per day, in the "ON-" and "OFF-status" and time spent experiencing dyskinesias, were evaluated using annotated motor complication diaries.

### Quantitative assessment of feasibility of the DHTS and motor complications diary

The WHO report (18) defines feasibility as "[…] whether the digital health system works as intended in a given context."

To test whether the DHTS and motor complications diary will be feasible for individuals with PD, we explored the feasibility of the DHTS to measure mobility (IMU) and assess self-reported medication adherence (smartwatch), and the feasibility of the smartphone and diary to collect contextual data and track motor complications ("ON," "OFF" periods, dyskinesia), respectively. In reference to the WHO definition of feasibility, we assessed whether the intended data had been collected by each device in the system (18).

Concerning medication adherence, the number of interactions expected corresponded to the number of prescribed medication intakes, excluding PRN intakes. As the overall aim of this project is to model mobility and motor complications in response to medication intake and this will include PRN doses, interactions recorded per day included PRN intakes. Duplicates (second intake separated by 30 minutes or less from initial intake) were excluded from the analysis.

Table 2 summarises the measures of feasibility and outcomes extracted.

### Quantitative assessment of usability of the DHTS

The WHO report (18) defines usability as "[…] whether the digital health system can be used as intended by users."

TABLE 2 Measure of feasibility and outcomes extracted for each device of the DHTS and motor complications diary.

| Device | Measure of feasibility | Outcomes extracted |
|---|---|---|
| IMU | Percentage of IMU datasets collected over 7 days | Gait speed and number of steps per day. |
| Smartphone | Percentage of datasets collected over 7 days and percentage of days missing. | Number of steps taken outside the home per day. |
| Smartwatch | Percentage of participants interacting with the smartwatch over 7 days. | Number of interactions recorded. |
| Motor complications diary | Percentage of diaries returned and legible. | Time spent in ON or OFF state and dyskinesia. |

The usability of the DHTS was evaluated through analysis of the quantitative part of the usability questionnaire. To test our second hypothesis that usability of the DHTS's devices will be affected by participants' demographic and clinical characteristics, we ran Spearman's rho correlations between the overall usability score of the DHTS provided by participants and their demographic and clinical characteristics. Considering the lack of normality of the sample's DHTS usability score, we used bootstrapping correlations with bias corrected and accelerated 95% confidence interval (BCa 95% CI) to improve the accuracy of the confidence interval [for information on bootstrapping, please see Wright, London and Field's paper (39)]. It was anticipated that usability of the DHTS would decrease with age or disease progression. Therefore, correlation analysis was run between the overall DHTS score (0–100) and demographic (age) ($\alpha = 0.05$), as well as clinical characteristics (disease duration, number of medication doses prescribed per day, SPPB score, MDS-UPDRS II and MDS-UPDRS III scores, frailty phenotype and total NFoG-Q score) characteristics. Concerning the correlation between the overall DHTS score and participants' clinical characteristics, because we would reject the null hypothesis should any of the seven clinical characteristics be correlated with the overall DHTS score, a Bonferroni correction was performed and $\alpha$ adjusted to 0.007.

### Qualitative assessment of feasibility and usability of the DHTS

To identify opportunities to improve the DHTS, we evaluated the qualitative part of the usability questionnaire (19, 40, 41). To analyse these responses, we took a hybrid approach using both deductive and inductive methods, originally grouping qualitative feedback into feasibility, usability, and recommendations for improvement. From exploration of responses, acceptability was included as an additional theme and, based on a previous definition (42), refers to the extent to which the DHTS is perceived as agreeable. Finally, the quantitative part of the usability questionnaires was analysed again with questions grouped according to the identified theme. Question 3 was the only question relating to the feasibility theme. Questions 1, 2, 7, and 8 related to the usability theme and the remaining questions (4, 5, 6, 9, 10, 11, and 12) related to the acceptability theme.

## Results

### Demographic and clinical characteristics

Thirty participants (22 males, 63 ± 9 years, levodopa equivalent daily dose 676 ± 370 mg·day$^{-1}$) who met the inclusion criteria (Table 1) were included in this study. Most ($n = 29$) participants were at Hoehn and Yahr stage II (97%), and one was at Stage I (3%). Participants' clinical and demographic characteristics are presented in Table 3.

No serious adverse event was reported.

TABLE 3 Demographic and clinical characteristics of participants recruited for the study.

| Characteristics | Mean ± SD | Median (Min–Max) | Frequency |
|---|---|---|---|
| Males/females | | | 22/8 |
| Age (years) | 63 ± 9 | | |
| BMI (kg·m$^{-2}$) | 26.2 ± 4.2 | | |
| Education (years) | 13 ± 3 | | |
| Disease duration (years) | | 5 (1–17) | |
| N° doses prescribed per day | | 5 (3–13) | |
| Hoehn and Yahr stage, stage: *n* (%) | | | I: 1 (3%)<br>II: 29 (97%) |
| LLFDI function (0–160) | 132 ± 19 | | |
| LLFDI function walking device (0–40) | | 33 (32–35) | |
| LLFDI disability frequency (0–80) | | 56 (43–70) | |
| LLFDI disability limitation (0–80) | 66 ± 9 | | |
| LEDD (mg·day$^{-1}$) | 676 ± 370 | | |
| Frailty Phenotype, phenotype: *n* (%) | | | 0: 16 (53%)<br>I: 10 (33%)<br>II: 3 (10%)<br>III: 1 (3%) |
| MDS-UPDRS Part II (0–52) | | 11 (2–33) | |
| MDS-UPDRS Part III (0–132) | | 30 (7–43) | |
| NFoG-Q (0–33) | | 0 (0–26) | Score ≥ 1: $n = 10$ |
| MoCA (0–30) | | 28 (21–30) | |
| SPPB (0–12) | 10 ± 1 | | |

Outcomes are reported as mean and standard deviation (SD) when normally distributed and median with minimum and maximum values (Min–Max) when they lack normality.
BMI, body mass index; LLFDI, late-life function and disability instrument; MDS-UPDRS, movement disorder society-unified Parkinson's disease rating scale; NFoG-Q, new freezing of gait questionnaire; MoCA, Montreal Cognitive Assessment; SPPB, short physical performance battery test.

### Quantitative assessment of the feasibility of the DHTS and motor complications diary

#### IMU to monitor DMOs

IMU data was collected for 93% of participants ($n = 28$) over the 7-day monitoring period. Two data sets were missing because one DHTS was recalled due to technical issues with the smartwatch and one participant removed it on day 3 due to skin irritation. Averaged over the 7 days monitored, the median gait speed collected from the IMUs was 1.04 m·s$^{-1}$ and ranged from 0.90 to 1.28 m·s$^{-1}$. The median number of steps (indoor and outdoor) recorded per day by the IMU ranged from 11,228 to 13,693.

Table 4 shows participants' gait speed and number of steps per day recorded by the IMU from day 1 to day 7.

## Smartphone to contextualise DMOs

Contextual data for one participant was missing for the whole monitoring period (Day 1–7), therefore contextual data was recorded for 97% ($n = 29$) of participants. No data was recorded (phone off) for eight participants for 1–5 days [total number of days without contextual data = 23 (11%)]. The median number of steps (outdoor) recorded per day by the smartphone ranged from 313 to 3,307.

Table 5 shows participants' number of steps outside their home environment recorded by the smartphone from day 1 to day 7 (different from the IMU that continuously collected steps per day indoors and outdoors).

## Smartwatch to assess self-reported medication intake

Three participants (10%) did not interact with their smartwatch during the monitoring period, whilst the other 27 participants (90%) interacted with it at least once. Due to technical issues, eight participants (27%) stopped using the smartwatch during the monitoring period, therefore only 22 participants (73%) had smartwatch data recorded over the monitoring period. Delayed ("No" interaction followed by late additional interaction to report intake) and PRN intakes mean that some participants interacted with their smartwatch more than expected. Ninety expected interactions were missing from the records and 191 duplicates were excluded from analysis.

Figure 2 shows the number of interactions recorded vs. expected per day for (A) the whole sample ($n = 30$), and (B) participants ($n = 22$) who used the smartwatch throughout the monitoring period.

TABLE 4 Gait speed and number of steps per day measured from the IMU's data ($n = 28$).

| | Gait speed m·s$^{-1}$ | Number of steps per day (inside and outside) |
|---|---|---|
| | Median (Min–Max) | Median (Min–Max) |
| Day 1 | 1.05 (0.76–1.16) | 13,235 (3,688–24,556) |
| Day 2 | 1.05 (0.76–1.18) | 13,092 (2,935–24,099) |
| Day 3 | 1.04 (0.83–1.16) | 13,693 (4,360–38,655) |
| Day 4 | 1.03 (0.75–1.20) | 11,919 (2,387–29,719) |
| Day 5 | 1.05 (0.82–1.14) | 11,228 (917–33,403) |
| Day 6 | 1.05 (0.85–1.17) | 13,399 (1,896–30,872) |
| Day 7 | 1.06 (0.85–1.40) | 11,823 (1,755–27,394) |

TABLE 5 Number of steps taken outside the home, per day, recorded by the smartphone ($n = 29$).

| | Median (Min–Max) |
|---|---|
| Day 1 | 3,307 (0–12,068) |
| Day 2 | 2,218 (0–15,932) |
| Day 3 | 1,437 (0–19,184) |
| Day 4 | 1,521 (0–9,014) |
| Day 5 | 313 (0–11,915) |
| Day 6 | 2,425 (0–10,342) |
| Day 7 | 1,873 (0–19,452) |

## Diary to track motor complications

Twenty-nine participants (97%) returned their motor complication diaries, among these, two diaries could not be analysed (not legible) and were excluded from analysis; therefore data from 27 participants (90%) was analysed. Participants spent most of their time in the "ON" state during the monitoring period, with participants' median time in the "ON" state being 108 h, ranging from 56.5 to 112 h. Participants' median time in the "OFF" state was 2 h, ranging from 0 to 55.5 h, over the seven days monitored 19 out of 27 participants reported "OFF" periods. Participants' median time over which they reported dyskinesia was 0 h and ranged from 0 to 30.5 h, 10 out of 27 participants reported dyskinesia over the monitoring period.

Table 6 displays the time spent in each state from Day 1 to Day 7 in 27 participants for whom diary data could be analysed.

# Quantitative assessment of usability of the DHTS

Twenty-eight participants (93%) returned their usability questionnaires. Briefly, 82% of those who returned their questionnaires had little to no trouble getting started with the DHTS (Q1), 64% found the system easy to put on and take off (Q2), and 59% reported experiencing technical issues (Q3). Additionally, the DHTS did not interfere with normal activities in 89% of participants (Q4), with 93% of them felt comfortable wearing the DHTS (Q5), none of the participants felt embarrassed wearing the smartwatch (Q6), and over 68% of participants found that the instructions were clear and that the daily use of the DHTS was easy (Q7 and Q8). According to 75% of participants the system was not bulky or heavy (Q9). Eight percent of them felt that the DHTS bothered them in bed (Q10), and 7% of participants felt that their privacy was invaded by the DHTS (Q11). Finally, 43% of participants reported that they would be happy to wear the DHTS for over a week if their doctor asked them to, 43% of them reported that they would be happy to wear it for a week and the remaining ones less than a week (Q12).

Results of the usability questionnaire are presented in Figure 3.

The median overall usability score given to the DHTS was 80% and ranged from 10 to 100%, on a scale ranging from 0 (worst) to 100% (best score). Responses were ranked over 25% intervals, which showed that 61% of participants ($n = 17$) provided scores in the highest rank (score above 75%) and overall, 86% of participants ($n = 24$) found the DHTS usable (score 50% and above) (Figure 4).

A significant correlation was found between the overall usability score and participants' age ($\rho = -0.560$, $p = 0.002$,

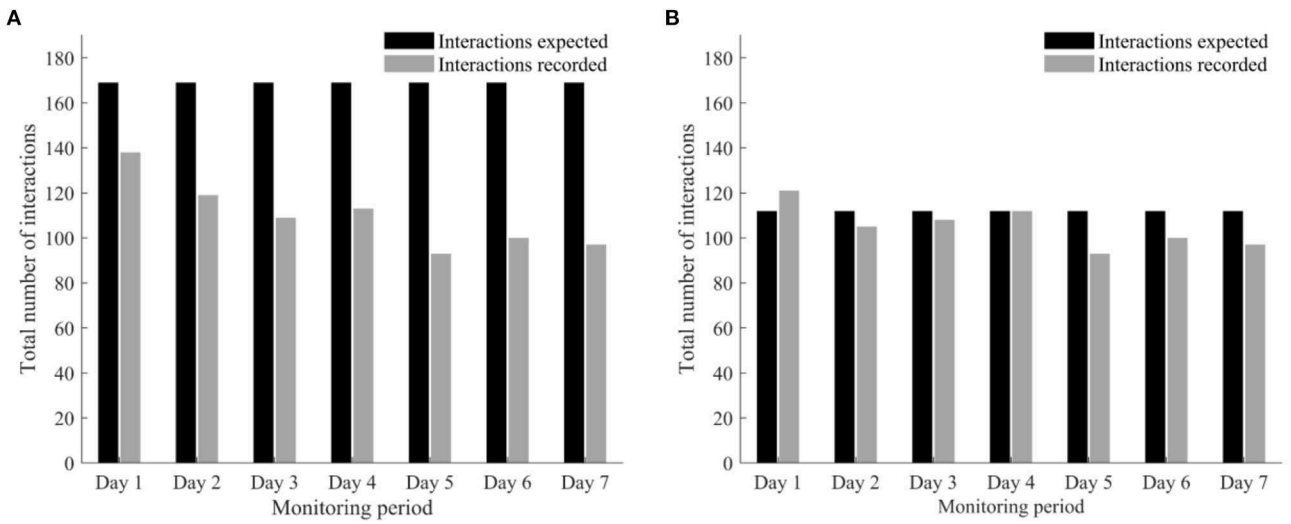


FIGURE 2
Bar chart representing the number of interactions with the smartwatch expected (black) vs. recorded (grey) per day for all 30 participants **(A)** and only the 22 participants who recorded medication intake for seven days **(B)**.

TABLE 6 Time (hours) in each medication state (ON, OFF, dyskinesia) recorded from the medication diary ($n = 27$).

| | ON | OFF | Dyskinesia |
|---|---|---|---|
| | Median (Min–Max) | Median (Min–Max) | Median (Min–Max) |
| Day 1 | 15.3 (8.5–16.0) | 0.5 (0.0–7.0) | 0.0 (0.0–3.5) |
| Day 2 | 15.5 (8.5–16.0) | 0.5 (0.0–7.5) | 0.0 (0.0–4.0) |
| Day 3 | 15.5 (6.5–16.0) | 0.3 (0.0–9.5) | 0.0 (0.0–5.0) |
| Day 4 | 15.5 (8.0–16.0) | 0.0 (0.0–8.0) | 0.0 (0.0–4.5) |
| Day 5 | 15.5 (6.5–16.0) | 0.0 (0.0–9.5) | 0.0 (0.0–5.5) |
| Day 6 | 15.5 (8.5–16.0) | 0.5 (0.0–7.5) | 0.0 (0.0–3.5) |
| Day 7 | 15.8 (8.5–16.0) | 0.3 (0.0–6.5) | 0.0 (0.0–4.5) |

BCa 95% CI [−0.791, −0.207]). A scatter plot of the significant correlation is presented in Figure 5; Table 7 shows all the correlation results.

## Qualitative assessment of feasibility and usability of the DHTS

Three themes (feasibility, usability, and acceptability) were identified from analysis of participants' feedback of the DHTS and individual devices (open text questions of the usability questionnaire). Responses to the questionnaire (classified into themes and subthemes) are presented in the Supplementary material 3.

### Feasibility

Feasibility comments were split into two sub-themes: technical and non-technical. Overall, most comments referred to technical issues with the smartwatch, especially concerning its expected function, with some participants reporting that notifications were not delivered at the correct time "*notifications sometimes late*." Two participants felt the notification vibrations were not strong enough to be felt "*couldn't feel the vibration*." Non-technical comments encompassed all the devices and reflected the overall satisfaction of participants. Commonly reported comments indicating no issues with feasibility included "*No problems*" and "*All good*."

### Usability

Usability was split into three sub-themes: ease of use, disease specific comments and requirement for external support. Usability comments generally reflected issues experienced with the IMU and smartwatch.

Ease of use comments generally concerned the IMU and smartwatch. Regarding the IMU, participants commented on whether they had to replace the attachment during the monitoring period. Most participants who commented on the usability of the IMU were satisfied by the product "*No maintenance! Okay in shower*," "*Easy to wear*," but one reported having to "*reapply twice during the 7 days*." Concerning the smartwatch, two participants found it easy to use, but three expressed their concern about how it is "*easy to get confused*" or the watch being "*over complicated*." Another participant provided mixed feedback, stating that it was "*Difficult to fasten and unfasten* [...] *Clear readable face. Easy to recharge*."

Disease specific comments related to the participants' tremors adversely influencing their capacity to interact with the smartwatch "*screen is quite small, especially hard with a tremor*" and to reach the IMU (i.e., on their lower back) "*needed help reapplying after showers as could not reach*." Linking with this, four participants required, or expressed the need for external support to reattach individual devices, "*tricky to attach without help*."

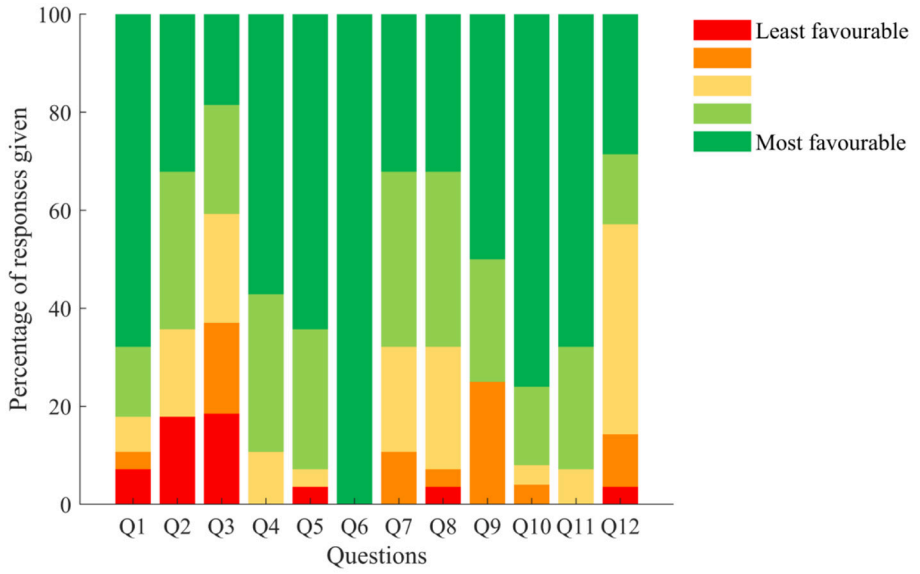


FIGURE 3
Responses given to the usability questionnaire (%). Q1: How much trouble did you have getting started with the wearable technology system? Q2: The wearable technology system was easy to put on/take off. Q3: I experienced technical problems with the wearable technology system. Q4: The wearable technology system interfered with my normal activities. Q5: I felt comfortable wearing the wearable technology system. Q6: I felt embarrassed wearing the wearable technology system. Q7: The instructions on how to use the wearable technology system were clear. Q8: Using the wearable technology system on a daily basis was easy. Q9: The wearable technology system was bulky/heavy. Q10: The wearable technology system bothered me in bed. Q11: I felt my privacy was invaded by the wearable technology system. Q12: If my doctor would like to use the wearable technology system to assess my activity and medication adherence I would be willing to wear it and use it for. Colour code from red (score = 1 for least favourable response) to green (score = 5 for most favourable response). For this questionnaire, the term "wearable technology system" refers to the DHTS.

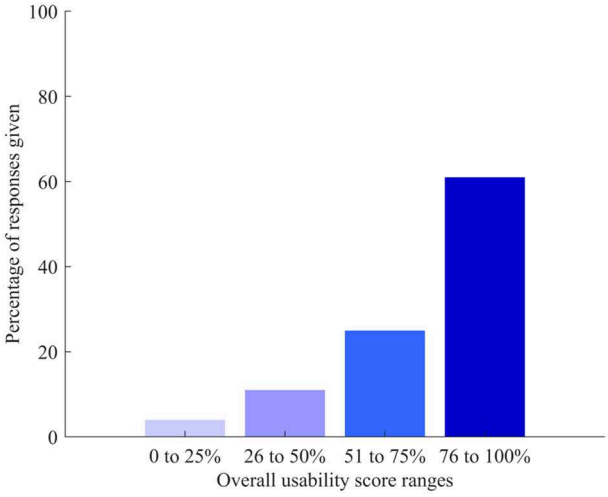


FIGURE 4
Ranges of overall score given to usability of the DHTS (from 0 worse to 100 best score).

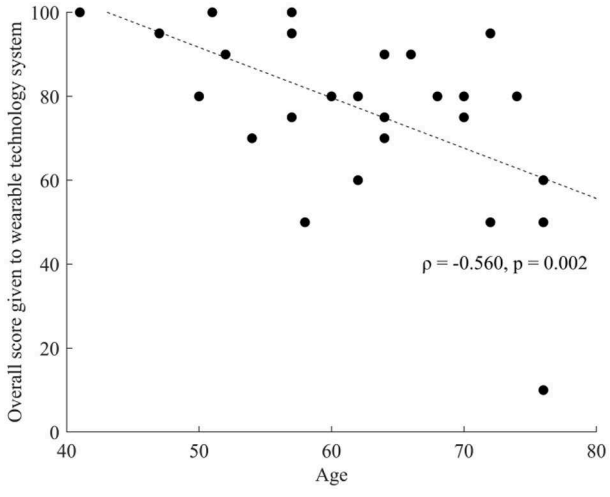


FIGURE 5
Spearman's rho correlation between overall usability score and age.

## Acceptability

Acceptability was split into four sub-themes: appearance, perception of the device, routine and wearability. Overall, the acceptability comments on the DHTS were positive, with the devices described as "*great to monitor people*" and "*ideal for use*."

Comments on appearance solely concerned the smartwatch and smartphone. Participants reported that the smartwatch was "*bulky*" or "*too large*" for their wrist. Two participants reported that the watch was "*nice looking*" and had a "*clear screen*." Concerning the smartphone, participants also found it "*a bit bulky*" and "*too big*" to be carried in a handbag or pocket. One participant commented

TABLE 7 Correlations between the overall usability score provided by participants on the DHTS in the usability questionnaire and demographic and clinical characteristics.

| Correlation with overall usability score | Spearman's rho | Sig. (*p*) | $\alpha$ | BCa 95%CI | |
|---|---|---|---|---|---|
| | | | | Lower boundary | Upper boundary |
| Age | **−0.560** | **0.002** | **<0.05** | **−0.791** | **−0.207** |
| Disease duration | −0.269 | 0.167 | <0.007 | −0.643 | 0.145 |
| Number of medication doses per day | −0.309 | 0.109 | <0.007 | −0.680 | 0.153 |
| SPPB score | 0.412 | 0.029 | <0.007 | 0.018 | 0.712 |
| MDS-UPDRS II | −0.218 | 0.266 | <0.007 | −0.536 | 0.193 |
| MDS-UPDRS III | 0.093 | 0.638 | <0.007 | −0.285 | 0.500 |
| Frailty phenotype | −0.224 | 0.251 | <0.007 | −0.582 | 0.142 |
| NFoG-Q | −0.259 | 0.184 | <0.007 | −0.581 | 0.144 |

Bold values are significant.

that the DHTS "*would be a very helpful piece of technology if watch was smaller*."

Concerning participants' perception of the devices, they liked that the IMU was "*waterproof*." The smartwatch was reported as "*handy*" and participants liked having a "*reminder to take medication*," one participant reported having invested in their own smartwatch as a result of the study: "*Seemed like a good idea as I regularly need an alarm reminder. I like the theory. Have invested in my own vibrating alarm watch*" and one participant felt that the notifications helped them realise that their medication "*ran out sooner*" "*No problems just made me realise my meds ran out sooner before next dose*." Concerning the smartphone, one participant reported that they "*Didn't feel any benefit from this device. A nuisance*."

Relative to the sub-theme of routine, many participants felt the IMU was "*small*" enough that it could be forgotten about. One participant reported no issues sleeping with the IMU device on "*No problem sleeping. Kept it on all week*." One participant reported having reservations before wearing it, but quickly forgot this once attached "*Had reservations before wearing it. However, after it was fitted, I soon forgot about it, and it was no trouble*." One participant felt that "*When working full-time it was annoying having to keep setting the watch*." Concerning the smartphone, two participants reported either forgetting to take their smartphone with them "*Ok I forgot to take it twice*" or that "*Having to remember to have it with me all the time was annoying*." In contrast, two participants reported that they were not concerned by having the smartphone with them "*I did not need to do anything with the phone other than have it with me all the time*," "*Most people carry a phone these days, so no problem for me*." Participants felt that overall, the DHTS "*didn't interfere with daily life too much*" and that it was "*quite easy to live with*," with "*little impact on day-to-day activities*."

Concerning wearability, many participants felt that the IMU was "*comfortable*" and "*unobtrusive*" although some reported occasional itching and skin irritation due to the adhesive. One participant reported that the smartwatch was the "*least comfortable*" device, and one that it was "*a bit big for me*," but two participants reported being overall satisfied "*Ok to wear*," "*Not heavy*" by the smartwatch. Three participants reported that the smartphone was "*too heavy*" or "*on the heavy side*." One participant reported that the overall system was "*Wearable for a week*" with another reporting that they had "*no problems wearing it*."

Overall, the DHTS was well accepted and usable, but technical issues with the smartwatch affected participants' opinion on the system. Re-analysis on the questionnaire and grouping of each question within the feasibility, usability and acceptability themes, showed that the DHTS was deemed acceptable and usable with 83 and 71% of participants responding with the 2 most favourable answers, respectively. Reflecting the responses given to Q3, only 41% of participants responded with the 2 most favourable answers to the feasibility question. Figure 6 shows the percentage of responses given for each theme.

## Discussion

This study aimed to provide evidence that a new multicomponent DHTS and a motor complications diary could monitor mobility and contextual factors, assess self-reported medication adherence and track motor complications in people with mild-moderate Parkinson's disease, and to identify potential means to improve the DHTS for future use. Results showed that the DHTS is both feasible and usable for remote monitoring of PwP, but the smartwatch was prone to technical issues making it the least feasible and usable component.

### Feasibility

For this feasibility study, the performance of the DHTS was not directly compared to other systems. However, previous research assessing the feasibility of a DHTS in PwP found a completion rate between 62 and 68% over 6 and 13 weeks, respectively, in people mostly scoring II on the Hoehn & Yahr scale (43). Therefore, as previously done by others over longer time periods (12 weeks) in people with a median Hoehn & Yahr score of II, a completion rate of 68% was used as feasibility threshold in the present study (44). Here, this threshold was exceeded for all devices which was expected as the monitoring period was much shorter. Specifically, 97 and 93% of the smartphone and IMU data was collected,

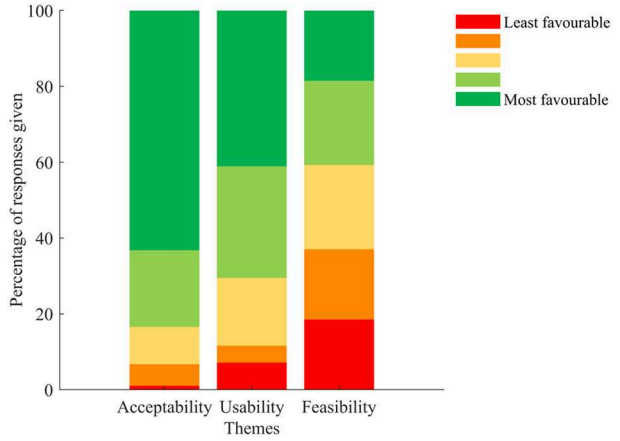


FIGURE 6
Percentage of responses given to the usability questionnaire classified according to the acceptability (Q4, Q5. Q6, Q9, Q10, Q11, and Q12), usability (Q1, Q2, Q7, and Q8), and feasibility (Q3) themes. Colour code from red (least favourable) to green (most favourable).

respectively, 90% of the motor complications diaries were legible, and 73% of participants reported medication intakes over the 7-day monitoring period. This last completion rate, although lower than that of the smartphone and IMU, remains in line or slightly higher than the compliance to a DHTS use measured over the first week by other authors (about 75% on Day 1 and down to about 65% after few days) (43). Therefore, this study showed that it is feasible to assess self-reported medication adherence and monitor mobility in PwP using this DHTS, and to track motor complications with the diary. However, participants experienced technical issues existed, particularly with the smartwatch, which reduced the feasibility of the DHTS to assess self-reported medication adherence. Importantly, some participants reported not receiving or feeling the smartwatch vibrations, or notifications being late. At this stage, it is difficult to evaluate whether these failures were due: to participants not noticing the vibration, possibly due to a disease related higher threshold to vibrations of the sensory system (45); to the vibration not being strong enough; or to technical failures, leading to notifications not being sent to and/or received by the smartwatch. To appropriately control motor symptoms and complications in PD, strict adherence to prescribed medication timing is crucial. Therefore, the late delivery of smartwatch notifications is a prominent issue that will need to be addressed before this smartwatch can be utilised in future work monitoring medication adherence in PD.

Contextual data (obtained from the smartphone) were missing for 23 days in total (11% of total number of days monitored). Out of these 23 days with missing contextual data, 21 days correspond to participants ($n = 6$) who stopped interacting with their smartwatch during the monitoring period. This may be due to participants forgetting to take the phone with them when leaving their home, and/or them not being aware of the importance of taking the phone with them when they leave their home. As contextual data was collected when the smartphone was on and movement was detected, even when they did not leave their home, missing data for the remaining 2 participants (1 day missing for each participant) may mean that the smartphone was turned off, either voluntarily or because it had run out of battery, and/or that the phone was not moved that day. This may be due to participants not endorsing the purpose or benefit of the device: exemplified in the questionnaire response "*Didn't feel any benefit from this device. A nuisance.*" This is supported by previous research on DHTS observing that older adults and PwP better adhere to device use when they understand their benefits (46, 47). Therefore, to improve participants' adherence to smartphone usage, research should emphasise to participants the importance and purpose of collecting contextual data using a smartphone when monitoring PD symptoms. As technology progresses and sensors reduce in size, we expect the smartwatch to collect contextual data independently and therefore the smartphone to become redundant, which would resolve this issue.

Finally, two diaries were not legible. One because the participant coloured the slots of the diary instead of differentiating between OFF-status or dyskinesia with an O or D, and one because the "O"s and "D"s were not distinguishable. Future work should utilise devices which distinguish between these medication phases. Although this is possible with the PKG (17), as previously stated, it is limited in other outcomes it can produce. Therefore, an optimal device should independently monitor motor symptoms and complications, mobility, contextual factors and self-reported medication adherence.

## Usability

Overall, participants in this study considered the DHTS usable, however the usability score given by participants was negatively correlated with age, indicating that younger adults felt more at ease using the DHTS. This may be a consequence of the lack of experience with DHT associated with advanced age (48), or a lack of confidence associated with handling new technology observed in older adults with PD (49). This suggests that participants may have benefitted from more practice time. No correlation was found between the overall usability score of the DHTS and clinical characteristics of participants. This is surprising since two participants reported having issues interacting with the IMU or smartwatch due to their tremor (see Supplementary material). These results may suggest that a larger and more diverse sample will be necessary to understand the usability of this DHTS in participants with more severe PD, impaired motor function and dexterity issues. Therefore, any attempt to assess self-reported medication adherence in participants with more advanced PD using this DHTS should be preceded by an appropriate usability study.

## Acceptability

Previous research highlighted that for a DHTS to be acceptable, it should, among others, be easy to wear and be aesthetically pleasing (9). Concerning wearability, many participants commented on the "bulky" nature of the smartwatch.

We received mixed feedback about the devices, particularly the smartwatch was considered "*too big*" and "*bulky*" by some participants but too small to use with a tremor by others. These findings follow previous research that suggests that wearable devices should be adjusted to individuals' needs and motor symptoms (49). Participants should therefore be offered a range of models between which they are free to choose based on personal preference. This would require careful study design to avoid variations in response due only to a specific choice of DHTS, but may encourage greater compliance, given active participation in model selection.

Forty-three percent of participants would be happy to wear the DHTS for a week and another 43% would be happy to wear it for over a week. This is lower than previously reported (36). In the present study, this was explored for the DHTS as a whole whereas it was investigated for individual devices in Rabinovich et al.'s study. Hence, the acceptability of the DHTS here was probably lowered by the issues experimented with the smartwatch. The COVID-19 pandemic highlighted the need for long-term remote monitoring of people with chronic disease, such as PD, therefore an independent feasibility study of longer duration would be required to apply these results for clinical management of PwP. Previous work (50) observed that the majority of participants with PD would not feel at ease wearing sensors, such as the Axivity sensor in public on visible body locations. Although our study did not specifically ask about wearing the devices in public, wearing a device for a week or longer would most probably involve wearing it in public, as participants in our study did. The greater acceptance of using our DHTS may result from our devices being small, and easily hidden by clothing. Additionally, although many participants in our study were willing to utilise the DHTS, previous studies have highlighted that they do not want this as a replacement for clinical consultations with participants often prioritising communication with their clinician (47, 49).

Despite utilising medical grade adhesive to secure the IMU, one participant stopped the trial due to skin irritations and three others reported mild symptoms of contact dermatitis (itchy skin or irritation) on the location of the IMU. Future work will include screening for history of allergy, skin reaction to adhesive, or skin condition that could be triggered by contact with adhesive (e.g., eczema) as exclusion criteria.

## Recommendations for improvement

This study was part of a larger project aiming to model motor symptoms and mobility in response to medication intake in PwP and has provided vital insights for the future. Firstly, technical issues (notifications received late, not received, or received more than once) with the smartwatch need to be addressed. To this aim, we will update the smartphone to the latest version of the android mobile operating system and upgrade the smartwatch to the most recent model, which may improve the timing of notification delivery. We could not identify why many expected interactions were missing ($n = 90$), or received multiple times ($n = 191$) with the current system. These might be due to a system failure, with either no notification or multiple ones being sent to, or received by, the smartwatch. The Aeqora application will be updated which should improve notification delivery. Alternatively, these missing or repeated interactions might be due to participants not acknowledging their medication intake or inputting the same intake several times. With the current system there were only two possible outcomes for medication intake, either "Yes" when participants acknowledged medication intake or "No" when participants acknowledged not taking their medication. We will add a "No interaction" outcome so that in the future we can distinguish whether participants received the notification but ignored it ("No interaction") or if the notification had not been sent to or received by the smartwatch (system error). In addition, participants may have received their notifications but not felt the watch vibration, possibly due to a higher sensory threshold (45). To minimise this potential risk of losing data, in the future, we will trial different notification types with participants and let them choose which pattern they better detect (vibration only, auditory alarm only, vibration and auditory alarm). Finally, we will add a "thank you" message confirming to participants that their input has been recorded which should prevent repeated inputs.

## Limitations

The present study utilised an indirect approach to assess medication intake which relies on participants self-reporting their intakes and may be considered less accurate than direct observation of intakes, or invasive and potentially expensive laboratory detection of the active substance (15). This indirect method was chosen because it is easily applicable to large cohorts, but it requires reliable interactions with the smartwatch which may be difficult to achieve for individuals with advanced PD and may be susceptible to active deception (i.e., participant choosing not to consume the medication whilst acknowledging its intake) (15). In the future to reduce this risk, our system could be associated with medication specific upper arm movement detection algorithms, such as those developed by other authors (51–53).

Improvements made to the smartwatch should improve both the feasibility and usability aspect of the DHTS but further work is needed to quantify the progress made. In the future, additional practice time will be scheduled to ensure participants have sufficient understanding of how to use the devices, and for technical issues to be identified and resolved.

This study presents data collected from a relatively small sample, which only included participants at stage I ($n = 1$) and II ($n = 29$) of the Hoehn and Yahr Scale. The majority of participants ($n = 16$) were classified as not frail (only four participants had two or more frailty characteristics), with little OFF-time (median time = 2 h) or dyskinesia periods (median time = 0 h) and did not have severe cognitive impairment (all participants scored $\geq$21/30 on the MoCA). Additionally, multimorbidity frequently coexists with PD (54), but this was not recorded in the present study. Furthermore, the sample was recruited from a regional movement disorder clinic with specialised PD expertise. Therefore, this study only reflects people in the early stages of the disease with mild to moderate motor and cognitive symptoms and findings cannot be generalised to the wider PD population. Hence, any attempt at utilising this DHTS with people in the later stage of the disease should be preceded by a feasibility study conducted with the

intended population. Similarly, this DHTS may not be adapted to the study of people in the very early stages of the disease (prodromal and Hoehn and Yahr stage I) as it may be seen as too constraining and of limited relevance to them if prescribed less complex medication regimens.

## Conclusion

This study demonstrated that assessing self-reported medication adherence, tracking motor complications, and monitoring mobility in people with mild-to-moderate Parkinson's disease are feasible using this novel DHTS and a motor complications diary. Analysis of questionnaire answers and qualitative feedback highlighted contrasting opinions on the DHTS's usability. Specifically, the IMU and smartphone were considered usable by most participants, but difficulties arose when interacting with the smartwatch due to technical issues, lack of familiarity with the system and motor symptoms (tremor). In the future, the DHTS will be improved to allow for more reliable monitoring of medication intakes, which should enhance our capacity to model motor symptoms, complications, and their fluctuation in response to medication intake. This will provide greater insights for clinicians to optimise complex medication regimens in individuals with PD, potentially improving their quality of life.

## Data availability statement

The datasets supporting the conclusions of this article can be made available by the corresponding author upon reasonable request.

## Ethics statement

The studies involving human participants were reviewed and approved by London—Westminster Research Ethics Committee (REC reference: 21/PR/0469). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

Study design: SDD, LA, AY, and LR. Data collection and pre-processing of the data: HB, PB, HH, and LA. Ethical approval, people with Parkinson's recruitment, and clinical oversight: SDD, HB, PB, HH, LA, AY, and LR. Data analysis, statistical analyses, and tables creation: HD, EP, and EB. Figures preparation and drafting of the manuscript: HD and EP. Data interpretation: HD, EP, LA, and SDD. Intellectual contribution: HD, EP, EB, HB, RMA, RD, JE, MN, FC, NI, JS, AY, LR, LA, and SDD. All authors have provided critical intellectual input during the revision of the manuscript, have reviewed the manuscript, and approved the submitted version.

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## Conflict of interest

FC was CEO and shareholder of Aeqora Ltd. McRoberts is the manufacturer of the DynaPort. MN and JE are employees of McRoberts. SDD reports consultancy activity with Hoffmann-La Roche Ltd outside of this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1111260/full#supplementary-material

# References


1. Armstrong MJ, Okun MS. Diagnosis and treatment of parkinson disease: a review. *JAMA*. (2020) 323:548–60. doi: 10.1001/jama.2019.22360

2. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. (2021) 397:2284–303. doi: 10.1016/S0140-6736(21)00218-X

3. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA*. (2014) 311:1670–83. doi: 10.1001/jama.2014.3654

4. Nyholm D, Stepien V. Levodopa fractionation in Parkinson's disease. *J Parkinsons Dis*. (2014) 4:89–96. doi: 10.3233/JPD-130244

5. Poewe W, Antonini A, Zijlmans JC, Burkhard PR, Vingerhoets F. Levodopa in the treatment of Parkinson's disease: an old drug still going strong. *Clin Interv Aging*. (2010) 5:229–38. doi: 10.2147/CIA.S6456

6. Straka I, Minár M, Škorvánek M, Grofik M, Danterová K, Benetin J, et al. Adherence to pharmacotherapy in patients with Parkinson's disease taking three and more daily doses of medication. *Front Neurol*. (2019) 10:799. doi: 10.3389/fneur.2019.00799

7. Fasano A, Antonini A, Katzenschlager R, Krack P, Odin P, Evans AH, et al. Management of advanced therapies in parkinson's disease patients in times of humanitarian crisis: the COVID-19 experience. *Mov Disord Clin Pract*. (2020) 7:361–72. doi: 10.1002/mdc3.12965

8. Soilemezi D, Roberts HC, Navarta-Sánchez MV, Kunkel D, Ewings S, Reidy C, et al. Managing Parkinson's during the COVID-19 pandemic: perspectives from people living with Parkinson's and health professionals. *J Clin Nurs*. (2022) 17:1637. doi: 10.1111/jocn.16367

9. Keogh A, Taraldsen K, Caulfield B, Vereijken B. It's not about the capture, it's about what we can learn": a qualitative study of experts' opinions and experiences regarding the use of wearable sensors to measure gait and physical activity. *J Neuroeng Rehabil*. (2021) 18:78. doi: 10.1186/s12984-021-00874-8

10. Del Din S, Godfrey A, Rochester L. Validation of an accelerometer to quantify a comprehensive battery of gait characteristics in healthy older adults and Parkinson's disease: toward clinical and at home use. *IEEE J Biomed Health Inform*. (2016) 20:838–47. doi: 10.1109/JBHI.2015.2419317

11. Del Din S, Elshehabi M, Galna B, Hobert MA, Warmerdam E, Suenkel U, et al. Gait analysis with wearables predicts conversion to parkinson disease. *Ann Neurol*. (2019) 86:357–67. doi: 10.1002/ana.25548

12. Del Din S, Galna B, Godfrey A, Bekkers EM, Pelosin E, Nieuwhof F, et al. Analysis of free-living gait in older adults with and without Parkinson's disease and with and without a history of falls: identifying generic and disease-specific characteristics. *J Gerontol A Biol Sci Med Sci*. (2019) 74:500–6. doi: 10.1093/gerona/glx254

13. Del Din S, Godfrey A, Galna B, Lord S, Rochester L. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. *J Neuroeng Rehabil*. (2016) 13:46. doi: 10.1186/s12984-016-0154-5

14. Roth N, Wieland GP, Küderle A, Ullrich M, Gladow T, Marxreiter F, et al. Do we walk differently at home? A context-aware gait analysis system in continuous real-world environments .*IEEE*. (2021) 43:1932–5. doi: 10.1109/EMBC46164.2021.9630378

15. Aldeer M, Javanmard M, Martin RP, A. review of medication adherence monitoring technologies. *Appl Syst Innov*. (2018) 1:14. doi: 10.3390/asi1020014

16. Aungst TD, Franzese C, Kim Y. Digital health implications for clinical pharmacists services: a primer on the current landscape and future concerns. *J Am Coll Clin Pharm*. (2021) 4:514–24. doi: 10.1002/jac5.1382

17. Joshi R, Bronstein JM, Keener A, Alcazar J, Yang DD, Joshi M, et al. PKG movement recording system use shows promise in routine clinical care of patients with Parkinson's disease. *Front Neurol*. (2019) 10:1027. doi: 10.3389/fneur.2019.01027

18. World Health Organization. *Monitoring and Evaluating Digital Health Interventions: A Practical Guide to Conducting Research and Assessment*. Geneva: Worl Health Organization (2016).

19. Keogh A, Argent R, Anderson A, Caulfield B, Johnston W. Assessing the usability of wearable devices to measure gait and physical activity in chronic conditions: a systematic review. *J Neuroeng Rehabil*. (2021) 18:138. doi: 10.1186/s12984-021-00931-2

20. Manta C, Mahadevan N, Bakker J, Irmak SO, Izmailova E, Park S, et al. EVIDENCE publication checklist for studies evaluating connected sensor technologies: explanation and elaboration. *Dig Biomark*. (2021) 5:127–47. doi: 10.1159/000515835

21. Mikolaizak AS, Rochester L, Maetzler W, Sharrack B, Demeyer H, Mazzà C, et al. Connecting real-world digital mobility assessment to clinical outcomes for regulatory and clinical endorsement-the Mobilise-D study protocol. *PLoS ONE*. (2022) 17:e0269615. doi: 10.1371/journal.pone.0269615

22. COSMIN. *COnsensus-Based Standards for the Selection of Health Measurement INstruments*. Moldavia: COSMIN. Available online at: https://www.cosmin.nl/ (accessed November 23, 2022).

23. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent*. (2014) 81:14–8. doi: 10.1001/jama.2013.281053

24. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424

25. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Ser A*. (2001) 56:M146–57. doi: 10.1093/gerona/56.3.M146

26. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movem Disord*. (2008) 23:2129–70. doi: 10.1002/mds.22340

27. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. (1994) 49:M85–94.

28. Hoehn MM, Yahr MD. Parkinsonism. *Neurology*. (1967) 17:427.

29. Jette AM, Haley SM, Coster WJ, Kooyoomjian JT, Levenson S, Heeren T, et al. Late life function and disability instrument: I. Development and evaluation of the disability component. *J Gerontol Ser A*. (2002) 57:M209–16. doi: 10.1093/gerona/57.4.M209

30. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriat Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x

31. Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture*. (2009) 30:459–63. doi: 10.1016/j.gaitpost.2009.07.108

32. Schade S, Mollenhauer B, Trenkwalder C. Levodopa equivalent dose conversion factors: an updated proposal including opicapone and safinamide. *Mov Disord Clin Pract*. (2020) 7:343–5. doi: 10.1002/mdc3.12921

33. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movem Disord*. (2010) 25:2649–53. doi: 10.1002/mds.23429

34. Ciravegna F, Gao J, Ireson N, Copeland R, Walsh J, Lanfranchi V. Active 10: Brisk Walking to Support Regular Physical Activity. In: *13th EAI International Conference on Pervasive Computing Technologies for Healthcare*. Trento: Association for Computing Machinery (2019). doi: 10.1145/3329189.3329208

35. Marcianò V, Bertuletti S, Bonci T, Mazzà C, Ireson N, Ciravegna F, et al. A deep learning model to discern indoor from outdoor environments based on data recorded by a tri-axial digital magnetic sensor. *Gait Posture*. (2022) 97:5. doi: 10.1016/j.gaitpost.2022.09.015

36. Rabinovich RA, Louvaris Z, Raste Y, Langer D, Van Remoortel H, Giavedoni S, et al. Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J*. (2013) 42:1205–15. doi: 10.1183/09031936.00134312

37. Hickey A, Del Din S, Rochester L, Godfrey A. Detecting free-living steps and walking bouts: validating an algorithm for macro gait analysis. *Physiol Measur*. (2017) 38:N1. doi: 10.1088/1361-6579/38/1/N1

38. Hiden H, Woodman S, Watson P, Cala J. Developing cloud applications using the e-Science Central platform. *Philos Trans A Math Phys Eng Sci*. (2013) 371:20120085. doi: 10.1098/rsta.2012.0085

39. Wright DB, London K, Field AP. Using bootstrap estimation and the plug-in principle for clinical psychology data. *J Exp Psychopathol*. (2011) 2:252–70. doi: 10.5127/jep.013611

40. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol*. (2013) 13:117. doi: 10.1186/1471-2288-13-117

41. Keogh A, Dorn JF, Walsh L, Calvo F, Caulfield B. Comparing the usability and acceptability of wearable sensors among older irish adults in a real-world context: observational study. *JMIR Mhealth Uhealth*. (2020) 8:e15704. doi: 10.2196/15704

42. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ Br Med J*. (2013) 347:f6753. doi: 10.1136/bmj.f6753

43. Silva de Lima AL, Hahn T, Evers LJ, De Vries NM, Cohen E, Afek M, et al. Feasibility of large-scale deployment of multiple wearable sensors in Parkinson's disease. *PLoS ONE*. (2017) 12:e0189161. doi: 10.1371/journal.pone.0189161

44. Bendig J, Wolf AS, Mark T, Frank A, Mathiebe J, Scheibe M, et al. Feasibility of a multimodal telemedical intervention for patients with parkinson's disease: a pilot study. *J Clin Med*. (2022) 11:1074. doi: 10.3390/jcm11041074

45. Nolano M, Provitera V, Estraneo A, Selim MM, Caporaso G, Stancanelli A, et al. Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. *Brain.* (2008) 131:1903–11. doi: 10.1093/brain/awn102

46. Moore K, O'Shea E, Kenny L, Barton J, Tedesco S, Sica M, et al. Older adults' experiences with using wearable devices: qualitative systematic review and meta-synthesis. *JMIR mHealth uHealth.* (2021) 9:e23832. doi: 10.2196/23832

47. Ozanne A, Johansson D, Hällgren Graneheim U, Malmgren K, Bergquist F, Alt Murphy M. Wearables in epilepsy and Parkinson's disease: a focus group study. *Acta Neurol Scand.* (2018) 137:188–94. doi: 10.1111/ane.12798

48. Kekade S, Hseieh CH, Islam MM, Atique S, Khalfan AM Li YC, et al. The usefulness and actual use of wearable devices among the elderly population. *Comput Methods Prog Biomed.* (2018) 153:137–59. doi: 10.1016/j.cmpb.2017.10.008

49. Kenny L, Moore K, O'Riordan C, Fox S, Barton J, Tedesco S, et al. The views and needs of people with Parkinson disease regarding wearable devices for disease monitoring: mixed methods exploration. *JMIR Format Res.* (2022) 6:e27418. doi: 10.2196/27418

50. Botros A, Schütz N, Camenzind M, Urwyler P, Bolliger D, Vanbellingen T, et al. Long-term home-monitoring sensor technology in patients with Parkinson's disease: acceptance and adherence. *Sensors.* (2019) 19:5169. doi: 10.3390/s19235169

51. Chen C, Kehtarnavaz N, Jafari R, A. medication adherence monitoring system for pill bottles based on a wearable inertial sensor. *Annu Int Conf IEEE Eng Med Biol Soc.* (2014) 2014:4983–6. doi: 10.1109/EMBC.2014.6944743

52. Kalantarian H, Alshurafa N, Sarrafzadeh M. Detection of gestures associated with medication adherence using smartwatch-based inertial sensors. *IEEE Sens.* (2016) 16:1054–61. doi: 10.1109/JSEN.2015.2497279

53. Wang R, Sitová Z, Jia X, He X, Abramson T, Gasti P, et al. Automatic identification of solid-phase medication intake using wireless wearable accelerometers. *Annu Int Conf IEEE Eng Med Biol Soc.* (2014) 2014:4 168–71. doi: 10.1109/EMBC.2014.6944542

54. Tenison E, Henderson EJ. Multimorbidity and frailty: tackling complexity in Parkinson's disease. *J Parkinsons Dis.* (2020) 10:S85–s91. doi: 10.3233/JPD-202105

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# Need for personalized monitoring of Parkinson's disease: the perspectives of patients and specialized healthcare providers

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**Background:** Digital tools such as wearable sensors may help to monitor Parkinson's disease (PD) in daily life. To optimally achieve the expected benefits, such as personized care and improved self-management, it is essential to understand the perspective of both patients and the healthcare providers.

**Objectives:** We identified the motivations for and barriers against monitoring PD symptoms among PD patients and healthcare providers. We also investigated which aspects of PD were considered most important to monitor in daily life, and which benefits and limitations of wearable sensors were expected.

**Methods:** Online questionnaires were completed by 434 PD patients and 166 healthcare providers who were specialized in PD care (86 physiotherapists, 55 nurses, and 25 neurologists). To gain further understanding in the main findings, we subsequently conducted homogeneous focus groups with patients ($n$ =14), physiotherapists ($n$ =5), and nurses ($n$ =6), as well as individual interviews with neurologists ($n$ =5).

**Results:** One third of the patients had monitored their PD symptoms in the past year, most commonly using a paper diary. Key motivations were: (1) discuss findings with healthcare providers, (2) obtain insight in the effect of medication and other treatments, and (3) follow the progression of the disease. Key barriers were: (1) not wanting to focus too much on having PD, (2) symptoms being relatively stable, and (3) lacking an easy-to-use tool. Prioritized symptoms of interest differed between patients and healthcare providers; patients gave a higher priority to fatigue, problems with fine motor movements and tremor, whereas professionals more frequently prioritized balance, freezing and hallucinations. Although both patients and healthcare providers were generally positive about the potential of wearable sensors for monitoring PD symptoms, the expected benefits and limitations varied considerably between groups and within the patient group.

**Conclusion:** This study provides detailed information about the perspectives of patients, physiotherapists, nurses and neurologists on the merits of monitoring PD in daily life. The identified priorities differed considerably between patients and professionals, and this information is critical when defining the development and research agenda for the coming years. We also noted considerable differences in priorities between individual patients, highlighting the need for personalized disease monitoring.

KEYWORDS

Parkinson's disease, remote monitoring, self-monitoring, wearable sensors, personalized care, disease monitoring

# 1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease with complex clinical presentation (1, 2). Patients may experience motor symptoms such as bradykinesia, rigidity, tremor and balance impairments, but also a wide range of non-motor symptoms, such as mood changes, cognitive decline, pain and sleep disturbance, and side effects of medication such as dyskinesia. Symptoms can differ considerably between patients, and both the nature and the impact of symptoms can vary markedly throughout the course of the disease (3). In current clinical practice, we mainly use self-reports (history taking, sometimes supplemented by diaries) and in-clinic observations to monitor the presence and severity of symptoms, as well as the response to treatment. These episodic assessments do not always provide a representative and complete picture of the patient's actual functioning in daily life, for example due to recall bias (4) and observer effects (5). Remote monitoring tools such as wearable sensors may partly fill this gap and provide opportunities for personalized care, telemedicine and improved self-management (6, 7).

To deliver on these promises, it is essential that such tools address specific needs experienced by PD patients and their healthcare providers. This requires a thorough understanding of the diverse perspectives on symptom monitoring and wearable sensors of all stakeholders involved (8). PD patients vary in terms of experienced symptoms, but also with regard to coping strategies and personal treatment goals (9). Moreover, professionals from multiple disciplines can be involved in PD care, including neurologists, physiotherapists, nurses, speech therapists, general practitioners and many others, with each discipline focusing on different aspects (10). Our current understanding of the motivations and barriers for symptom monitoring of PD and for using wearable sensors is fragmented, and the focus has thus far mainly been on the perspective of patients (11, 12).

Because health monitoring behavior is not limited to patients, some useful insights can be obtained from studies in the general population. Using a survey among 150 self-trackers, five different motivations for self-tracking were identified, consisting of self-design (possibilities of self-optimization), self-discipline (self-gratification possibilities), and self-healing (independence of traditional medical treatment), self-entertainment (pleasure-bringing aspects), and self-association (sharing results with others and being part of a community) (13). This framework has not yet been evaluated in PD patients, but other studies have shown that specific motivations of PD patients with experience in self-tracking include the desire to better understand their disease, understand the effects of medication intake, and share information with healthcare providers (11, 12). The symptoms of interest among patients varied between studies, often including slowness of movements, tremor, stiffness, lack of energy, and sleep (11, 12, 14). In these studies, the barriers among patients who did not engage in self-tracking activities (36 to 51%) were not investigated. A better understanding of experienced barriers could provide useful strategies to engage and support these patients as well, and offer useful insights in the potential (and limitations) of monitoring tools such as wearable sensors.

The perspective of different PD healthcare providers on symptom monitoring, and how this relates to the perspective of patients has received little attention so far. Studies on symptom monitoring in PD that included healthcare providers did not differentiate between different disciplines (i.e., neurologists, physiotherapists, etc.) (14, 15), or aimed to reach consensus between healthcare providers and patients (14). We approach the problem from a different angle, and hypothesize that the different groups may represent unique needs, potentially requiring different solutions.

The aim of this study is to provide insights that can fuel the development of remote monitoring tools that address specific needs experienced by patients and/or healthcare providers. Specifically, our objectives were to identify the motivations for and barriers to monitoring PD symptoms, and to better understand the expected benefits and limitations of wearable sensors. In addition, we aimed to assess which aspects of PD are considered most important to be monitored in daily life. Finally, we aimed to compare the perspectives of PD patients and healthcare providers specialized in PD (physiotherapists, nurses, and neurologists).

# 2. Methods

## 2.1. Study design

We used a two-phase, explanatory mixed method design, consisting of online surveys, and subsequent homogeneous focus groups and interviews among the different stakeholders to gain further understanding in the domains of interest that were identified in the preceding surveys (16, 17). We focus on the perspective of PD patients, as well as that of healthcare providers that are most frequently involved in PD care in the Netherlands, i.e., neurologists, physiotherapists and Parkinson nurses. The study was approved by the local medical ethics committee (Commissie Mensgebonden Onderzoek, regio Arnhem-Nijmegen; file number 2015–1776). All participants provided informed consent prior to participation.

## 2.2. Participants

Seven hundred and eleven persons with PD were invited by email to participate in the online survey. All invitees were on the waiting list to be included in the Parkinson@Home study (18). Various recruitment strategies were used, including advertisements in the Dutch Parkinson Patient Association magazine and on social media, visits to support groups, and through physiotherapists specialized in PD care. Inclusion criteria were broad; participants were only asked

TABLE 1 Characteristics of the early PD (<6 years since diagnosis) and late PD (≥6 years since diagnosis) groups.

| | Early PD patients (*n* =207) | Late PD patients (*n* =222) |
|---|---|---|
| Age (years), mean (SD) | 67.3 (8.6) | 69.1 (8.1) |
| Gender (men), *n* (%) | 146 (71%) | 136 (61%) |
| Use of PD medication (% yes) | 201 (97%) | 221 (99%) |
| Time since diagnosis of PD (years), mean (SD) | 3.8 (1.5) | 12.6 (7.3) |
| Healthcare providers seen in past year for PD (% yes) | | |
| Neurologist | 204 (99%) | 215 (97%) |
| Physiotherapist | 161 (78%) | 189 (85%) |
| Parkinson nurse | 143 (69%) | 164 (74%) |
| General practitioner | 80 (39%) | 95 (43%) |
| Occupational therapist | 45 (22%) | 56 (25%) |
| Speech therapist | 51 (25%) | 44 (20%) |
| Dietitian | 20 (10%) | 32 (14%) |
| Other (including psychologist, revalidation specialist, neurosurgeon) | 32 (16%) | 40 (18%) |

PD, Parkinson's disease; SD, standard deviation.

to confirm that they were diagnosed with PD by a neurologist at the start of the survey. At the end of the survey, participants were invited to participate in subsequent focus groups.

We also included healthcare providers who were specialized in PD care. We chose to focus on the perspectives of neurologists, physiotherapists and Parkinson nurses, because the survey among patients showed that these healthcare providers are most frequently involved in PD care in the Netherlands (Table 1). To ensure that all included healthcare providers had sufficient experience in PD care, we only included members of the Dutch ParkinsonNet, a nationwide network of healthcare professionals who have received dedicated training in managing persons with PD (19). The invitations for the online survey were sent by email to 85 neurologists, 156 physiotherapists and 163 nurses. Participants for the focus groups and interviews with healthcare providers were recruited from the responses to the survey and *via* ParkinsonNet.

## 2.3. Survey development

We developed two surveys: one for patients and one for healthcare providers. The surveys consisted of a combination of validated questionnaires and custom-developed questions, on the following domains: current use of monitoring tools, motivations for and barriers to monitoring PD, relevant aspects to monitor, and expected benefits and limitations of wearable sensors for monitoring PD.

First, the surveys addressed the participants' experience with symptom monitoring, including the use of PD monitoring tools. Among patients, we assessed motivations for and barriers to self-monitoring PD symptoms using open-ended questions, and using the validated 19-item motivations for self-tracking scale (13). This scale consists of 19 items answered on a Likert scale ranging from 0 ("disagree strongly") to 4 ("agree strongly"). A five-factor structure was identified by the developers, consisting of self-entertainment (five items, e.g., "I enjoy getting lost in totally in self-tracking activities"), self-association (four items, e.g., "I want to help/inspire others"), self-design (five items, e.g., "I want to control what I am doing with my life,") self-discipline (three items, e.g., "It motivates me to keep on working for a goal"), and self-healing (two items, e.g., "I do not trust the healthcare system/classic therapies"). Next, we asked both patients and healthcare providers to indicate which symptoms, and which factors that influence symptoms, they found most useful to monitor in daily life. Participants were instructed to select a top 3 from a predefined list. The symptom list was based on the Non-Motor Symptom Questionnaire (NMS-Quest) (20) and the MDS-UPDRS part II, with some additions from the patient survey used by Mathur et al. (11). All items were phrased in understandable language, and medical terms for symptoms were avoided as much as possible. To facilitate the comparison, the items were identical between the patient and healthcare provider surveys. For patients, the items were personalized according to which symptoms they had ever experienced. To assess which factors explained the selection of specific symptoms, patients were also asked to make a top 3 of the most troublesome and a top 3 of the most strongly fluctuating symptoms. Finally, we explored the interest of healthcare providers in wearable sensors, including the expected benefits and limitations of this technology, using a combination of open- and closed-ended questions.

To assess whether participants could understand the questions and formulate appropriate answers, we performed cognitive interviews prior to deployment (21). These interviews were conducted face-to-face or by telephone, with five PD patients and four healthcare providers (two physiotherapists, one nurse, and one neurologist). During each session the assessor asked the participant to complete the draft survey, and to think out loud while doing so. Based on the assessor's observations and the feedback from participants, we updated the survey after each session, until all questions were correctly understood.

The surveys were implemented using SurveyGizmo[1], which allowed for the inclusion of advanced functionalities such as personalized drag-and-drop lists. The required completion time was approximately 30 min. The full surveys can be found in Appendix A.

## 2.4. Survey analysis

All data were analyzed separately for each stakeholder group. Persons with PD were divided into early (≤5 years since diagnosis) and late PD groups (>5 years since diagnosis) (3). All answers to open-ended questions were analyzed using thematic analysis with inductive coding (17). Quantitative outcomes were analyzed using descriptive statistics. Specifically, from the responses to the motivations for self-tracking scale, we calculated subtotals according to the identified five-factor structure (13). For each symptom, and for each factor that influences symptoms, we determined the percentage of participants who selected the item for their top 3. To examine differences between

1 www.surveygizmo.com

patients and healthcare providers, the average percentages of patients (early and late PD) were compared with the average percentages of healthcare providers (neurologists, physiotherapists and nurses). To assess which factors explained the patients' selected three most important symptoms to monitor, we examined the correlation with the selected three most troublesome and three most strongly fluctuating symptoms (using Spearman's ρ, applied to the percentages). We performed the quantitative analyses using SPSS (version 22.0), and we used Atlas.Ti (version 8.2.29) to support the qualitative analyses.

## 2.5. Design of focus groups and individual interviews

To gain a deeper understanding of the results of the survey and collect illustrative examples, we conducted homogeneous, semi-structured focus group discussions; two groups were organized with persons with PD, one group with physiotherapists specialized in PD, and one group with Parkinson nurses. We opted for focus groups because we expected that a group setting would stimulate further discussion about items that were considered relevant by more than one group member (22). The choice for *homogeneous* focus groups matches our hypothesis that the different stakeholders represent unique needs, which may require different solutions (i.e., the goal was not to reach consensus between the different groups). For logistical reasons, we conducted individual, semi-structured interviews with five neurologists. Because the goal of the focus groups and interviews was to further explore the findings of the surveys, we did not aim for data saturation.

The Value Proposition Canvas, a framework for matching proposed solutions to experienced needs (23), was used to develop the topic guide. Participants were invited to share their views regarding the following general themes: (1) goals participants wanted to achieve by monitoring symptoms, (2) experienced challenges ("pains") and benefits ("gains") of currently used monitoring tools, (3) potential advantages and limitations of wearable sensors, and (4) what the ideal tool to monitor PD in daily life would look like. These themes were discussed within a specific domain of interest, which varied per stakeholder group, and was based on the most important symptoms and motivations identified by the surveys. The full interview guides can be found in Appendix B.

## 2.6. Analysis of focus groups and interviews

All focus groups and interviews were audio recorded and transcribed verbatim. One researcher coded the transcripts using the four themes of the topic guide as pre-defined framework. Within these general themes, thematic analysis based on inductive coding was used. A second, independent researcher commented on the codes to improve their validity. In case of disagreement, the researchers discussed their interpretation of the codes until consensus was reached. Atlas.Ti (version 8.2.29) was used to facilitate the qualitative analysis.

# 3. Results

We will first discuss the results of the online surveys, including the current use of monitoring tools, motivations and barriers for monitoring PD, the most important PD aspects to monitor, and the expected benefits of wearable sensors for monitoring PD. Then we will zoom into different promising contexts for using wearables sensors for each group, discussing the theme's emerging from the analysis of the focus groups and interviews. Finally, we present expected barriers of wearable sensors, identified in the surveys, focus groups and interviews combined.

The online surveys were completed by 429 PD patients (response rate 60%), 86 physiotherapists (response rate 55%), 55 nurses (response rate 34%) and 25 neurologists (response rate 29%). The background characteristics of the included PD patients are shown in Table 1. From the participating healthcare providers, 96% of the neurologists, 94% of the nurses and 78% of the physiotherapists treated at least 10 individual PD patients per year, most often more than 15 PD patients. The remaining healthcare providers, except for one nurse, treated at least five individual PD patients annually.

## 3.1. Use of monitoring tools (survey)

Approximately one third of the patients had tracked their PD symptoms during the previous year, with no differences between early PD (33, 95% CI: 27–40%) and late PD (34, 95% CI: 28–41%). Most healthcare providers used self-collected information from patients; almost all specialized nurses (94%) recommended at least some of their patients to record the course of symptoms, versus 80% of physiotherapists, and 68% of neurologists. Various modalities of paper diaries were the most frequently used tools among all patient and healthcare provider groups (range: 62–96%). Common examples included free notes, on/off state diaries and falls diaries. The use of digital tools was less prevalent; 14% of patients who monitored their PD used a website [most often the "Parkinson's Well-Being Map" (24)], 12% used a smartphone or tablet (e.g., digital notes or apps for tracking physical activity), and only 4% of all patients had used a monitoring device or sensor [e.g., Parkinson KinetiGraph (25) or activity tracker] to monitor their PD during the previous year. Differences in tracking tools between early and late PD were negligible. The use of digital tools among healthcare providers was more prevalent: 24% of the neurologists, 23% of the nurses, and 10% of the physiotherapists who recommended their patients to keep track of their symptoms, had already used a wearable sensor in their clinical practice (e.g., Parkinson KinetiGraph or activity tracker). Moreover, 42% of nurses, 24% of neurologists, and 16% of physiotherapists recommended a symptom tracking website such as the "Parkinson's Well-Being Map."

## 3.2. Motivations and barriers for self-monitoring (survey)

Among patients who tracked their PD symptoms during the previous year ($n = 145$), we identified various themes describing their motivations to do so (Figure 1). To support the communication with healthcare providers was frequently mentioned by both early and late PD patients. One patient wrote: *"I do it to have an overview of the increase/decrease of complaints for the neurologist and Parkinson nurse."* Obtaining insights in the effect of medication and other treatments was another important motivation for many patients: *"To gain insight*

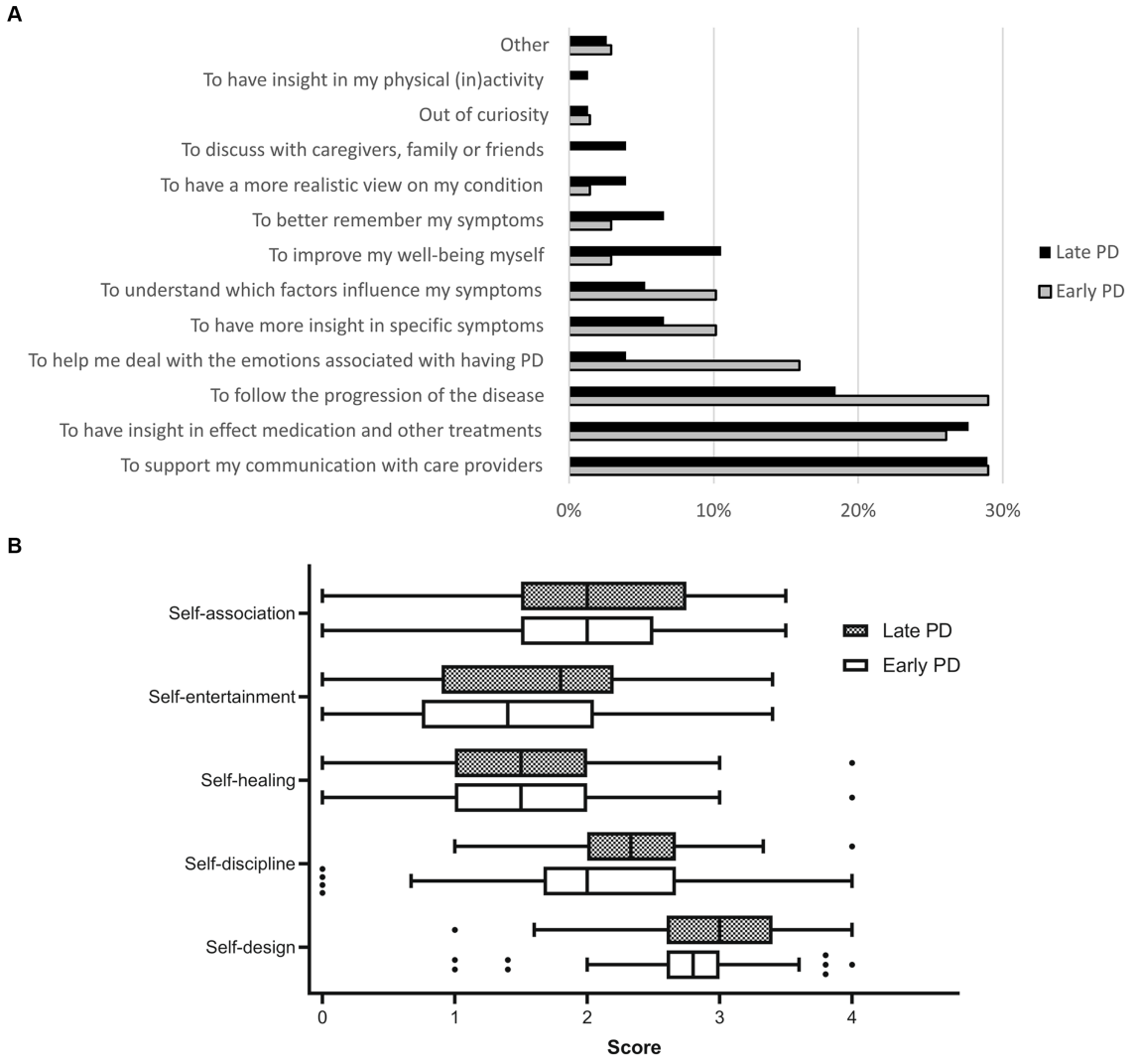


FIGURE 1
**(A)** Motivations for self-monitoring PD among early PD ($n$ =69) and late PD patients ($n$ =76) who had tracked their PD symptoms during the previous year. Presented categories are based on thematic analysis of open-ended responses to the online patient survey. **(B)** Motivations for self-monitoring among early PD ($n$ =67, 2 missing values) and late PD patients ($n$ =69, 7 missing values) who kept track of their PD symptoms during the previous year, based on five factors of the motivations for self-tracking scale. We show the distribution (median, 25th percentile, 75th percentile and range) of each patient's average score of all relevant items (0: "disagree strongly," 4: "agree strongly"; all items were phrased positively).

*into the efficacy of medications! Especially the variation between on and off moments was difficult to measure!,"* and *"I have kept track of relevant items since the start, now 13 years. Therefore I can see the influence of actions taken."* More prevalent motivations in the early PD group were (1) following the disease progression over longer time periods (*"To better interpret any decline over a longer time period, and use this to have a potential prognosis, to be able to anticipate on supportive measures"*), and (2) dealing with the emotions associated with having PD (*"To keep having control on the disease, and to deal with it as well as possible"*). Motivations mentioned more often by the late PD group were (1) to better remember symptoms (*"because you cannot remember the many complaints that you come across during the day"*), and (2) to be able to undertake actions yourself to improve your well-being (*"The goal was to split my day into energy blocks, so I can do the most difficult activities during the hours with the most energy,"* and *"to limit the use of medications as much as possible"*).

On the "motivations for self-tracking" scale, both early and late PD patients scored highest on the self-design dimension (the possibilities of self-optimization), whereas self-healing (independence of traditional medical treatment) and self-entertainment (the pleasure-bringing aspects) were the least important motivations at the group level. On most dimensions, considerable variation was observed between patients (Figure 2).

Among patients who had not tracked their PD symptoms during the previous year (early PD: $n$ = 138, late PD: $n$ = 146), we identified various themes describing reasons for this (Figure 3). The desire not to focus too much on having PD was an important barrier for many early and late PD patients. Different patients wrote: *"I do not want to become mister Parkinson,"* *"The tide cannot be turned. I rather look at the positive experiences that I would not have had without Parkinson. Such as new social contacts and friendships through volunteer work, and contact with children and grandchildren as babysit,"* and *"Confrontation*

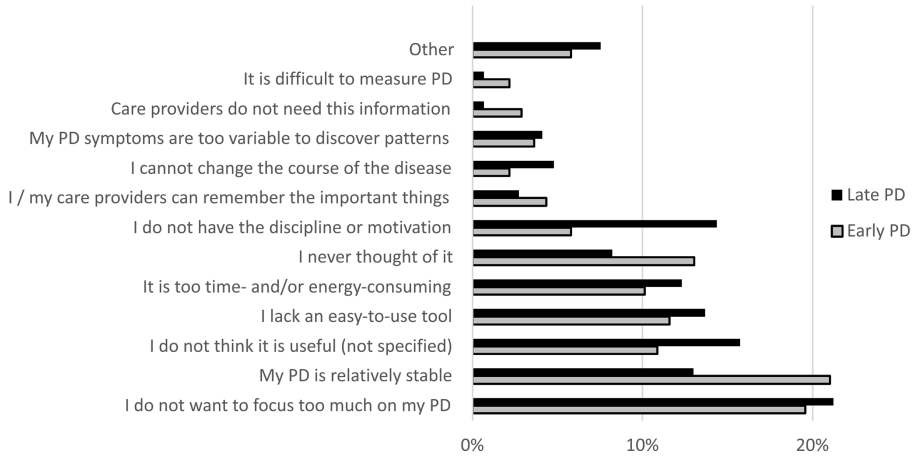


FIGURE 2
Barriers to self-monitoring PD among early PD ($n$ =138) and late PD patients ($n$ =146) who have not tracked the course of their disease in the last year. Presented categories are based on thematic analysis of responses to open-ended questions in the online patient survey.

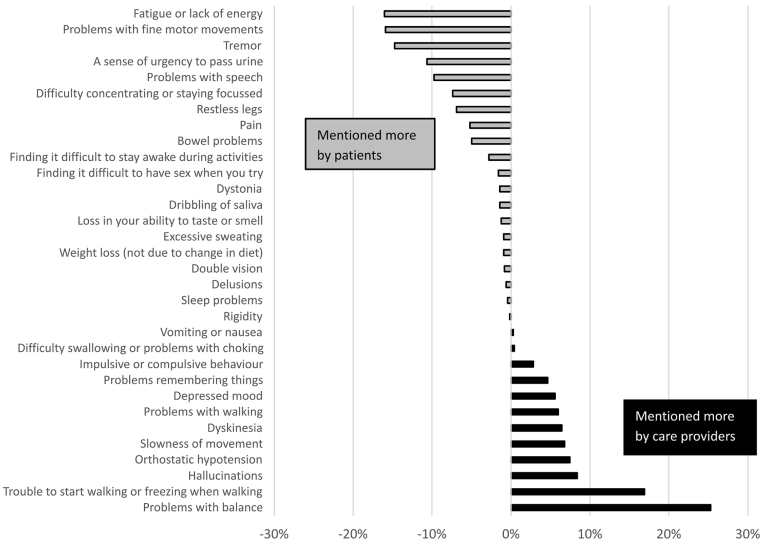


FIGURE 3
Differences between PD patients and healthcare providers in how frequently symptoms were selected for the three most important symptoms to monitor. Difference is expressed in percent point difference between the average percentage of the patient groups, and the average percentage of the healthcare provider groups.

*with the disease and receiving more info makes me depressed. I put my head in the sand, according to my neurologist much better for me!.*" The most common barrier among early PD patients was the fact that their PD was relatively stable: "*The picture of each day is almost identical. Differences are barely noticeable, also not between medication intakes. I do not notice that the medication wears off, or that I need to take the next dose.*" A common barrier among late PD patients was a lack of discipline or motivation: "*I have tried it once or twice, but I'm not a go-getter, sometimes too tired.*" Some patients thought that keeping track of their PD was too energy-consuming: "*I've had Parkinson for almost 14 years now, and my husband died 6 years ago so I'm on my own. I need all my time and energy.*" Other patients missed an easy-to-use self-monitoring tool: "*I do not know a smartphone app,*" and "*Making notes is difficult for me: my hand-writing is very small, typing takes too much time because of repeating keys.*" Last, some patients had never thought about tracking their PD: "*The question only now gives me the idea.*" The fact that some patients mainly experienced "practical" barriers or never thought of tracking their PD, aligns with the fact that two-third (68%) of patients who had not tracked their PD during the previous year indicated to be interested in self-monitoring.

## 3.3. Most important aspects of PD to monitor (survey)

The patients who indicated to be interested in monitoring their PD ($n$ = 326, 76%), and all healthcare providers were asked for their

TABLE 2 Most frequently mentioned symptoms and factors that influence PD by the different stakeholder groups.

| | Early PD** (*n* =165) | Late PD** (*n* =161) | Physiotherapists (*n* =86) | PD nurses (*n* =55) | Neurologist (*n* =25) |
|---|---|---|---|---|---|
| **Symptoms** | | | | | |
| 1st | Tremor | Rigidity | Balance and falls | Balance and falls | Slowness of movement |
| 2nd | Slowness of movement* | Problems with walking | Problems with walking | Slowness of movement | Dyskinesia |
| 3rd | Fatigue* | Tremor* | Freezing of gait | Freezing of gait | Freezing of gait |
| 4th | Rigidity | Balance and falls* | Rigidity | Rigidity | Balance and falls |
| 5th | Problems with fine motor movements | Fatigue | Slowness of movement | Sleep problems | Rigidity |
| **Other factors** | | | | | |
| 1st | PD medication | PD medication | Physical exercise | PD medication | PD medication |
| 2nd | Physical exercise | Physical exercise | PD medication | Physical exercise | General sense of well-being |
| 3rd | Sleep | Stress | General sense of well-being | General sense of well-being* | Physical exercise |
| 4th | Stress | Sleep | Stress | Mood* | Sleep |
| 5th | Time of the day | Time of the day | Pain | Sleep | Time of the day |

*Equal percentages. **Only completed by patients who indicated to be interested in monitoring their PD.

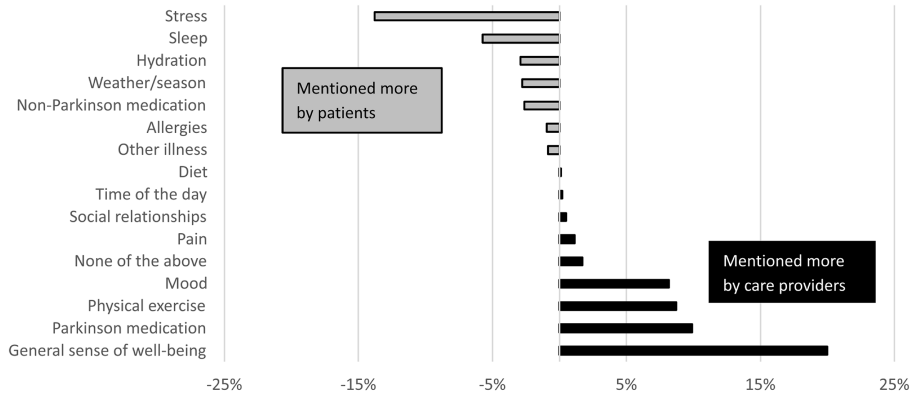


FIGURE 4
Differences between PD patients and healthcare providers in how frequently factors that influence PD were selected for the three most important aspects to monitor. Differences are expressed as percent point difference between the average percentage of the patient groups, and the average percentage of the care provider groups.

three most important symptoms and other factors that would merit monitoring in daily life. The five most frequently selected items per group are shown in Table 2. The complete item lists, including all percentages, can be found in Appendix C. The selection made by patients differed from the selection of healthcare providers, which is highlighted in Figures 4, 5. On average, healthcare providers valued information about balance problems and freezing of gait more, whereas patients showed a larger interest in monitoring fatigue, problems with fine motor movements and tremor. Regarding factors that influence symptoms, patients showed more interest in the effects of stress, whereas healthcare providers were relatively interested in monitoring the general well-being of patients. The selection of symptoms by patients was largely explained by how burdensome (early PD: $\rho = 0.95$, late PD: $\rho = 0.96$) and how strongly fluctuating symptoms were (early PD: $\rho = 0.96$, late PD: $\rho = 0.95$). Healthcare providers mentioned several considerations for their selection, including (1) whether they expected that the symptom had a high impact on the patient's quality of life and/or daily life functioning, (2) whether they could effectively treat the symptom, and (3) whether there is a "knowledge gap," for example because there is a need for frequent information (e.g., for managing response fluctuations), or because the reliability of in-clinic anamnesis is limited (e.g., for managing falls). Some healthcare providers also mentioned increasing the patients' self-awareness of symptoms as a motivation for their selection.

## 3.4. Expected benefits of wearable sensors (surveys)

Respondents in all healthcare provider groups generally had a positive attitude toward using wearable sensors in PD care; on a seven point Likert scale ranging from 1 ("strongly disagree") to 7 ("strongly agree"), they responded to the statement "I believe that wearable sensors have the potential to help me monitor my

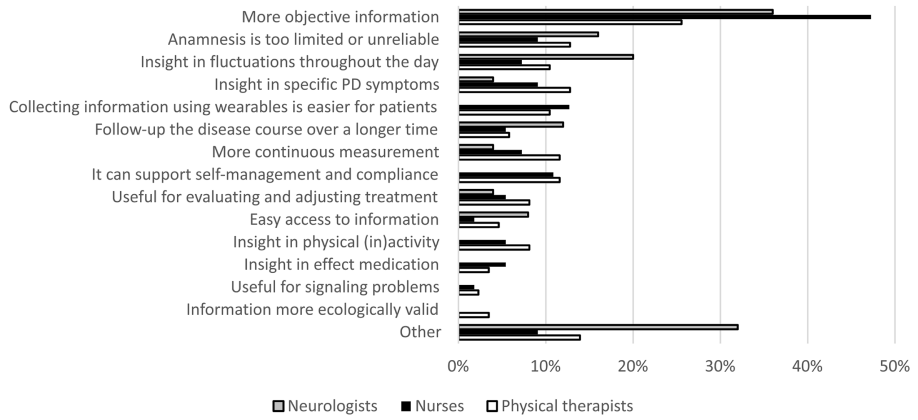


FIGURE 5
Expected benefits of wearable sensors among neurologists (*n* =25), nurses (*n* =55), and physiotherapists (*n* =86). Presented categories are based on thematic analysis of open-ended responses to the online care provider survey. The prevalence of the "other" category is high in the neurologists group; this is mainly because some neurologists mentioned "better monitoring" as a benefit, but did not specify this further.

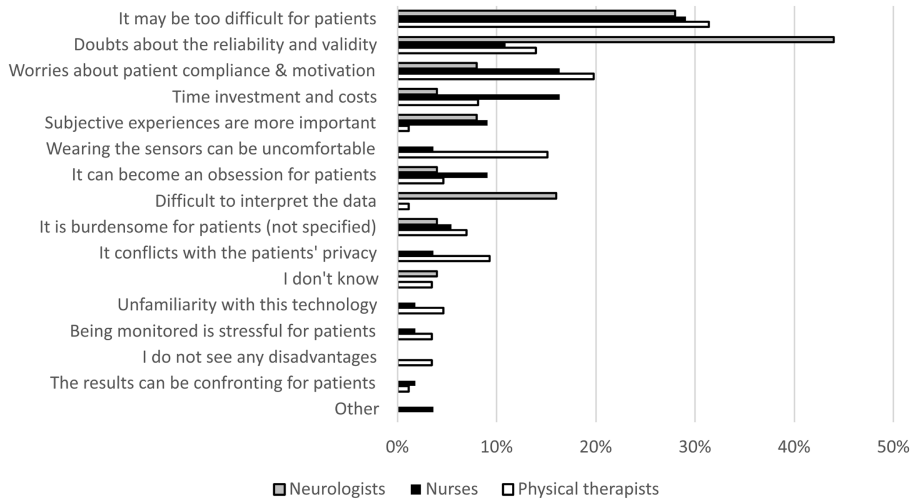


FIGURE 6
Expected limitations of wearable sensors among neurologists (*n* =25), nurses (*n* =55), and physiotherapists (*n* =86). Presented categories are based on thematic analysis of open-ended responses to the online care provider survey.

Parkinson patients" with a mean score of 5.5 (neurologists), 5.5 (physiotherapists), and 5.4 (nurses). Figure 6 summarizes the most frequently identified themes of expected benefits. Obtaining more objective measurements was the most frequently mentioned theme across all groups. *"It helps to translate complaints into symptoms,"* according to a neurologist. A nurse wrote: *"Often my patient category cannot clearly put into words what I would like to know. If I could see it myself, that would at least tell me something about what actually happened to someone."* Different physiotherapists mentioned: *"Patients are inclined to downplay problems, with measurements you obtain a better picture,"* and *"It adds objectivity to my own observations and the responses of the patient."*

In addition, different nurses and physiotherapists emphasized that wearable sensors could make it easier for patients to track their disease: *"If they are unobtrusive for the patient, it hardly affects their activities and thinking,"* and *"Then the patients do not need to actively make notes."* Nurses and physiotherapists also saw opportunities for wearable sensors to support self-management and treatment compliance. Different nurses wrote: *"People obtain more insight into the course of their disease, and receive guidance for self-management,"* and *"It can motivate patients, increase their involvement, and make things more insightful for patients themselves."* Physiotherapists mentioned: *"It can help patients to see for themselves what they can and cannot do,"* and *"It provides people with feedback. And that could well be very different from how people currently see things."*

For neurologists, one of the main expected benefits of wearable sensors was obtaining more detailed measurements of symptom fluctuations throughout the day: *"It can help to obtain better insights into the level of functioning, and fluctuations in time."*

## 3.5. Further exploration of each group's main interest (focus groups and interviews)

Based on the most important symptoms and motivations identified by the surveys, the domains of interest for the focus groups and interviews were chosen: the physiotherapists ($n = 5$) elaborated on the management of balance problems and falls, the neurologists ($n = 5$) on the management of response fluctuations, the nurses ($n = 6$) on supporting self-management, and the patients on communication with their healthcare providers ($n = 14$, divided into two groups). Below we describe the main findings related to the experienced challenges ("pains") of currently used monitoring tools and the potential advantages of wearable sensors (all identified themes within the Value Proposition Canvas can be found in Appendix D).

### 3.5.1. Physiotherapists' view: improved fall risk monitoring

Three main "pains" were identified in the current treatment of falls and balance problems: (1) it is difficult to find out what precedes fall incidents in the patient's daily life, especially in patients with cognitive impairments or without a partner: "*Often patients say: all of a sudden I was lying on the floor,*" (2) the in-clinic performance measured with standardized assessments (such as the mini-BEST) does not fully explain why some patients fall frequently and others do not: *"On the balance board they perform quite well, their strength is rather good, their catch response is good, and still they fall 3 times per week. That is quite frustrating,*" and (3) patients tend to forget applying strategies to prevent falling that the therapists teach them in-clinic: *"When I am standing next to them, they perform things very differently. Last time a patient stepped over everything, but when I walked next to him he carefully walks around obstacles and takes the right path.*"

According to the physiotherapists, wearable sensors worn in daily life could help by increasing the self-awareness of the fall frequency and situations with a high fall-risk, as a starting point for therapy: *"If I as a therapist see someone who has reached his limit and I can talk with the patient about that: on these moments in your daily life you take risks.*" Objective data about what precedes a fall incident could help to identify different "fall profiles" that would enable more targeted therapy. One physiotherapist said: *"Together with the tests with patients we already perform, I would like to make a sort of risk analysis, of which factors are causing the fall. Then, based on the patient profiles, I can give my patients tailored verbal instructions. That would be a good example of using wearable sensors and connecting data."* Sensor devices could also be used to coach patients, for example by detecting situations with high fall risk and providing warnings or reminders to apply the right movement strategy: *"If it has to do with selective attention and the sensor can recognize the movements before a fall occurs, then a warning signal may make someone alert so that he makes the right decision,*" or coach patients to maintain a healthy gait pattern: *"I can imagine that you have a sensor that in some situations sends a verbal message: pay attention, big steps, keep on stepping.*" In addition, the therapists saw benefits for stimulating patients to do balance exercises: *"It think it can be motivating for balance exercises which they need to perform at home, and they receive a signal when it goes well.*"

### 3.5.2. Neurologists' view: better management of response fluctuations

Three main "pains" regarding managing response fluctuations were identified. First, neurologists often find it difficult to understand the daily patterns of response fluctuations based on the patient's story. One neurologist said: *"Often patients say I am not doing well doctor, and then you need to figure out why: is it because of motor problems? And if this is the case, is it rigidity, dyskinesia or tremor?."* Self-reported on–off diaries are often not very helpful: *"The patients who can accurately describe it are also capable of filling out such a dairy, it's mostly the patients who find it hard to explain it, they also have problems completing the on–off diaries.*" A complicating factor is that some patients find it difficult to distinguish between tremor and dyskinesias. Second, it is difficult to rely on in-clinic observations: *"The situation here in the consultation room is always different than at home, so you rely on what patients experience at home.*" Third, it can be challenging to determine who is eligible for advanced therapies: *"I often refer them to Nijmegen for that, and then they also find it difficult. It is very difficult to get an accurate picture. Now patients are often admitted to the hospital for that.*"

Objectively quantifying response fluctuations in real-life could help neurologists to find the right medication dosage more efficiently: *"That you can give the right medication dosage more quickly, that you can go through the process of adjusting the medication schedule faster,*" and *"Then you can see at a glance whether the patient responds to the treatment or not.*" Specifically, it could be helpful to find out whether motor symptoms are the main problem: *"It would give a nice impression of how patients are doing in terms of motor symptoms, and if you see that patients are doing well motorically, then you know something else is going on. I think that that is a huge benefit.*" In addition, it might help to identify patients who would benefit from advanced therapy: *"That you can identify the phase when the medication really does not work anymore earlier. And that you can use this to refer patients for advanced therapies in an earlier stage.*" The ability to provide care proactively was also seen as an important benefit: *"I think that you can also use it to signal problems in an early stage, …, that you receive an early signal when a patient falls outside a certain range, when we should schedule an earlier check-up, or when the GP or local Parkinson nurse should have a look, to prevent certain problems, for example falls, confusion, or delirium."* In addition to these forms of decision support, neurologists also mentioned benefits for their communication with patients. Wearable sensors may help to increase the self-awareness of patients: *"You may give a patient more insights into his own functioning if you can monitor him for a longer time than when you briefly discuss things in the consultation room.*" It may also help to focus the conversation: *"It makes the conversation much more concrete, because you can focus very timely on the current problems of a patient.*"

### 3.5.3. Parkinson nurses' view: educate patients and stimulate self-management

Three main "pains" were identified among Parkinson nurses. First, some patients find it difficult to reflect on and understand their own symptoms. Different nurses mentioned: *"If we ask very specifically, what do you experience and how does it present itself, patients often find it difficult to pinpoint,*" and *"I saw a patient and when she goes into an off state, she really panics. She does not recognize the off phenomenon yet, which makes her hyperventilate.*" In addition, for some patients understanding the difference between tremor and dyskinesias is difficult: *"If you are dyskinetic, and you take extra dopamine, it only becomes worse."* Some patients also have the tendency to underestimate their sleep duration: *"Sometimes it is the experience of a patient that*

*he sleeps for only 3 h, while it appears to be different. I always find this a difficult point to discuss.*" Second, the nurses emphasized that completing diaries is often burdensome for patients: *"The partner or someone else constantly looks over your shoulder and says: "you still need to fill it in," and that drives some people crazy.*" For some PD patients, this may even become an obsession: "*The people who become very rigid in their behavior because of their PD and who want to rationalize everything in numbers, they sometimes show up with whole packages of information and then the partners tell us: "we cannot leave the house without taking pen and paper with us," or they bring extensive tables and graphs. That is real obsessive behavior.*" This makes some nurses also question how representative the diaries are: *"I wonder, how realistic is it, because the stress that comes with filling in the diaries also makes symptoms different than they normally are."* Third, some patients in the early stages struggle with accepting the diagnosis: *"Patients visit the neurologist and he says: "you have Parkinson's." Then people think, that cannot be true, nothing has been done. That's why many patients keep on wondering: is the diagnosis true, because we cannot do imaging.*"

The nurses thought that wearable sensors could help to increase the patients' self-awareness. One nurse mentioned: *"I could mention tens of patients of whom I think: yes, that would actually be nice to make it insightful: what really happened and discuss that together.*" About the patient who panicked during off phases, the nurse said: *"It could help her if she could say: last week I had such an attack, and that we can then discuss: it really looks like an off phase, which is confirmed in a graph.*" Self-awareness about the cause of falls may help the patient to help himself: *"Then you could say: you should have stood up less quickly. If someone has a gap in his memory and does not know it anymore, they also cannot help themselves.*" Nurses also emphasized that wearable sensors could make it easier for patients to tell their story: *"They already have less dopamine, so a conversation costs a lot of energy. I can imagine that it helps if you already have some numbers and the patient does not have to tell the whole story."* In addition, they saw a role for wearable sensor to activate patients: *"If a sensor gives certain stimuli for loss of initiative, that could unburden caregivers a little because he does not continuously have to stimulate the partner and be in the caregiver role, and can be more of a partner.*" Last, having objective measurements could help with accepting the diagnosis: *"Often patients feel like: is the diagnosis true, because I cannot confirm it with imaging. This* (i.e., *feedback from wearable sensors*) *is something that patients can really see, something that is being measured.*"

### 3.5.4. Patients' view: communication with healthcare providers

How patients communicated about their symptoms with healthcare providers varied per individual. Some patients already made notes about the most important changes or questions before meeting with their healthcare providers: *"Before I visit my neurologist, I always make one sheet with what I want to say, so I do not forget anything.*" Some patients regularly used an online questionnaire ("Parkinson Monitor," developed by the Dutch Parkinson Association) to identify the biggest changes in their symptoms compared to the last appointment. For some patients, the partner's support during consultations was very important: *"I have a very good partner who joins me with a memory like an elephant."* Others did not feel the need to track their Parkinson symptoms, either because their situation was relatively stable or because they felt like their disease course was too unpredictable to identify useful patterns: *"I started with it, only for me every day is different. There is no logic to it, so at a certain point I felt like: what's the use of keeping track of it."* Identified facilitators ("gains") for communicating with healthcare providers about symptoms included (1) an open attitude to using self-collected information: *"My neurologist says: "I am happy you brought a form, because I am depending on you." She can only help if I say something,*" and (2) whether their healthcare providers were easy to approach: *"We have the best feeling with the Parkinson nurse. She maybe does not know 100% about my patient record, but she does have eye for the social aspects and thinks with you if you say: "I went on a holiday and it was so nice." It feels closer.*"

Three main "pains" were identified with respect to the communication about symptoms with care providers. First, some patients thought it was difficult to collect reliable information to share. The Parkinson Monitor was considered as too subjective: *"I tried it and I thought it was much too subjective. You need to give a number, and if I selected a 6 last time, I do not remember why I choose a 6 then."* In addition, patients who wanted to try a smartphone applications, found it difficult to know which one was reliable: *"If I look for Parkinson's in the app store, there are so many applications. I do not know which ones are any good.*" Second, some patients thought it was burdensome to self-track their PD, either because it required a lot of time or because they did not want to focus too much on their PD: *"I am very eager to learn, so I thought I want to know everything about the disease. It made me very sad day by day, I did not sleep anymore, and I became depressed.*" Third, some patients had the impression that their care providers are not open for self-collected information: *"The neurologists inspects how I walk when I come in and looks at my facial expression and says: you are doing well. That is what he relies on.*" Another patient mentioned: *"I know the Parkinson Monitor, but the neurologist thinks it's nonsense and he does not cooperate, so then there is no point.*" Patients thought that the limited time for consultations was an important factor in this.

Patients who were interested in symptom monitoring, agreed that wearable sensors could provide more objective information, which would be useful to share and discuss with healthcare providers. First, patient thought that it could help to find the right treatment, for example by adjusting the medication schedule more quickly: *"Imagine that you agree during a consultation that the medication needs to be increased because you are too passive. Then you can see during the next 2 weeks: has it changed or not. Now you wait for 3 months until you go back."* Similarly, one patient thought that it could help with adjusting the intraduodenal levodopa infusion: *"If you get it, you need to go for a week to the hospital to see: how are the settings. That should work much better with such a device.*" Patients also saw benefits for non-pharmacological interventions: "*With walking, sometimes it goes smoothly and sometimes I think: "flap, flap, flap." So then I think: we should analyze the movements with sensors, and then get an advice which exercises you should do.*" Second, some patients thought that it could help healthcare providers to proactively signal changes that need attention: *"Then they might be able to see in the data in an earlier stage: something is not going well, maybe we should schedule a check-up earlier.*" Third, sensors could facilitate the communication during consultations: *"I think that they are even more prepared for what happened, that they can read in before the appointment. Then you do not need to mention everything, because everyone is up-to-date.*"

## 3.6. Expected barriers and contextual considerations for use of wearable sensors (mixed methods)

The most frequently identified barriers to using wearable sensors among healthcare providers are shown in Figure 7 (the percentages were based on the survey, whereas the illustrative quotes below were based on the survey, focus groups and interviews combined). Concerns about the usability of wearable sensors, in particular for the PD population, was a common theme. Some healthcare providers commented on the motor skills required for using the devices: *"It may be difficult for patients to put the sensors on and take them off,"* one physiotherapist wrote, and one nurse mentioned: *"Patients often have problems with fine motor skills."* Cognitive problems were a common concern as well: *"Patients may forget that we agreed to wear the device, or how to use the device,"* according to one of the nurses. A physiotherapist mentioned: *"Some patients with Parkinson's disease are not teachable anymore."*

Both patients and healthcare providers, neurologists in particular, emphasized the importance of reliable and well-validated sensor-based outcomes: *"It is important whether it actually reflects the condition of the patient"* (neurologist), and *"A sensor only gives objective data if it is really good. A system of a few years ago could not detect biking, then it does not work, then it is not a complete, objective picture"* (patient). Some healthcare providers would only trust the measurements if recognized by the patient: *"I would trust it if you look at it together with the patient and he says multiple times: yes that is true, I also experience it that way"* (nurse). A neurologist noted that he needs to able to rely on measurements, also when findings are unexpected: "*On the other hand, if it completely matches one-on-one with what I already thought myself, then the added value is of course zero*" (neurologist). Some healthcare providers emphasized the importance of transparency: *"I think it's difficult if you cannot look under the hood. If it does not seem to match with what you think about this patient, you cannot really see why it does not match."* The scope of what could be measured with wearables was also a concern: *"Only limited measurements are possible: for example one arm or one symptom"* (neurologist), and "*We talk a lot about cognitive problems. The sensors measure movements, so there is already some friction*" (physiotherapist).

Another common theme was the compliance with using wearable sensors: "*The devices will not always be used by the patient, so information will not be complete, which can make patients very nervous*" (nurse), and *"Patients may take them off and forget to put them on again"* (physiotherapist). Some healthcare providers thought that the patients' motivation to wear the devices is an important hurdle: *"It asks a lot of discipline from patients"* (physiotherapist), and *"Patients must benefit from it themselves"* (neurologist).

Healthcare providers were also concerned about the time investment and costs. A physiotherapist wrote: "*Reading out the sensors requires extra time which is not there, or it comes at the expense of treatment time,*" and a neurologist expressed the concern that it may raise more questions: *"Then they tell me in the app I see this and that. Cannot you increase the medication even more?"* (neurologist). In addition, healthcare providers stressed the importance of the subjective experiences of patients: *"You do not treat graphs, but patients. So how the patient eventually experiences it remains most important"* (nurse), and *"It is very important that patients can indicate via a simple button how they feel from time to time, for example whether they are feeling comfortable, miserable, stressed,* etc. *That is important for the interpretation of the data. The combination of subjective and objective data is important"* (neurologist). Last, some participants mentioned the risk that self-monitoring can become an obsession, in particular for patients with PD: *"A disadvantage could be that you let your life be ruled by the sensors. I would not be happy with that"* (patient).

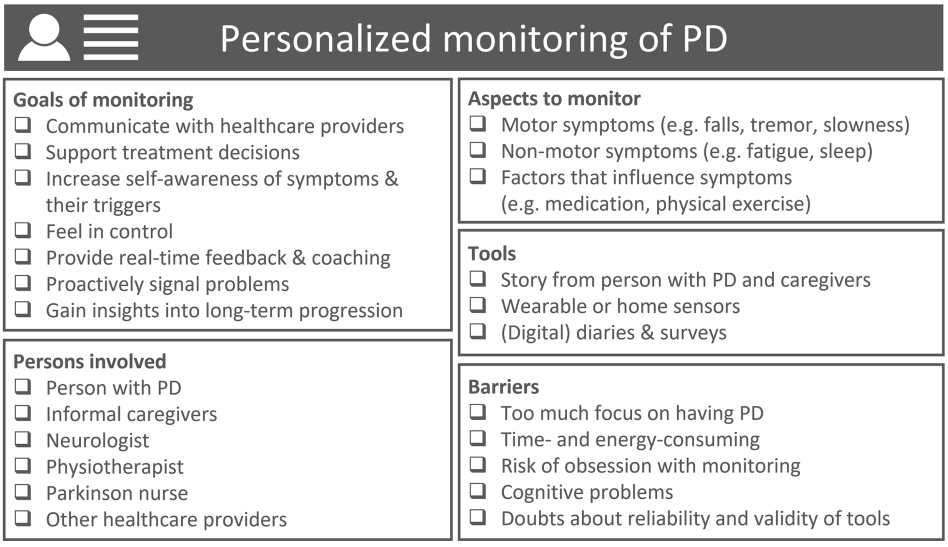


FIGURE 7
Visualization of personalized monitoring of PD, providing a non-exhaustive overview of aspects that should be considered when developing PD monitoring solutions to address specific needs of specific target groups of patients and healthcare providers. Categories are inspired by the results from the surveys, focus groups and interviews.

In the focus groups, additional themes regarding the design and implementation of wearable sensors were identified ("the ideal tool" in the Value Proposition Canvas). Below we highlight highly prevalent themes; for all identified themes and illustrative quotations we refer to Appendix D.

### 3.6.1. Use for specific indications

Healthcare providers mainly saw benefits for specific target groups: *"On the long term, I think we will mainly use it for the vulnerable patient with little informal care, or with cognitive problems when you think, I cannot get a good impression of how the patient functions at home, and that you have doubts about the medication or activities of such a patient"* (neurologist), and *"It is particularly important for patients living by themselves and in nursing homes: here we often do not have a clear picture of the patients' functioning"* (nurse). Both patients and healthcare providers also mentioned that there need to be specific goals and the use of wearable sensors should not be standard: *"I find everything that's standard a bit tricky. In contrast, we aim for personalized care, and if you say: we will do certain things as standard when they have Parkinson's for 5 years, I would hate that."* A patient mentioned: *"Yes, the data are very nice, but you can quickly drown in all the information, so you need to have a thread or a goal. I have a goal: stay active."*

### 3.6.2. Active versus passive monitoring

Because of the need to obtain (continuous) insights into how the patients move in real-life, healthcare providers generally preferred passive registrations in the background over performing active tasks: *"Otherwise patients focus on the exercise and not on the environment and why he stands up. He stands up for a reason, not to do that test, but he needs to go to the toilet. You can measure that in a very natural way"* (physiotherapist), and *"At the end of the day you would still do artificial measurements then. That's not what it's really about. They are still snapshots"* (neurologist). Some patients were also more enthusiastic about passive monitoring: *"I think you should not do extra movements for it. It needs to measure automatically, I should not have to say: now you measure me and now you do not."* Physiotherapists were interested in active tasks if these also served as an exercise: *"It can be valuable if you say: I think this is an important exercise for this patient to repeat often."* Patient expressed the desire that the schedule of tasks should be personalized and that sensors should sense when the patient is not available: *"A smart sensor knows from your movements that you are in a car, so it would be smart if it does not send you an alert then."* Nevertheless, some patients doubted whether they had the discipline to do repetitive tasks: *"In every test that I participated in I always needed to do the same thing. Counting back from 100 with steps of 7, always the same test. Once in a while you should think about something else."* Some healthcare providers thought it would be valuable to combine the sensor data with subjective self-reports: *"It is very important that patients can use a simple button from time to time to indicate how they feel: for example if they feel good, miserable, stressed,* etc. *That would really help interpreting the data. The combination of subjective and objective data is important"* (neurologist).

### 3.6.3. Privacy

Healthcare providers were generally more concerned about privacy than the patients themselves: *"Well, it feels a bit like big brother is watching you, I think a patient may experience that as unpleasant. It depends a little bit on how you measure it. You are already a patient and if you are also being monitored continuously, I can imagine if a patient would not like that"* (neurologist), and *"It should not work like: let us have a look at how mister X is doing tonight, whether he is sitting on the couch or he is doing his exercises. That is a bridge too far for me"* (physiotherapist). Patients were generally very open to share information with their healthcare providers, and mainly emphasized the positive aspects of data being available: *"Imagine that something happens and I have a question, then he can have a look at how I am doing. It is available. It is not a bad thing if it is available for people you trust."* Patients did emphasize they would like to have control on who has access to the data: *"If I can say who and when, then I think it's fine. My physiotherapist can see it for sure, because I see him every 14 days, maybe someone else not."* Some patients mentioned that data should not be shared with insurance companies. According to healthcare providers, it is important to give detailed information to PD patients and their caregivers about monitoring tools, by whom and how they are used, and to obtain informed consent. The nurses emphasized that respect for the patient's autonomy is essential, and it needs to be evaluated in each individual case if and what kind of home monitoring is useful and desirable: in some cases, directly transferring the data to healthcare providers could help signaling problems and be experienced as supportive, whereas in other cases, this might be experienced as not respecting the patient's privacy.

## 4. Discussion

### 4.1. Main findings

This mixed methods study provides detailed information about the perspectives of patients, physiotherapists, Parkinson nurses and neurologists on monitoring PD in daily life. One third of the patients had self-monitored their PD symptoms in the past year, most commonly using a paper diary. Key motivations for monitoring among patients are sharing information with healthcare providers, obtaining insight into the effect of medication and other treatments, and following the long-term disease progression. Key barriers are not wanting to focus too much on having PD, symptoms being relatively stable, and lacking an easy-to-use tool. Symptoms of interest differed between patients and healthcare providers; patients gave a higher priority to fatigue, problems with fine motor movements and tremor, whereas healthcare providers more frequently prioritized balance, freezing and hallucinations. PD patients as well as healthcare providers were in general positive about using wearable sensors to improve PD care and self-management, although the specific context and expected benefits varied considerably between the different stakeholders. For each group we provide further ideas about one promising context where wearable sensors could add value: treatment of balance and falls (physiotherapists), self-management and patient education (Parkinson nurses), treatment of response fluctuations (neurologists), and communication with healthcare providers (patients). Last, we discuss barriers for the use of wearable sensors as identified by the different groups (e.g., questions about usability, reliability, and compliance), as well as suggestions for the design and implementation of wearable sensors.

## 4.2. Toward personalized monitoring

We observed a large heterogeneity among PD patients and healthcare providers regarding their views on monitoring PD, which underlines the need for solutions tailored to specific contexts. The observed heterogeneity is reflected in multiple ways. First, although patients and healthcare providers share interest in the classical motor symptoms of PD, which is in line with earlier studies (11, 14), interesting differences also appeared. Fatigue, problems with fine motor movements, tremor, and stress were mentioned more commonly by patients, whereas healthcare providers gave a higher priority to monitoring balance, freezing of gait, and general sense of well-being. On the one hand, these differences could encourage professionals to pay more attention to symptoms frequently mentioned by patients, especially since interventions to treat fatigue (26) and stress (27, 28) in PD patients are increasingly available. On the other hand, we need to acknowledge that the perspectives of patients and healthcare providers may be inherently different: patients mainly tend to focus on aspects that are most burdensome for them, whereas the different healthcare providers mainly focus on areas where they can have an impact by providing tailored treatments, and where accurate information to support such treatment decisions is presently missing.

Second, healthcare providers expressed different ideas about how monitoring PD using wearable sensors could contribute to improving PD care. Wearable sensors were not only seen as tools to support treatment decisions and proactively signal problems, but also as tools to educate patients, increase their self-awareness of symptoms and triggers, increase their participation, and support treatment compliance. The latter could be particularly relevant for treatments that require a substantial active contribution from patients such as physiotherapy exercises, where wearable sensors could help by visualizing the achieved progress, or even by providing real-time feedback about the execution of exercises (29). In addition, wearable sensors could assist in the challenging transition from practicing movement strategies in a supervised setting to correctly applying them in daily life, by providing real-time feedback in daily life (30, 31).

Third, patients expressed different motivations for self-monitoring their PD. In addition to sharing information with healthcare providers, patients also saw added value of self-monitoring independent of their relationship with healthcare providers. Many patients expressed an interest in gaining more insight themselves into the course of their symptoms and into the effect of medication or other interventions. An important perk of this was the opportunity to feel more in control, and being able to optimize aspects of their lives themselves (self-design), which is in line with findings of Riggare et al. (12). Also, some patients found it useful to self-monitor symptoms to communicate about their PD with family and friends (self-association). Some patients expressed the hope that wearable sensors could be used to coach them, for example to maintain a healthy gait pattern (self-discipline). As such, self-monitoring using wearable sensors offers various opportunities to support self-management when properly integrated into treatment programs (32). However, the added value of self-monitoring will likely depend on whether it fits with the patient's personal coping strategies, and it is important to find a balance between the benefits and burdens (e.g., the required time and energy, and the fact that self-monitoring can be confrontational) (12, 33).

Taken together, we conclude that it is unrealistic that a one-size-fits all monitoring solution will be able to address the different needs of PD patients and healthcare providers involved in PD care. Instead, we believe that different PD monitoring solutions should be designed to address specific needs experienced by specific target groups of patients and healthcare providers (6), with close involvement of the users in all phases of the product's design (15, 34).

## 4.3. Impact on interaction between patients and healthcare providers

Patients and healthcare providers expected that the use of sensor-based monitoring tools will impact their interaction. On the positive side, being able to discuss measurements together could serve as a memory aid, trigger patients to share their experiences, and help to focus the conversation. Jointly discussing measurements was also seen as a way to increase the patients' self-awareness. In addition, by reducing the dependence on in-clinic observations to evaluate the severity of symptoms, wearable sensors provide opportunities for telemedicine (35), in which the COVID-19 crisis triggered a revived interest (36).

However, the use of sensor-based monitoring tools also comes with challenges for the communication between patients and healthcare providers. Focusing too much on numbers was identified as a potential risk. Healthcare providers agreed that the subjective experiences of the patient remain vital to guide treatment decisions, as wearable sensors cannot measure the limitations experienced by the patient. This stresses the importance of providing patients ample opportunity to comment on the measurements, and only act upon them if jointly agreeing on the conclusions, which is in line with findings of the focus group study of Ozanne et al. (37). Future clinical trials on the effectiveness of specific remote monitoring tools should include more elaborate evaluations of their impact on the relationship and communication between patients and healthcare providers (38).

## 4.4. Uptake of wearable sensors

Despite an increasing availability of sensor-based monitoring tools, both our survey and the survey of Mathur et al. (11) showed that paper diaries are currently the most commonly used tool among patients and healthcare providers. This may be partly explained by the lack of convincing evidence for the benefits of wearable sensors. A few pilot trials using sensor-based remote monitoring systems have demonstrated positive effects on clinical decision-making and motor symptoms of PD patients (34, 39, 40). However, these studies had different methodological shortcomings (including lack of randomization, small sample size, and no assessment of user experiences), and were conducted by the groups who also developed and commercialized the systems. The field would benefit from independent randomized controlled trials and qualitative process evaluations of mature versions of remote monitoring systems. In addition, systems are often evaluated in broad PD populations. Based on the observed heterogeneity in needs that we identified among patients and healthcare providers, it is unlikely that all PD patients will benefit from such solution. Instead, it would be more appropriate to conduct evaluations in well-defined, specific use cases. Randomized controlled trials such as the ongoing MoMoPa-EC

study are an important step in this direction (41). In addition, the focus has been on supporting clinical decisions around the prescription of medication, whereas opportunities also exist for supporting non-pharmacological interventions (e.g., by physiotherapists) and self-management. Finally, given that concerns about the reliability and validity were commonly mentioned as barriers for using sensor-based monitoring tools, building trust in newly developed sensor-based outcomes is essential (42).

### 4.5. Strengths and limitations

This study has a few limitations. First, a relatively small number of patients and healthcare providers participated in the focus groups and interviews. Because we did not aim for data saturation, the identified themes cannot be assumed to be exhaustive, also given the observed large variation in individual perspectives. Instead, our aim was to enrich the findings of the online surveys by further exploring promising contexts where wearable sensors could be of added value. Second, the organization of PD care in some other countries differs from the Netherlands, where, for example, PD patients are often seen by physiotherapists and Parkinson nurses, in addition to neurologists. Therefore, the roles of different healthcare providers should be considered when translating the findings of this study to other countries. At the same time, the Netherlands lends itself well for studying innovations in PD care, because of the nation-wide network of healthcare providers specialized in PD (19). Third, it should be noted that, because patients signed up to participate in a wearable sensor study, our study population may be relatively interested in this topic. We believe this did not affect the generalizability of our findings, as approximately two-third of the participants did not perform self-tracking activities. Finally, although we involved the most frequently involved healthcare providers in PD care, future research may explore the perspectives of other relevant disciplines, such as speech and language therapists, occupational therapists and dietitians (10).

Strengths of this study include the combination of surveys with subsequent focus groups, and the involvement of both patients and different healthcare providers. The alignment of the survey questions allowed for a comparison of perspectives, highlighting interesting differences between the different stakeholder groups. In addition, by not limiting the input of participants to the development of a specific solution, we aimed to identify universal needs, not limited to what is currently technically possible. Finally, we aimed to provide a nuanced view on the potential of new monitoring solutions, by not only focusing on motivations for self-monitoring and expected benefits of wearable sensors, but also on barriers and expected limitations. More insights into the different perspectives on symptom monitoring and wearable sensors of all stakeholders involved will hopefully contribute to the successful design and implementation of PD monitoring solutions.

## Data availability statement

The anonymized raw data supporting the conclusions of this article can be shared by the authors upon request, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Commissie Mensgebonden Onderzoek, regio Arnhem-Nijmegen; file number 2015-1776. Participants in the online survey study provided informed e-consent; participants in the focus groups and interviews provided written informed consent.

## Author contributions

LE, BB, and MM were responsible for the conception of the research idea and design of the study. BB and MM obtained the funding for the study. LE and MM wrote the research protocol and obtained approval from the ethical committee. LE developed the surveys and the topic guides for the focus groups and interviews. LE and JP collected the data, performed the analyses, and drafted the initial manuscript. MM and BB helped with interpreting the results, and thoroughly reviewed the manuscript. All authors read and approved the final version of the manuscript.

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## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1150634/full#supplementary-material

## References

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. (2015) 386:896–912. doi: 10.1016/S0140-6736(14)61393-3

2. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. (2021) 397:2284–303. doi: 10.1016/S0140-6736(21)00218-X

3. Politis M., Wu K., Molloy S., Bain P., Chaudhuri K.R., Piccini P., Parkinson's disease symptoms: the patient's perspective. *Mov Disord*, (2010). 25, 1646–1651, doi: 10.1002/mds.23135

4. Papapetropoulos SS. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Ther*. (2012) 18:380–7. doi: 10.1111/j.1755-5949.2011.00253.x

5. Hillel I, Gazit E, Nieuwboer A, Avanzino L, Rochester L, Cereatti A, et al. Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gaps between gait performance in the lab and during 24/7 monitoring. *Eur Rev Aging Phys Act*. (2019) 16:6. doi: 10.1186/s11556-019-0214-5

6. Klucken J, Krüger R, Schmidt P, Bloem BR. Management of Parkinson's disease 20 years from now: towards digital health pathways. *J Parkinsons Dis*. (2018) 8:S85–94. doi: 10.3233/JPD-181519

7. Caballol N, Bayés À, Prats A, Martín-Baranera M, Quispe P. Feasibility of a wearable inertial sensor to assess motor complications and treatment in Parkinson's disease. *PLoS One*. (2023) 18:e0279910. doi: 10.1371/journal.pone.0279910

8. Friedman B, Kahn PH, Borning A. Value sensitive design and information systems. *Hum Comput Interact Manage Inform Syst*. (2006) 5:348–72. doi: 10.1007/978-94-007-7844-3_4

9. Scott Duncan T, Engström J, Riggare S, Hägglund M, Koch S. Meeting the burden of self-management: qualitative study investigating the empowering behaviors of patients and informal caregivers. *J Particip Med*. (2022) 14:e39174. doi: 10.2196/39174

10. Radder DLM, de Vries NM, Riksen NP, Diamond SJ, Gross D, Gold DR, et al. Multidisciplinary care for people with Parkinson's disease: the new kids on the block! *Expert Rev Neurother*. (2019) 19:145–57. doi: 10.1080/14737175.2019.1561285

11. Mathur S, Mursaleen L, Stamford J, DeWitte S, Robledo I, Isaacs T. Challenges of improving patient-Centred Care in Parkinson's disease. *J Parkinsons Dis*. (2017) 7:163–74. doi: 10.3233/JPD-160922

12. Riggare S, Scott Duncan T, Hvitfeldt H, Hägglund M. "You have to know why you're doing this": a mixed methods study of the benefits and burdens of self-tracking in Parkinson's disease. *BMC Med Inform Decis Mak*. (2019) 19:175. doi: 10.1186/s12911-019-0896-7

13. Gimpel H., Nißen M., Görlitz R., Quantifying the quantified self: a study on the motivations of patients to track their own health. Thirty fourth international conference on information systems, Milan, (2013).

14. SENSE-PARK ConsortiumSerrano JA, Larsen F, Isaacs T, Matthews H, Duffen J, et al. Participatory design in Parkinson's research with focus on the symptomatic domains to be measured. *J Parkinsons Dis*. (2015) 5:187–96. doi: 10.3233/JPD-140472

15. Cancela J, Fico G, Arredondo Waldmeyer MT. Using the analytic hierarchy process (AHP) to understand the most important factors to design and evaluate a telehealth system for Parkinson's disease. *BMC Med Inform Decis Mak*. (2015) 15:S7. doi: 10.1186/1472-6947-15-S3-S7

16. Schoonenboom J, Johnson RB. How to construct a mixed methods research design. *Kolner Z Soz Sozpsychol*. (2017) 69:107–31. doi: 10.1007/s11577-017-0454-1

17. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. (2006) 3:77–101. doi: 10.1191/1478088706qp063oa

18. Silva de Lima AL, Hahn T, Evers LJW, de Vries NM, Cohen E, Afek M, et al. Feasibility of large-scale deployment of multiple wearable sensors in Parkinson's disease. *PLoS One*. (2017) 12:e0189161. doi: 10.1371/journal.pone.0189161

19. Bloem BR, Munneke M. Revolutionising management of chronic disease: the ParkinsonNet approach. *BMJ*. (2014) 348:g1838. doi: 10.1136/bmj.g1838

20. Rios Romenets S, Wolfson C, Galatas C, Pelletier A, Altman R, Wadup L, et al. Validation of the non-motor symptoms questionnaire (NMS-quest). *Parkinsonism Relat Disord*. (2012) 18:54–8. doi: 10.1016/j.parkreldis.2011.08.013

21. Beatty PC, Willis GB. Research synthesis: the practice of cognitive interviewing. *Public Opin Q*. (2007) 71:287–311. doi: 10.1093/poq/nfm006

22. Morgan DL, Krueger RA. When to use focus groups and why In: . *Successful focus groups: Advancing the state of the art*, Sage Publications, Inc. vol. 1 (1993). 3–19.

23. Osterwalder A, Pigneur Y, Bernarda G, Smith A, Papadakos T. *Value proposition design: how to create products and services customers want*. Hoboken, New Jersey: John Wiley & Sons (2014).

24. UCB. Parkinson's Well-Being Map. (n.d.). Retrieved November 2022, from https://www.ucb.com/patients/Support-tools/Parkinson-s-Well-Being-Map.

25. Horne MK, McGregor S, Bergquist F. An objective fluctuation score for Parkinson's disease. *PLoS One*. (2015) 10:e0124522. doi: 10.1371/journal.pone.0124522

26. Akbar U, Friedman JH. Treatment of Fatigue in Parkinson's Disease. In: *Therapy of Movement Disorders*, eds. S. Reich, S. Factor 2019). Humana, Cham: Current Clinical Neurology.

27. Kwok JY, Kwan JCY, Auyeung M, Mok VCT, Lau CKY, Choi KC, et al. Effects of mindfulness yoga vs stretching and resistance training exercises on anxiety and depression for people with Parkinson disease: a randomized clinical trial. *JAMA Neurol*. (2019) 76:755–63. doi: 10.1001/jamaneurol.2019.0534

28. van der Heide A, Meinders MJ, Speckens AEM, Peerbolte TF, Bloem BR, Helmich RC. Stress and mindfulness in Parkinson's disease: clinical effects and potential underlying mechanisms. *Mov Disord*. (2021) 36:64–70. doi: 10.1002/mds.28345

29. Gordt K, Gerhardy T, Najafi B, Schwenk M. Effects of wearable sensor-based balance and gait training on balance, gait, and functional performance in healthy and patient populations: a systematic review and meta-analysis of randomized controlled trials. *Gerontology*. (2018) 64:74–89. doi: 10.1159/000481454

30. Ginis P, Nieuwboer A, Dorfman M, Ferrari A, Gazit E, Canning CG, et al. Feasibility and effects of home-based smartphone-delivered automated feedback training for gait in people with Parkinson's disease: a pilot randomized controlled trial. *Parkinsonism Relat Disord*. (2016) 22:28–34. doi: 10.1016/j.parkreldis.2015.11.004

31. Corzani M, Ferrari A, Ginis P, Nieuwboer A, Chiari L. Motor adaptation in Parkinson's disease during prolonged walking in response to corrective acoustic messages. *Front Aging Neurosci*. (2019) 11:265. doi: 10.3389/fnagi.2019.00265

32. Chiauzzi E, Rodarte C, DasMahapatra P. Patient-centered activity monitoring in the self-management of chronic health conditions. *BMC Med*. (2015) 13:1–6. doi: 10.1186/s12916-015-0319-2

33. Ancker JS, Witteman HO, Hafeez B, Provencher T, van de Graaf M, Wei E. "You get reminded you're a sick person": personal data tracking and patients with multiple chronic conditions. *J Med Internet Res*. (2015) 17:e202. doi: 10.2196/jmir.4209

34. Elm JJ, Daeschler M, Bataille L, Schneider R, Amara A, Espay AJ, et al. Feasibility and utility of a clinician dashboard from wearable and mobile application Parkinson's disease data. *NPJ Digit Med*. (2019) 2:95. doi: 10.1038/s41746-019-0169-y

35. Dorsey ER, Achey MA, Beck CA, Beran DB, Biglan KM, Boyd CM, et al. National Randomized Controlled Trial of virtual house calls for people with Parkinson's disease: interest and barriers. *Telemed J E Health*. (2016) 22:590–8. doi: 10.1089/tmj.2015.0191

36. Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Parkinsons Dis*. (2020) 10:351–4. doi: 10.3233/JPD-202038

37. Ozanne A, Johansson D, Hällgren Graneheim U, Malmgren K, Bergquist F, Alt Murphy M. Wearables in epilepsy and Parkinson's disease—a focus group study. *Acta Neurol Scand*. (2018) 137:188–94. doi: 10.1111/ane.12798

38. Noah B, Keller MS, Mosadeghi S, Stein L, Johl S, Delshad S, et al. Impact of remote patient monitoring on clinical outcomes: an updated meta-analysis of randomized controlled trials. *NPJ Digit Med*. (2018) 1:1–12. doi: 10.1038/s41746-017-0002-4

39. Farzanehfar P, Woodrow H, Braybrook M, McGregor S, Evans A, Nicklason F, et al. Objective measurement in routine care of people with Parkinson's disease improves outcomes. *NPJ Parkinsons Dis*. (2018) 4:10. doi: 10.1038/s41531-018-0046-4

40. Isaacson SH, Boroojerdi B, Waln O, McGraw M, Kreitzman DL, Klos K, et al. Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting transdermal rotigotine patch: a pilot study. *Parkinsonism Relat Disord*. (2019) 64:132–7. doi: 10.1016/j.parkreldis.2019.01.025

41. Rodríguez-Molinero A, Hernández-Vara J, Miñarro A, Pérez-López C, Bayes-Rusiñol À, Martínez-Castrillo JC, et al. Multicentre, randomised, single-blind, parallel group trial to compare the effectiveness of a Holter for Parkinson's symptoms against other clinical monitoring methods: study protocol. *BMJ Open*. (2021) 11:e045272. doi: 10.1136/bmjopen-2020-045272

42. Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov Disord*. (2019) 34:657–63. doi: 10.1002/mds.27671

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# Toward objective monitoring of Parkinson's disease motor symptoms using a wearable device: wearability and performance evaluation of PDMonitor®

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Parkinson's disease (PD) is characterized by a variety of motor and non-motor symptoms. As disease progresses, fluctuations in the response to levodopa treatment may develop, along with emergence of freezing of gait (FoG) and levodopa induced dyskinesia (LiD). The optimal management of the motor symptoms and their complications, depends, principally, on the consistent detection of their course, leading to improved treatment decisions. During the last few years, wearable devices have started to be used in the clinical practice for monitoring patients' PD-related motor symptoms, during their daily activities. This work describes the results of 2 multi-site clinical studies (PDNST001 and PDNST002) designed to validate the performance and the wearability of a new wearable monitoring device, the PDMonitor®, in the detection of PD-related motor symptoms. For the studies, 65 patients with Parkinson's disease and 28 healthy individuals (controls) were recruited. Specifically, during the Phase I of the first study, participants used the monitoring device for 2–6 h in a clinic while neurologists assessed the exhibited parkinsonian symptoms every half hour using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III, as well as the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia severity assessment. The goal of Phase I was data gathering. On the other hand, during the Phase II of the first study, as well as during the second study (PDNST002), day-to-day variability was evaluated, with patients in the former and with control subjects in the latter. In both cases, the device was used for a number of days, with the subjects being unsupervised and free to perform any kind of daily activities. The monitoring device produced estimations of the severity of the majority of PD-related motor symptoms and their fluctuations. Statistical analysis demonstrated that the accuracy in the detection of symptoms and the correlation between their

severity and the expert evaluations were high. As a result, the studies confirmed the effectiveness of the system as a continuous telemonitoring solution, easy to be used to facilitate decision-making for the treatment of patients with Parkinson's disease.

KEYWORDS

**Parkinson's disease, telemonitoring, wearable devices, digital health, automatic ambulatory monitoring, inertial measurement unit sensors**

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a high prevalence among those aged $\geq$ 45 years (572 patients per 100,000 people) (1). It is characterized by motor and non-motor symptoms, with a progressively worsening course. The main motor manifestations of the disease are bradykinesia, rigidity and resting tremor, with accompanying gait impairment and reduced manual dexterity (2). Non-motor symptoms include autonomic nervous system disorders, dementia, as well as neuropsychiatric disorders (3–5). To date, treatment is based on dopamine replacement drugs but there are numerous biological strategies under development including active and passive immunization aimed at testing disease modification (2, 6). In the early stages, drug treatment results in sustained benefits and improves quality of life throughout the day. However, as disease progresses, levodopa effects shorten, and patients experience motor and non-motor fluctuations, as well as, in some occasions, levodopa induced dyskinesia (LiD) and freezing of gait (FoG). To optimize and personalize the treatment strategy, it is necessary to accurately monitor their symptoms, as they vary widely from day-to-day, and also differ significantly between different patients (7). Rating scales for clinical evaluation, internet-based tools, completed by physicians, and diaries/questionnaires, completed by patients and caregivers have been developed to improve disease assessment of the clinical features of the disease (8, 9). However, the information from the diaries is often unclear and the limited time of the neurological assessment, during patient encounters, does not provide sufficient information to accurately determine the severity of symptoms that patients experience in their daily living and their own environment. This often results in underestimating or overestimating the symptoms of the disease and could lead to sub-optimal therapeutic interventions (10).

To address this issue, sensor-based systems have been developed for the quantitative evaluation of motor symptoms' severity, and some of them have been specifically designed for tracking PD symptoms (11–14). The idea of telemedicine is not new (15), but during the last 20 years, technological advancements and enhancement of telecommunication infrastructure, have made the accurate remote monitoring of patients with diverse disorders, such as PD, possible (16, 17). For neurodegenerative diseases, affecting both motor and cognitive functions, technological health services have emerged as useful tools for tackling the challenge of patient-physician contact, in cases where patients' visits to medical centers are laborious (18). Especially during the COVID-19 pandemic, a number of restrictions were imposed, forcing patients, caregivers and healthcare professionals toward limiting their interactions, thus encouraging the use of healthcare practices supported by electronic processes (eHealth) (19). This practice resulted in better healthcare technologies and related services, and led to their widespread adoption (20–22). Apart from remote delivery of health services to overcome barriers in communication and transportation, telemedicine in PD also involves accurate objective symptom detection, monitoring and improvement of follow-up care (18, 23). Different telemedicine modalities have been successfully employed in patients' care, including:

1. virtual visits via video conferencing (24),
2. non-motor symptom assessment/treatment via phone (25),
3. monitoring through wearable devices (23),
4. health applications on mobile phones (mHealth) (26),
5. virtual reality rehabilitation (27) and
6. online speech assessment and rehabilitation (28).

Telemedicine technology enables a patient-centric approach and has been proven to be reliable in the management of specific disease aspects, having comparable results with current medical practice (29, 30). Furthermore, the cost-effectiveness of telemedicine in PD has been analyzed in several studies that show considerable resource savings stemming from technology enhanced and home-based monitoring (31–34). Of course, disadvantages do exist, since telemedicine may limit the diagnostic ability and the patient-physician relationship, however, healthcare technology devices are currently recommended for use in response to existing clinical needs and have been integrated in the PD multidisciplinary care (19, 35). Wearable devices are the spearhead of eHealth modalities in PD. The reason for this lies mainly in the fact that symptoms' fluctuations in patients with PD cannot be reliably addressed with the current clinical limited assessment, while wearables can offer prolonged objective measurements of motor symptoms (11, 23).

Most of these wearable systems are based on inertial sensors that consist of accelerometers and gyroscopes. Griffiths et al. (36) presented a wearable system composed of a single sensor in the form of a wrist-worn watch and reported high accuracy in the detection of bradykinesia and dyskinesia, compared to clinical examination (37). The system was further validated in subsequent studies for fluctuation detection (38, 39), impairment in activities of daily living (40) and overall therapeutic management of patients with PD (41). However, since this system is worn on a single wrist, it can only measure a subset of PD symptoms, and specifically those related to that limb. Thus, gait impairment, dyskinesia, as well as freezing of gait, cannot be detected as they would require additional sensors (42–44). As a result, the presented system lacked the ability to extract information comparable with patient diaries,

or more importantly, with a full neurological examination. Ferreira et al. (37) introduced another system based on wearable sensors and accompanied by a mobile app, for which they evaluated its wearability and usability (45). The clinical validity of the system was also evaluated and high accuracy was reported in leg dyskinesia assessment and fluctuation detection, without any report about the detection of other parkinsonian symptoms (13). For the detection of specific symptoms, other sensors have been developed as well (12, 46). A recent systematic review described wearable solutions developed for PD and summarized their advantages and disadvantages (47). Although the advancements in telemonitoring solutions are significant, monitoring technologies for PD haven't yet gained wide acceptance among physicians, patients and caregivers. The reason lies in the lack of adequate evidence for validating their clinical utility in specific conditions, including their use in the selection of suitable patients for invasive therapies (48–50). During the last couple of years, a paradigm shift in the monitoring of patients with PD is taking place. But, in order to be successful, it needs further support that can only be provided by the development of devices that can accurately monitor parkinsonian symptoms and evaluate their fluctuations in the long term. Perhaps the most important aspect of this process is to prove that the output of the monitoring devices is accurate, thus extensive validation is necessary (23). Preliminary data on acceptability originating from patients of these systems are encouraging and have helped define outcome measures for clinical studies (51).

To that end, the PDMonitor® system (PD Neurotechnology Ltd.) was developed for the continuous monitoring of Parkinson's disease symptoms, designed to be used by patients in their own environment. The PDMonitor® is an innovative device consisting of five wearable sensors, to be worn on the trunk and then limbs, and is able to detect remotely most motor manifestations of PD, including the daily activity of patients in their home. It is also intended for long term follow-up monitoring of each patient with the goal of objectively assessing the course of the disease. The aim of this work was to use complementary data from 2 multi-site clinical studies, described in Section 2.3, as a first systematic validation of the usability and the performance detected of the PDMonitor® system in the identification, quantification and monitoring of PD motor symptoms. More specifically, the main questions this works aimed to answer, were:

- *Is the device feasible to be used by patients and caregivers without supervision?*
- *Is the device reliable when compared to expert assessment of PD symptoms?*

# 2. Materials and methods

Section 2.1 describes the body-worn system used for the evaluation of PD motor symptoms. Section 2.2 briefly describes the methods and algorithms used by the system. Section 2.3 briefly describes the data collection used for the initial algorithm verification, as well as the studies performed for the validation of the device.

## 2.1. The PDMonitor® system

The PDMonitor® system developed by PD Neurotechnology® Ltd. is a class IIa CE-marked medical device, intended to be used by patients diagnosed with PD, for continuous home monitoring. The system is comprised of a base, a set of monitoring devices, a set of mounting accessories, a mobile application, a physician web dashboard and a cloud service. The PDMonitor® provides an ecosystem (Figure 1) enabling long term continuous remote monitoring of patients with Parkinson's disease (PwPs).

Physicians have full access to patients' symptom reports at any time, with comprehensive information about almost all PD-related motor symptoms *via* the physicians' web dashboard. Two different patient cases from the study, with different symptoms, as they appear in the web portal, are presented in Figure 2. The PDMonitor® report consists of a heatmap, illustrating the severity of a symptom for a 30-minute interval and a chart with the average symptom intensity for any time of day. The reports also provide the medication schedule and the actual medication intake (as well as nutrition information) reported by the patient via the PDMonitor® mobile application. Although the web dashboard is the default way of accessing the outputs of the system, if there is a need for direct access to the raw IMU data, then one would need to contact PD Neurotechnology Ltd. beforehand, i.e., before the patient uses the device. The components of the PDMonitor® system are the following (Figure 3A):

1. The PDMonitor® SmartBox, used to collect, process and upload data to the cloud. The SmartBox also acts as a docking station for charging the wearable sensing devices (Monitoring Devices) after they have been used. The SmartBox has a size of $170 \times 80 \times 17$ mm and a weight of $\approx 280$ g.
2. Five wearable sensing monitoring devices, used to collect movement data. Each monitoring device has a size of $41 \times 30.6 \times 12.85$ mm, a weight of $\approx 16$ g and contains a 9-degree inertial measurement unit (IMU) sensor (accelerometer, gyroscope and magnetometer), the LSM9DS1 from ST Microelectronics. The monitoring devices record data with a sampling frequency of 59.5 Hz, which they store internally, until they are docked to the SmartBox, at which point the data are transferred and uploaded to the Cloud. The LSM9DS1 has a linear acceleration full scale of $\pm 2/\pm 4/\pm 8/\pm 1$ g, a magnetic field full scale of $\pm 4/\pm 8/\pm 12/\pm 16$ gauss and an angular rate of $\pm 245/\pm 500/\pm 2000$ dps.
3. PDMonitor® accessories (i.e., ClipFrame, StrapFrame, Wristband and Velcro straps), used to attach the monitoring devices to the patient's body, and more specifically, near the ankles, wrists and waist. Regarding the ankles, the monitoring devices are attached to the lateral compartment of the leg, slightly above the ankle, whereas the wrist monitoring devices are attached to the posterior compartment of the forearm around the wrist, much like a watch. The waist monitoring device is placed near the anterior midline of the body at the height of the waist. The waist sensor can be mounted, either with a velcro band paired with a StrapFrame, or with a ClipFrame, based on the patient's preferences. The proper device placement is presented in Figures 3B, C.

Each PDMonitor® monitoring device produces raw measurements from its embedded IMU sensor. Subsequently,

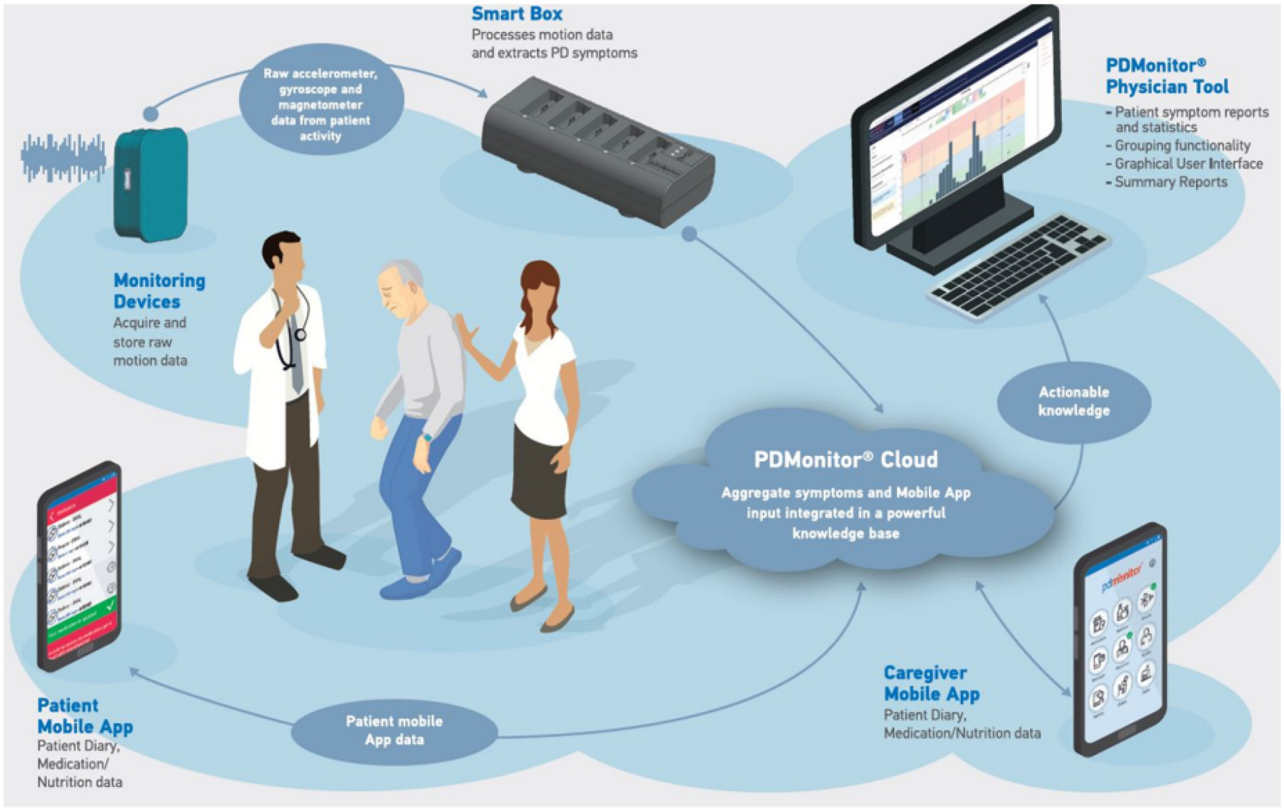


FIGURE 1
The PDMonitor® ecosystem.

all 5 are synchronized and their data are uploaded to the Cloud when docked to the SmartBox. Then, the symptom evaluation process transforms the raw IMU signals from all monitoring devices to a unique set of movement features, which are in turn converted to symptom estimations for 30-minute windows, correlated to UPDRS or other relevant scales' items. The final movement items estimations are the output of the PDMonitor® device to the cloud. The PDMonitor® symptom evaluation involves data analysis with digital signal processing techniques, feature extraction algorithms, and machine learning. The final outcome is the automated quantification of basic daily activities (walking, resting/sitting, lying), main parkinsonian motor symptoms (tremor, bradykinesia, gait and balance impairments), and the most important motor complications associated with the antiparkinsonian therapy (ON/OFF fluctuations, LiD and FoG). Based on the system's intended use, the 5 monitoring devices must be worn by the patients during their waking hours, and then docked for data transfer and recharging during the rest of the day. However, the sensors have a battery duration of up to 50 h and thus this is considered the maximum recording duration.

Although there are 5 monitoring devices to be attached to a patient's body, PDMonitor® is easy to use, due to its ability to automatically identify the placement of each sensing device on the waist and limbs (52). As a result, the users (patients and/or caregivers), do not need to match each sensor, individually, to a corresponding body position, thus, reducing both the time necessary for mounting the sensors and the probability of user error. Moreover, PDMonitor's® sensor-mounting accessories (i.e., the Wristbands, StrapFrames and ClipFrames) act as active measures against inappropriate use (i.e., placing them in a wrong orientation). However, caution by the users remains a prerequisite to place, both the wrist, and the ankle sensors facing outwards, to prevent misidentification between the left and right limbs. An inwards placement of the limb monitoring devices would be improbable, given the awkward and uncomfortable nature of this configuration, especially for the wrist sensors.

## 2.2. The PDMonitor® algorithms

The PDMonitor® algorithms were initially designed, and preliminary developed, during the PERFORM project (53–55). Subsequently, they were further/mainly developed and verified in a Pilot study performed at the University Hospital of Ioannina (see Section 2.3.3).

The symptom evaluation process is similar for all PDMonitor® symptom assessment algorithms (Figure 4). More specifically, all devices collect IMU sensor raw measurements (accelerometer, gyroscope, magnetometer). Each sensor has three axes (X, Y, Z),

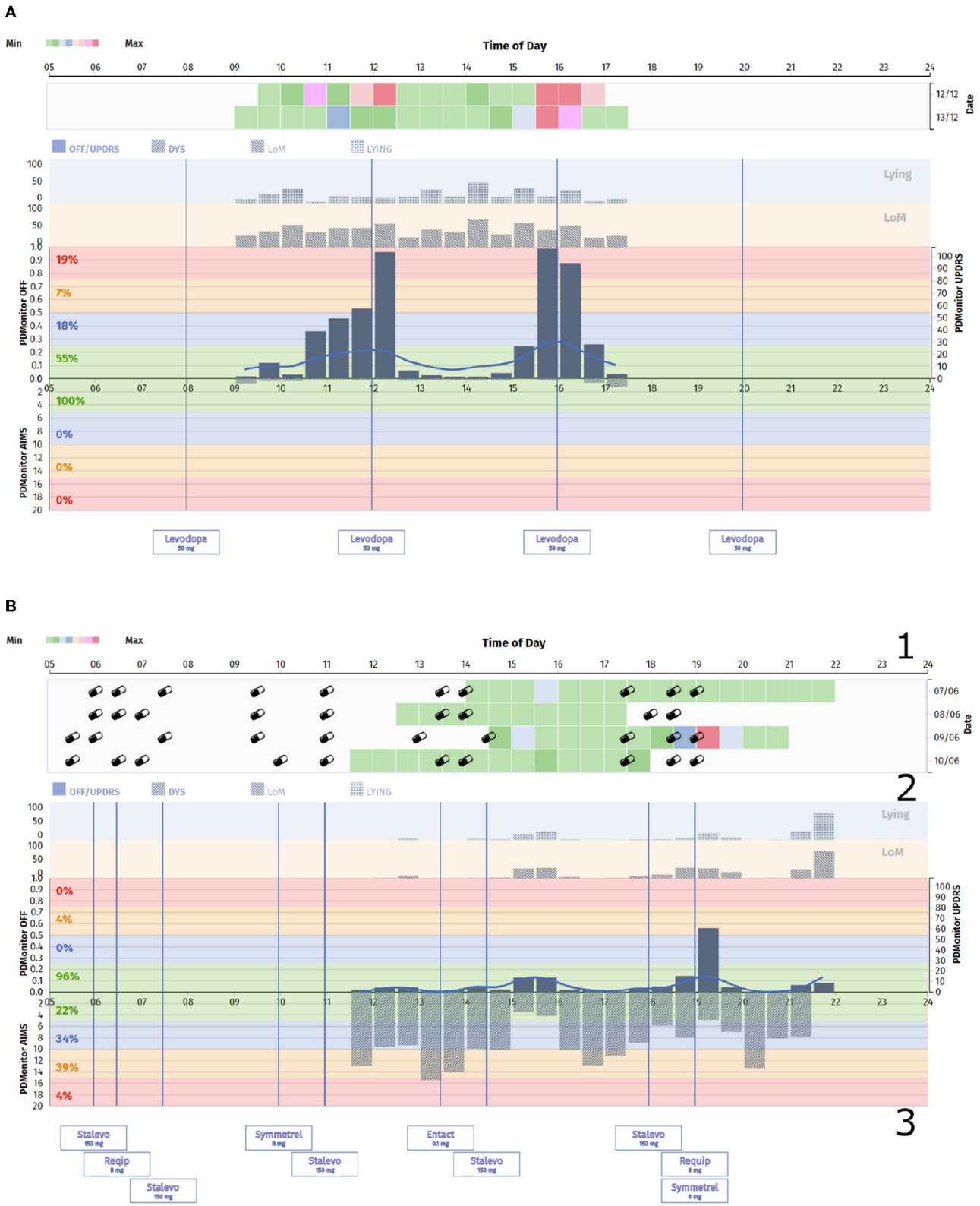


FIGURE 2
**(A)** PDMonitor® OFF/Dyskinesia chart for a patient with clear fluctuations. **(B)** PDMonitor® OFF/Dyskinesia chart for a patient with significant dyskinesia. In this report the different areas of interest have been marked. Specifically, the area 1 illustrates the severity of a symptom for a 30-min interval, including medication and nutrition information, the area 2 presents a chart with the average symptom intensity for any time of the day, while the area 3 lists the medication the patient receives.

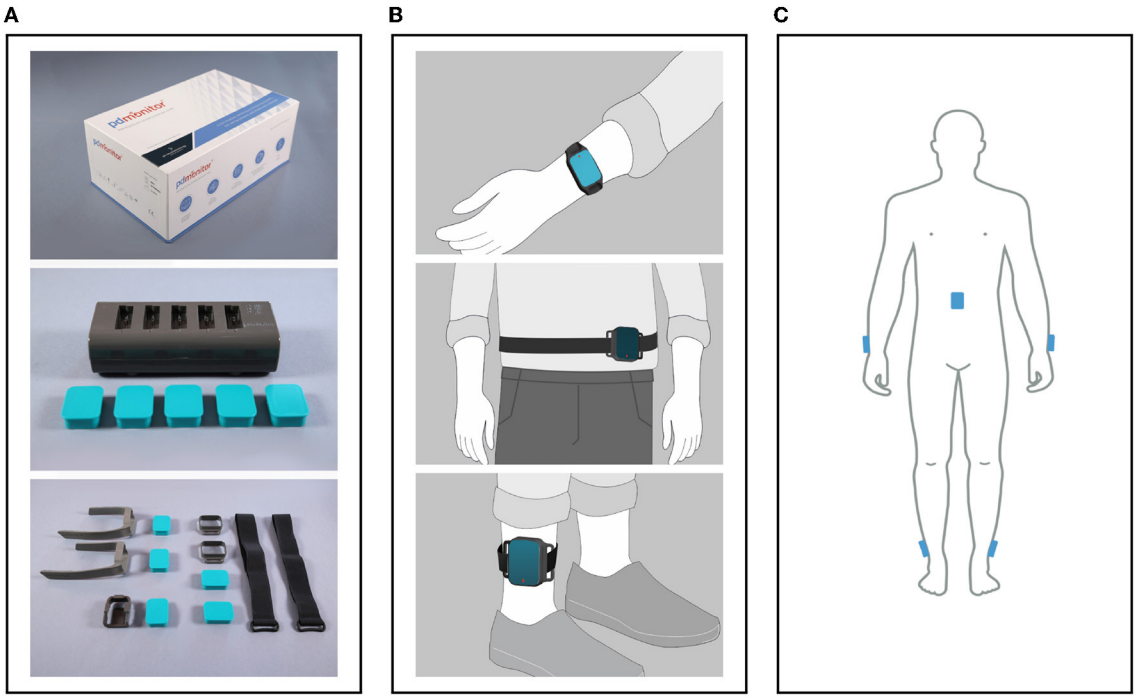


FIGURE 3
**(A)** The PDMonitor® box, docking station, monitoring devices and accessories. **(B)** The PDMonitor® monitoring devices' placement on the wrists, torso and ankles. In the middle image, the waist sensor has been placed to the waist with a velcro band and a StrapFrame, but there is also the option to be mounted on a belt using a ClipFrame accessory. **(C)** The placement of all monitoring devices on the appropriate body position at the same time.

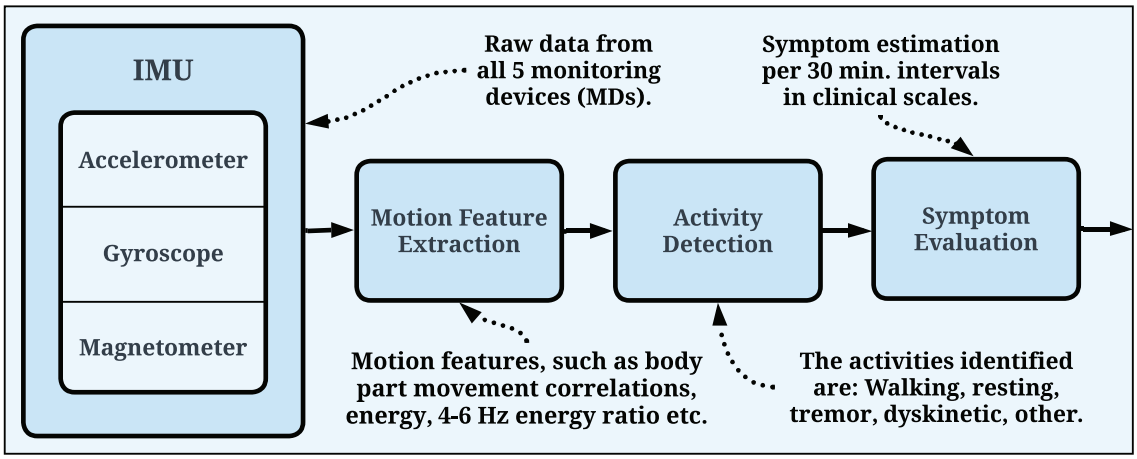


FIGURE 4
General pipeline used by the PDMonitor® algorithms. The raw IMU signals are used for motion feature extraction, which are, in turn, utilized for symptom evaluation. The evaluation is generated every 30 min and the symptoms are presented in relevant clinical scales.

therefore it is a 9-degree measurement system. The PDMonitor® symptom evaluation process transforms the raw IMU signals from all monitoring devices to a unique set of movement features, which are in turn converted to UPDRS, or other clinical scales' items, estimated in 30-minute windows. The first step in the overall PDMonitor® symptom evaluation methodology is activity detection as described in Section 2.2.1. After activity detection, symptom-specific processing is used to address the challenging task of detecting, quantifying and assessing each of the cardinal PD motor symptoms. Machine learning is mainly applied in this step in order to discriminate different types of body movement (walking, normal activity, leg tremor and dyskinesia) and in every case a different kind of symptom assessment takes place. In the following sections, the methods and algorithms used in the PDMonitor® system will be briefly described, mainly focusing on activity and posture detection, dyskinesia, bradykinesia, gait, tremor and

ON/OFF fluctuations. Due to space limitations, algorithms are not presented in detail. Nonetheless, the main features used by each method are described.

### 2.2.1. Activity detection

The PDMonitor® symptom evaluation process for symptom detection and severity assessment follows a hierarchical approach. The main idea is to first identify "regions of interest" based on the activity, where each symptom can be evaluated with high accuracy. For example, regions in the signal identified as rest are used to detect resting tremor, while regions that include climbing of stairs are used to detect gait impairment. This requires accurate activity detection algorithms. The main activities identified were: Walking, Resting, Tremor, Dyskinetic and Other. Walking pertains to free walking (excluding stair climbing), however the patients that took part in the generation of the dataset, were free to move without restrictions. Hence, the dataset itself, and as a result the symptom evaluation process, take into account numerous other activities (i.e., rehabilitation activities), which were not explicitly annotated. Those activities are included in the "Other" category.

The PDMonitor® activity detection is based on motion features extracted from all body parts, as well as from both time (signal energies, average values, standard deviations, jerk, correlation of signals from different body parts etc.) and frequency domain (energies of gyroscope signals within different frequency bins). The objective of the activity detection is to evaluate different activities based on the quantification of body movement, movement coordination (walking is a coordinated body motion whereas dyskinesia is not) and posture (by discriminating between standing, sitting and lying). In total, over 140 features are extracted. A wrapper feature selection method (56) is applied to identify the best feature set for Bayes classification. The activity detection method was developed and verified with data from the pilot study. A Naive Bayes classifier is applied using a leave-one-out technique, which minimizes the risk of overfitting and bias. With this approach, PDMonitor® managed to identify the different body movements with high accuracy ($> 90\%$). The identification of each activity spawns further analysis for different symptoms and motor characteristics. Gait disturbances are evaluated exclusively during the "Walking" activity, dyskinesia severity is assessed during the "Dyskinetic" activity, whereas (wrist) tremor and arm bradykinesia are assessed during the "Resting" or "Other" activities. The general pipeline used by the PDMonitor® algorithms is presented in Figure 4.

### 2.2.2. Dyskinesia

The dyskinesia evaluation algorithm requires activity detection to be implemented first. Dyskinesia severity is better assessed while resting, therefore walking regions are excluded. The first step is to find dyskinetic regions in 5-minute window intervals. In a 5-minute window, the initial detected activity is combined with motion features from all body parts into a new feature vector enabling the detection of dyskinesia and the assessment of its severity.

### 2.2.3. Bradykinesia

The PDMonitor® method for the detection and assessment of bradykinesia is based on the evaluation of a patient's movement speed. However, to assess movement capacity, actual movement must occur and be detected. Therefore, bradykinesia evaluation starts with the detection of specific movements and the estimation of their speed. Movements that are slower than those calculated for the control group are considered as bradykinetic movements. The percentage of the bradykinetic movements for a 30-minute window is the so-called "PDMonitor® bradykinesia score" which is significantly correlated with the UPDRS score of arm bradykinesia (items 23, 24 and 25).

### 2.2.4. Gait

The gait assessment requires the identification of walking regions and the detection of individual steps. The main parts of the method are: signal acquisition and filtering, activity detection, consecutive candidate walking regions' merging, steps detection, gait features extraction and gait impairment score extraction based on gait features. The detection of gait is based on the activity detection method. The basic window used for activity detection is 4 s. Consecutive windows classified as "Walking" are merged into larger walking regions in order to improve the statistical estimation of gait parameters. After walking region detection and merging, a step detection procedure is applied. Three peaks are identified for each step: Terminal Contact (TC), corresponding to heel off, Max Rotational Speed (RS), corresponding to mid-stance and Initial Contact (IC), corresponding to heel strike. Then, a number of features are estimated based on the detected peaks for each step. A number of gait features are extracted (shanks' sagittal range of movement, cadence, swing time, swing time variability among others) and combined in order to build a linear model with the purpose of translating gait features to the gait corresponding item of the UPDRS scale. The feature that dominates the gait impairment estimation is the shanks' range of motion (RoM). This feature is related to the step length, which has been demonstrated to be levodopa responsive (57). Said property (i.e., responsiveness to levodopa) is significant, given that the main purpose of devices such as the PDMonitor® is to equip physicians with the means to better evaluate symptom response to medication, and as a result have finer control over medication dose adjustments and time intake.

### 2.2.5. Freezing of gait

Freezing of Gait (FoG) is a phenomenon described by PD patients as a sensation of their feet being "glued to the ground." FoG is of episodic and unpredictable nature and as such, it is detected as an event, potentially with a duration of just a few seconds, rather than being considered a symptom. FoG is expressed when a patient is either shuffling forward with tiny steps, or suddenly being incapable of starting to walk, or failing to move forward. FoG can also be expressed by the complete absence of movement.

Moore et al. (58) presented a method for the calculation of an index of FoG, based on the principle that FoG is usually combined with short hesitation steps that could be detected. However, this is not always the case. A comprehensive definition of FoG such as the one used by Djurić-Jovičić et al. (59), differentiating between FoG

paired with trembling and FoG paired with complete motor blocks, seems to address the problem by incorporating different types of FoG events. Nonetheless, FoG events expressed with full motor blocks are difficult to accurately detect in a home environment and they would most likely introduce a lot of false positives. Marcante et al. (60) used a system based on a pair of pressure insoles equipped with a 3D accelerometer in order to detect FoG episodes. Using it in a controlled environment they were able to report a 90% accuracy in FoG detection. The PDMonitor® evaluates the presence of FoG events before the initiation of walking, during pausing phases. FoG is then detected based on the freezing index introduced by Moore et al. (58), which is estimated using data from the ankle gyroscope, as well as other features necessary for the discrimination between FoG and other kinds of activity (i.e., tremor an/or dyskinesia).

### 2.2.6. Tremor

PDMonitor® evaluates resting tremor occurring in a body segment while maintained at rest. Action (or kinetic) tremor are not evaluated by the current version of PDMonitor®.

Leg tremor detection is based on the activity detection method and specifically on the activities classified as "Tremor." The activity detector is a probabilistic classifier which provides a posterior probability of a sample X belonging to a specific class, that is $P(Class|X)$. The posterior probability of the activity detection classifier for the "Tremor" class, i.e., $P(Class = Tremor|X)$ represents mainly leg activity and is averaged over a 30-minute window.

Wrist tremor assessment is based on the method presented by Cancela et al. (45), which mainly relies on the gyroscope's signal. The method consists of: signal preprocessing, tremor detection, tremor amplitude estimation and rest/posture detection. Both wrist tremor detection and amplitude estimation are based on 3-s windows. Typically, tremor has a dominant frequency on the 3.5 to 8 Hz frequency band, whereas the voluntary movement frequency's range is below $2.5 - 3$ Hz. A number of features are extracted, including the energy of low-pass and high-pass gyroscope signals, defined, as a reference, as following:

$$En = \sum_i \sqrt{s_x^2(i) + s_y^2(i) + s_z^2(i)} \quad (1)$$

In Equation 1, $s_k(i)$ is the $i$-th sample of the $k$ axis of the signal.

A C4.5 decision tree was employed for wrist tremor detection. The wrist tremor amplitude estimation and consequently its translation to UPDRS item scores follows the approach of Rigas et al. (53) and uses a fuzzy linear function to correlate with the score of the UPDRS item 20.

### 2.2.7. ON/OFF and fluctuations

Motor fluctuations refer to the transitions between the ON and the OFF periods. During the ON periods, medication is in effect and patients with a well-adjusted treatment plan should not experience any motor symptoms. An exception is dyskinesia, which occurs in more advanced stages of the disease. During the OFF periods, medication is not alleviating the symptoms, although is should. In advanced stages of the disease, most PD patients will experience OFF periods, with increased symptom severity, manifested unpredictably during the day.

The time during which a patient is in an OFF state is an important parameter used to assess interventions. As a result, obtaining precise information, such as the onset and the duration of OFF states, on the long term evolution of ON/OFF fluctuations is essential to optimize therapy. Currently, the only available method to collect such information is self-reported diaries. A wearable device capable of collecting PD motor fluctuations in an objective and reliable way would help overcome the limitations of those diaries and as a result would provide physicians with a valuable tool for reducing OFF periods and dyskinesia.

PDMonitor® estimates the probability of a patient being in the OFF state based on a Naive Bayes classifier, taking as input the rest of the PDMonitor outputs. A feature importance technique based on the Relief method (61) is conducted in order to evaluate the importance of each feature in the detection of OFF. The features used, can be sorted into groups of interest as presented in Table 1. For the purposes of this work, a similar analysis was performed based on study data including patient diaries and UPDRS expert evaluations, in order to estimate the importance of each feature. The results for the accuracy of OFF detection are presented in Section 3.2.1.

TABLE 1 The features used by the PDMonitor® for the detection of OFF, sorted into groups of interest.

| Group name | PDMonitor® | UPDRS items |
|---|---|---|
| Activity | Lack of movement, Activity, Resting time | - |
| Gait | Gait, Gait with no dyskinesia | 29 |
| Tremor | Tremor score for LL, RL, LW, RW | 20, 21 |
| FoG/PI | Freezing of gait/Postural instability | 14, 30 |
| Rigidity | - | 22 |
| Body Bradykinesia | - | 31, 27 |
| Arm Bradykinesia | Bradykinesia score for LW, RW | 23, 24, 25 |

In the last column, there is a set of UPDRS items that correspond to the same groups. LL, RL, LW, RW stand for Left/Right Leg and Left/Right Wrist, respectively.

## 2.3. Study description

The data used in this work to validate PDMonitor® originated from two studies (Figure 5). Specifically:

1. A study with PD patients (PDNST001) for the evaluation of the PD motor symptom assessment algorithms of the PDMonitor®, as well as for the wearability and usability of the PDMonitor device (Section 2.3.1).
2. A study with age-matched healthy subjects (PDNST002) for the evaluation of the wearability/usability of the device, as well as for collecting data in order to evaluate the sensitivity of the device's algorithms (Section 2.3.2).

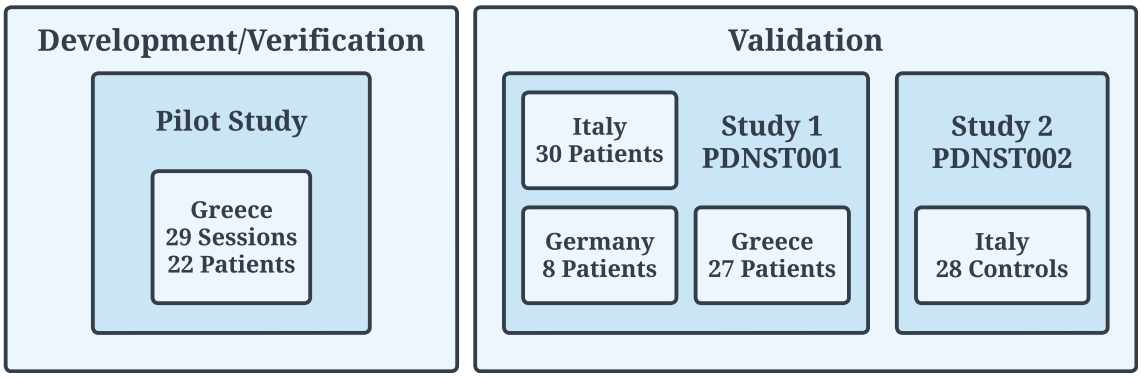


FIGURE 5
Clinical trials (Pilot, PDNST001, and PDNST002) that took place for the generation of datasets used for the development/verification and validation of the algorithms of the PDMonitor® device. The PERFORM project, used for the initial development of the algorithms, is not related to the studies described in the body of this manuscript.

As mentioned in Section 2.2, the data for the main development and verification of the PDMonitor® algorithms were generated during a Pilot study which is described in Section 2.3.3.

### 2.3.1. Clinical study with PD patients (PDNST001)

The PDMonitor® system was used in the study PDNST001, entitled "Assessment of Parkinson's Disease's Motor Symptoms Using Inertial Measurement Devices", in which sixty-five (65) PD patients were recruited. The total duration of the study was 5 months and it included the following two phases:

1. Phase I: Data collection for inpatients, with a participation duration not exceeding 6 h. During that time expert evaluations based on clinical scales were also regularly conducted.
2. Phase II: Data collection from continuous monitoring of outpatients at their home, or in care facilities, with a duration not exceeding seven (7) days and at least 7 h per day.

Phase II participants were a subset of patients who already participated in Phase I. The aim of the study was the assessment of PDMonitor®, as an integrated monitoring system for Parkinson's disease, ultimately intended to increase patients' independence, improve their quality of life and reduce the costs associated with the disease.

**Phase I.** During the Phase I of the study, the patients wore the system while staying at the hospital. At the beginning of the recording with the PDMonitor®, a clinical examination based on the Unified Parkinson's Disease Rating Scale (UPDRS) (62), and the Abnormal Involuntary Movement Scale (AIMS) (63) took place, preferably while patients were in an "OFF" state. If a patient was in an "ON" state, the clinical examination was postponed and rescheduled. Each patient was examined at regular intervals (30 minutes) by a physician and the whole session was recorded by a camera. The video obtained was used for the identification and evaluation of symptoms by third-party physicians (expert evaluations). The duration of the PDMonitor® recording in Phase I was between 3 and 6 h for each patient. For the proper evaluation of the patients' symptoms, a diary was kept by their caregivers or nurses. Every half hour the specialized nurse or the physician asked the patient to perform specific motor tests and recorded their symptoms. During each session, patients were instructed to perform random activities that could last several minutes, for example, climbing up and down a set of stairs, making turns, lying down, standing up, walking while carrying a glass of water, carrying a heavy object, drinking a glass of water, opening and closing a door, taking a walk outside. Also there were more complex activities conducted, such as setting a table for a meal, having a meal, or even using a computer, tablet, or smartphone, etc. Normal daily activities were required in order to reduce the possible bias in symptom assessment introduced by the reduced range of patients' activity in a hospital environment.

**Phase II.** Data collected during Phase II were used to evaluate usability, validate the outcomes of the PDMonitor® system vs. patient diaries as well as to evaluate day-to-day variability. The overall recording run for 1–3 days and with at least 7 h per day, whether a caregiver was present or not. Patients were trained on how to wear and use the system during their participation in Phase I.

Data from Phase I (i.e., gathered from inpatients wearing the device) were used in order to compare PDMonitor® outcomes with both expert annotations (available only in Phase I) and diaries.

**Sites and Participants.** This study took place in three sites:

1. the Technische Universität Dresden (TU Dresden) in Dresden, Germany,
2. the General University Hospital of Ioannina in Ioannina, Greece and
3. the Ospedale San Camillo IRCCS, and the Padua University Hospital in Italy.

In total, sixty-five (65) PD patients were recruited. The study protocols were approved by the corresponding ethical committees and all recruited individuals signed an informed consent form. The patients' demographics are shown in Table 2.

**Scales and Questionnaires.** For the purposes of the study, the following scales and questionnaires were used:

TABLE 2 Demographics of patients participating in the PDNST001 (top) and PDNST002 (bottom) studies.

| Patient population | |
|---|---|
| Number of participants | 65 |
| Age (Mean ± SD) | 65.8 ± 9 |
| Gender (Male/Female) | 33/30 |
| Years with PD (Mean ± SD) | 8.8 ± 4.9 |
| **Healthy population** | |
| Number of participants | 28 |
| Age (Mean ± SD) | 63.2 ± 9.9 |
| Gender (Male/Female) | 10/19 |

1. Unified Parkinson's Disease Rating Scale (UPDRS) (62). A full UPDRS evaluation was conducted in the start of the session, while the Part III of the UPDRS was performed every 30 minutes.
2. Abnormal Involuntary Movement Scale (AIMS) (63). An AIMS questionnaire was filled by physicians every 30 minutes to evaluate dyskinesia exhibited by the study participants.
3. Patient/Nurse Symptom Diary (64). Diaries were filled every 30 minutes by patients, or nurses, in order to assess ON/OFF states, Dyskinesia, Bradykinesia, Tremor, FoG and general activity.
4. Comfort Rating Scale (CRS) (45). A CRS questionnaire was filled once at the end of the session in order to evaluate whether the device was comfortable to use.

### 2.3.2. Clinical study with healthy individuals (PDNST002)

This study only included a procedure similar to that of Phase I of the PDNST001, and as such, during its course only healthy individuals (controls) used the PDMonitor® device.

**Sites and Participants.** This study took place in the Ospedale San Camillo IRCCS, and the Padua University Hospital in Italy. In total, 31 healthy individuals were recruited, with data being available for 28 subjects. The healthy participants used the device for up to 3 days in a hospital environment, but they were free to move and perform any kind of daily activity, mimicking home daily living scenarios. The data resulting from this study were used mainly for evaluating the robustness of the system's algorithms in order to properly discriminate normal activities and movements from PD symptoms. The study protocols were approved by the corresponding ethical committee and all recruited individuals signed an informed consent form. The participants' demographics are shown in Table 2.

### 2.3.3. Pilot study

The pilot study took place, chronologically, after the PERFORM project and before the PDNST001 and PDNST002 studies described herein with the purpose of data acquisition for developing the algorithms used in the PDMonitor® device. The pilot study used the same protocol as the Phase I of the PDNST001 study, and it included 30 sessions performed by patients staying in the hospital between 4 and 8 h. Each session was recorded on video, and every 30 minutes a UPDRS examination (62) was performed. Moreover, a trained nurse kept a symptom diary for the entirety of each session. For monitoring the pilot study participants, a Shimmer device[1] with 5 sensing elements was used. The sensing elements, were mounted on the ankles, wrists and the torso, in the exact same configuration as the PDMonitor®. The Shimmer device was used for data collection given that the PDMonitor® hardware was still under development at that time.

## 2.4. Statistical analysis

### 2.4.1. Assessment of wearability

The wearability of the device was evaluated based on the Comfort Rating Scale (CRS), filled by patients after completing the Phase II of the PDNST001 study, as well as by the control subjects of the PDNST002. The questions of the CRS are provided in Table 3. The average ratings, resulting from the responses of the patients and the control subjects, were quantitatively and qualitatively analyzed.

### 2.4.2. Assessment of accuracy

The validation of the PDMonitor® system in the identification and quantification of PD motor symptoms, as well as in the complications stemming from PD, in a statistically significant manner, is assessed based on measures of accuracy (for the detection) and measures of correlation (for the severity). Initially, the symptoms extracted through the PDMonitor® were compared against the UPDRS and the AIMS scores resulting from physicians' clinical examinations, conducted in 30-minute intervals.

**Agreement with Expert on the Detection of Specific Symptoms**. For the statistical analysis, a dataset was created for each symptom, which included pairs of PDMonitor® 30-minute estimations, as well as the corresponding UPDRS/AIMS items. The UPDRS/AIMS items were converted to a binary scale based on the clinical thresholds for defining a mild (or more severe) presence of a symptom. Cases with a slight symptom presence were ignored for this analysis. Then, for each symptom, an analysis based on a receiver operating characteristic (ROC) curve (65) was used to evaluate the corresponding thresholds to be set in the PDMonitor®. Given the thresholds obtained from the ROC analysis, a confusion matrix was computed. Accuracy, specificity and sensitivity measures were estimated and reported (Section 3.2.1).

For each symptom, specific groups of different symptoms' intensity were defined. Group differences were evaluated using the *t*-test method and box plots were generated using the Seaborn Python library (66). The created box plots are

1 http://www.shimmersensing.com

TABLE 3 All the questions included in the Comfort Rating Scale (CRS), a standardized questionnaire used in our work as a tool of assessing the wearability of the PDMonitor® system.

| Section | Description | Controls | Patients |
|---|---|---|---|
| Emotion | I feel worried and embarrassed. | 0.8/20 | 1.9/20 |
| | I feel tense. | 0.1/20 | 1.8/20 |
| | I would wear the device if it was invisible. | 7.4/20 | 7.1/20 |
| Attachment | I feel the device on the body. | 2.3/20 | 3.5/20 |
| | I feel the device moving. | 1.8/20 | 3.0/20 |
| | I was not able to move as usual. | 0.0/20 | 2.6/20 |
| | I have difficulty in putting on the device. | 1.1/20 | 5.9/20 |
| Harm | The attached device causes me some kind of harm. | 0.0/20 | 0.0/20 |
| Perceived change | I feel more bulky. | 1.0/20 | 0.9/20 |
| | I feel change in the way people look at me. | 2.0/20 | 3.0/20 |
| Movement | The device obstructs my movements. | 0.3/20 | 2.6/20 |
| Anxiety | I do not feel secure with the device. | 0.0/20 | 0.5/20 |
| | I feel that I do not have the device properly attached. | 0.5/20 | 1.1/20 |
| | I feel that the device is not working properly. | 0.0/20 | 0.8/20 |

In the "Controls" and "Patients" columns, we present the average ratings that resulted from the responses of the control subjects of the PDNST002 study, as well as the patients of the Phase II of the PDNST001 study to the CRS questionnaire.

presented in Section 3. Group differences in some cases included measurements from the same patient. Therefore, patients do not belong to a specific group, neither have the same number of measurements in the same group. As a result, given this degree of variability and non-determinism, the assumption of the samples being independent, as well as the use of the t-test is justified.

**Total time estimation**. Subsequently, the thresholds indicating a significant symptom presence were employed to extract, per session, the total time of its presence, as measured by both the experts and the PDMonitor® (Section 3.2.2) respectively.

A Bland Altman analysis (67) was also performed and is presented in Section 3. The intra-class correlation of PDMonitor® estimation of the total time of a symptom's presence was also evaluated. To that end, the data from Phase II of the PDNST001 study were employed. The total symptom presence was estimated, for the same patient, over a number of different days, resulting in a dataset containing those estimations in pairs, forming a dataset of day-to-day symptom presence estimations. Both Pearson and Spearman correlation were used as measures of correlation and a Bland Altman analysis (67) is also reported for the bradykinesia case. The Bland Altman analysis was performed using the Matlab implementation (68). The Standard error (SSE), the Coefficient of Variation (CV) and the RPC reproducibility coefficient ($1.96 * SD$) are included in the analysis.

**Agreement on Day-To-Day Symptom Evaluation.** For the evaluation of the day-to-day agreement of PDMonitor® measures, two sets of data were used. The first, was patient data from the Phase II of the PDNST001 study, while the second, was data of healthy individuals from the PDNST002 study. The agreement was evaluated for all those patients, and control subjects (healthy individuals), having more than 1 day of monitoring activity. For each symptom, the average severity was estimated per day, and then pairs of different days were compared. Similar to the case of the total time estimation, for the day-to-day symptom evaluation, a Bland Altman analysis was performed, and both Pearson and Spearman measures of correlation were employed to evaluate the day-to-day agreement.

# 3. Results

## 3.1. Assessment of wearability

The results of the Comfort Rating Scale (CRS) for both patient and control subjects are presented in Table 3. On top of the results from the CRS questionnaire, some key findings regarding the wearability of the system, acquired through the interaction with the patients of the study, are presented below. First, it took patients about 5 minutes on average (5.3±2 minutes ranging from 2 to 10.25 minutes evaluated on 39 patients), to put on all five monitoring devices (monitoring device). The procedure was recorded on video and the reported time durations were estimated based on those recordings. The wide spread in the time necessary to put on the device, was expected, and it is attributed to some patients exhibiting significant movement impairment or being in an OFF state when they were instructed to wear the device. Second, the study subjects indicated that the monitoring device worn on the waist seems to be more inconvenient compared to the devices worn on other body parts. Third, disease duration did not affect the time patients needed to put on the monitoring devices. For all patients, when comparing the time to put on the sensors to the disease duration, the Pearson's correlation coefficient (R), and its p-value, indicated that there was no significant correlation ($r = -0.123$ with $p = 0.77$,

TABLE 4 Evaluation of the accuracy of PDMonitor® vs. 30-min expert evaluations (UPDRS/AIMS) or diaries (for the OFF case).

| PDMonitor® | Scale item | Thres.[a] | Conf. Matrix[b] | Pos./Neg. | Acc./Spec./Sens.[c] |
|---|---|---|---|---|---|
| Arm brad. (UPDRS) | $23 + 24 + 25 > 4$ | 0.7 | 208/41/137/781 | 249/918 | 0.85/0.85/0.84 |
| Gait (UPDRS) | $29 > 1$ | 1.6 | 70/39/7/903 | 109/910 | 0.99/1.0/0.67 |
| Wrist tremor (UPDRS) | $20 > 1$ | 1.64 | 90/17/2/2,858 | 107/2860 | 0.99/0.99/0.84 |
| Leg tremor (UPDRS) | $20 > 1$ | 0.16 | 28/2/1/1,440 | 30/1441 | 0.99/0.99/0.93 |
| Dyskinesia (AIMS) | AIMS $> 4$ | 1.66 | 68/15/9/1,607 | 83/1616 | 0.99/0.99/0.82 |
| OFF (Diaries) | OFF | 0.5 | 29/5/18/571 | 34/589 | 0.96/0.97/0.85 |
| FoG (UPDRS) | $14 > 1$ | 0.02 | 10/2/1/61 | 12/62 | 0.96/0.98/0.83 |

The threshold derived by a ROC curve analysis (Thres.), the confusion matrix, the number of positives (true positives plus the false negatives), negatives (true negatives plus false positives), as well as the accuracy, specificity and sensitivity are also provided. The last line of the table presents the accuracy of the freezing of gait discrimination for the "Freezing" patients compared to the "No freezing" patients and the control subjects. The freezing of gait is evaluated per patient, instead of the 30-minute evaluations of the other outputs presented in this table.

[a]Threshold for the corresponding PDMonitor® measure extracted from the ROC analysis.

[b]True positive/False negative/False positive/True negative.

[c]Accuracy/Specificity/Sensitivity PDMonitor® measures are compared against specific scale items provided in the column "Scale Item."

for Germany, $r = -0.195$ with $p = 0.38$, for Greece and $r = 0.67$ with $p = 0.32$, for Italy). As expected, patients who had no help putting on the sensors, needed more time than patients assisted by a caregiver (6.28 vs. 4.67 minutes).

## 3.2. Assessment of accuracy

### 3.2.1. Agreement with expert on the detection of specific symptoms

In this section, the results regarding the agreement of the device with the expert assessments (UPDRS/AIMS evaluations performed every 30 minutes), and the symptom diaries, are presented.

**Bradykinesia.** PDMonitor® arm bradykinesia estimation for 30-minute windows had significant correlation with the UPDRS arm bradykinesia subscore ($r = 0.68$) and had a rather high accuracy (0.85) in detecting patients with a sum of the bradykinesia UPDRS subscore (sum of UPDRS items 23, 24 and 25) larger than 4, as presented in Table 4. In order to further evaluate the device's performance in discriminating bradykinesia impairment, 4 bradykinesia groups were considered:

1. control individuals (referring to healthy subjects),
2. patients with 0 bradykinesia UPDRS subscore,
3. patients with $< 4$ bradykinesia UPDRS subscore,
4. patients with $> 4$ bradykinesia UPDRS subscore.

The PDMonitor® bradykinesia estimation distributions for those groups are presented in Figure 6A. All groups have statistically significant different means, indicating the rather good correlation between the PDMonitor® estimation and the arm bradykinesia, annotated by the experts.

**Dyskinesia**. Based on the method described in Section 2.2.2, the accuracy of the dyskinesia detection method was evaluated for the discrimination of 30 minutes' regions where the patients' AIMS score, as annotated by experts, had a value greater than 4, compared to that of those participants (control and patients) with no dyskinesia. The threshold of 4 is the minimum AIMS score for which the device can provide the most accurate results regarding the sensitivity and specificity of the detection. The accuracy obtained (Table 4) was 0.99 with an excellent specificity (0.99) and sensitivity (0.82). A high specificity is paramount, considering that the device is intended to be used in daily living and during free activities where normal movements could be confused with dyskinesia.[2] To this end, the use of healthy subjects for the evaluation of the algorithms was rather important in order to ensure that dyskinesia can be accurately discriminated. Similarly to bradykinesia, 5 groups were considered based on their AIMS score. Those groups were:

1. control individuals (healthy),
2. patients with a 0 AIMS score,
3. patients with $< 4$ AIMS score,
4. patients with $4 - 12$ AIMS score,
5. patients with $> 12$ AIMS score.

The PDMonitor® dyskinesia estimation distributions for those groups are presented in Figure 6C. All groups have statistically important differences indicating a rather good performance of the device in discriminating dyskinesia. It should be noted that PD patients with no dyskinesia have significantly lower dyskinesia estimations compared to both patients with slight dyskinesia (AIMS $< 4$) as well as healthy subjects. The only shortcoming observed with our method was the underestimation of dyskinesia in the rare case of patients having significant dyskinesia on the head or the neck and less dyskinesia in their extremities.

**Gait**. The PDMonitor® gait score was evaluated for the detection of gait impairment in 30-minute windows taking into account mild and severe gait impairment according to the score of the UPDRS item 29. For the evaluation, annotations with a score of 1 in the UPDRS item 29, as well as regions with dyskinesia, were excluded. The accuracy of gait impairment detection is presented in Table 4. A rather high accuracy is achieved (0.99 accuracy with $>0.99$ specificity and 0.67 sensitivity). PDMonitor® gait score distributions for the different expert UPDRS assessments are provided in Figure 6B.

2 It should be noted that according to the device's instructions for use, the device is not intended to be worn during intense activities (i.e., any activity other than walking). The reason being, signals logged by the IMU sensors during intense activities would contain abrupt changes that would contaminate the system's output.

10.3389/fneur.2023.1080752

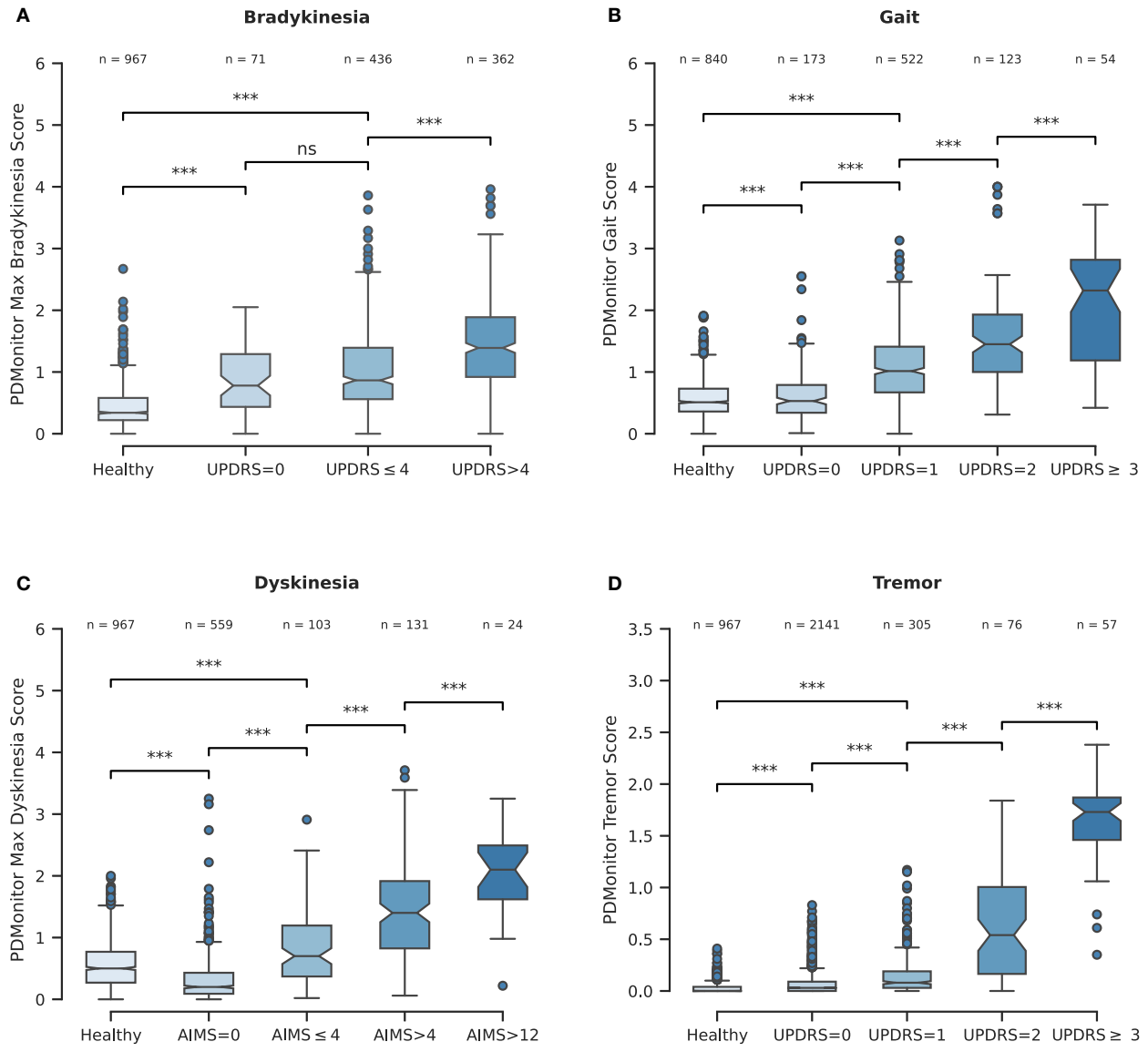


FIGURE 6
**(A)** Boxplot representing the PDMonitor® bradykinesia score distribution for the different subgroups based on expert UPDRS bradykinesia evaluations. **(B)** Boxplot of PDMonitor® gait score distribution for the different subgroups based on expert UPDRS gait evaluation. **(C)** Boxplot of PDMonitor® dyskinesia score for the different subgroups based on expert AIMS dyskinesia evaluation. **(D)** Boxplot of PDMonitor® tremor (wrist) score distribution for the different subgroups based on expert UPDRS tremor evaluation. The dots represent outliers in the dataset, while the asterisks represent statistical significance. On top of each box there is the number of data points contained within each group. Every data point represents an estimation of the respective symptom for a 30-min window. Regarding the underlying rules for the generation of the box plots, the "whiskers" extend to all points that belong within 1.5 IQR (interquartile range). The rest of the points, lying outside this range, are considered as outliers and are depicted as dots. The asterisks (*) that are drawn on top of the box plots, denote statistical significance and correspond to $p$-values' ranges. Specifically, 4 asterisks would denote $p \leq 0.0001$, 3 asterisks $p \leq 0.001$, 2 asterisks $p \leq 0.01$, 1 asterisks $p \leq 0.05$ while ns denotes $p > 0.05$.

**Freezing of gait**. During the Phase I of the PDNST001 study, 30-minute, in-clinic, sessions were annotated by experts for each patient as "Freezing" or "No-Freezing," based on whether they identified freezing of gait in their UPDRS evaluations. The expert annotations were also compared to symptom diaries, when available. Cases where diaries and expert annotations were in disagreement were excluded, taking into account mainly cases where FoG was not observed during the UPDRS examination. It should be noted that the clinical examination included a walking test requiring the subjects to open a door and pass through it. However, the protocol neither included specific tests or activities to elicit freezing events, nor called for patients to be monitored throughout the session (recorded on video), thus limiting our ability to fully assess FoG events. As a result, the PDMonitor® was evaluated in terms of discriminating between "Freezing" and "No freezing" patients based on a ROC (Receiver Operating Characteristic) analysis. To that end, first the device produced the ratio of the "*number of freezing of gait events*" compared to the "*total number of freezing of gait regions, per 30-minute periods*," and then aggregated those ratios, per patient, for the whole session. Finally

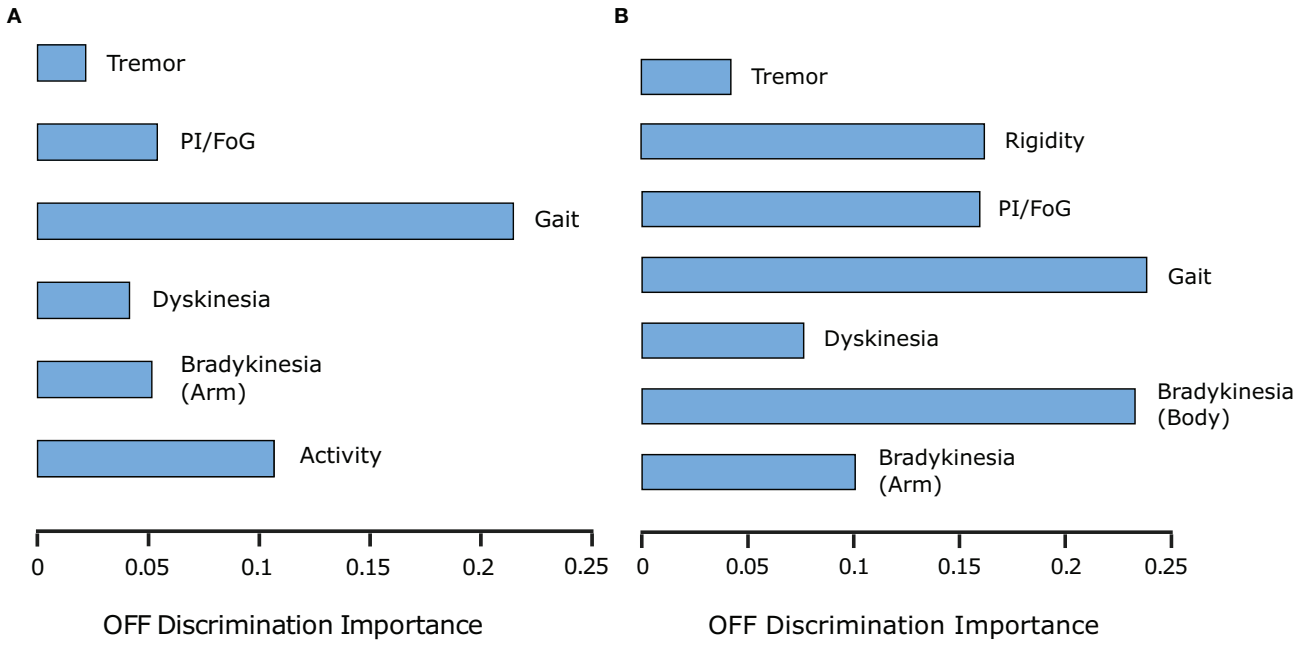


FIGURE 7
**(A)** PDMonitor® output importance for OFF detection (per group defined in Table 1). **(B)** UPDRS item importance for OFF detection (per group in Table 1).

the ROC analysis for the evaluation of the discriminating power of the device was conducted. The results are presented in Table 4, in which it can be seen that the device had an excellent accuracy in the discrimination of patients exhibiting freezing of gait.

**Tremor**. Wrist tremor with a 30-minute constancy was evaluated compared to the patients' symptom diary. The accuracy of the wrist tremor detection method was initially evaluated. All 30-minute intervals with RW (right wrist) or LW (left wrist) tremor score ($> 1$) in the UPDRS item 20 (tremor at rest) were considered as cases with tremor, whereas 30-minute windows without tremor (taking into account both the legs and the wrists) were considered as negative cases. Again, neighboring windows of different tremor classification where excluded. The confusion matrix is presented in Table 4. The specificity of tremor detection is very high ($> 0.99$) with a significant sensitivity ($> 0.85$). Based on the method described in the corresponding part of Section 2.2.6, the accuracy of leg tremor was also evaluated. Accuracy, sensitivity and specificity, along with the confusion matrix are presented in Table 4. The accuracy of the PDMonitor® in the discrimination between those patients that exhibit more than slight leg tremor compared to those patients that exhibit no tremor in 30-minute intervals is 0.99. As presented in Figure 6D the device is able to accurately discriminate tremor rated with a UPDRS item 20 score of $> 1$. It should be noted that neighboring samples with different UPDRS annotations were not excluded in the box-plot and therefore the overlapping between the distributions could be even smaller in practice.

**ON/OFF and Fluctuations**. PDMonitor® OFF estimation is based on a method combining the individual symptoms and measures produced by the device. The results of the Relief method for assessing the importance of each symptom in estimated OFF periods are presented in Figure 7A. As discussed in Section 2.2.7, a similar analysis was performed trying to estimate OFF periods as were reported in symptom diaries. The results are presented in Figure 7B for PDMonitor® and UPDRS annotations respectively. Features related to gait, postural instability and gait difficulties (PIGD) have the highest importance in discriminating between ON and OFF states consistently in both the PDMonitor® and the UPDRS estimations. The UPDRS body bradykinesia (UPDRS items 27 and 31) had similar importance with gait. However, this was expected since the correlation of gait (UPDRS item 29) with the rising from chair activity (UPDRS item 27) in our study was very high ($r = 0.88$). Therefore, the order of the symptoms' importance is consistent between the PDMonitor® and the expert annotations, highlighting again the rather good agreement between the device and the expert raters. The accuracy, the sensitivity and the specificity of the OFF score produced from the PDMonitor® compared to the UPDRS annotations and the symptom diaries was evaluated in 30-minute windows and is presented in Table 4. The evaluation included exclusively 30-minute intervals where estimations for gait from the PDMonitor® were available. It should be noted that for one site, diaries were not filled in during the Phase I of the PDNST001 study. Moreover, neighboring 30-minute intervals with different OFF evaluations where excluded, in order to reduce possible errors due to the transition between OFF and ON states (and vice versa). The accuracy and the specificity of the OFF detection method was excellent (0.96 and 0.97 respectively).

### 3.2.2. Agreement on the total time of presence of specific symptoms

**OFF Time.** For each session, the percentage of each patient in the OFF state was calculated. The percentage of time while a patient was in the OFF state was estimated as the ratio of the *"number of evaluations where the probability for being in an OFF state was higher than* 0.55," to the *"total number of evaluations."* A

high correlation, $r^2 = 0.75$, between the PDMonitor® estimations and the combination of UPDRS evaluations and symptom diaries is observed, as it can be seen in Table 5. Correlation and Bland-Altman plots are presented in Figure 8A.

**Dyskinesia Time.** The time with Dyskinesia is estimated in a similar fashion, considering the percent of expert annotations in which the AIMS scores were higher than 4. A total of 80 subjects were included in this analysis and the correlation of the variable called "Time with dyskinesia" as produced by the PDMonitor®, compared to the expert assessments was $r^2 = 0.63$ (Table 5).

TABLE 5 Correlation of the measures "Time with OFF" and "Time with dyskinesia," as were estimated by the PDMonitor® system, compared to expert annotations (and diaries in the case of "Time with OFF") per recording/session.

| PDMonitor® | No. of patients | Correlation ($r^2$) | Spearman's Rho |
|---|---|---|---|
| Time with OFF | 54 | 0.75 | 0.65 |
| Time with dyskinesia | 80 | 0.63 | 0.77 |

The "Time with OFF" was calculated from expert annotations using the ratio of the *"number of evaluations where the probability for being in an OFF state was higher than* 0.55", to the *"total number of evaluations."* "Time with dyskinesia". On the other hand, the "Time with dyskinesia" was calculated as the percent of expert annotations in which the AIMS scores were higher than 4.

### 3.2.3. Agreement on day-to-day symptom evaluation

The day-to-day agreement was evaluated for those patients of PDNST001, Phase II and those controls (healthy individuals) of PDNST002, having more than 1 day of monitoring activity. For each symptom, the average severity was estimated per day, and then pairs of different days were compared. Correlation and Bland-Altman plots of the results are presented, for bradykinesia, in Figure 8B. The ICC correlations are presented in Table 6. Considering the fact that there is an intrinsic variation in the PD symptoms, the device's ICCs could be considered rather high.

## 4. Remarks

During the course of the first study (PDNST001), the UPDRS annotations were performed by one physician, although different in each site. Diaries were not filled in one site during the Phase I of the PDNST001 study and as a result, for this site, we were not able

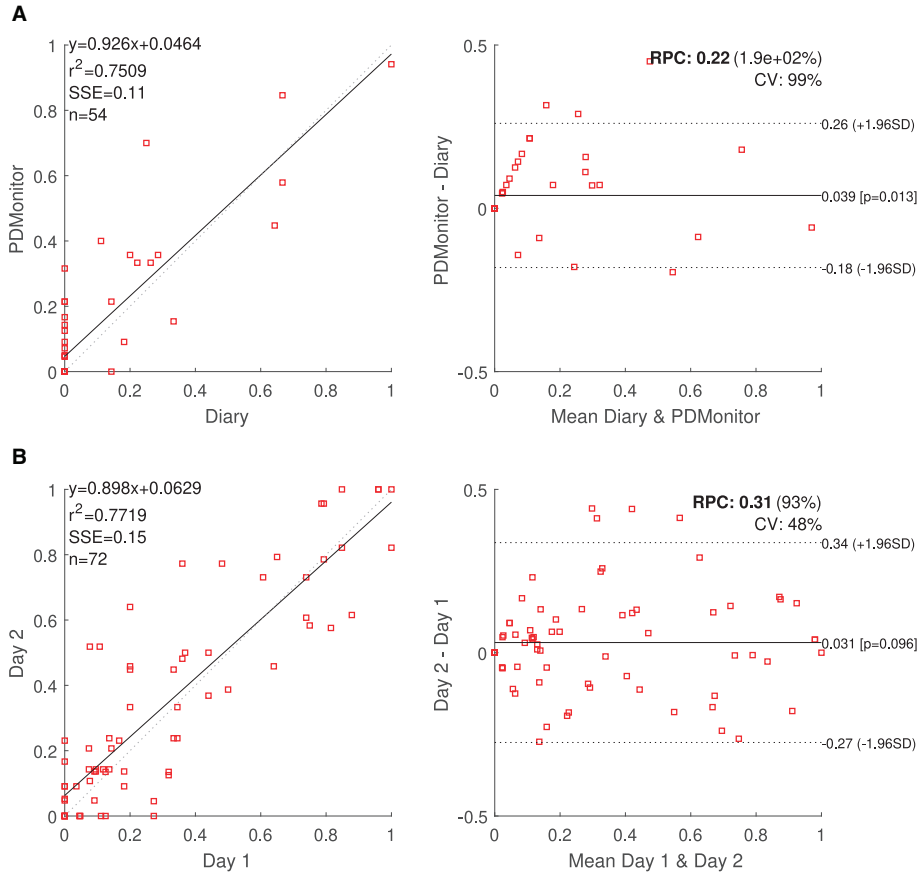


FIGURE 8
**(A)** PDMonitor® OFF estimation and Bland Altman plot for the patient diaries. **(B)** Correlation and Bland-Altman plots for day-to-day agreement of PDMonitor® estimated time percentage, where (left leg) bradykinesia score was more than 1 (UPDRS).

TABLE 6 Intra-class correlation coefficients of PDMonitor® estimated measures for different recording days.

| PDMonitor® | ICC ($r^2$) | Spearman's Rho |
|---|---|---|
| Time spent with bradykinesia (LL) > 1 | 0.77 | 0.83 |
| Time spent with dyskinesia (LL) > 1 | 0.82 | 0.45 |
| Time spent with gait > 1 | 0.71 | 0.83 |

This analysis evaluated the day-to-day agreement for those patients of PDNST001, Phase II and those controls (healthy individuals) of PDNST002, having more than one day of monitoring activity. For each symptom, the average severity was estimated per day, and then pairs of different days were compared.

to compare the UPDRS evaluations with the corresponding diaries. The majority of the recordings were performed inside hospitals, but the subjects were free to perform any kind of activity. For example, in one site, many patients also performed rehabilitation exercises. Therefore, even if the recordings were not in the patients' actual environment, the conditions during the studies were quite close them. Moreover, since patients are instructed not to use the device during intense activities, the actual conditions they encounter during their everyday lives, while wearing the PDMonitor®, were expected to be quite similar to the ones they experienced during the studies. Intense activities were defined as any activity other than walking. The patients were advised not to wear the monitoring devices during intense activities as there would be abrupt signal changes logged by the IMU sensors, which would contaminate the system's output.

## 5. Discussion

PDMonitor® is a monitoring system that has been developed for the detection and follow-up monitoring of parkinsonian symptoms based on wearable monitoring devices. Although, it should be noted, that the device does not replace, neither a clinical examination, nor a patient's symptoms report, and any findings should be always verified with the patients and their caregivers. The aim of the studies presented herein, was to validate the system's usability and efficacy in the detection of motor symptoms manifested in Parkinson's disease.

The first significant outcome of the PDNST001 study was the confirmation that PDMonitor® can be effectively, and easily, used by patients and caregivers. As a reference, in order to use the system, about 5 minutes are required, in average, for mounting all sensors, although patients in the OFF state may need more time or additional help. This finding is also confirmed by the CRS questionnaire in which the question "I have a difficulty in putting on the device" received a higher score by the patients compared to the control subjects. It should be noted that the PDMonitor® device has a number of features that enable its unsupervised use in hospital and home environments. The first important feature, is the ability to automatically identify the position of each of the 5 monitoring devices on a patient's body, thus, significantly reducing the complexity/burden of wearing the 5 sensors, as well as the probability of device misuse. Another important feature is that no user interaction is needed to start a recording, apart from undocking and wearing the monitoring devices, as well as putting them back overnight for data transfer and charging. A point to note is that, in terms of usability, the question "I would wear the device if it was invisible" of the CRS, received an increased score. This question is probably answered by patients having in mind the stigma around medical conditions, and thus it denotes a wish for discreet "invisible" medical devices in general. As a result, this is a well known aspect of similar devices (45) and PDMonitor® design aims to reduce such concerns. More data from real world use may be needed to further evaluate the effect of such issues on the usability of the device. The effective use of the system was also demonstrated in the study performed by Bendig et al. (69), where 12 subjects used the monitoring devices for 3 months and demonstrated significant adherence and satisfaction (both being prerequisites for effective use).

The second major outcome of the study is related to the performance of the device in the detection of PD related motor symptoms. Statistical analysis comparing the symptoms detected by the PDMonitor®, to those identified through clinical evaluation and patient diaries, revealed the system's capacity to accurately detect the majority of PD motor symptoms and their fluctuations. Table 4 summarizes all PDMonitor® outcomes and their accuracy measures, compared to the detection and severity estimation of PD motor symptoms based on the expert evaluations or diaries. In all cases, the outcomes of the PDMonitor® algorithms were translated to clinically relevant scales which are familiar to movement disorders healthcare professionals, aiming to immediately offer actionable knowledge. Even in cases where the accuracy was moderate, the specificity was very high. This was an important requirement of the device, considering the fact that it is intended to be used at home, as well as in general unconstrained, environments with a need of avoiding false positives occurring during daily activities. The significant day-to-day correlation between symptoms presented in Section 2.4.2 is also very important as it depicts the repeatability of the device's outcomes. This is also further supported by the fact that both bradykinesia and gait impairment were statistically different between control subjects (healthy individuals) and PD patients with a UPDRS score of 0 on the respective UPDRS items (Figures 6A, B). The results for both OFF and dyskinesia time estimation are also very important ($r^2 = 0.75$ and $r^2 = 0.63$ respectively) considering the sparse evaluations (30-minute intervals) and a typical duration of each session between 4 and 8 h. Therefore, PDMonitor® provides a rather comprehensive, and accurate, evaluation of the main parkinsonian symptoms. Each one symptom worths a further evaluation, in greater technical and clinical detail, in which there will be also presentations of specific cases. However, this was not possible in the context of this work due to space limitations. We will focus on this task in a future work.

Moreover, there are specific cases where the limitations of the physical examination were highlighted, even though they were not systematically evaluated in the studies. For example, some patients did have significant altered symptom manifestations before and during the clinical examination, including gait difficulty, which was however clearly depicted in the PDMonitor® report as it is

not based only on a specific time period in which the symptoms may have subsided. This further supports the need of using remote monitoring in clinical practice. Also, a very interesting fact is that features related to gait, postural instability and gait difficulties (PIGD) seem to be better indicators of OFF, compared to arm bradykinesia. This may further highlight the importance of ambulatory gait evaluation for assessing PD patient monitoring.

The progression of the neurodegeneration process in PD is related to the emergence of motor complications, such as fluctuations and dyskinesia, which are often difficult to predict and manage, especially in advanced patients (14, 70). The treatment strategies that are currently available for PD, as it advances, include lifestyle changes, fine tuning of oral medication, different routes of drug administration, and deep brain stimulation (13, 71). However, the efficacy of these treatments is limited and it relies mainly on the information that physicians manage to acquire regarding each patient's symptomatology, which does not always depict with accuracy the patient's overall state and disease progression. A study performed by Erb et al. (72) found that 38% of all participants who were asked to complete an electronic motor diary at home missed approximately 25% of all possible entries. Also, the entries the participants made had an average delay of more than 4 h. During clinical evaluations by PD specialists, self reports of dyskinesia were marked by approximately 35% false negatives and 15% false positives. Compared to the live examinations, the video evaluations of the Part III of the UPDRS significantly underestimated the subtle features of tremor and extremity bradykinesia, suggesting that these aspects of the disease may be misjudged during remote assessments. On the other hand, based on the results of this study, PDMonitor® can effectively detect the majority of PD related motor symptoms, with high test-retest reliability. The device also provides a highly accurate estimation of OFF and dyskinesia time, which is crucial for any therapeutic decision.

Other systems previously reported to detect parkinsonian symptoms in PD (36, 73, 74), do provide useful information to physicians leading to improved therapeutic decisions and patient outcomes (41, 75). However, PDMonitor® has the main advantage of evaluating all motor symptoms and their complications, including gait, freezing of gait and postural instability. The detection of freezing of gait along with other problems related to postural instability and gait difficulties (PIGD) is a key component when we try to optimize pharmacological and non-pharmacological treatment in Parkinson's (13, 71). These symptoms also have a strong effect on a patient's quality of life. The recent COVID-19 pandemic has further highlighted the importance of telemedicine and remote monitoring as a way to hamper the impact of social and mobility restrictions, particularly in patients in advanced stages of the disease and those that have undergone invasive treatments (19, 76).

PDMonitor® is designed for long-term continuous monitoring, enabling a new paradigm in PD management. Long-term and continuous monitoring facilitates the early detection of fluctuations (wearing off) and PIGD in patients, which the treating physicians could not otherwise identify. Timely detection and treatment could help patients better understand their status (77) and improve the probability of living a normal life while staying effective in their work. This is expected to have a serious impact to the Health Economics of the System and the patients' Quality of Life. Tsamis et al. (22) presented two specific cases where the potential of PDMonitor® to accurately capture the diverse clinical manifestations of advanced PD was demonstrated, thus reducing the need for prolonged in-person examinations or hospitalization. Both presented cases, included significant difficulties in the diagnostic approach, due to missing information regarding the time course of symptoms throughout the day. With the use of PDMonitor®, physicians had access to an objective assessment of the patients' motor symptoms, as these were manifested in their daily home environments, managing to reach a final diagnosis and making the right treatment decisions.

PDMonitor® also offers the possibility to be used for advanced therapy selection based on a set of patient eligibility criteria. For example, Antonini et al. (9) have developed a screening tool for identifying patients eligible for deep brain stimulation (DBS). The tool consists of a number of questions regarding PD motor symptoms and their fluctuations, such as:

- *Do you have* $\geq$ *2 h of OFF time per day?*
- *Do you experience unpredictable fluctuations?*

Objective measurements and measures like the ones suggested, based on PDMonitor (78), may complement such screening tools and provide a valuable instrument for a timely and accurate patient selection eligible for advanced therapies.

Furthermore, PDMonitor® can be used for post-DBS monitoring and tuning. The challenge in post-DBS management is to find the proper stimulation paradigm along with the proper medication treatment. The problem increases when the patients go home and after 3–4 weeks they start losing the acute effect of their therapy, creating the need for further medication optimizations. This is a use case when a medical device, like PDMonitor®, could be really useful, as it can guide the medication adjustment through precise monitoring, fulfilling a true unmet need of moving the patients' care away from the hospital and to the home.

Dorsey et al. (79) also supported that in order to improve PD care, more of it must be delivered at home. Emerging care models will combine remote monitoring, self-monitoring, and multidisciplinary care in order to enable the provision of patient-centered care at home and decrease the need for in-clinic assessments. It should be noted that PDMonitor® also provides an accompanying mobile app with important features like medication and medication intake, as well as a symptom diary. All logged information is also available in the PDMonitor® reports as those presented in Figures 2A, B. The mobile app also includes educational material and provides to each patient a form of an one-way communication with their physician. It is known that mHealth solutions tend to increase patient awareness and disease self-management, as demonstrated in similar applications (80). Therefore, based on the results of the studies (PDNST001 and PDNST002) and considering the usability, the performance and the clinical need, PDMonitor® could be considered as a tool that could be essential in daily practice and in the management of Parkinson's disease. New and ongoing studies are expected to provide additional evidence about the clinical benefits of this new paradigm, that PDMonitor® is a part of, enabling a wider adoption (81). Physicians and healthcare systems may need to adopt and embrace this new paradigm in order to overcome current barriers

(77, 82) as well as to unlock the full potential of continuous patient monitoring.

## 6. Conclusions

Objective symptom monitoring in Parkinson's disease can be a groundbreaking tool for the proper management of the disease and the therapeutic decision making process. Monitoring the most important PD motor symptoms with high accuracy, may contribute to better, more precise and more effective treatment interventions. The results of these studies demonstrated that PDMonitor® can provide a comprehensive evaluation of the majority of motor symptoms, with significant accuracy, as compared to expert assessments and patient/caregiver diaries, and also that it can be easily used by the patients and their caregivers. PDMonitor® enables longitudinal objective monitoring of patient symptoms and their lifestyle, unlocking important patient management potential.

## Related patents

The following patent has been filed and published: WO2020120999A1 Monitor system of Multiple Parkinson's Disease Symptoms And Their Intensity.

## Data availability statement

The datasets presented in this article are not readily available due to being property of PD Neurotechnology Ltd. Requests to access the datasets should be directed to PD Neurotechnology Ltd. (info@pdneurotechnology.com).

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the TU Dresden University, the Ethical Committee of the University Hospital of Ioannina and the Ethical Committee of the IRCCS San Camillo Research Hospital. The participants were fully informed about all aspects of their participation in the studies and provided a written informed consent form.

## Author contributions

AA, HR, and SK: study design, conceptualization and supervision, as well as patient enrolment. BF, AF, and KT: manuscript review and editing. GG, MG, and CT: study conceptualization, patient enrolment, data collection, curation, and validation. GR: study design, original draft preparation, statistical analysis, and data visualization. NK: original draft preparation and manuscript review. AN: manuscript review and editing, as well as data visualization. CP: manuscript writing, review and editing. All authors approved the submitted version of the manuscript.

## Conflict of interest

AA and HR participate in the Medical Advisory Board of PD Neurotechnology Ltd., KT served as a consultant for PD Neurotechnology Ltd., GR, NK, and AN are employees of PD Neurotechnology Ltd., while SK is a co-Founder of PD Neurotechnology Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Marras C, Beck J, Bower J, Roberts E, Ritz B, Ross G, et al. Prevalence of Parkinson's disease across North America. *Npj Parkinsons Dis.* (2018) 4:1–7. doi: 10.1038/s41531-018-0058-0

2. Poewe W, Mahlknecht P. Pharmacologic treatment of motor symptoms associated with Parkinson disease. *Neurol Clin.* (2020) 38:255–67. doi: 10.1016/j.ncl.2019.12.002

3. Chaudhuri KR, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: the non-motor issues. *Parkinsonism Related Disord.* (2011) 17:717–23. doi: 10.1016/j.parkreldis.2011.02.018

4. Pfeiffer RF. Autonomic dysfunction in Parkinson's disease. *Neurotherapeutics.* (2020) 17:1464–79. doi: 10.1007/s13311-020-00897-4

5. Biundo R, Weis L, Antonini A. Cognitive decline in Parkinson's disease: the complex picture. *NPJ Parkinsons Dis.* (2016) 2:1–7. doi: 10.1038/npjparkd.2016.18

6. Antonini A, Bravi D, Sandre M, Bubacco L. Immunization therapies for Parkinson's disease: state of the art and considerations for future clinical trials. *Expert Opinion Invest Drugs.* (2020) 29:685–95. doi: 10.1080/13543784.2020.1771693

7. Tarakad A, Jankovic J. Diagnosis and management of Parkinson's disease. *Seminars Neurol.* (2017) 37:118–26. doi: 10.1055/s-0037-1601888

8. Antonini A, Martinez-Martin P, Chaudhuri RK, Merello M, Hauser R, Katzenschlager R, et al. Wearing-off scales in Parkinson's disease: critique and recommendations. *Mov Disord.* (2011) 26:2169–75. doi: 10.1002/mds.23875

9. Antonini A, Odin P, Schmidt P, Cubillos F, Standaert DG, Henriksen T, et al. Validation and clinical value of the MANAGE-PD tool: a clinician-reported tool to identify Parkinson's disease patients inadequately controlled on oral medications. *Parkinsonism Related Disord.* (2021) 92:59–66. doi: 10.1016/j.parkreldis.2021.10.009

10. Mantri S, Wood S, Duda JE, Morley JF. Comparing self-reported and objective monitoring of physical activity in Parkinson disease. *Parkinsonism Related Disord.* (2019) 67:56–9. doi: 10.1016/j.parkreldis.2019.09.004

11. Ossig C, Antonini A, Buhmann C, Classen J, Csoti I, Falkenburger B, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's disease. *J Neural Transmission.* (2016) 123:57–64. doi: 10.1007/s00702-015-1439-8

12. Lones MA, Alty JE, Cosgrove J, Duggan-Carter P, Jamieson S, Naylor RF, et al. A new evolutionary algorithm-based home monitoring device for Parkinson's dyskinesia. *J Med Syst*. (2017) 41:1–8. doi: 10.1007/s10916-017-0811-7

13. Bayés À, Samá A, Prats A, Pérez-López C, Crespo-Maraver M, Moreno JM, et al. A "HOLTER" for Parkinson's disease: Validation of the ability to detect on-off states using the REMPARK system. *Gait Posture*. (2018) 59:1–6. doi: 10.1016/j.gaitpost.2017.09.031

14. García DS, Ariztegui NL, Cubo E, Aragón AV, García-Ramos R, Borrué C, et al. Clinical utility of a personalized and long-term monitoring device for Parkinson's disease in a real clinical practice setting: an expert opinion survey on STAT-ON™. *Neurologia*. (2020) 24:S0213-4853(20)30339-X. doi: 10.1016/j.nrl.2020.10.013

15. Ryu S. History of telemedicine: evolution, context, and transformation. *Healthcare Inf Res*. (2010) 16:65–6. doi: 10.4258/hir.2010.16.1.65

16. Shah ND, Krupinski EA, Bernard J, Moyer MF. The evolution and utilization of telehealth in ambulatory nutrition practice. *Nutr Clin Pract*. (2021) 36:739–49. doi: 10.1002/ncp.10641

17. Pagliani L, Elisa N, Eduardo RD, Antonini-Canterin F, et al. Role of new technologies in supporting the treatment of complex patients. *Heart Failure Clin*. (2021) 17:279–87. doi: 10.1016/j.hfc.2021.01.009

18. De Marchi F, Contaldi E, Magistrelli L, Cantello R, Comi C, Mazzini L. Telehealth in neurodegenerative diseases: opportunities and challenges for patients and physicians. *Brain Sci*. (2021) 11:237. doi: 10.3390/brainsci11020237

19. Fasano A, Antonini A, Katzenschlager R, Krack P, Odin P, Evans AH, et al. Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: the COVID-19 experience. *Mov Disord Clin Pract*. (2020) 7:361–72. doi: 10.1002/mdc3.12965

20. Langer A, Gassner L, Flotz A, Hasenauer S, Gruber J, Wizany L, et al. How COVID-19 will boost remote exercise-based treatment in Parkinson's disease: a narrative review. *Npj Parkinsons Dis*. (2021) 7:1–9. doi: 10.1038/s41531-021-00160-3

21. Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinski K, et al. Parkinson's disease remote patient monitoring during the COVID-19 lockdown. *Front Neurol*. (2020) 11:567413. doi: 10.3389/fneur.2020.567413

22. Tsamis KI, Rigas G, Nikolaos K, Fotiadis DI, Konitsiotis S. Accurate monitoring of Parkinson's disease symptoms with a wearable device during COVID-19 pandemic. *In Vivo*. (2021) 35:2327–30. doi: 10.21873/invivo.12507

23. Ancona S, Faraci FD, Khatab E, Fiorillo L, Gnarra O, Nef T, et al. Wearables in the home-based assessment of abnormal movements in Parkinson's disease: a systematic review of the literature. *J Neurol*. (2021) 2021:1–11. doi: 10.1007/s00415-020-10350-3

24. Vaswani PA, Tropea TF, Dahodwala N. Overcoming barriers to Parkinson disease trial participation: increasing diversity and novel designs for recruitment and retention. *Neurotherapeutics*. (2020) 17:1724–35. doi: 10.1007/s13311-020-00960-0

25. Dobkin RD, Mann SL, Gara MA, Interian A, Rodriguez KM, Menza M. Telephone-based cognitive behavioral therapy for depression in Parkinson disease: a randomized controlled trial. *Neurology*. (2020) 94:e1764–73. doi: 10.1212/WNL.0000000000009292

26. Artusi CA, Imbalzano G, Sturchio A, Pilotto A, Montanaro E, Padovani A, et al. Implementation of mobile health technologies in clinical trials of movement disorders: underutilized potential. *Neurotherapeutics*. (2020) 17:1736–46. doi: 10.1007/s13311-020-00901-x

27. Lai B, Bond K, Kim Y, Barstow B, Jovanov E, Bickel CS. Exploring the uptake and implementation of tele-monitored home-exercise programmes in adults with Parkinson's disease: a mixed-methods pilot study. *J Telemed Telecare*. (2020) 26:53–63. doi: 10.1177/1357633X18794315

28. Griffin M, Bentley J, Shanks J, Wood C. The effectiveness of Lee Silverman Voice Treatment therapy issued interactively through an iPad device: a non-inferiority study. *J Telemed Telecare*. (2018) 24:209–15. doi: 10.1177/1357633X17691865

29. Grimes D, Antonini A, Ferreira JJ, Sanchez-Ferro Á, Lynch T, Rascol O, et al. Patient-centred management of Parkinson's disease. *Lancet Neurol*. (2020) 19:887–8. doi: 10.1016/S1474-4422(20)30359-8

30. Dorsey ER, Bloem BR, Okun MS. A new day: the role of telemedicine in reshaping care for persons with movement disorders. *Mov Disord*. (2020) 35:1897–902. doi: 10.1002/mds.28296

31. Munoz DA, Kilinc MS, Nembhard HB, Tucker C, Huang X. Evaluating the cost-effectiveness of an early detection of Parkinson's disease through innovative technology. *The Eng Econ*. (2017) 62:180–96. doi: 10.1080/0013791X.2017.1294718

32. Samii A, Ryan-Dykes P, Tsukuda RA, Zink C, Franks R, Nichol WP. Telemedicine for delivery of health care in Parkinson's disease. *J Telemed Telecare*. (2006) 12:16–18. doi: 10.1258/135763306775321371

33. Cubo E, Mariscal N, Solano B, Becerra V, Armesto D, Calvo S, et al. Prospective study on cost-effectiveness of home-based motor assessment in Parkinson's disease. *J Telemed Telecare*. (2017) 23:328–38. doi: 10.1177/1357633X16638971

34. Albani G, Ferraris C, Nerino R, Chimienti A, Pettiti G, Parisi F, et al. An integrated multi-sensor approach for the remote monitoring of Parkinson's disease. *Sensors*. (2019) 19:4764. doi: 10.3390/s19214764

35. Luis-Martínez R, Monje MH, Antonini A, Sánchez-Ferro Á, Mestre TA. Technology-enabled care: integrating multidisciplinary care in Parkinson's disease through digital technology. *Front Neurol*. (2020) 11:575975. doi: 10.3389/fneur.2020.575975

36. Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *J Parkinsons Dis*. (2012) 2:47–55. doi: 10.3233/JPD-2012-11071

37. Ferreira JJ, Godinho C, Santos AT, Domingos J, Abreu D, Lobo R, et al. Quantitative home-based assessment of Parkinson's symptoms: the SENSE-PARK feasibility and usability study. *BMC Neurol*. (2015) 15:1–7. doi: 10.1186/s12883-015-0343-z

38. Horne MK, McGregor S, Bergquist F. An objective fluctuation score for Parkinson's disease. *PLoS ONE*. (2015) 10:e0124522. doi: 10.1371/journal.pone.0124522

39. Klingelhoefer L, Rizos A, Sauerbier A, McGregor S, Martinez-Martin P, Reichmann H, et al. Night-time sleep in Parkinson's disease-the potential use of Parkinson's KinetiGraph: a prospective comparative study. *Eur J Neurol*. (2016) 23:1275–88. doi: 10.1111/ene.13015

40. Knudson M, Thomsen TH, Kjaer TW. Comparing objective and subjective measures of Parkinson's disease using the Parkinson's KinetiGraph. *Front Neurol*. (2020) 11:570833. doi: 10.3389/fneur.2020.570833

41. Woodrow H, Horne MK, Fernando CV, Kotschet KE. A blinded, controlled trial of objective measurement in Parkinson's disease. *Npj Parkinsons Dis*. (2020) 6:1–10. doi: 10.1038/s41531-020-00136-9

42. Ramsperger R, Meckler S, Heger T, van Uem J, Hucker S, Braatz U, et al. Continuous leg dyskinesia assessment in Parkinson's disease-clinical validity and ecological effect. *Parkinsonism Related Disord*. (2016) 26:41–6. doi: 10.1016/j.parkreldis.2016.02.007

43. Joshi R, Bronstein JM, Keener A, Alcazar J, Yang DD, Joshi M, et al. PKG movement recording system use shows promise in routine clinical care of patients with Parkinson's disease. *Front Neurol*. (2019) 10:1027. doi: 10.3389/fneur.2019.01027

44. Höglund A, Hagell P, Broman JE, Pålhagen S, Sorjonen K, Fredrikson S, et al. Associations between fluctuations in daytime sleepiness and motor and non-motor symptoms in Parkinson's disease. *Mov Disord Clin Pract*. (2021) 8:44–50. doi: 10.1002/mdc3.13102

45. Cancela J, Pastorino M, Tzallas AT, Tsipouras MG, Rigas G, Arredondo MT, et al. Wearability assessment of a wearable system for Parkinson's disease remote monitoring based on a body area network of sensors. *Sensors*. (2014) 14:17235–55. doi: 10.3390/s140917235

46. Gao C, Smith S, Lones M, Jamieson S, Alty J, Cosgrove J, et al. Objective assessment of bradykinesia in Parkinson's disease using evolutionary algorithms: clinical validation. *Transl Neurodegenerat*. (2018) 7:1–8. doi: 10.1186/s40035-018-0124-x

47. Channa A, Popescu N, Ciobanu V. Wearable solutions for patients with Parkinson's disease and neurocognitive disorder: a systematic review. *Sensors*. (2020) 20:2713. doi: 10.3390/s20092713

48. Urso D, Chaudhuri K, Qamar MA, Jenner P. Improving the delivery of levodopa in Parkinson's disease: a review of approved and emerging therapies. *CNS Drugs*. (2020) 34:1149–1163. doi: 10.1007/s40263-020-00769-7

49. Prakash N, Simuni T. Infusion therapies for Parkinson's disease. *Curr Neurol Neurosci Rep*. (2020) 20:1–13. doi: 10.1007/s11910-020-01062-2

50. Deuschl G, Antonini A, Costa J, Śmiłowska K, Berg D, Corvol JC, et al. European Academy of Neurology/Movement Disorder Society-European Section guideline on the treatment of Parkinson's disease: I. Invasive therapies. *Eur J Neurol*. (2022) 2022:15386. doi: 10.1111/ene.15386

51. Antonini A, Gentile G, Giglio M, Marcante A, Gage H, Touray MM, et al. Acceptability to patients, carers and clinicians of an mHealth platform for the management of Parkinson's disease (PD_Manager): study protocol for a pilot randomised controlled trial. *Trials*. (2018) 19:1–11. doi: 10.1186/s13063-018-2767-4

52. Kostikis N, Rigas G, Konitsiotis S, Fotiadis DI. Configurable offline sensor placement identification for a medical device monitoring Parkinson's disease. *Sensors*. (2021) 21:7801. doi: 10.3390/s21237801

53. Rigas G, Gatsios D, Fotiadis DI, Chondrogiorgi M, Tsironis C, Konitsiotis S, et al. Tremor UPDRS estimation in home environment. In: *2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. Orlando, FL: IEEE (2016). p. 3642–5.

54. Tripoliti EE, Tzallas AT, Tsipouras MG, Rigas G, Bougia P, Leontiou M, et al. Automatic detection of freezing of gait events in patients with Parkinson's disease. *Comput Methods Programs Biomed*. (2013) 110:12–26. doi: 10.1016/j.cmpb.2012.10.016

55. Tsipouras MG, Tzallas AT, Rigas G, Tsouli S, Fotiadis DI, Konitsiotis S. An automated methodology for levodopa-induced dyskinesia: assessment based on gyroscope and accelerometer signals. *Artif Intell Med*. (2012) 55:127–35. doi: 10.1016/j.artmed.2012.03.003

56. Jović A, Brkić K, Bogunović N. A review of feature selection methods with applications. In: *2015 38th International Convention on Information and Communication Technology, Electronics and Microelectronics (MIPRO)*. Opatija: IEEE (2015). p. 1200–5.

57. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease. *Mov Disord*. (2015) 30:1361–70. doi: 10.1002/mds.26269

58. Moore ST, Yungher DA, Morris TR, Dilda V, MacDougall HG, Shine JM, et al. Autonomous identification of freezing of gait in Parkinson's disease from lower-body segmental accelerometry. *J Neuroeng Rehabil*. (2013) 10:1–11. doi: 10.1186/1743-0003-10-19

59. Djurić-Jovičić MD, Jovičić NS, Radovanović SM, Stanković ID, Popović MB, Kostić VS. Automatic identification and classification of freezing of gait episodes in Parkinson's disease patients. *IEEE Trans Neural Syst Rehabil Eng*. (2013) 22:685–94. doi: 10.1109/TNSRE.2013.2287241

60. Marcante A, Di Marco R, Gentile G, Pellicano C, Assogna F, Pontieri FE, et al. Foot pressure wearable sensors for freezing of gait detection in Parkinson's disease. *Sensors*. (2020) 21:128. doi: 10.3390/s21010128

61. Kira K, Rendell LA. A Practical Approach to Feature Selection. In: Sleeman D, Edwards P, editors. *Machine Learning Proceedings*. San Francisco, CA: Morgan Kaufmann (1992). p. 249–56.

62. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's disease rating scale (UPDRS): Status and recommendations. *Mov Disord*. (2003) 18:738–50. doi: 10.1002/mds.10473

63. Colosimo C, Martínez-Martín P, Fabbrini G, Hauser RA, Merello M, Miyasaki J, et al. Task force report on scales to assess dyskinesia in Parkinson's disease: Critique and recommendations: scales to assess dyskinesia in Parkinson's disease. *Mov Disord*. (2010) 25:1131–42. doi: 10.1002/mds.23072

64. Hauser RA, Deckers F, Lehert P. Parkinson's disease home diary: further validation and implications for clinical trials. *Mov Disord*. (2004) 19:1409–13. doi: 10.1002/mds.20248

65. Moskowitz CS, Pepe MS. Quantifying and comparing the predictive accuracy of continuous prognostic factors for binary outcomes. *Biostatistics*. (2004) 5:113–27. doi: 10.1093/biostatistics/5.1.113

66. Waskom ML. seaborn: statistical data visualization. *J Open Source Software*. (2021) 6:3021. doi: 10.21105/joss.03021

67. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician*. (1983) 32:307. doi: 10.2307/2987937

68. Klein R. *Bland-Altman and Correlation Plot* (2023).

69. Bendig J, Wolf AS, Mark T, Frank A, Mathiebe J, Scheibe M, et al. Feasibility of a multimodal telemedical intervention for patients with Parkinson's disease-a pilot study. *J Clin Med*. (2022) 11:1074. doi: 10.3390/jcm11041074

70. Fabbri M, Coelho M, Abreu D, Guedes LC, Rosa MM, Costa N, et al. Do patients with late-stage Parkinson's disease still respond to levodopa? *Parkinsonism Related Disord*. (2016) 26:10–16. doi: 10.1016/j.parkreldis.2016.02.021

71. Antonini A, Moro E, Godeiro C, Reichmann H. Medical and surgical management of advanced Parkinson's disease. *Mov Disord*. (2018) 33:900–8. doi: 10.1002/mds.27340

72. Erb MK, Karlin DR, Ho BK, Thomas KC, Parisi F, Vergara-Diaz GP, et al. mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's disease. *Npj Digital Med*. (2020) 3:1–10. doi: 10.1038/s41746-019-0214-x

73. Rodríguez-Martín D, Cabestany J, Pérez-López C, Pie M, Calvet J, Samà A, et al. A new paradigm in Parkinson's disease evaluation with wearable medical devices: a review of STAT-ONTM. *Front Neurol*. (2022) 13:912343. doi: 10.3389/fneur.2022.912343

74. Pulliam CL, Heldman DA, Brokaw EB, Mera TO, Mari ZK, Burack MA. Continuous assessment of levodopa response in Parkinson's disease using wearable motion sensors. *IEEE Trans Biomed Eng*. (2018) 65:159. doi: 10.1109/TBME.2017.2697764

75. Isaacson SH, Boroojerdi B, Waln O, McGraw M, Kreitzman DL, Klos K, et al. Effect of using a wearable device on clinical decision-making and motor symptoms in patients with Parkinson's disease starting transdermal rotigotine patch: a pilot study. *Parkinsonism Related Disord*. (2019) 64:132–7. doi: 10.1016/j.parkreldis.2019.01.025

76. Luis-Martínez R, Di Marco R, Weis L, Cianci V, Pistonesi F, Baba A, et al. Impact of social and mobility restrictions in Parkinson's disease during COVID-19 lockdown. *BMC Neurol*. (2021) 21:1–8. doi: 10.1186/s12883-021-02364-9

77. Basholli A, Lagkas T, Bath PA, Eleftherakis G. Sensor-based platforms for remote management of chronic diseases in developing regions: a qualitative approach examining the perspectives of healthcare professionals. *Health Inform J*. (2021) 27:9360. doi: 10.1177/14604582209793 50

78. Rigas G, Kakalou D, Tachos N, Tsamis K, Kostikis N, Marcante A, et al. Instrumented detection of fluctuations with wearable devices in Parkinson's disease. *Mov Disord*. (2020) 35 (Suppl 1).

79. Dorsey ER, Vlaanderen FP, Engelen LJ, Kieburtz K, Zhu W, Biglan KM, et al. Moving Parkinson care to the home. *Mov Disord*. (2016) 31:1258–62. doi: 10.1002/mds.26744

80. Bao Y, Wang C, Xu H, Lai Y, Yan Y, Ma Y, et al. Effects of an mHealth intervention for pulmonary tuberculosis self-management based on the integrated theory of health behavior change: randomized controlled trial. *JMIR Public Health Surveill*. (2022) 87:34277. doi: 10.2196/preprints.34277

81. AlMahadin G, Lotfi A, Zysk E, Siena FL, Carthy MM, Breedon P. Parkinson's disease: current assessment methods and wearable devices for evaluation of movement disorder motor symptoms - a patient and healthcare professional perspective. *BMC Neurol*. (2020) 20:419. doi: 10.1186/s12883-020-01996-7

82. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's disease: challenges and opportunities. *Mov Disord*. (2016) 31:1272–1282. doi: 10.1002/mds.26642

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# Balance and gait in progressive supranuclear palsy: a narrative review of objective metrics and exercise interventions

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**Background:** The use of objective gait and balance metrics is rapidly expanding for evaluation of atypical parkinsonism, and these measures add to clinical observations. Evidence for rehabilitation interventions to improve objective measures of balance and gait in atypical parkinsonism is needed.

**Aim:** Our aim is to review, with a narrative approach, current evidence on objective metrics for gait and balance and exercise interventions in progressive supranuclear palsy (PSP).

**Methods:** Literature searches were conducted in four computerized databases from the earliest record up to April 2023: PubMed, ISI's Web of Knowledge, Cochrane's Library, and Embase. Data were extracted for study type (cross-sectional, longitudinal, and rehabilitation interventions), study design (e.g., experimental design and case series), sample characteristics, and gait and balance measurements.

**Results:** Eighteen gait and balance (16 cross-sectional and 4 longitudinal) and 14 rehabilitation intervention studies were included. Cross-sectional studies showed that people with PSP have impairments in gait initiation and steady-state gait using wearable sensors, and in static and dynamic balance assessed by posturography when compared to Parkinson's disease (PD) and healthy controls. Two longitudinal studies observed that wearable sensors can serve as objective measures of PSP progression, using relevant variables of change in turn velocity, stride length variability, toe off angle, cadence, and cycle duration. Rehabilitation studies investigated the effect of different interventions (e.g., balance training, body-weight supported treadmill gait, sensorimotor training, and cerebellar transcranial magnetic stimulation) on gait, clinical balance, and static and dynamic balance assessed by posturography measurements. No rehabilitation study in PSP used wearable sensors to evaluate gait and balance impairments. Although clinical balance was assessed in 6 rehabilitation studies, 3 of these studies used a quasi-experimental design, 2 used a case series, only 1 study used an experimental design, and sample sizes were relatively small.

**Conclusion:** Wearable sensors to quantify balance and gait impairments are emerging as a means of documenting progression of PSP. Robust evidence for improving balance and gait in PSP was not found for rehabilitation studies. Future powered, prospective and robust clinical trials are needed to investigate the effects of rehabilitation interventions on objective gait and balance outcomes in people with PSP.

KEYWORDS

**progressive supranuclear palsy, balance, gait, objective measurements, rehabilitation**

## Introduction

Progressive supranuclear palsy (PSP) is a relatively rare and rapidly progressive neurodegenerative disease classified among atypical Parkinsonisms (1, 2), but evidence suggests that the clinical spectrum of PSP is larger than originally described. The most frequent form of the disease, PSP-RS (PSP Richardson syndrome), is characterized by vertical supranuclear gaze palsy and backward postural instability with early falls (2), while the second most common form of disease is characterized by a parkinsonian syndrome resembling Parkinson's disease (PD) especially in the earliest stages (3). The 2017 Movement Disorder Society criteria recognize multiple subtypes of PSP (4), and these subtypes encompass a spectrum of degree of gait and balance deficits. PSP-RS, PSP-P, and PSP-progressive gait freezing (PSP-PGF) display prominent gait and balance abnormalities, while other subtypes and stages of PSP, such as probable PSP frontal presentation (probable PSP-F) and possible PSP speech and language (possible PSP-SL), are characterized primarily by deficits other than gait and balance impairment.

It has long been recognized that particular clinical exam findings and history questions serve as a red flag for gait and balance in atypical parkinsonism disorders, such as PSP and multiple system atrophy (MSA). For example, Nonnekes et al. (5) highlighted the *tandem gait sign* and *bicycle sign* as indicative of atypical parkinsonism versus idiopathic PD (iPD): if a patient has impaired tandem gait or states that early in their disease course that they were no longer able to ride a bicycle, one should be concerned for possible atypical parkinsonism. This reflects the clinical observation of a wider-based gait and earlier balance troubles as reflective of atypical parkinsonism.

The use of objective gait and balance metrics is rapidly expanding for evaluation of atypical parkinsonism, and these measures add to clinical observations. For example, Raccagni et al. (6) used inertial sensors on the feet to compare a group of subjects with PSP and MSA to a group with iPD and found reduced gait speed and stride length in the atypical parkinsonism subjects compared to subjects with iPD.

Although advances in technology of small, body-worn, inertial sensors have objectively quantified balance and gait impairments in the clinic for research trials and clinical practice in people with PD (7–9), this approach has not been explored in PSP. Objective balance and gait metrics may eventually provide useful biomarkers for PSP, clinical efficacy of new treatments, in place of counting falls from diaries or clinical balance rating scales. Objective balance and gait biomarkers also may be helpful in clinical practice to monitor effects of interventions and prognosis. Biomarkers of balance control could be especially useful to monitor PSP progression and fall risk as well as to differentiate PSP subtypes.

In this narrative review, we examine current evidence for objective metrics of gait and balance in people with PSP. We summarize cross-sectional studies examining gait initiation, steady state gait, and balance in PSP, as well as studies that use gait and balance data mining approaches for classification of PSP, and studies examining radiological correlations with gait and balance metrics in PSP. We then discuss the emerging use of objective gait and balance measures for longitudinal monitoring in PSP and objective gait and balance measures as endpoints for rehabilitation intervention trials in PSP.

## Methods

Literature searches were conducted in the following four computerized databases from the earliest record up to April 2023: PubMed, ISI's Web of Knowledge, Cochrane's Library, and Embase. Inclusion criteria were: any study design (cross-sectional, longitudinal, and rehabilitation interventions) published in peer-reviewed journal, published in English, available in full text, with or without rehabilitation interventions [e.g., physical exercise, virtual reality, and repetitive transcranial magnetic stimulation (rTMS)], population with diagnosis of PSP, mixed PSP subtypes, gait and/or balance assessment. Exclusion criteria were: no gait and/or balance assessment and invasive brain stimulation.

The search was limited to English language. All the identified and retrieved electronic search titles, selected abstracts, and full-text articles were independently evaluated by two of the authors (FOA and CSB) to assess their eligibility. In case of disagreements, a consensus was adopted or, if necessary, a third reviewer evaluated the article (MD). The search process is depicted in Figure 1.

## Results

### Gait and balance as a diagnostic tool: cross-sectional studies

Sixteen cross-sectional studies were included in this review (Table 1). These studies compared gait initiation, steady state gait, and balance between people with and without PSP. In addition, some studies used radiological correlations with gait and balance measures in PSP and mixed PSP phenotypes. We have separated the following discussion of cross-sectional studies according the type of gait and balance assessment.

#### Gait initiation in PSP

In an elegant 2015 study Amano and colleagues examined the mechanics of gait initiation in PSP using a combination of force platforms embedded in a walkway and a 3D motion capture system (11). Twelve subjects with PSP-Richardson syndrome (PSP-RS), 12 subjects with PD, and 12 age- and gender-matched healthy controls (HC) performed 5 gait initiation trials at a self-selected speed, and their anticipatory postural adjustments (APAs) were examined in detail. Whereas subjects with Parkinson's disease and HCs displayed the normal APA with an initial backward and lateral center of pressure shift to initiate gait, subjects with PSP could not tolerate the initial destabilization of the APA imbalance phase. In other words, subjects with PSP displayed an inefficient gait initiation strategy because they were unable to initially shift their center of pressure to generate momentum for forward movement, but rather moved their swing foot forward more robotically without the normal, anticipatory weight shift that moves the center of body mass forward and over the stance leg.

The authors proposed that gait initiation in PSP prioritizes stability over mobility, and suggested possible strategies for rehabilitation including focusing on medio-lateral balance to overcome the minimal lateral weight shift and staggering the initial swing foot posteriorly to try to promote the physiological weight shift of a normal APA. Limitations of this study include a lack of accounting

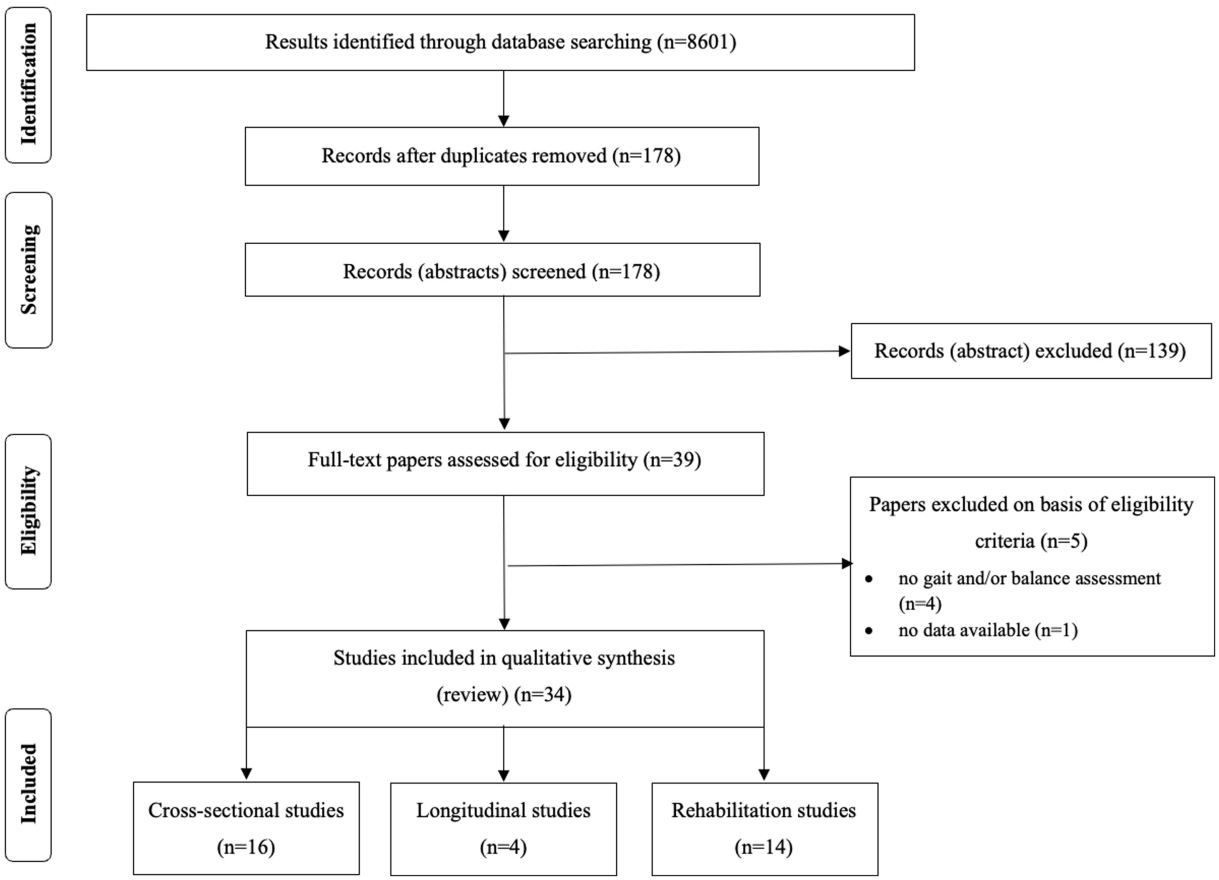


FIGURE 1
PRISMA flowchart for inclusion into the review.

for baseline anthropometric measurements and width of the initial base of support, and the fact that all subjects were evaluated *on* levodopa, likely preferentially improving APAs in the iPD group (25). The study was also conducted prior to the 2017 Movement Disorder PSP Criteria (4), and thus only included subjects with the Richardson syndrome variant of PSP (PSP-RS).

## Steady state gait in PSP-RS

In the same Amano study discussed above, PSP, iPD, and HC subjects also performed 10 steady state gait trials at a self-selected speed, and gait analysis revealed a slower, and more variable, gait in PSP-RS compared to iPD (11). Hatanaka et al. also compared steady state gait in 20 PSP-Richardson syndrome, 124 PD, and 24 HC subjects, using triaxial accelerometers for 10-meter, self-selected straight walking (15). Their study replicated the finding of slower gait in PSP, showing an overall hypokinetic gait pattern with decreased velocity, step length, cadence, and mean acceleration in PSP. They additionally found that the subjects with PSP demonstrated an especially small vertical displacement but larger vertical acceleration than PD patients when comparing subjects with the same cadence.

Selge et al. applied straight walking on a gait mat, with and without cognitive and motor dual tasks, to differentiate PSP-RS from normal pressure hydrocephalus (NPH) (20). Clinically, gait in NPH is considered to be even wider-based and slower than in PSP with an additional "magnetic" quality, but in certain cases the gait patterns of the two diseases approximate each other and contribute to a differential diagnosis that includes both NPH and PSP. In the Selge study, 27 subjects with idiopathic NPH and 38 subjects with PSP performed straight walking at their preferred speed, at a slow speed, and at their maximum speed, as well as dual-task walking at their preferred speed with the serial 7 s cognitive task or while carrying a tray as a motor dual task. Importantly, the PSP and NPH subjects were initially matched on a clinical, functional gait assessment scale. The authors found that gait was slower and more broad-based in NPH, and gait in PSP was more variable and more sensitive to dual-task conditions. They interpreted the increased sensitivity to dual- task conditions in PSP to increased cortical attention for walking. A limitation of this (and many other dual-task studies) was that prioritization of the dual-task was not assessed, so it was not known to what degree the subjects were focused on walking versus on the cognitive task during the assessments.

## Steady state gait in mixed PSP phenotypes

After establishment of the 2017 Movement Disorder Society Criteria for PSP (4), several groups examined steady state gait in multiple phenotypic variants of PSP. Amboni et al. (12) included variants of PSP to compare with iPD specifically in early diagnostic stages. The iPD subjects were enrolled less than a year from symptom onset and had confirmed positive DAT scans. The subjects with PSP met MDS PSP diagnostic criteria and included 11 with PSP-RS, 5 with

TABLE 1 Summary characteristics of the cross-sectional included studies.

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ali et al. (20) USA | PSP: *n*=16, age (70.4±7.1 years), disease duration (4.4±2.8 years), men (*n*=10), women (*n*=6) HC: *n*=25, age (72.7±6.6 years), women (*n*=25) | PSPRS UPDRS-III Richardson's syndrome (*n*=10), Cortico-basal syndrome (*n*= 3), Parkinsonism predominant (*n*=2), Speech and language disorder (*n*=2), Frontal predominant (*n*=1) | Not Reported | Patients were not on any dopaminergic medications. | Not reported | Force plate, 3D motion system | UPDRS-III scores were average 50 (range: 20, 85) for PSP, while PSPRS scores average was 39 (range:24, 58). | PSP patients walked with a slower velocity, lower cadence, shorter stride, and step lengths, and reduced single support times compared to healthy older adults. Total sagittal plane ROM in the hip, knee and ankle showed significant decreased ROM ($p<0.05$) when comparing patients with PSP to healthy adults | PSP exhibited significantly larger amplitudes of COP displacement (7.0±3.9) compared to the healthy individuals (3.4±2.2) for the eyes open task ($p<0.01$). PSP patients exhibited less displacement in the ML (2.2±1.1) but significantly increased displacement in the AP (7.2±4.0) direction compared to the healthy individuals (5.1±1.6) in the eyes closed task ($p<0.04$). | There were significant correlations between PSPRS and UPDRS with gait velocity, (rs=0.597, $p$=0.015; rs=0.756, $p$=0.001), total support (rs=0.591, $p$=0.016; rs=0.546, $p$=0.029), single support (rs=0.557, $p$=0.025; rs=0.500, $p$=0.049), and step length (rs=0.561, $p$=0.024; rs=0.764, $p$=0.001). Significant correlations were also found for UPDRS only and initial double support (rs=0.582, $p$=0.018) and hip ROM (rs=0.728, $p$=0.003). | Patients with PSP have increased anteroposterior sway, slower gait velocity, wider stance, and lower cadence. The gait stability ratio and Romberg ratio was high consistent with postural imbalance and increased reliance on vision for stability, experienced by PSP patients. Motion analysis metrics correlated with clinical scales reflecting that they are a marker of disease severity. |
| Amano et al. (10) USA | PSP: *n*= 12, age (66 ± 8.0 years), disease duration (6.5 ± 4.9 years), men (*n*=5), women (*n*=7) PD: *n*=12, age (64 ± 7 years), disease duration (7.8 ± 7.1 years), men (*n*=5), women (*n*=7) HC: *n*=12, age (67 ± 7 years), men (*n*=5), women (*n*=7) | NINDS-SPSP UPDRS Subtypes not reported | Not reported. | ON-assessment | Not reported | 3D motion system | UPDRS-III (PSP: 49.6±10.4; PD: 23.5±8.5). UPDRS PIGD (PSP:6.33±2.46; PD:3.33±2.42) | The PSP group exhibited significantly reduced cadence, gait velocity, step length, and step duration compared to the other two groups. | COP displacement AP (PSP 0.71±1.55, PD −1.14±0.71, HC −2,61±1.56) COP displacement ML (PSP 2.46±3.62, PD −0.81±1.03, HC −1.85±1.28) The maximum distance between COP and COM significantly differed among the groups. | Not reported. | The study identified significant differences in specific biomechanical characteristics during gait initiation and gait between PSP and PD. Abnormally shorter and slower step during GI in PSP was observed and may result from the inability to execute APAs. The compensatory GI strategy, characterized by diminished posterior COP shift and weight shift toward the stance limb, is therefore very distinct from PD and paradoxically induces lateral postural instability. PSP gait, which prioritizes stability over mobility, may be compensatory and could be the consequence of lateral instability and fear of falling. |

*(Continued)*





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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Amboni et al. (14) Italy | PSP Total: *n*= 21, age (67.8 ± 7.4 years), disease duration (2.5 ± 1.1 years), men (*n*=11), women (*n*=10) PD Total: *n*=83, age (63.2 ± 8.5 years), disease duration (3.4 ± 3.2 years), men (*n*=55), women (*n*=28) Early PSP: *n*= 12, age (63.5 ± 5.9 years), disease duration (1.7 ± 0.4 year), men (*n*=7), women (*n*=5) De novo PD: *n*=27, age (63.3 ± 8.7 years), disease duration (< 1 year), men (*n*=17), women (*n*=10) | PSPRS NDS-UPDRS-III Richardson's syndrome (*n*=11), Parkinsonism predominant (*n*=5), Freezing of gait predominant (*n*=4) | MMSE: PSP Total (25.1 ± 3.0), PD Total (26.8 ± 2.3), Early PSP (25.5 ± 2.7), De novo PD (26.9 ± 2.2) | *ON-assessment* | No | SMART DX system (3D motion system + force plate) | MDS-UPDRS-III (PD Total): 19.46±8.99; MDS-UPDRS-III (De novo PD): 12.85±6.17; PSP-RS-V (PSP total): 5.81±2.73; PSP-RS-VI (PSP total): 7.28±4.55; PSP-RS-V (Early PSP): 5,.3±2.87 PSP-RS-VI (Early PSP): 6.58±3.73 | Compared to PD, PSP patients exhibited reduced velocity and cadence, shortened step and cycle lengths, increased cycle duration mainly due to longer double support stance phase duration, and increased swing duration variability during single task. During dual task, PSP patients exhibited the same gait features as those displayed during the single task, except for swing duration and step length variability. Compared to newly diagnosed PD patients, early PSP patients exhibited reduced velocity and cadence, shortened step and cycle length, and increased cycle duration; these patients tended to rely on a longer double support stance phase during single task. During dual task, early PSP patients exhibited a gait pattern similar to that during the single task except for swing duration and swing duration variability. | Not reported. | Not reported. | The study demonstrates that quantitative gait evaluation clearly distinguishes PSP patients from PD patients since the earliest stages of disease. These findings indicate that gait analysis could be a candidate as a reliable biomarker in both clinical and research setting. In addition, results may offer speculative clues for conceiving early disease-specific rehabilitation strategies. |

*(Continued)*





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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dale et al. (19) USA | PSP: *n*= 12, age (70 ± 6.3 years), disease duration (2.6 ± 1.5 years), men (*n*=6), women (*n*=6) PD: *n*=12, age (67.8 ± 7.3 years), disease duration (8.1 ± 5.6 years), men (*n*=6), women (*n*=6) HC: *n*=12, age (not reported), men (not reported), women (not reported) | NINDS-SPSP UPDRS Subtypes not reported | Not reported | *OFF*-assessment | Not reported | NeuroCom Balance Master Clinical Research System | UPDRS-III (PD): 33.7 ± 7.5; UPDRS-III (PSP): 34.4 ± 9.1; PSP-RS: 26.9 ± 11.9 | Not reported | PSP displaced their CoP significantly less than PD subjects ($p \leq 0.006$) and slightly less than healthy subjects during the forward translation of the platform. The CoP of subjects with PSP remained more posterior after the platform shifted back to the initial position compared to subjects with PD ($p \leq 0.01$), while only a slight difference was found compared to healthy subjects. When the body was displaced backward by toes-up platform rotation, PSP exerted a significantly larger destabilizing plantar-flexion torque (as evidenced by forward CoP displacement) than subjects with PD ($p \leq 0.008$), and only slightly larger compared to healthy subjects. | Not reported | The study demonstrates inappropriate adaptive postural motor control with excessive forward CoP displacement in response to toes-up surface tilts in PSP. |
| De Vos et al. (22) United Kingdom | PSP: *n*= 21, age (71 years), disease duration (2 years), men (*n*=12), women (*n*=9) PD: *n*=20, age (66.4 years), disease duration (11.4 years), men (*n*=11), women (*n*=9) Healthy Control: *n*=39, age (67.1 years), men (19), women (20) | UPDRS-III Richardson's syndrome (*n*=4), Parkinsonism predominant (*n*=17) | MoCA: PSP (mean 22), PD (mean 26.6), HC (mean 28.5). MMSE: PSP (mean 25.8), PD (mean 26.6), HC (mean 27.6). | *ON*-assessment | Not reported | IMUs | UPDRS-III (PSP: 44.6; PD: 27.9) | Gait cadence distinguished PSP from PD and HC showing a high specificity (90 %) when using 6 sensors (Mobility Lab™, APDM) over the lumbar spine, sternum, left and right wrists, and left and right feet. | Mean postural sway velocity in the coronal plane during the sway test, mean time taken to sit from standing during the timed up-and-go (TUG) task, mean time taken to turn during the gait task, mean time taken to turn during the TUG task, standard deviation of time taken to turn during the gait task distinguished PSP from PD and HC showing a high specificity (90 %) when using 6 sensors (Mobility Lab™, APDM) over the lumbar spine, sternum, left and right wrists, and left and right feet. | Not reported | A wearable inertial measurement unit array and machine learning methods can accurately differentiate PSP from PD and from control. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hatanaka et al. (12) Japan | PSP: *n*= 20, age (71,8 ±5.9 years), disease duration (3.4±1.8 years), men (*n*=14), women (*n*=6) PD: *n*=124, age (68.4 ± 11.2 years), disease duration (6.7±7.4 years), men (*n*=64), women (*n*=60) HC: *n*=24, age (73.7 ± 3.8 years), men (5), women (19) | NINDS-SPSP Subtypes not reported | Not Reported | *ON*-assessment | No | Portable triaxial accelerometer rhythmogram device | Not reported | Compared with the accelerogram of HC, both PSP and PD patients showed a smaller amplitude (acceleration) and increased shuffle frequency over a certain period, indicating a reduced acceleration and shorter step time. Compared with HC (1.10 ± 0.22 m/s), velocity was reduced in PSP patients (0.83 ± 0.23 m/s, $p < 0.01$ vs. control) and in all PD patients (0.89 ± 0.24 m/s, $p < 0.01$). The cadence of the PSP patients (100.5 ± 11.5 steps/min, $p < 0.01$ vs. control) was significantly lower than HC (115.9 ± 11.2 steps/min) and of PD patients (109.3 ± 15.9 steps/min, # $p < 0.05$ vs. PSP). The vertical displacement of PSP patients (2.3 ± 1.1 cm) was significantly lower than HC (5.6 ± 1.7 cm, $p< 0.01$ vs. PSP), all PD patients (4.4 ± 2.2 cm, $p< 0.01$ vs. PSP). | Not reported | There was a close relationship between cadence and acceleration for all groups. The relationships were positive and linear with $R^2$ values > 0.4 (controls, $R^2 = 0.54$; PSP patients, $R^2 = 0.56$; PD patients, $R^2 = 0.48$). | Lower vertical displacement could be a feature of gait disturbance in PSP patients, and which could be used to better discriminate PSP from PD patients. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Liao et al. (17) USA/Germany | PSP-tVOR: *n*=9, age (median 68 years, range 61-75), men (*n*=5), women (*n*=4) PSP-VEMPs: *n*=10, age (median 68 years, range 60-76), men (*n*=7), women (*n*=3) HC-tVOR: *n*=9, age (median 67 years, range 60-72), men (*n*=6), women (*n*=3) HC-VEMPs: *n*=30, age (median 67 years, range 56-80), men (*n*=19), women (*n*=11) | NINDS-SPSP Subtypes not reported | Not reported | Not reported | Not reported | Magnetic search coil + Infrared reflection system | Not reported | Not reported | *Vestibulo-ocular reflex:* Patients with PSP tend to show smaller values of aVOR RR than control subjects, but with some overlap of data. For tVOR, patients with PSP's RR were smaller than controls during far viewing, but with overlap of data. However, during near-viewing conditions, PSP RR values for tVOR were significantly smaller than controls, with no overlap of data. The range of tVOR RR of our control subjects was similar to those previously reported during rapid oscillatory head translations, but responses of patients with PSP during near viewing were, on average, only 12% of controls. *Vestibulo-spinal reflex*: The median P1-N1 amplitude of all 60 ears of the HC was 149 μV (range: 11.6 to 466); that of all 20 ears of the patients with PSP 54.3 μV (range: 16.8 to 214). | Not reported | The study results indicate that abnormal otolith-mediated reflexes may be at least partly responsible for frequent falls in progressive supranuclear palsy. |
| Ondo et al. (18) USA | PSP: *n*= 20, age (68 ±5.4 years), disease duration (3.5±1.5 years), men (*n*=8), women (*n*=12) PD: *n*=20, age (65.4 ± 5.3 years), disease duration (4.4±1.5 years), men (*n*=13), women (*n*=7) HC: *n*=20, age (69 ± 3 years), men (8), women (12) | Clinical criteria Subtypes not reported | Not reported | *OFF*-assessment | Not reported | Computerized posturography | PSP group was significantly worse than both other groups (POAG, z = −5.13 [*P*<.001]; POAB, z = −5.02 [*P*<.001]). The FR measures showed significant differences among the groups (F2 = 48.2; *P*<.001, univariate ANOVA). PSP group scores were significantly lower than those of both other groups (*P*<.001), and that PD group scores were significantly lower than those of controls (*P*= .003). | Not reported. | The total stability score (SOT) showed that PSP group total scores were worse than those of both other groups (*P*<.001). CT sway was greater in the PSP than in the PD or control groups (*P*=.02); and total LOS measures of path time to target (*P*<.001) and path sway from a straight line to target (*P*<.001) were significantly prolonged in the PSP compared with the PD and control groups. The PSP group tended to have better performance with lateral movement and worse with anterior/posterior movements | Total LOS correlated with total POA scores (Pearson correlation, 0.67). | Results demonstrate significant abnormalities of postural control in patients with PSP that were markedly worse than those seen in a PD group matched for age and disease duration, and in age-matched healthy controls. Although clinical assessments also showed significant differences among the groups, CP more accurately discriminated early PSP from early PD. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Palmisano et al. (24) Italy | PSP: *n*= 20, age (66.6 ±4.7 years), disease duration (5.3±3.1 years), men (*n*=6), women (*n*=14) HC: *n*=25, age (65.1 ± 3.4 years), men (9), women (14) | PSPRS All had Richardson's Syndrome | Not reported | *OFF*-assessment | Not reported | Force plate, 3D motion system | PSPRS Total (33 ± 9,7); PSPRS limb motor (5.6± 1.9); PSPRS gait and midline (9.3 ± 2.7) *Brain metabolic measures:* there are six hypometabolic brain regions in the PSP group: the right dorsolateral prefrontal cortex, the left supplementary motor area, the middle cingulate cortex, the left caudate Nucleus, the medial thalamus and the Midbrain. | Not reported. | CoM movement was significantly impaired in the PSP group as revealed by lower values of the velocity and acceleration of the CoM at the unloading phase end, as well as the velocity and position of the CoM with respect to the CoP at the stance foot toe-off. Patients with PSP also showed a significantly reduced first step length, average and maximum velocity compared to HC. | In healthy controls, the velocity, acceleration and position of the CoM with respect to the CoP at IMB end were influenced by AM and BoS parameters. In the same cohort, during the unloading phase the CoP displacement and the average and maximum velocity of the CoP in the ML direction were influenced by the BoS. In the PSP group, no correlations of GI parameters with BoS measurements were found. The study also showed a significant correlation between the PSPRS subscores related to motor impairment (i.e., Limb motor, and Gait and midline) and the kinematic measurements of all GI phases. The caudate nucleus, together with the middle cingulate cortex, correlated with the velocity of the CoM at the end of the unload phase and, together with the thalamus, with the distance between CoP and CoM at stance foot toe-off. | The results of the study provide evidence to support the hypothesis that dysfunctional postural control at GI in PSP patients involves poor APA programming and execution. Multiple brain regions of the supraspinal locomotor network specifically contributes in a principled, controlled manner to an efficient GI. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pasha et al. (23) India | PSP: *n*= 29, age (60.8 ± 8.2 years), disease duration (2.2±1.2 years), men (*n*=21), women (*n*=8) HC: *n*=30, age (59.8 ± 7.6 years), men (17), women (13) | NINDS-SPSP Richardson's syndrome (17); Parkinsonism predominant (12) | MMSE: PSP (24.8±5.04); HC (29.7 ± 1.0) | ON and OFF-assessments | Not reported | Dynamic posturography | PSPRS, TPG, and TPT scores were found to be statistically significant among the subtypes of PSP (*P*=0.045; *P*=0.031; and *P*=0.037) while UPDRS-III was not significant (*P*=0.7). The PSP-R subtype performed poorly in comparison to the PSP-P subtype on these scales. *MRI measures:* The PSP-R subtype, compared to the PSP-P subtype, had more often radiological signs such as HBS (P < 0.001), MGS (P <0.008), and GCA (P <0.001). | | The mean values of balance indices were almost similar between the subtypes of PSP as compared to controls. The most significant of all the parameters in DP was LOS (P < 0.001) and the PSP-R subtype had lower scores. | There was a significant correlation of PSPRS with BBS (r = −0.642, P < 0.001), TPT (r = −0.516, *P*=0.004), TPG (r = −0.449, *P*=0.013), and TPB (r = −0.505, *P*=0.004). LOS-BW-LT had significant positive correlation with BBS (r = 0.381, *P*=0.038), TPB (r = 0.417, *P*=0.022), and TPT scores (r = 0.362, *P*=0.049). There was a significant correlation of the midbrain axial AP diameter (r = 0.4; *P*=0.03) and the ratio of midbrain to pons with BBS (r = 0.4; *P*=0.02), indicating that these are worse in patients with midbrain atrophy. In DP, API correlated negatively with the midbrain axial AP diameter (r = −0.5; *P*=0.01) and midbrain area (−0.39; *P*=0.03). The LOS-BW correlated positively with the area of midbrain (r = 0.49; *P*=0.001) and the midbrain to pons ratio (r = 0.57; r = 0.001). In addition, LOS-BW-LT correlated with the midbrain to pons ratio (r = 0.37; *P*=0.43) | The study shows that the measurements of balance severity in the PSP-P group correlate with the predominant pathology of the midbrain (midbrain atrophy); while in PSP-R subtype, the balance abnormalities could be a result of pathology in different or overlapping areas. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Picillo et al. (16) Italy | PSP-RS: *n*= 10, age (69.9 ±7.6 years), disease duration (2.5 ± 1.17 years), men (*n*=5), women (*n*=5) PSP (other subtypes): *n*=9, age (66.5 ± 5.9 years), disease duration (2.33 ± 1 years), men (*n*=6), women (*n*=3) | MDS-UPDRS-III PSPRS Richardson's syndrome (*n*=10), Parkinsonism predominant (*n*=5), Freezing of Gait predominant (*n*=4) | MoCA: PSP-R (15.3 ± 5.7), PSP-other (19.5 ± 4.2). | Not Reported | No | SMART DX system (3D motion system + force plate) | PSPRS (PSP-R: 34.9 ± 13.8; PSP-other: 28.33 ± 9.38) | PSP-R showed worse gait parameters than did other subtypes of PSP during single task. In detail, PSP-RS exhibited reduced cadence and increased cycle duration ($p$=0.018), mainly due to longer stance duration ($p$=0.034). For the dual task analysis, PSP-RS continued to roughly show the same gait features displayed during the single task. In addition, PSP-RS showed increased stance phase and reduced swing phase ($p$=0.031). There was a trend for significance for greater variability in step length ($p$=0.069) and lower velocity ($p$= 0.098) in PSP-RS. | Not reported | In patients with PSP-RS, constructional apraxia and right ideomotor apraxia presented an inverse relationship with cycle and swing duration and a direct correlation with cadence ($p$<0.05). TMT parts A and B showed a direct correlation with swing duration and cycle duration, respectively ($p$<0.05). No significant correlations were shown for other subtypes of PSP. | PSP-RS presents greater gait dynamic instability since the earliest stages of disease compared with other subtypes of PSP. In addition, these findings indicate that gait quantitative evaluation can help to distinguish PSP-RS from other subtypes of PSP. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Raccagni et al. (6) Austria | PSP: *n*= 12, age (67.4 ±8.7 years), disease duration (5.0±3.6 years), men (*n*=9), women (*n*=3) PD: *n*=25, age (66.6 ± 7.9 years), disease duration (7.5±4.5 years), men (*n*=13), women (*n*=12) HC: *n*=25, age (63.7 ± 9.7 years), men (13), women (12) | MDS-UPDRS-III PSPRS Subtypes not reported | Not reported | *ON*-assessment | Not reported | Wearable sensor-based gait analysis system | MDS-UPDRS-III (PSP: 41.7±15.5; PD: 31.7±9.3) | Gait speed was significantly reduced in PD patients (1.20 ± 0.23m/s) compared to controls 1.38 ± 0.20 m/s; *p*=.011) and even more impaired in APD patients (0.98 ± 0.18 m/s). 1.38 ± 0.20 m/s; *p*=.011) and even more impaired in APD patients (0.98 ± 0.18 m/s). Results showed significant difference for stride length in controls (1.47 ± 0.15 m), PD (1.27 ± 0.22 m) and APD (1.11 ± 0.18m). Maximum toe clearance was significantly reduced in PD (7.8 ± 2.6 cm; *p*=.001) and APD patients (6.9 ± 2.8 cm; *p*=.000) compared to controls (10.8 ± 3.3 cm) | Not reported | Stride length correlated with PSP-RS scores in the PSP patients (r=0.59, *p*=.021). There was a significant correlation between maximum toe clearance and MDS-UPDRS-3 (r =−.444, *p*=.026) in APD. | The significant difference of objective gait parameters among patient groups suggests that sensor-based technology may support and complement the clinical assessment provided by validated rating scales. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ricciardi et al. (21) Italy | PSP: *n*= 7, age (70.5 ±8.9 years), disease duration (2.6±0.5 years), men (*n*=3), women (*n*=4) De novo PD: *n*=15, age (63.3 ± 6.7 years), disease duration (0), men (*n*=11), women (*n*=4) Stable PD: *n*=24, age (61.9 ± 6.7 years), disease duration (5.9±2.5), men (17), women (7) | MDS-UPDRS-III PSPRS Richardson's syndrome (*n*=4); Parkinsonism predominant (*n*=3) | Not reported | Not reported | No | SMART DX system (3D motion system + force plate) | MDS-UPDRS-III (De novo PD: 14.3±7.5; Stable PD: 21.3±6.3), PSPRS (16.8±3.3) | The PSP group showed the highest sensitivity and specificity among all patients, both overcame the threshold of 90% and, particularly, the specificity went beyond 95%. De Novo PD's sensitivity and specificity scores were remarkable as well as the previous group, getting close to the value of 90%. The Stable PD group achieved the lowest sensitivity (between 65% and 70%) but high specificity; this metric, that represents the capacity to classify correctly the examined group but not the others, overcame the value of 90%. | Not reported | Not reported | The study's methodology allowed a good overall accuracy and re- markable sensitivities in the classification of PSP and De Novo PD patients. This indicates that the present approach could provide the clinician with a reliable, low-cost, non-invasive tool to distinguish early PSP from PD, in the first phases of the diseases' courses when the diagnosis of atypical forms of Parkinsonism is challenging. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Selge et al. (13) Germany | PSP: *n*= 38, age (69 ±6.3 years), disease duration (3.5 ± 2.2), men (*n*=20), women (*n*=18) iNPH: *n*=27, age (63.3 ± 6.7 years), disease duration (1.9 ± 1.6), men (*n*=21), women (*n*=6) HC: *n*=38, age (68.9 ± 7.6 years), men (20), women (18) | NINDS-SPSP Subtypes not reported | MMSE (PSP: 27.3 ± 3.1; iNPH; 23.4 ± 3.3) and FAB (PSP: 13.9 ± 2.3) | Not reported | No | GAITRite (6.7-m-long pressure-sensitive carpet system) | PSPRS (31.1±8.9) | Compared to HC, both patients with PSP and those with iNPH had a significantly inferior gait performance. Compared with patients with PSP, the gait of patients with iNPH was characterized by a lower velocity ($p$=0.001) and shorter stride length ($p < 0.001$). The main differences were a more broad-based gait in iNPH ($p < 0.001$) and a higher CV of stride time in PSP ($p$=0.009). Cognitive dual task led to a significant impairment of gait in all 3 groups. Patients with PSP were significantly more sensitive to dual-task perturbation than patients with iNPH. Especially gait velocity was clearly more reduced in patients with PSP, while the reduction in patients with iNPH was comparable to that in HC. Motor dual task led to a significant decrease of gait velocity and stride length in patients with PSP, but to a lesser extent than cognitive dual task. | Not reported | In patients with PSP, the CV of stride length increased at the time when the CV of step width decreased ($r = -0.338$). This correlation was not seen in patients with iNPH or HC. | Compared with patients with PSP, the gait of patients with iNPH was slower and broader based; gait variability was higher in patients with PSP; and patients with PSP were more sensitive to dual-task perturbation. Under motor dual task, patients with iNPH tended to even improve. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sintini et al. (25) USA | PSP: *n*= 19, age (71 ±7 years), disease duration (4.7 ± 2.6), men (*n*=11), women (*n*=8) | MDS-UPDRS-III PSPRS Richardson's syndrome (*n*=13), Parkinsonism predominant (*n*=3), Cortico-basal syndrome (*n*= 1), Speech and language disorder (*n*=2) | Not reported | Not reported | No | Force plate, 3D motion system | PSPRS (39 ± 10); MDS-UPDRS-III (49 ± 17) *Neuroimaging measures:* MRI atrophy, white matter tracts degeneration and flortaucipir-PET uptake were measured. Typically, DTI-FA and MRI volumes are reduced in PSP relative to healthy controls, while DTI-MD and flortaucipir SUVR are increased. | Stride length, cadence, velocity and step width were measured. Compared to HC, velocity, cadence and stride length are typically lower in PSP patients, while step width and stride length coefficient of variation are typically higher. | Gait stability ratio, total support, initial double support, postural imbalance and dynamic stability were measured. Compared to HC, velocity, cadence, stride length and dynamic stability are typically lower in PSP patients, while step width, gait stability ratio, total support, initial double support, postural imbalance, and stride length coefficient of variation are typically higher. | PSP rating scale and MDS-UPDRS III scores strongly correlated to velocity, stride length, gait stability ratio and dynamic stability. The gait midline sub-scale score of the PSP rating scale strongly correlated to velocity, dynamic stability, and stride length CV. Velocity was negatively correlated to DTI-MD in the cerebellar peduncle and positively correlated to volume in the supplementary motor area, superior frontal, and lateral parietal cortex. Velocity was positively correlated to subcortical flortaucipir-PET uptake (subthalamic nucleus, pallidum, caudate, red nucleus). Cadence was positively associated with DTI-MD in various tracts, especially the sagittal stratum and the cingulum (hippocampus). Stride length was strongly associated with DTI-MD in the body and splenium of the corpus callosum and with volume in the precentral, superior, and medial frontal, and parietal cortex. Step width was strongly related to DTI-MD in the superior cerebellar peduncle and flortaucipir-PET uptake in the dentate nucleus, cerebellum, and pons. Total support time was higher (i.e., more impaired gait) in patients with lower DTI-FA in many tracts, particularly the posterior thalamic radiation, sagittal stratum, external capsule and splenium of the corpus callosum. Greater postural imbalance with eyes open correlated to reduced metabolism in the cerebellar crus and lateral parietal cortex and greater postural imbalance with eyes closed correlated to reduced metabolism in the dentate nucleus. Lower dynamic stability strongly correlated with lower volume in the lateral parietal cortex. | The study showed that gait and postural impairments in PSP are associated with imaging abnormalities on different sets of regions and tracts that belong to the PSP system of neurodegeneration and the supraspinal locomotor network. The results suggest that gait and balance impairments might be driven by different mechanisms in PSP. |

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TABLE 1 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids (YES/NO) and type | Measurement Tool | Clinical motor outcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Correlational analysis | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Takamatsu et al. (15) Japan | PSP: *n*= 27, age (73.4 ± 5.3 years), disease duration (5.0±4.4 years), men (*n*=19), women (*n*=8) PD: *n*=25, age (74.2 ± 5.3 years), disease duration (4.7±3.4 years), men (*n*=14), women (*n*=11) HC: *n*=25, age (73.1 ± 5.3 years), men (11), women (14) | UPDRS-III PSPRS-V and VI Richardson's syndrome (*n*=19), Progressive gait freezing (*n*=5) Parkinsonism predominant (*n*=3) | Not reported | Not reported | Not reported | WalkWay MW-1000 (2.4-m-long pressure-sensitive carpet system) | PSPRS-V mean (3); PSPRS-VI mean (9); UPDRS-III mean (25) | Walking speed (PSP:75.1± 19.1, HC: 119±21, P < 0.001), CV of cadence (PSP: 5.3 ± 3.9, HC: 2.6±2.5, *P*=0.001), step length (PSP: 42.2 ± 8.9, HC: 62.2 ± 7.1, P < 0.001), step width (PSP:10.6 ± 3.5, HC:7.7 ± 3.4, *P*=0.007), foot angle (PSP: 9.6 ± 6.9, HC: 5,8 ± 4.8, *P*=0.010), time of stance phase (PSP: 0.73±0,12, HC: 0.63± 0,08, *P*=0.031), and double supporting phase (PSP: 0.15±0,04, HC: 0.11±0,02, P < 0.001) showed significant differences between PSP and HC. CV of cadence (PSP: 5.3 ± 3.9, PD: 2.8±2.6, *P*=0.015) and foot angle (PSP: 9.6 ± 6.9, PD: 5.1±4.7, *P*=0.016) showed significant differences between PSP and PD. | Not reported | Not reported | Results suggests that the gait of patients with PSP was unstable with parkinsonism and wide-based, which might be similar to combining features of PD and cerebellar disorders. |

A*P*=anteroposterior; APAs = anticipatory postural adjustments; aVOR = angular vestibulo-ocular reflex; BBS = Berg Balance scale; BOS = base of support; CO*P*=center of pressure; COM = center of mass; C*P*=Computerized posturography; CV = coefficient of variation; D*P*=dynamic posturography; DTI-FA = Diffusion tensor imaging—fractional anisotropy; DTI-MD = Diffusion tensor imaging—mean diffusivity; GI = gait initiation; HC = Healthy Control; iNPH = idiopathic normal pressure hydrocephalus; LOS = limits of stability; MDS-UPDRS-III = Movement Disorders Society Unified Parkinson's Disease Rating Scale part III motor subscale score; ML = mediolateral; MMSE = Mini Mental state examination. MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; NINDS-SPS*P*=National Institute of Neurological Disorders and Society for Progressive Supranuclear Palsy criteria for PSP; PD = Parkinson's disease; POA = performance-oriented assessments; POAB = performance-oriented assessment for balance; POAG = performance-oriented assessment for gait; PS*P*=Progressive Supranuclear Palsy; PSPRS = PSP rating scale; PSPRS-V = PSP rating scale-limb motor subscale; PSPRS-VI = PSP rating scale—gait and midline subscale; RR = responsivity ratio; SOT: sensory organization testing; SUVR = standard uptake value ratios; TPB, TPG and TPT = Tinetti performance-oriented mobility assessment (POMA) balance, gait and total; tVOR = translational vestibular-ocular reflex; UPDRS-III = Unified Parkinson's Disease Rating Scale part III motor subscale score.





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PSP-parkinsonism (PSP-P), and 4 with PSP-progressive gait freezing (PSP-PGF). Objective gait analysis revealed a longer stance phase in all PSP variants compared to iPD.

While some groups have compared the gait characteristics of PSP-RS, PSP-P, and PSP-PGF to each other and to iPD, other groups have pooled the variant subtypes to compare as a group to the traditional PSP-RS type, leading to slightly different conclusions. Takamatsu et al. compared gait mat measurements in 27 patients with PSP (including PSP-RS, PSP-PGF, and PSP-P variants) to patients with iPD and to healthy controls (24). They found an overall longer gait cycle time and a larger step width in PSP compared to iPD and HC. They also found a trend toward a faster walking speed in PSP-PGF compared to PSP-RS, and a trend toward a slower walking speed in PSP-P compared to PSP-RS. Low subgroup numbers did not allow for full statistical analysis. Picillo et al. performed a gait analysis in 19 patients with PSP in single and dual tasks (21) and compared the PSP-RS group to a pooled variant group of PSP-P and PSP-PGF (vPSP). Ten of the 19 PSP subjects had the PSP-RS subtype, 5 had PSP-P, and 4 had PSP-PGF. The authors found reduced cadence and increased cycle duration with a longer stance duration in PSP-RS compared to vPSP. With the dual task condition, they found an additional increase in stance phase in PSP-RS compared to the vPSP group. In addition to different methodologies for comparison groups, another important limitation of these studies is that straight walking on a gait mat may not elicit freezing episodes that are fully representative of real-world mobility impairments.

## Balance in PSP-RS

Despite the fact that postural instability and falls are classic features of PSP, fewer studies have focused on static and dynamic balance compared to the number of studies of gait in PSP. Early studies focused on the contribution of vestibular dysfunction to balance impairment in PSP. In 2008 Liao et al. combined otolith-ocular reflexes (VORs) and vestibular-evoked myogenic potentials (VEMPs) while subjects with PSP-RS were seated on a dynamic chair capable of translations and rotation and found smaller translational VORs and smaller VEMPs in PSP compared to control subjects (16). The authors concluded that abnormal otolith reflexes may contribute to frequent falls in PSP. Using the sensory organization test (SOT), during which subjects stand in 6 conditions on a moveable force plate (Neurocom) platform (1. eyes open with stationary platform, 2. eyes closed with stationary platform, 3. eyes open with visual background movement, 4. eyes open with platform movement, 5. eyes closed with platform movement, and 6. eyes open with both background and platform movement), Ondo et al. showed that subject with PSP-RS performed worse than subjects with iPD on the total SOT score (17).They also found that subjects with PSP-RS had specific impairments in a pattern that they concluded suggested vestibular dysfunction (conditions 3, 4, 5, and 6 of the SOT). However, these are also the most challenging balance conditions in the SOT, nonspecific for vestibular loss.

Our group subsequently compared the sensory and motor responses of 12 subjects with PSP-RS, 12 postural instability and gait disturbance (PIGD)-matched subjects with iPD, and 12 healthy controls while sitting and standing on the same Neurocom moveable force plate platform system (13). We specifically examined subjects' reactions to forward platform translations and toes-up platform tilts that resulted in backward sway. Compared to subjects with iPD, we found that subjects with PSP accurately perceived gravity when standing on a tilting surface, but could not accurately perceive toes-up platform tilts, and furthermore exerted less postural corrective motor responses in response to forward platform translations and toes up surface tilts. Taken together, we postulated that balance dysfunction in PSP is the result of abnormal central sensory integration, rather than a result of a primary vestibular deficit.

## Combined gait and balance in mixed PSP phenotypes

More recently, Ali et al. combined gait and postural sway in a small number of PSP phenotypes versus age-matched controls using a 3D motion capture system (10). Sixteen patients with PSP (11 PSP-RS, 2 PSP-P, 2 PSP-SL, and 1 PSP-CBS) were compared with healthy controls using a 10-camera motion capture system and 41 body markers and ground-embedded force plates. They found a slower gait velocity, slower cadence, and longer double-support time in PSP that correlated with clinical disease severity on the PSP Rating Scale (PSPRS). They also noted larger antero-posterior sway, but there was no relationship between the clinical PSPRS scores and standing postural sway tasks. The findings suggest that static standing sway tasks may not fully capture dynamic balance impairments in PSP.

## Data mining studies for classification of PSP versus PD

Machine learning approaches to classify gait in people with PSP from PD are the focus of two studies, one by Ricciardi (22) that uses data from a motion analysis system, and the other data from wearable Opal inertial sensors (APDM) by De Vos in 2020 (14). In the motion analysis study, straight walking data from 46 subjects with a mix of *de novo* PD, moderate PD, and unspecified PSP subtypes was compared. Freezing and turning data was excluded. In the initial machine learning classification attempt by Ricciardi, random forest and gradient boosted tree models correctly discriminated gait in those with PSP from iPD, with a sensitivity and specificity of 92.6 and 96.3 (random forest) and 96.3 and 92.6 (gradient boosted), respectively. However, because the disease duration differed largely between groups, the clinical utility of such classification is unclear. The subsequent machine learning study by deVos, 2020 used 6 wearable Opal sensors (placed on feet, wrists, sternum, and the lumbar region) to examine data from 4 PSP-RS subjects, 17 PSP-P subjects, 20 iPD subjects, and 30 healthy controls during a 2-min walk, sway on a firm surface with eyes closed, and a 3-m timed up and go task (14). The Opal triaxial sensors include accelerometers, gyroscopes, and a magnetometer. Subjects were tested on dopaminergic medication. The authors found that a random forest model with combined gait, sway, and timed up and go data predicted PSP versus PD with 86% sensitivity and 90% specificity. Sway, alone, did not discriminate the groups. This study was also limited by a variable disease duration in subjects. The average disease duration in the subjects with PD was 11.4 years, and only 2 years in the subjects with PSP. Additionally, machine learning approaches for classification of diseases can be of limited clinical utility when differences in the clinical features of the diseases under investigation are clinically apparent at baseline.

## Radiological correlations with gait and balance measures in PSP

A 2016 study by Pasha et al. compared balance and radiological features in 17 PSP-RS and 12 PSP-P patients using a Biodex

posturography system, which is a platform capable of tilting 20 degrees from the horizontal in all directions (19). They compared static limits of stability and dynamic stability in response to surface tilts with structural MRI features in PSP-RS and PSP-P and found that balance and radiological abnormalities were overall more severe in PSP-RS. This is consistent with evolution of the disease course, as we see that variants of PSP evolve with time and disease progression. In PSP-RS, they did not find any significant correlations between the PSPRS and specific areas of atrophy or between balance measures and imaging features. In PSP-P, the midbrain axial anterior–posterior diameter significantly correlated with the Tinetti Mobility Assessment total score and Gait subscore, but not with any dynamic posturography measures.

Palmisano et al. used a 3D motion capture system to examine anticipatory postural adjustments (APAs) for gait initiation in 26 subjects with PSP-RS and 14 age-matched controls and then correlates APA measures with metabolic activity on fluoro-D glucose (FGD) PET (18). Their study supported the findings of Amano and colleagues showing impaired APAs in people with PSP (11). Metabolic correlations were not significant after controlling for multiple comparisons, but the data suggested several trends toward significance such as an association between decreased regional caudate uptake and impaired APA control. The study was limited by a high rate of exclusion due to falls or total absence of the imbalance phase of the APA (8 out of 26 patients were excluded), and this highlights the major limitation of severity of disease in clinical trials in PSP.

A subsequent, multimodal imaging study in 19 subjects with PSP analyzed 3 T MRI markers of atrophy and white matter integrity on diffusion tensor imaging (DTI) and fortaucipir-PET metabolic imaging with principal components analysis (23). Various subtypes of PSP were represented including PSP-RS, PSP-P, PSP-SL, and PSP-CBS. Gait features of decreased stride length, increased step width, and longer double-support time related to DTI measures in the posterior thalamic radiation, external capsule, superior cerebellar peduncle, superior fronto-occipital fasciculus, body and splenium of the corpus callosum, and the sagittal striatum, to MRI volumes in frontal and precentral regions, and to flortaucipir-PET uptake in the precentral gyrus. Postural sway in standing, alone, did not correlate with imaging abnormalities, but this may be due to the mix of PSP phenotypes studied. In PSP-RS, alone, imaging and postural sway abnormalities did correlate. The authors note that a limitation of the study relates to the somewhat controversial use of flortaucipir PET in PSP, as it was optimized for the paired helical tau fragments in Alzheimer's and is known to have off-target binding in PSP.

## Gait and balance as a biomarker of progression: longitudinal studies

Four longitudinal studies were included in this review (Table 2). These studies evaluated longitudinal changes in gait, balance, and cognition up to 1.5 years. Two studies observed that wearable sensors can serve as sensitive measures of PSP progression.

An early study by Ghosh et al. (27) previously examined PSPRS and oculomotor function changes in 23 subjects with PSP Richardson syndrome over 14 months. They found significant changes on both the PSPRS and vertical eye movements *via* saccadometry during that period, but objective gait and balance outcomes were not used.

As part of a larger, longitudinal study in the United Kingdom, the "OxQuip" study, Pereira et al. examined longitudinal changes in motor and cognitive symptoms on clinical scales in PSP (28), and then Sotirakis et al. (29) built upon this background with longitudinal monitoring of PSP with 6 body-worn, inertial measurement units (IMU) sensors ("Opals," by APDM). Pereira analyzed the PSPRS, MDS-UPDRS 3, MOCA, and MMSE in 28 subjects with possible or probable PSP by 2017 MDS criteria (with symptom onset at an average of 1.9 years prior to enrollment, but PSP subtypes were not specified) at visits every 3 months for 18 months. The gait and midline sub-score of the PSPRS was the earliest score to change and this change was observed at *6 months*. This study experienced a drop-out rate of approximately 50% due to progression of illness, death, or change in diagnosis (the latter in only one subject). Other limitations of this study were the lack of pathological diagnoses and the fact that dopaminergic medication use was not accounted for at the time of assessments.

Sotirakis et al. then applied 6 wearable IMU Opal sensors to the wrists, feet, sternum, and lumbar region for longitudinal measurement in 27 subjects with PSP of the PSP-RS and PSP-P subtypes. The Opal sensors were applied for a 2-min walk with 180 degree turns and for a postural sway task for 30 s with eyes closed. Data from 17 participants was sufficient for analysis of visits at 3-month intervals for 12 months. Linear regression revealed that a model incorporating turn velocity, stride length standard deviation, and toe off angle detected statistically significant progression at visit 4, which was *3 months earlier* than the clinical PSP Rating Scale, alone. This was an important first study to quantify disease progression in PSP using wearable sensors. An important limitation of this study is the lack of accounting for the potential influence of physical therapy interventions on progression.

A subsequent study by Abate et al. (26) also examined disease progression in PSP using Opal inertial sensors, and correlated kinematic data to the PSPRS. Twenty-three subjects were assessed for progression, and PSP phenotypes included in this study were PSP-RS (80%), PSP-P (14%), and PSP-PGF (6%). In this study Opals were applied to the feet and lumbar area only. At the 3-month follow-up, cadence and gait cycle duration from a two-minute walking task worsened significantly, although the total PSPRS did not worsen significantly, except for the specific "arising from chair" sub-item that did worsen significantly. A strength of this study is the use of fewer sensors, which improve ease of clinical use. An important limitation of this study is that only 29% of the subjects with PSP needed unilateral assistance for gait (i.e., a cane or a helper holding onto one limb), so the population only encompassed relatively mild disease presentations of PSP.

The Sotrirakis and Abate studies (26, 29) both suggest that wearable sensors may be important and more sensitive detectors of disease progression than the PSPRS. Both studies also found that dynamic gait parameters, rather than balance parameters, are related to disease progression. The authors hypothesize that dynamic instability outweighs static instability for assessment of progression, at least in the relatively early stages of the disease. It is important to acknowledge that more wearable sensor assessment of static balance is needed to better understand progression, particularly in more advanced stages of PSP.

TABLE 2 Summary characteristics of the longitudinal included studies.

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids | Follow-up | Clinical motor utcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Abate et al. (26) Italy | PSP: $n = 35$, age (68.1 ± 5.4 years), disease duration (4.2 ± 2.5 years), men ($n = 27$), women ($n = 8$) | MDS PSP criteria. Richardson's syndrome ($n = 28$), parkinsonism predominant ($n = 5$), freezing of gait predominant ($n = 2$) | Not reported | PSPRS, Wearable sensors (one on the back and one on each foot) | Ten (29%) participants required unilateral support to complete at least one of the required tasks. | Three-month follow-up for PSPRS and each objective variable | PSPRS total score did not show a significant change over the follow-up (0.78% increase), but significant differences were detected for the "emotional lability" item (36.54% decrease) and the "arising from chair" item (16.31% increase). PSPRS total showed moderate inverse correlations with gait speed ($r = -0.434$; $p < 0.001$), and with stride length, swing and turning velocity, 360° angle and 360° turning velocity and moderate correlations with gait double support, stance and turning duration. PSPRS gait/midline subscore presented a strong inverse correlation with gait turning velocity, moderate inverse correlations with gait speed, stride length, swing, 360° angle, 360° duration and 360° turning velocity and moderate direct correlations with gait double support time and stance. | The analysis from baseline to 3-month follow-up showed that cadence and cycle duration from the 2-min walking test presented a significant increase over time (by 3.69 and 3.94% respectively). | Not reported. | Results from the study demonstrated the change of objective gait parameters over a short-term follow-up. Wearable sensors can provide an objective, sensitive quantitative evaluation and immediate notification of gait changes in PSP. |

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TABLE 2 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids | Follow-up | Clinical motor utcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Ghosh et al. (27) United Kingdom | PSP: *n* = 23, age (71.1 ± 8.6 years), disease duration (3 years), men (*n* = 14), women (*n* = 9) Healthy Control: *n* = 22, age (71.4 ± 7.6 years), disease duration (N/A) | PSPRS Richardson's syndrome | ACE-R = 76.4 ± 10.9 FAB = 10.8 ± 3.9 VOS*P*=7.6 ± 3.2 | PSPRS, UPDRS-III, Saccadometry | Not reported | 1.2 years for PSPRS, UPDRS-III, Saccadometry and cognitive status | PSPRS showed a mean change over a year of 11.3 points ($p < 0.001$). UPDRS-III showed a mean change of 8.3 points ($p$=0.003) and mu (the inverse median latency for saccades) showed a mean decrease of 0.4 $s^{-1}$(equivalent to an increase in latency of 0.02 s) ($p$=0.01). Cognition did not change significantly during the study period. | Not reported | Not reported | Patients show significant deterioration over one year using the PSPRS severity measure. Oculomotor function changed over one year, including the range of vertical gaze in the PSPRS. |
| Pereira et al. (28) United Kingdom | PSP: *n* = 28, age [69.2 (52–68) years], disease duration [1.9 (0.2–6.3) years], men (*n* = 15), women (*n* = 12) Healthy Control: *n* = 28, age [66.2 (56–72) years], disease duration (N/A) | MDS PSP criteria. Subtypes not reported | MoCA = 22.4 (12–30) MMSE = 26 (20–30) Fluency test (Semantic) = 21.8 (6–41) Fluency test (Phonemic) = 19.9 (6–50) | PSPRS UPDRS-III | Not reported | 1.5 years for PSPRS and MDS-UPDRS-III and cognitive status. Assessment visits were done every 3 months. | The increase in MDS-UPDRS-III was statistically significant after 12 months ($\Delta = 11.75$, SD = 12.31, $p < 0.008$) while the increase in PSPRS became significant 15 months after baseline assessment ($\Delta = 7.42$, SD = 7.63, $p < 0.008$). The MoCA and MMSE scores did not show any enduring changes in scores over time. | Not reported | Not reported | Motor decline in PSP is consistently captured by clinical rating scales. These results support the inclusion of multiple follow-up time points in longitudinal studies in the early stages of PSP. |

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TABLE 2 (Continued)

| Study and Country | Participants | Subtypes of PSP and criteria for PSP | Cognitive and Mood status | Assessment | Walking aids | Follow-up | Clinical motor utcomes/other outcomes | Objective gait outcomes | Objective balance outcomes | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Sotirakis et al. (29) United Kingdom | PSP: *n* = 17, age [63 (51–73) years], disease duration [1.6 (0–6) years], men (*n* = 9), women (*n* = 8) | MDS PSP criteria. Subtypes not reported | MMSE = 26.2 (20–30) | Kinematic gait and posture features collected by a body-worn IMU | Not reported. | 1 year, over five visits at 3-month intervals. | Not reported. | There was a significant change in mean turn velocity, SD of Stride length and mean toe off angle. These three features served exclusively as predictors of progression on a mathematical model used to predict MDS-UPDRS-III and PSPRS-motor. Strongly significant differences from baseline were apparent 3 months earlier in these models than in the actual scores | Not reported. | Data from wearable IMU arrays coupled with mathematical modeling can be used to track progression of PSP, complementing established clinical rating scales. In this study, the reduced variability in the modeled data allowed a progression signal to be discerned 3 months earlier than would otherwise be expected. |

ACE-R = Addenbrooke's Cognitive Examination—revised; FAB = Frontal Assessment Battery; MDS-UPDRS-III = Movement Disorders Society Unified Parkinson's Disease Rating Scale part III motor subscale score; MoCA = Montreal Cognitive Assessment; MMSE = Mini-mental State Examination; NINDS-SPSP: National Institute of Neurological Disorders and Society for Progressive Supranuclear Palsy criteria for PSP; PSPRS = PSP rating scale; UPDRS-III = Unified Parkinson's Disease Rating Scale part III motor subscale score; VOS*P*=Visual Object and Space Perception Battery.





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## Rehabilitation intervention studies

Fourteen rehabilitation intervention studies were included in this review (Table 3). These studies evaluated the effect of different interventions (balance training, home-gait exercise body-weight supported treadmill gait, virtual reality intervention, Robot-assisted walking, and cerebellar rTMS) on gait and balance outcomes in people with PSP. No study used wearable sensors to evaluate gait and balance impairments.

### Effect of rehabilitation interventions on spatiotemporal gait metrics in PSP

Changes in spatiotemporal gait metrics were observed in six rehabilitation studies (31, 38, 39, 41–43). Of these studies, only one had a sample size of 19 people with PSP (43), the other studies were case report that investigated the effects of treadmill training and boxing (31), robot-assisted walking (38), virtual reality (39), treadmill training with body weight support (41), and cueing step-training (42) on spatiotemporal gait parameters such as gait speed, stride length, and cadence. Although these studies have shown changes in gait speed, stride length, and cadence after a short period of intervention, ranging from 8 (42) to 24 sessions (41), it is important to emphasize that the data from these case studies do not allow causal conclusions on the effects of these mode of rehabilitation in PSP. Therefore, caution should be exercised when interpreting these findings as they cannot be generalized to the entire PSP population. Thus, robust clinical trials are needed to investigate the effects of rehabilitation intervention on spatiotemporal gait parameters in people with PSP.

Zampieri et al. (43) assessed the effect of a rehabilitation intervention in PSP on kinematic gait parameters (stance time, swing time, and step length) by tracking foot motion using electromagnetic sensors. Nineteen people moderately affected by the PSP were assigned to either a treatment group (balance plus eye movement exercises, $n = 10$) or a comparison group (balance exercises only, $n = 9$). Although the authors did not find a difference between groups for any gait parameter, the within-group analysis revealed significant improvements in stance time and walking speed for the treatment group, whereas the comparison group showed improvements in step length only. These preliminary findings support the use of eye movement exercises as a complementary therapy for balance training in the rehabilitation of some gait parameters in people with PSP; however, future clinical trials powered at a higher level are needed to confirm these results.

### Effect of rehabilitation interventions on clinical balance in PSP

Changes in clinical balance were observed in 6 rehabilitation studies (30, 32, 33, 35, 36, 40). These studies had a sample size ranging from 1 (40) to 24 (30). The number of sessions ranged from 10 (40) to 24 sessions (33). Most studies used the Berg Balance Scale (BBS) to assess clinical balance, while one study used the Mini-BESTest (40). Different interventions were used such as treadmill training (30), body-weight supported treadmill gait training (33), balance and resistance training (35), cueing balance-exercises (36), and backward gait training combined with gait-synchronized transcranial alternating current stimulation (tACS) (40).

Clerici et al. (30) observed that 20 sessions of treadmill training with visual cues and auditory feedback, both with ($n = 12$) and without ($n = 12$) the use of a robotic device, significantly improved the BBS scores in people with PSP. The authors concluded that both interventions have similar effects on clinical balance of this population, thus, the usefulness of an aerobic, sensory-feedback approach for the rehabilitation of patients suffering from PSP may be implemented in future clinical trials. Di Pancrazio et al. (33) tested the effect of 24 sessions of a rehabilitative program combining sensorimotor exercises (postural control, vibration, and cues) on postural instability of ten people with PSP. The authors observed that the combined rehabilitative program produced improvement in the BBS score and this clinical balance improvement persisted also in the follow-up phase after 30 days. Although the authors suggest that this specific rehabilitation program could improve postural instability in people with PSP due to intensive sensory stimulation involved in the intervention protocol, the failure to use a control group can make it impossible to draw meaningful conclusion from this study. Likewise, Matsuda et al. (35) applied 20 sessions of balance and resistance training in 20 people with PSP without the use of a control group. They also observed beneficial effects on the BBS score.

Although we do not know exactly the positive effects of progressive resistance strength training on people with PSP, there is strong evidence of benefit of this intervention in people with PD (44, 45). Two years of progressive resistance strength training were more effective than 2 years of non-progressive exercise in decreasing the motor symptoms of patients with mild-to-moderate PD (44). Our previous studies have demonstrated that combining balance exercises with progressive resistance strength training is more effective than progressive resistance strength training alone in decreasing motor symptoms of PD (46), as well improving clinical balance on the Balance Evaluation Systems Test (BESTest), mobility (timed-up-and-go test), and fear of falling in people with mild-to-moderate PD (47). Thus, a combined balance and progressive resistance training intervention would be more effective for people with PSP than progressive resistance training alone. Future controlled and randomized studies should test this intervention in PSP.

Nicolai et al. (36) tested the effects of 18 sessions of audio-biofeedback training on the BBS score in 8 people with PSP. This study used a new device that was well accepted for the participants and no adverse events occurred. Although the authors observed a significant improvement in the BBS score, which remained significant at the 4-week follow-up, the lack of a control group makes it difficult to be certain that the improvement in the BBS scores was caused by the audio-biofeedback training and not by other variables in the intervention. Thus, future powered and robust clinical trials are necessary to investigate the effects of sensory-feedback rehabilitation intervention on the clinical and objective balance of people with PSP.

Only one study investigated the effects of rehabilitation on freezing of gait (FOG) in people with PSP (34). We know FOG negatively impacts balance and functional gait in this population (48, 49). Irons et al. (34) observed that 24 sessions of a motor-assisted elliptical trainer with body weight support decreased FOG in a 67-year-old man with PSP. However, 1 month without training revealed worsening of his FOG, although the improved oxygen cost during training was sustained at 1-month follow-up. This case study is the first to document FOG improvement after a motor-assisted, elliptical training program for an individual with PSP, and future studies with a larger sample size are needed to investigate the possible benefits of this structured rehabilitation for people with PSP.

TABLE 3 Summary characteristics of the rehabilitation interventions included studies.

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Clerici et al. (30) Italy | *n* = 24 PSP patients *Experimental group:* age 69.9 ± 5.2, disease duration 4.1 ± 1.4 years *Control group:* age 72.5 ± 6.1; disease duration 4.0 ± 1.2 years | Lokomat® Training (20 min), maximum velocity tolerated, not exceeding 2.5 km/h, 5 times/week for 4 weeks. | Treadmill Training with visual and auditory cues (20 min), maximum velocity tolerated, not exceeding 2.5 km/h 5 times/week for 4 weeks. | PSPRS, BBS, 6MWT and number of falls | Not reported | Total PSPRS, PSPRS-gait, BBS, 6MWT and number of falls improved significantly by the end of the training programs in both groups. PSPRS-limb score improved significantly only in control group. | Not reported | Not reported | Not reported | Aerobic, motor-cognitive and goal-based rehabilitation treatments based on a multidisciplinary and intensive approach are useful for PSP patients, even without the support of expensive robotic technologies such as Lokomat® |
| Croarkin et al. (31) United States | *n* = 1 atypical PSP patient Age 63 years old, disease duration 11 years | Boxing, stepping tasks and treadmill training, 20 min for each 2 times/week, for 6 weeks | No | Computerized posturography, 10 camera DX system (Vicon Motion Systems), performance-based tests of timed stepping and unilateral squats | Not reported | Gains in strength were noted by improvements in his home exercise regimen. | Not reported. | Foot clearance scores increased around 0.2 to 2 cm bilaterally. Results on the repeated stepping test and the squats during unilateral stance also improved. Increased speed, symmetry, and accuracy were recorded. | Not reported | The intervention improved balance, eye-body coordination and strength in a high functioning patient with PSP. |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Dale et al. (32) United States | *n* = 2 PSP patients Age and disease duration not reported | 10 days of active Cerebellar rTMS (4,000 pulses were delivered with a 70 mm figure-of-8 coil at 10 Hz, 4 s on, 8 s off, 100 trains, machine output 90e110% of RMT, pending tolerability) plus 10 days of Sham treatment | No | Cerebellar brain inhibition (CBI) assessment, posturography. | Not reported | CBI increased by 50% in subject 1 and by 32% in subject 2. | Not reported | Subjects' backward stability improved when standing on a force plate, as evidenced by reduction of the backward center of pressure excursion (less sway in the posterior direction). | Not reported | Cerebellar rTMS with neuronavigation may result in improved postural stability in PSP. |
| Di Pancrazio et al. (33) Italy | *n* = 10 PSP patients Age 69 ± 7 years, disease duration not reported | 20–30% body-weight supported treadmill gait training (20 min) plus mechanical acoustic vibrations 3 times/week, for 8 weeks | No | PSPRS, BBS, Baropodometry static and dynamic, Stabilometry | Not reported | PSPRS showed improvement of the motor score posture item ($p$=0.01), and in the motor score postural stability item ($p$=0.01). BBS score varied from a 37.7 ± 12.1 at the baseline to a score of 47,6 ± 9.2 at the end of treatment ($p$=0.02). | Not reported | Stabilometry test showed a significant improvement of the distribution of the load in percentage. | Not reported. | The rehabilitation program was efficient on posture and on walking quality. The patients showed an increase in walking speed, greater stability and a consequent reduction in the risk of falling. |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Irons et al. (34) United States | *n* = 1 PSP patient Age 67 years old, disease duration 1.5 years | 17–21% body-weight supported motor-assisted elliptical training, time and speed progressively increased to 30 min and 50 rpm. 3 times/ week, for 8 weeks | No | 6MWT, FOG-Q, SSC (self-selected comfortable treadmill speed (m/min)) Oxygen cost of SSC walk speed | Not reported | Improvement of 82.9 m from pretraining on the 6MWT distance. The oxygen cost of SSC gait speed improved 6.8% between pretraining ($0.44\ mL{\cdot}kg^{-1}{\cdot}m^{-1}$) and post training ($0.41\ mL\ kg^{-1}\ m^{-1}$). This improvement in oxygen cost was sustained 1 month later ($0.41\ mL{\cdot}kg^{-1}{\cdot}m^{-1}$). | Not reported | Not reported | Not reported. | The intervention resulted in improved gait efficiency (oxygen cost of SSC gait speed) and distance traversed (6MWT). |
| Matsuda et al. (35) Japan | *n* = 20 PSP patients Age 72.3 ± 6.2 years, disease duration 2.4 ± 1.5 years | Balance training, resistance training, range of motion (ROM) exercises, stretching, walking exercises, and ADL training, 60–80 min/ day 5 times/week, for 4 weeks | No | PSPRS, BBS, TUG, Pull test, comfortable and maximum gait speed | Not reported | Improvements of PSPRS gait and midline total scores ($p$=0.004, r = 0.645), were found after intervention. BBS showed significant improvements in the items of reaching forward with outstretched arm ($p$=0.011, r = 0.566), turning to look behind ($p$=0.039, r = 0.461), turning 360 degrees ($p$=0.046, r = 0.447), standing with one foot in front ($p$=0.047, r = 0.445), and standing on one foot ($p$=0.009, r = 0.588). | No statistically significant difference was found for comfortable and maximum gait speed. | Not reported. | Not reported | A multiple therapeutic exercise program can improve the balance function in patients with PSP. |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Nicolai et al. (36) Germany | *n* = 8 PSP patients Age 66.4 ± 6.2 years, disease duration 6.2 ± 4 years | Balance exercises (sitting, standing, stepping) plus auditory cues (45 min) 3 times/ week, for 6 weeks | No | BBS, TUG, 5CR, UPDRS-III | Five participants used a walking aid, and two participants were wheelchair-bound but able to stand upright without another person's help. | Median values of the BBS improved by 25.7% ($p$=0.016) from pre to post intervention. | Not reported | Not reported | No adverse events. | The intervention is both feasible and associated with functional and psychosocial improvements for PSP patients. |
| Pilotto et al. (37) Italy | *n* = 20 PSP patients Age 67.8 ± 11.7 years, disease duration 3.6 ± 1.8 years | Each patient received both rTMS and sham cerebellar single session stimulations in randomized order in two different sessions performed at the same time of the day, separated by at least 2 weeks. | No | Tinetti test, SPPB, TUG, FRT, IMUs | No | Not reported | Not reported | No differences in baseline performances in instrumented tests were detected for each task between real and sham stimulation. In both eyes closed conditions, the participants were able to stay longer without support after the real rTMS, compared to sham stimulation | Not reported | Results suggests a beneficial effect of a single session of cerebellar rTMS stimulation on measures of postural instability in PSP patients |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Sale et al. (38) Italy | *n* = 5 PSP patients Age 74 ± 4 years, disease duration 3.8 ± 1.2 years | Robot-assisted walking (45 min) 5 times/week, for 4 weeks | No | 3D-Gait analysis | Not reported | Not reported | Gait velocity and cadence improved, respectively, by 15 and 23.8%. It was also shown an improvement of 11% in step length left and of 35% in step length right, besides a decrease Of 9% of Step width. Due to a small sample size, no statistical significance was found in all the analyzed parameters. | Not reported | No adverse events. | The positive results on improvement in spatiotemporal parameter of the PSP subject by the Robot Therapy, the lack of side effects strongly recommends extending the use of a Robot Therapy in the recovery of gait performance. |
| Seamon et al. (39) United States | *n* = 1 PSP patient Age 65 years old, disease duration 5 years | Xbox Kinect virtual exergaming (60 min) 2 times/week, for 6 weeks | No | BBS, FFABQ, FGA, 10 Meter walk test, TUG | Not reported | | Fastest comfortable gait speed changed from 1.16 m/s to 1.05 m/s on the 10 Meter Walk Test. Balance function remained stable and no declines below fall risk cut offs listed for elderly individuals. | Not reported | Not reported | Results of the study demonstrates the feasibility of an intervention using a virtual gaming system to help maintain functional mobility, balance and independence for an individual with PSP. |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Shima et al. (40) Japan | *n* = 1 PSP patient Age 70 years old, disease duration 1.6 years | tACS plus 4-min self-paced backward gait on the treadmill. A combination of sham stimulation (Intervention A), gait-synchronized cerebellar tACS (Intervention B), and cerebellar tACS asynchronized with gait using the inverted phase as a control condition (Intervention C) was performed. The order of the interventions was A–C, with an interval of more than a week between the interventions. 10 times backward training, 2 times/ week, for 5 weeks | No | PSPRS, TUG, mini-BESTest, FES, modified FES ABC scale, VAS, CBI | No | The short-term intervention elucidated that Intervention B improved the time of TUG and the total score of the mini-BESTest, whereas interventions A and C did not. The VAS revealed the largest improvement in general motor symptoms in Intervention B and improvements in gait and balance functions evaluated using TUG and mini-BESTest. PSPRS was also improved, especially in the subscale of the "Gait and midline," along with the VAS improvement for general symptoms The FES and modified FES scores increased after long-term intervention. The ABC scale also showed an increase in scores: 490 at pre-intervention and 640 at post-intervention. CBI using paired TMS of the left M1 and right cerebellum was improved at inter-stimulus interval of 3,5, and 10 ms, suggesting that the function of the right cerebellum was recovered | Not reported | Not reported | No | The results demonstrates that backward gait training combined with synchronized cerebellar tACS can be a promising treatment for improving the motor symptoms of PSP |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Suteerawattananon et al. (41) United States | *n* = 1 PSP patient Age 62 years old, disease duration >5 years | 15% body-weight supported treadmill gait training (90 min) 3 times/week, for 8 weeks | No | BBS, TUG, 15.2-m (50-ft) walk test, FRT, LOS, spatiotemporal gait measures | Sometimes the patient carried a cane for better balance. | The BBS score increased from 45 at the beginning of the training to 49 at midpoint, but it decreased to 47 by the end of the program. | Gait speed increased from 73.40 ± 10.47 cm/s to 100.05 ± 0.78 cm/s after training. Step length of the left and right legs improved from 43.76 ± 5.52 cm and 49.66 ± 4.32 cm to 51.27 ± 0.44 cm and 58.74 ± 3.80 cm, respectively. | Static balance in reaching forward increased 3.63 cm. | Not reported | The intervention might be an appropriate apparatus to reduce falls and improve balance and mobility in patients with PSP. |
| Wittwer et al. (42) Australia | *n* = 5 PSP patients Age ranging from 54–74 years old, disease duration ranging from 1.1–12.8 years | Home-based gait and Step training plus music and auditory cues (60 min) 2 times/ week, for 4 weeks | No | Spatiotemporal gait measures (GAITRite) | 2 patients occasionally used walking aid (single point stick, 4 wheeled frame) | Not reported | Gait velocity and stride time improved for three patients. Stride time variability improved for four patients. Clinical significance was found for gait velocity in one patient. | Not reported. | No | The intervention was feasible for people living with mild to moderately severe PSP and was associated with improvements including reduced variability in temporal and spatial measures of walking. |

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TABLE 3 (Continued)

| Study and Country | Participants | Experimental | Control | Measurement tools | Walking aids | Clinical motor outcomes/ other outcomes | Objective gait outcomes | Objective balance outcomes | Adverse events | Author's conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Zampieri et al. (43) United States | *n* = 19 PSP patients *Experimental group:* age 71.2 ± 5.2, disease duration 3.4 ± 2.6 years *Control group:* age 67.5 ± 7.2; disease duration 4.4 ± 2.8 years | Balance exercises plus eye movement and visual awareness training (60 min) 3 times/week, for 4 weeks | Balance exercises only (60 min) 3 times/week, for 4 weeks | Kinematic gait measures through the 2.4 m (8 ft) walk test, TUG | Not reported | TUG score decreased more in the experimental group than in the control group. No statistically significant differences between the groups were observed. | A significant decrease in stance time was observed in the experimental group. There was a significant improvement in walking speed on the 8-ft walk test in the treatment group but not in the control group. | Not reported. | Not reported | Balance exercises coupled with eye movement exercises may improve gait in people with PSP. Improvements in spatial gait parameters, gait speed, and TUG scores were observed for participants who received balance and eye training. |

ABC scale = Activities-Specific Balance Confidence scale; BBS = Berg Balance Scale; CBI = Cerebellar brain inhibition; FES = falls efficacy scale; FFABQ = fear of falling avoidance belief questionnaire; 5CR = Five chair rise test; FOG-Q = Freezing of Gait Questionnaire; FGA = Functional gait analysis; FRT = Functional reach test; LOS = limits-of-stability test; PSPRS = PSP rating scale; SPPB = Short Physical Performance Battery; 6MWT = 6 Minutes Walking Test; tACS = transcranial alternating current stimulation; TUG = Timed-up and Go test; UPDRS-III = Unified Parkinson's Disease Rating Scale-motor subscale, VAS = visual analog scale.

Interventions that involve cognitive and balance exercises should be applied to decrease FOG in people with PSP. People with PSP have more fear of falling, cognitive and balance impairments, and falls compared to people with PD (50). Our previous studies have demonstrated that 36 sessions (47, 51) or 18 sessions (52, 53) of challenging motor-cognitive balance training improved spatiotemporal gait parameters, anticipatory postural adjustments, postural stability, as well decreased FOG severity (51) and improved cognitive function in people with mild-to-severe PD. These interventions are challenging and need to be applied individually. As people with PSP are at higher risk of falling compared to those without PSP (49, 50), these exercises would be performed individually and with a body-weight support system (e.g., ZeroG) (54), in an attempt to significantly improve gait, cognition, FOG, and balance in a safe way. Thus, future, randomized, clinical trials are encouraged to implement this motor-cognitive rehabilitation strategy.

Using a different intervention approach, Shima et al. (40) assessed the effect of 10 sessions of rehabilitation (backward gait training) combined with gait-synchronized, cerebellar transcranial alternating current stimulation (tACS) on the MiniBESTest score in a 70-year-old woman with PSP-Richardson's syndrome. Initially, the participant underwent short-term intervention with combined training of backward gait with synchronized cerebellar tACS, asynchronized, or sham stimulation according to the N-of-1 study design. Synchronized tACS training demonstrated an improvement in the MiniBESTest scores, whereas asynchronized or sham stimulation did not. The additional long-term interventions of combined backward gait training with synchronized cerebellar tACS demonstrated further improvement in MiniBESTest. Although this case study results can be difficult to replicate due to the sample size, it describes a novel approach for clinical balance in a patient with PSP-Richardson's syndrome, as backward gait training with synchronized cerebellar tACS may be a promising therapeutic approach due to pathophysiology of disease involving cerebellar dysfunction (55, 56) and backward falls. Robust, prospective clinical trials are needed to test this new approach in people with PSP.

Although clinical balance was assessed in 6 rehabilitation studies (30, 33–36, 40), 3 of these studies used a quasi-experimental design (33, 35, 36), 2 used a case report (34, 40, 44–47), and only one study used an experimental design (30). Thus, the effects of balance- and gait-focused rehabilitation for people with PSP are still unknown due to small sample sizes. Future powered, prospective and robust clinical trials are needed to investigate the effects of rehabilitation interventions on clinical balance of the people with PSP.

## Effect of rehabilitation interventions on objective balance measures in PSP

The effect of rehabilitation interventions on balance posturography has been investigated only in 2 studies, both of which used cerebellar transcranial magnetic stimulation (TMS) in people with PSP (32, 37). Neuroimaging and neuropathology studies have revealed a reduced volume of the cerebellum with tau accumulation (55, 56) that may be responsible for impaired balance and gait in patients with PSP. Thus, stimulatory cerebellar TMS may be a promising tool to improve balance and motor control in people with PSP.

Dale et al. showed that 10 sessions of cerebellar repetitive TMS (rTMS) improved backward postural stability when 2 subjects with PSP-RS stood on a force plate (Neurocom), as evidenced by reduction

of the backward center of pressure excursion (less sway in the posterior direction) (32). The authors also observed that the 10 sessions of cerebellar rTMS increased cerebellar-brain inhibition by 50% in subject 1 and by 32% in subject 2. The rTMS protocol was well tolerated. Cerebellar rTMS may improve postural stability, but larger future studies are needed. One such study is currently enrolling (NCT04468932).

A recent study of cerebellar TMS compared theta burst TMS with sham cerebellar, single session stimulation in a randomized order in 2 different sessions in 20 people with PSP (37). Before and after stimulation, static balance was evaluated with instrumented (lower back accelerometer) 30-s trials in semi-tandem and tandem positions. In tandem and semi-tandem tasks, active stimulation was associated with increase in time without falls. In addition, postural sway area, velocity, acceleration, and jerkiness was improved only after theta burst TMS, compared to sham stimulation. These preliminary data suggest that cerebellar theta burst TMS has significant effect on postural stability in people with PSP, when assessed with mobile digital technology. The authors suggest that these results should motivate larger and longer trials using non-invasive brain stimulation for people with PSP. Future powered, prospective and robust clinical trials are needed to investigate the effects of cerebellar TMS on outcomes of this population.

## Conclusion

Objective measurement to quantify gait and balance and effects of rehabilitation on gait and balance in PSP is a rapidly growing field, with potential uses to classify of early parkinsonism, monitoring progression, and documenting effects of rehabilitation. A natural tension exists between lab-based, comprehensive 3D motion capture of gait and force plate measures of postural sway and wearable inertial sensors (57). The former yields laboratory, gold-standard data, but is impractical for clinical trials. Wearable sensors are currently being used in clinical trials of balance and gait and have the potential for home-based daily life monitoring of mobility (7–9).

In this narrative review we examined: (a) cross-sectional studies in PSP focused on quantifying step initiation and steady state gait and postural sway for standing balance that relate to disease progression and imaging features, and (b) the use of objective gait and balance metrics as endpoints for rehabilitation and brain stimulation intervention studies in PSP. This review suggests several potential practical applications: for example, abnormal anticipatory postural adjustments when initiating gait suggest medio-lateral tasks should be a focus in rehabilitation for PSP, not just backward postural instability, and body-worn sensors for longitudinal monitoring may detect relevant gait changes 3 months earlier than the PSP Rating Scale.

However, studies of objective measurement of gait and balance in PSP suffer from several limitations common to studies of rare diseases: small sample sizes, no pathological confirmation of diagnoses, lack of multi-center studies, lack of replication, lack of long-term follow-up, and unclear subtyping of PSP classification. A particular note of caution when interpreting PSP classification studies: it is important to consider what particular mix of PSP subtypes is being evaluated and if it is reasonable to lump such variants together for analysis. PSP-RS, PSP-P, and PSP-PGF are the most represented variants, and these variants can look rather different clinically. Little is known about any subtle gait or balance abnormalities that objective metrics may elucidate in other categories of PSP, such as possible PSP speech and language, possible PSP with predominant corticobasal syndrome, and other categories that are suggestive of early PSP. It is also important not to consider variant subtypes of PSP as static categories, but rather milestones along a progression to eventual development of probable PSP-RS.

Regarding rehabilitation interventions, due to small sample sizes, low statistical power and comparatively low methodological rigor (lack of a control group and case series) in the studies included in this review, the effectiveness of rehabilitation interventions on objective measures of gait and balance and clinical balance still needs to be confirmed. Although we still do not know the optimal content of exercise (dosage, frequency, intensity, time, and type) for people with PSP, the most of the studies included in this review have used gait training, balance training, and sensory feedback training of gait and balance. Thus, there is a need to understand if rehabilitation interventions may have positive impact in a large population with PSP in future randomized clinical trials.

Looking forward, longitudinal monitoring with objective gait and balance metrics from body-worn sensors should be incorporated into future clinical trials with PSP, complementing the PSPRS clinical scale that has traditionally been used as the primary endpoint. Studies of correlations between objective measures of gait and balance and imaging features in PSP are in early stages, but are likely to grow in the coming years. Exercise regimens in PSP are often modified from PD or stroke regimens, and development of rehabilitation targeted specifically to the balance and gait impairments in people with PSP are needed. Exercise and other intervention studies benefit from objective gait and balance endpoints, but need replication with multisite application and long-term follow-up.

## Author contributions

MD conceived and designed the study. FA and CS-B collected and organized the data. MD and CS-B drafted the manuscript. FH critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

FH is a part-time employee of Clario, that makes APDM Opals for clinical trials. This potential conflict has been managed by Oregon Health and Science University.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogenous degeneration involving the brainstem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia, and dementia. *Arch Neurol*. (1964) 10:333–59. doi: 10.1001/archneur.1964.00460160003001

2. Golbe LI. Progressive supranuclear palsy. *Semin Neurol*. (2014) 34:151–9. doi: 10.1055/s-0034-1381736

3. Williams DR, de Silva R, Paviour DC, Pittman A, Watt HC, Kilford L, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain*. (2005) 128:1247–58. doi: 10.1093/brain/awh488

4. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord*. (2017) 32:853–64. doi: 10.1002/mds.26987

5. Nonnekes J, Aerts MB, Abdo WF, Bloem BR. Medio-lateral balance impairment differentiates between Parkinson's disease and atypical parkinsonism. *J Parkinsons Dis*. (2014) 4:567–9. doi: 10.3233/JPD-140436

6. Raccagni C, Gaßner H, Eschlboeck S, Boesch S, Krismer F, Seppi K, et al. Sensor-based gait analysis in atypical parkinsonian disorders. *Brain Behav* (2018);8:e00977. doi: 10.1002/brb3.977

7. Horak FB, Mancini M. Objective biomarkers of balance and gait for Parkinson's disease using body-worn sensors. *Mov Disord*. (2013) 28:1544–51. doi: 10.1002/mds.25684

8. Mancini M, Horak FB. Potential of APDM mobility lab for the monitoring of the progression of Parkinson's disease. *Expert Rev Med Devices*. (2016) 13:455–62. doi: 10.1586/17434440.2016.1153421

9. Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov Disord*. (2019) 34:657–63. doi: 10.1002/mds.27671

10. Ali F, Loushin SR, Botha H, Josephs KA, Whitwell JL, Kaufman K. Laboratory based assessment of gait and balance impairment in patients with progressive supranuclear palsy. *J Neurol Sci*. (2021) 429:118054. doi: 10.1016/j.jns.2021.118054

11. Amano S, Skinner JW, Lee HK, Stegemöller EL, Hack N, Akbar U, et al. Discriminating features of gait performance in progressive supranuclear palsy. *Parkinsonism Relat Disord*. (2015) 21:888–93. doi: 10.1016/j.parkreldis.2015.05.017

12. Amboni M, Ricciardi C, Picillo M, De Santis C, Ricciardelli G, Abate F, et al. Gait analysis may distinguish progressive supranuclear palsy and Parkinson disease since the earliest stages. *Sci Rep*. (2021) 11:33927317. doi: 10.1038/s41598-021-88877-2

13. Dale ML, Horak FB, Wright WG, Schoneburg BM, Nutt JG, Mancini M. Impaired perception of surface tilt in progressive supranuclear palsy. *PLoS One* (2017); 12:e0173351.; PMCID: PMC5340402, doi: 10.1371/journal.pone.0173351

14. De Vos M, Prince J, Buchanan T, FitzGerald JJ, Antoniades CA. Discriminating progressive supranuclear palsy from Parkinson's disease using wearable technology and machine learning. *Gait Posture*. (2020) 77:257–63. doi: 10.1016/j.gaitpost.2020.02.007

15. Hatanaka N, Sato K, Hishikawa N, Takemoto M, Ohta Y, Yamashita T, et al. Comparative gait analysis in progressive Supranuclear palsy and Parkinson's disease. *Eur Neurol*. (2016) 75:282–9. doi: 10.1159/000445111

16. Liao K, Wagner J, Joshi A, Estrovich I, Walker MF, Strupp M, et al. Why do patients with PSP fall? Evidence for abnormal otolith responses. *Neurology*. (2008) 70:802–9. doi: 10.1212/01.wnl.0000304134.33380.1e

17. Ondo W, Warrior D, Overby A, Calmes J, Hendersen N, Olson S, et al. Computerized posturography analysis of progressive supranuclear palsy: a case-control comparison with Parkinson's disease and healthy controls. *Arch Neurol*. (2000) 57:1464–9. doi: 10.1001/archneur.57.10.1464

18. Palmisano C, Todisco M, Marotta G, Volkmann J, Pacchetti C, Frigo CA, et al. Gait initiation in progressive supranuclear palsy: brain metabolic correlates. *Neuroimage Clin*. (2020) 28:102408. doi: 10.1016/j.nicl.2020.102408

19. Pasha SA, Yadav R, Ganeshan M, Saini J, Gupta A, Sandhya M, et al. Correlation between qualitative balance indices, dynamic posturography and structural brain imaging in patients with progressive supranuclear palsy and its subtypes. *Neurol India*. (2016) 64:633–9. doi: 10.4103/0028-3886.185417

20. Selge C, Schoeberl F, Zwergal A, Nuebling G, Brandt T, Dieterich M, et al. Gait analysis in PSP and NPH: dual-task conditions make the difference. *Neurology*. (2018) 90:e1021–8. doi: 10.1212/WNL.0000000000005168

21. Picillo M, Ricciardi C, Tepedino MF, Abate F, Cuoco S, Carotenuto I, et al. Gait analysis in progressive Supranuclear palsy phenotypes. *Front Neurol*. (2021) 12:674495. doi: 10.3389/fneur.2021.674495

22. Ricciardi C, Amboni M, De Santis C, Improta G, Volpe G, Iuppariello L, et al. Motion analysis "Schola Medica Salernitana" group; biomedical engineering unit. Using gait analysis' parameters to classify parkinsonism: a data mining approach. *Comput Methods Prog Biomed*. (2019) 180:105033. doi: 10.1016/j.cmpb.2019.105033

23. Sintini I, Kaufman K, Botha H, Martin PR, Loushin SR, Senjem ML, et al. Neuroimaging correlates of gait abnormalities in progressive supranuclear palsy. *Neuroimage Clin*. (2021) 32:102850. doi: 10.1016/j.nicl.2021.102850

24. Takamatsu Y, Matsuda N, Aiba I. The combination of short-step and wide-based gait is a gait characteristic in progressive supranuclear palsy: a retrospective, cross-sectional study. *Eur Geriatr Med*. (2019) 10:809–15. doi: 10.1007/s41999-019-00211-2

25. Bonora G, Mancini M, Carpinella I, Chiari L, Horak FB, Ferrarin M. Gait initiation is impaired in subjects with Parkinson's disease in the OFF state: evidence from the analysis of the anticipatory postural adjustments through wearable inertial sensors. *Gait Posture*. (2017) 51:218–21. doi: 10.1016/j.gaitpost.2016.10.017

26. Abate F, Russo M, Ricciardi C, Tepedino MF, Romano M, Erro R, et al. Wearable sensors for assessing disease severity and progression in progressive supranuclear palsy. *Parkinsonism Relat Disord*. (2023) 109:105345. doi: 10.1016/j.parkreldis.2023.105345

27. Ghosh BC, Carpenter RH, Rowe JB. A longitudinal study of motor, oculomotor and cognitive function in progressive supranuclear palsy. *PLoS One* (2013); 8:e74486.; PMCID: PMC3769232, doi: 10.1371/journal.pone.0074486

28. Pereira MF, Buchanan T, Höglinger GU, Bogdanovic M, Tofaris G, Prangnell S, et al. Longitudinal changes of early motor and cognitive symptoms in progressive supranuclear palsy: the OxQUIP study. *BMJ Neurol Open*. (2022) 4:35128403. doi: 10.1136/bmjno-2021-000214

29. Sotirakis C, Conway N, Su Z, Villarroel M, Tarassenko L, FitzGerald JJ, et al. Longitudinal monitoring of progressive Supranuclear palsy using body-worn movement sensors. *Mov Disord*. (2022) 37:2263–71. doi: 10.1002/mds.29194

30. Clerici I, Ferrazzoli D, Maestri R, Bossio F, Zivi I, Canesi M, et al. Rehabilitation in progressive supranuclear palsy: effectiveness of two multidisciplinary treatments. *PLoS One*. (2017) 12:e0170927. doi: 10.1371/journal.pone.0170927

31. Croarkin E, Robinson K, Stanley CJ, Zampieri C. Training high level balance and stepping responses in atypical progressive supranuclear palsy: a case report. *Physiother Theory Pract*. (2022):1–12. doi: 10.1080/09593985.2022.2032509

32. Dale ML, DeVries WH, Mancini M, George MS. Cerebellar rTMS for motor control in progressive supranuclear palsy. *Brain Stimul*. (2019) 12:1588–91. doi: 10.1016/j.brs.2019.07.017

33. Di Pancrazio L, Bellomo RG, Franciotti R, Iodice P, Galati V, D'Andreagiovanni A, et al. Combined rehabilitation program for postural instability in progressive supranuclear palsy. *NeuroRehabilitation*. (2013) 32:855–60. doi: 10.3233/NRE-130909

34. Irons SL, Brusola GA, Buster TW, Burnfield JM. Novel motor-assisted elliptical training intervention improves 6-minute walk test and oxygen cost for an individual with progressive supranuclear palsy. *Cardiopulm Phys Ther J*. (2015) 26:36–41. doi: 10.1097/CPT.0000000000000007

35. Matsuda N, Takamatsu Y, Aiba I. Effect of therapeutic exercise on the balance of patients with progressive supranuclear palsy: a pilot study. *Front Neurol*. (2022) 13:955893. doi: 10.3389/fneur.2022.955893

36. Nicolai S, Mirelman A, Herman T, Zijlstra A, Mancini M, Becker C, et al. Improvement of balance after audio-biofeedback. A 6-week intervention study in patients with progressive supranuclear palsy. *Z Gerontol Geriatr*. (2010) 43:224–8. doi: 10.1007/s00391-010-0125-6

37. Pilotto A, Rizzetti MC, Lombardi A, Hansen C, Biggi M, Verzeroli G, et al. Cerebellar rTMS in PSP: a double-blind sham-controlled study using Mobile health technology. *Cerebellum*. (2021) 20:662–6. doi: 10.1007/s12311-021-01239-6

38. Sale P, Stocchi F, Galafate D, De Pandis MF, Le Pera D, Sova I, et al. Effects of robot assisted gait training in progressive supranuclear palsy (PSP): a preliminary report. *Front Hum Neurosci*. (2014) 8:207. doi: 10.3389/fnhum.2014.00207

39. Seamon B, DeFranco M, Thigpen M. Use of the Xbox Kinect virtual gaming system to improve gait, postural control and cognitive awareness in an individual with progressive Supranuclear palsy. *Disabil Rehabil*. (2017) 39:721–6. doi: 10.3109/09638288.2016.1160444

40. Shima A, Tanaka K, Ogawa A, Omae E, Miyake T, Nagamori Y, et al. Case report: backward gait training combined with gait-synchronized cerebellar transcranial

alternating current stimulation in progressive supranuclear palsy. *Front Hum Neurosci*. (2023) 17:1082555. doi: 10.3389/fnhum.2023.1082555

41. Suteerawattananon M, MacNeill B, Protas EJ. Supported treadmill training for gait and balance in a patient with progressive supranuclear palsy. *Phys Ther*. (2002) 82:485–95. doi: 10.1093/ptj/82.5.485

42. Wittwer JE, Winbolt M, Morris ME. A home-based, music-cued movement program is feasible and may improve gait in progressive Supranuclear palsy. *Front Neurol*. (2019) 10:116. doi: 10.3389/fneur.2019.00116

43. Zampieri C, Di Fabio RP. Balance and eye movement training to improve gait in people with progressive supranuclear palsy: quasi-randomized clinical trial. *Phys Ther*. (2008) 88:1460–73. doi: 10.2522/ptj.20070302

44. Corcos DM, Robichaud JA, David FJ, Leurgans SE, Vaillancourt DE, Poon C, et al. A two-year randomized controlled trial of progressive resistance exercise for Parkinson's disease. *Mov Disord*. (2013) 28:1230–40. doi: 10.1002/mds.25380

45. Lamotte G, Skender E, Rafferty MR, Fabian DJ, Sadowsky S, Corcos DM. Effects of progressive resistance exercise training on the motor and nonmotor features of Parkinson's disease: a review. *Kinesiol Rev*. (2015) 4:11–27. doi: 10.1123/kr.2014-0074

46. Silva-Batista C, Corcos DM, Roschel H, Kanegusuku H, Gobbi LT, Piemonte ME, et al. Resistance training with instability for patients with Parkinson's disease. *Med Sci Sports Exerc*. (2016) 48:1678–87. doi: 10.1249/MSS.0000000000000945

47. Silva-Batista C, Corcos DM, Kanegusuku H, Piemonte MEP, Gobbi LTB, de Lima-Pardini AC, et al. Balance and fear of falling in subjects with Parkinson's disease is improved after exercises with motor complexity. *Gait Posture*. (2018) 61:90–7. doi: 10.1016/j.gaitpost.2017.12.027

48. Compta Y, Valldeoriola F, Tolosa E, Rey MJ, Martí MJ, Valls-Solé J. Long lasting pure freezing of gait preceding progressive supranuclear palsy: a clinicopathological study. *Mov Disord*. (2007) 22:1954–8. doi: 10.1002/mds.21612

49. Osaki Y, Morita Y, Miyamoto Y, Furuta K, Furuya H. Freezing of gait is an early clinical feature of progressive supranuclear palsy. *Clin Neurosci*. (2017) 5:86–90. doi: 10.1111/ncn3.12122

50. Brown FS, Rowe JB, Passamonti L, Rittman T. Falls in progressive Supranuclear palsy. *Mov Disord Clin Pract*. (2020) 7:16–24. doi: 10.1002/mdc3.12879

51. Silva-Batista C, de Lima-Pardini AC, Nucci MP, Coelho DB, Batista A, Piemonte MEP, et al. A randomized, controlled trial of exercise for Parkinsonian individuals with freezing of gait. *Mov Disord*. (2020) 35:1607–17. doi: 10.1002/mds.28128

52. Hasegawa N, Shah VV, Harker G, Carlson-Kuhta P, Nutt JG, Lapidus JA, et al. Clinical balance domain outcomes for exercise intervention in Parkinson's disease. *Front Neurol*. (2020) 11:940. doi: 10.3389/fneur.2020.00940

53. King LA, Mancini M, Smulders K, Harker G, Lapidus JA, Ramsey K, et al. Cognitively challenging agility boot camp program for freezing of gait in Parkinson disease. *Neurorehabil Neural Repair*. (2020) 34:417–27. doi: 10.1177/1545968320909331

54. Hidler J, Brennan D, Black I, Nichols D, Brady K, Nef T. ZeroG: overground gait and balance training system. *J Rehabil Res Dev*. (2011) 48:287–98. doi: 10.1682/jrrd.2010.05.0098

55. Dickson DW, Ahmed Z, Algom AA, Tsuboi Y, Josephs KA. Neuropathology of variants of progressive supranuclear palsy. *Curr Opin Neurol*. (2010) 23:394–400. doi: 10.1097/WCO.0b013e32833be924

56. Gellersen HM, Guo CC, O'Callaghan C, Tan RH, Sami S, Hornberger M. Cerebellar atrophy in neurodegeneration-a meta-analysis. *J Neurol Neurosurg Psychiatry*. (2017) 88:780–8. doi: 10.1136/jnnp-2017-315607

57. Dale ML, Prewitt AL, Harker GR, McBarron GE, Mancini M. Perspective: balance assessments in progressive Supranuclear palsy: lessons learned. *Front Neurol*. (2022) 13:801291. doi: 10.3389/fneur.2022.801291

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# The Parkinson's disease waiting room of the future: measurements, not magazines

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Utilizing technology to precisely quantify Parkinson's disease motor symptoms has evolved over the past 50 years from single point in time assessments using traditional biomechanical approaches to continuous monitoring of performance with wearables. Despite advances in the precision, usability, availability and affordability of technology, the "gold standard" for assessing Parkinson's motor symptoms continues to be a subjective clinical assessment as none of these technologies have been fully integrated into routine clinical care of Parkinson's disease patients. To facilitate the integration of technology into routine clinical care, the Develop with Clinical Intent (DCI) model was created. The DCI model takes a unique approach to the development and integration of technology into clinical practice by focusing on the clinical problem to be solved by technology rather than focusing on the technology and then contemplating how it could be integrated into clinical care. The DCI model was successfully used to develop the Parkinson's disease *Waiting Room of the Future (WROTF)* within the Center for Neurological Restoration at the Cleveland Clinic. Within the WROTF, Parkinson's disease patients complete the self-directed PD-Optimize application on an iPad. The PD-Optimize platform contains cognitive and motor assessments to quantify PD symptoms that are difficult and time-consuming to evaluate clinically. PD-Optimize is completed by the patient prior to their medical appointment and the results are immediately integrated into the electronic health record for discussion with the movement disorder neurologist. Insights from the clinical use of PD-Optimize has spurred the development of a virtual reality technology to evaluate instrumental activities of daily living in PD patients. This new technology will undergo rigorous assessment and validation as dictated by the DCI model. The DCI model is intended to serve as a health enablement roadmap to formalize and accelerate the process of bringing the advantages of cutting-edge technology to those who could benefit the most: the patient.

KEYWORDS

**Parkinson's disease, technology enablement, technology integration, healthcare transformation, clinical integration**

## 1. Introduction

Over the past several decades there has been an explosion in the development of technology and the "internet of things" aimed at providing objective and quantitative outcomes to accelerate the detection and improve the treatment of Parkinson's disease (PD) (1). Despite this explosion, the concept of using objective and quantitative measures to characterize PD symptoms and

motor and non-motor function is not new. In the early 1950's accelerometers were used to measure human gait (2) and in the 1970's the possibility of using accelerometers to characterize human movement in athletes was realized (3). The pioneering studies of George Stelmach (4) and Erwin Montgomery (5) were some of the first to apply biomechanical methods to better understand the effects of PD on motor control and potentially aid in disease detection. However, after decades of development and potential promise of using objective, quantitative outcomes from these and other technologies to enhance patient care, the gold standard of PD evaluation remains a subjective clinical scale. The goal of this paper is to introduce a cohesive model of technology development and clinical integration that we have used to effectively transition technology from the peak of inflated expectations through the trough of disillusionment and eventually to the plateau of productivity for the benefit of patient care and scientific advancement.

Gartner, Inc. (Stamford, CT), the advisory and information technology company, proposed a hype cycle "model" that characterizes technology adoption (Figure 1). The hype cycle consists of five phases: technology trigger, peak of inflated expectations, trough of disillusionment, slope of enlightenment, and plateau of productivity. The hype cycle is intended to conceptualize the maturity of technology and its adoption. While not a perfect model, it appropriately contextualizes the use of technology in evaluating PD motor and non-motor performance. We take the position that technology intended to aid clinical practice in PD has cycled between the first three phases of this hype cycle: an emerging technology triggers an explosion of enthusiasm and validation studies and maybe even a few case series studies are published and then that technology tumbles to its final resting place, the trough of disillusionment. Failure to integrate promising technology has stagnated the field of movement disorders neurology, visible by the continued reliance on the Unified Parkinson's disease Rating Scale (UPDRS), originally developed in the 1980s (6).

The field of clinical neurology, movement disorders in particular, is filled with examples of technology developed to quantify a single, isolated PD symptom via accelerometer or other technologies (7–11). In a review of technology solutions for the quantification of PD motor and non-motor symptoms, only six of more than 500 technologies were deemed at a technology readiness level for the integration into clinical care (12); of those six, it is unclear if any have been integrated into routine clinical care. The inability to integrate into clinical workflows provides clear evidence the field must critically reassess the model of technology development to ensure the technology has the best chance to pass through the trough of disillusionment. Hence, the expert Movement Disorders Society panel continues to call for the development of technology platforms that can be integrated into clinical workflows (13). Previous technology often times is valid and reliable; however, the focus has been on technology development with little regard to feasibility of clinical integration (14, 15). If the true value of technological approaches to quantifying motor and non-motor aspects of PD are to be realized, a fundamental shift in the approach to technology development and integration is necessary. We have created and successfully utilized the Develop with Clinical Intent (DCI) model, shown in Figure 2. Central to this model is that technology development is secondary to the clinical problem that the technology aims to solve.

The DCI model was used to guide the successful development and integration of the Multiple Sclerosis Performance Test (MSPT) mobile application (16). The MSPT application is the cornerstone to the multi-continent Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) which is the first example of a learning health system in MS (17). To date, more than 17,000 unique MS patients have completed the MSPT application as part of standard of care; approximately 88 percent of these patients have multiple assessments over time which has resulted in more than 93,000 quantitative assessments of motor and non-motor function in approximately six years. Data from the MSPT application has informed and augmented the care of the individual patients, enhanced

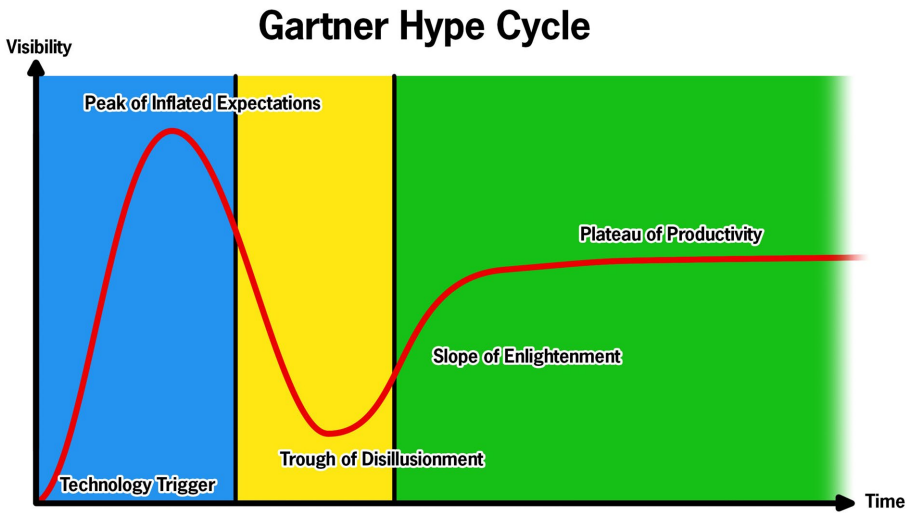


FIGURE 1
Representation of the Gartner Hype Cycle for technology with the corresponding components of the Develop with Clinical Intent (DCI) model. The blue represents the Technology Development and Validation Phase of the DCI model; the yellow represents the Clinical Viability and Design Iteration Phase; and green represents the Full-scale Clinical Integration.

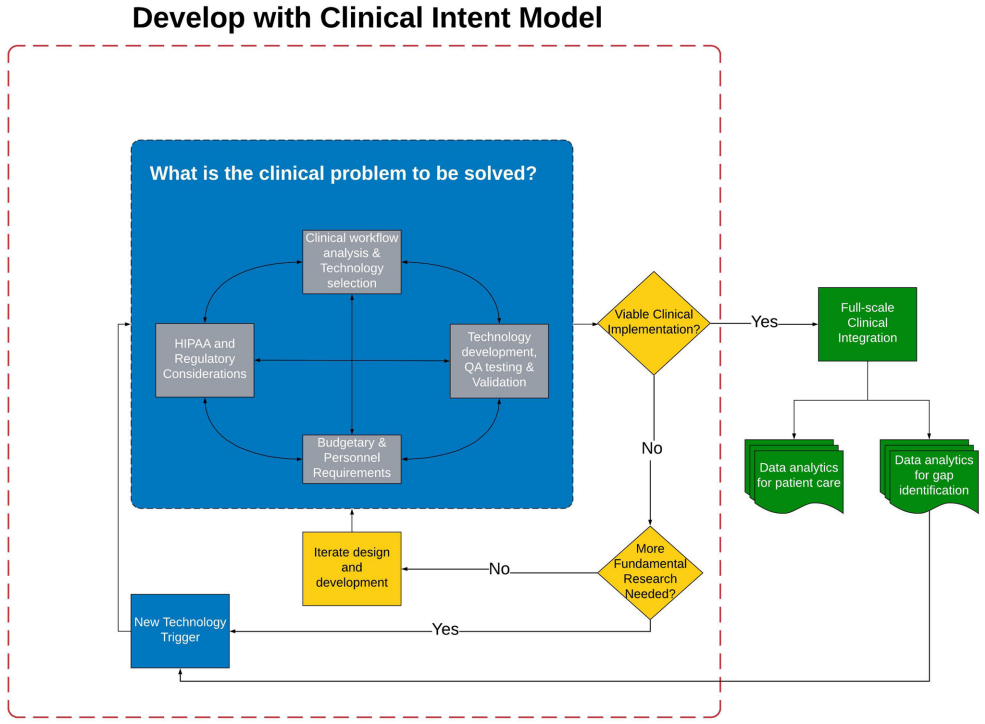


FIGURE 2
The Develop with Clinical Intent Model and decision-making points. Phase I, the blue section, represents the steps that must be considered during the initial phase of Technology Development and Validation. Once validation has occurred the technology is evaluated for Viability of Clinical Implementation in Phase II (represented by yellow decision points). Should the technology be viable for clinical integration, Full-scale Clinical Integration is Phase III (green section). HIPPA, Health Insurance Portability and Accountability Act; QA, Quality assurance.

care of MS patients from a population health perspective (18–21), and reduced provider documentation time in the electronic health record (22). Our experience in developing the MSPT application and involvement with the MS PATHS initiative was leveraged to create the PD-Optimize application for deployment into the Parkinson's disease Waiting Room of the Future for PD (PD-WROTF).

## 2. Operationalizing the Develop with Clinical Intent model to create the Parkinson's disease waiting room of the future

Building the PD-Optimize application and PD-WROTF was initiated in 2019; following pandemic related delays it was integrated into clinical practice and the Center for Neurological Restoration at the Cleveland Clinic in 2021. The remainder of this manuscript will detail the DCI model and processes, experience with the PD-WROTF and how analytics and clinical experience are shaping the development of new technology to better understand the effects of PD on non-motor performance and completion of instrumental activities of daily living (IADLs). It is envisioned that the DCI model serve as a roadmap for the development and integration of technology into routine clinical practice. The DCI model and decision-making process has three phases: (I) Technology Development and Validation (Figure 2, blue section), (II) Clinical Viability and Design Iteration (Figure 2, yellow section) and (III) Full-scale Clinical Integration (Figure 2, green section).

### 2.1. Phase I: technology development and validation

The critical first step of the DCI model is to bring providers, patients, engineers, IT professionals and data scientists together to clearly identify: *What is the clinical problem to be solved?* For PD, the clinical problem is well-known and has been expressed over multiple decades: how can one comprehensively and objectively quantify PD motor and non-motor symptoms for use in the long-term tracking of disease progression to optimize the clinical management of PD patients? While this clinical problem may be rather obvious to providers or scientists who are immersed in PD clinical care or investigation, it is likely not evident to those who will be developing, testing and evaluating, integrating and eventually using the technology. Having critical and open conversations with experts in their respective fields will ensure all important knowledge and experience will be evaluated and weighed to ensure that the proposed technology is the most suitable, scalable and sustainable to solve the clinical problem.

While the problem of quantifying PD motor and non-motor function is well-known to PD providers and researchers, software developers and IT professionals are likely not familiar with the problem. The *Clinical Workflow Analysis and Technology Selection* is an important early step that must have representation from all stakeholders. The active participation of all parties is necessary to ensure all teams have a clear understanding of the problem and how they can leverage their respective expertise to identify a technology

solution that can be scaled and sustained. It is necessary to engage engineers, software developers and IT specialists, including those affiliated at the enterprise level, in this initial phase as these preliminary discussions reinforce the concept that the project is not about the technology, rather that technology should enable the practice of better and more efficient medicine to benefit the patient. *Technology Selection* discussions between clinicians, researchers, and engineers are critical in this early phase of the DCI model as identifying the most appropriate technology to address the problem is critical. Our approach to the *Technology Selection* phase is to empower the engineers and software developers to lead this phase as they are familiar with the strengths and weaknesses of a given technology. If this phase is executed properly, the software and hardware developers will often propose technology that is typically "cutting edge," but may not be "bleeding edge." This phase takes time, commitment and discipline. Clinicians typically want to implement tomorrow, researchers want to use bleeding edge technology and if developers and IT are not actively participating in this phase, they want to finish the application and move to the next project.

Once the technology has been agreed upon, the *Clinical Workflow Analysis* phase is undertaken. The goal of this phase is to immerse the developers and engineers with all providers in the clinic to understand the current clinical workflow. Ideally, these teams will spend multiple days together initially and make frequent visits to the clinical setting during the technology development phase. Understanding the existing patient flow and how information is transmitted or not transmitted between nurses, physicians and patients will provide insight into the optimal integration points or may reveal that the technology can only be used if there is a reimagining of the clinical workflow.

A necessary precursor to the adoption of technology into the clinical workflow is provider trust of the data generated by the new technology. Providers must trust that the technology is accurate, reliable and provides data that will enhance treatment. During the *Technology Development, Quality Assurance (QA) Testing, and Validation Testing*, trust is established between the clinical team members, the technology team members, and the technology itself. We contend that the most appropriate technology validation study design is one in which outcomes from the proposed technology are compared to a gold standard biomechanical or non-motor outcome if possible. Notably, it is contended that the correlation of a measure of motor function to a clinical rating within the MDS-UPDRS III is not a gold standard comparison of motor performance. While MDS-UPDRS III items are the clinical gold standard for clinical use, they are not objective and lack resolution and a degree of quantification to serve as the best validation comparison to a new technology (23). If the outcome from the technology simply correlates with a subjective clinical rating, one must question if that is the best use of technology as providers will likely reject the technology as it is not providing new information that they could not derive from the traditional clinical assessment. Following rigorous validation, an analysis to understand how the outcomes of the technology may be related to clinical ratings to facilitate clinical understanding and adoption is recommended.

Once the team is aligned on the clinical problem, understands clinical workflow challenges and opportunities and validation strategy is established, the inevitable and unavoidable *Budgetary and Personnel Requirements* discussion must occur. Each institution will have resources unique to them that will shape these discussions. Seeking philanthropy for the support of a clinical technology integration project may an effective strategy or, as in the case of the MS PATHS, collaboration with a pharmaceutical partner. It is important to consider not only the technical development and validation of the potential technology, but also ongoing support in terms of maintenance, data storage, hardware and cost of integrating data into the electronic health record (EHR). The PD-Optimize and PD-WROTF were largely supported by philanthropic support.

Although it may seem premature during the initial development and validation phase, it is valuable to engage and contemplate the current *HIPPA and Regulatory Considerations* and future regulatory claims of the technology. During the initial phases of development, the most important activity is keeping and maintaining comprehensive documentation. Notably, documenting user requirements, technical requirements, software versioning, hardware versioning and quality assurance testing will save time and effort when deploying to the clinic as this information will be requested by enterprise IT and EHR teams. Further, any documentation of human factors testing, no matter how informal, will be important should one decide to pursue regulatory approval in the future.

## 2.2. Phase II: clinical viability and design iteration

Once the technology is at the point of moving out of the development phase, a piloting of the solution is necessary (Figure 2, yellow section). It is recommended that the beta version of the software/hardware should be tested within the clinical practice of one of the providers engaged in Phase I of the DCI model to determine if the technology is: *Viable for Clinical Implementation*. If the technology is not mature enough to meet the viability criteria (e.g., does it work reliably, is the user interface appropriate, can patients complete, are the data outputs valid and reliable, etc.), then one must determine if more fundamental research or validation or development is necessary. As shown in Figure 2, if the answer to this question is *No*, the technology should re-enter the development cycle and the stakeholders iterate on design or user interface or whatever factor(s) has been identified as a barrier to clinical integration. If more fundamental research is needed, one must critically evaluate if the current technology is capable of addressing the question or if alternative or new technology should be considered.

## 2.3. Phase III: full-scale clinical integration

If the technology is determined to meet clinical viability requirements, *Full-scale Clinical Integration* follows (Figure 2, green section). Prior to this implementation, the technology must be industrialized or hardened to ensure it is reliable and does not require a full-time engineer to monitor and troubleshoot. It is at this point the initial time and effort spent with the enterprise IT and EHR groups will pay dividends as their approval is necessary for the introduction of a new technology and for the integration of outcomes into the EHR. The transition from clinical viability to full-scale clinical integration is tenuous and failure to plan for this transition from Day 1 increases the probability of the technology getting stuck in the trough of disillusionment. An enterprise approved plan for continuous support and maintenance of the technology must be contemplated

and agreed upon prior to clinical implementation. Clear communication with enterprise IT to clearly understand who will be responsible for perpetual support and maintenance is critical. It is also important to facilitate continuous communication between the data analytics team, IT team and medical providers after clinical integration as it relates to the display of data outcomes and their formal analyses. While many EHRs are able to ingest data from mobile devices or external sources, the graphing and visual display capabilities of the EHR are far from that of typical analytic or statistical software packages. In our experience, integration with EHRs should be done as close to natively as possible. Native integration typically limits data exchange to raw data; however, it lends itself to reliability and good clinical utilization as providers are able to minimize the number of clicks between screens or data sources.

The successful clinical integration and utilization of the technology is a tremendous accomplishment: however, in order to sustain use of the technology proper utilization of these data are necessary. One must remember that patient appointments are likely a little longer to complete the technology assessment. It is critical that patients are informed of these changes in clinical workflow prior to their appointment so they know what to expect and can plan to bring their eyeglasses or hearing aid. By asking patients to complete these tests prior to their appointment there is an implied importance of these assessments. It is imperative that the provider review these data with the patient as part of their clinical visit. Failure to review the data with the patient will result in the patient feeling these data are not important and they are likely to not complete in future visits (24).

Finally, clinical interpretation and data analytics should be coupled to identify new questions and potentially trigger the revision of the technology or possibly trigger the development of new technology. This encourages continued use and improvement of the DCI model.

## 3. Experience with the PD waiting room of the future (PD-WROTF)

The Center for Neurological Restoration (CNR) is a PD Center of Excellence that serves Northeast Ohio. Across all of its locations, the CNR examines and treats over 10,000 unique patients annually from across the globe. The DCI model was used to create the PD-WROTF which aimed to gather objective and quantitative data to better understand, track and treat the motor and non-motor effects of PD. The PD-WROTF was introduced into clinical practice in two stages. The first stage was in late 2019. To evaluate the acceptance of using technology, PD patients completed quality of life and symptom severity questionnaires via an iPad after checking in for their appointment. These questionnaires were completed by the patient in the waiting area. Information from the questionnaires was then automatically uploaded to a HIPPA compliant cloud, hence the importance of getting enterprise IT and cybersecurity engaged early, and automatically integrated into a flowsheet within the EHR. The provider was able to review this information and discuss with the patient at that visit. The collection of these patient reported outcomes served as a "soft launch" to determine if technology could be successfully implemented into a patient visit without disrupting the overall clinical workflow and gather patient and clinician feedback.

Early in the *Technology Selection* and *Technology Development* discussions, there were valid concerns from providers, software developers and IT staff that individuals with PD tend to be older and exhibit physical limitations such as bradykinesia, tremor or cognitive impairments that would result in poor assessment compliance and high abandonment rates. To mitigate these concerns, a group of PD patients were engaged in the development process and assisted in developing instructions for the test that were understandable and that the user interface and experience contemplated the effects of potential motor and non-motor dysfunction. Early engagement of the end user has been critical in ensuring the assessment modules are completed as intended and that the outcomes are measuring the function of interest.

Another key concern from clinicians was the amount of oversite that would be required to ensure the patients were completing the modules as intended. During the *Clinical Workflow Analysis and Technology Selection,* the clinicians voiced the importance of self-administered modules to minimize staffing requirements and maximize workflow efficiency. The clinical and software teams addressed this need through the development of self-administered modules, ultimately resulting in one medical assistant overseeing as many as five PD patients simultaneously completing the PD-Optimize app. The cognitive modules include a practice session to ensure the patient understands the task. Algorithms were created during the *Technology Development, Quality Assurance (QA) Testing, and Validation Testing* to ensure understanding; if the patient makes too many errors on the practice portion, they are re-directed back to the instructions. The algorithms went through a rigorous quality assurance testing. This process ensured full understanding of the task prior to assessment initiation. Furthermore, the clinicians felt empowered that their clinical integration concerns had been heard and collaboratively addressed in the initial phase of the project.

Based on the success of this initial launch and with appropriate adaptions from clinician and patient feedback, the full suite of cognitive and motor assessment modules of PD-Optimize was developed and integrated into CNR clinical workflow for all PD patients. In 2021, four assessment modules, screenshot shown in Figure 3, and the MyHealth patient demographics questionnaire were completed and incorporated into the clinical workflow. Similar to the MS PATHS, assessment modules are delivered to the patient via iPad. Two motor and two non-motor modules are self-administered by the patient. Upper extremity function is evaluated with the Manual Dexterity Test (16, 22, 25), an electronically enabled version of the Nine-Hole Peg Test (26, 27). Lower extremity performance is monitored using the Walking Speed Test, an electronic adaptation of the 10 meter walk test (28). From a non-motor perspective, two validated and normed assessments of cognition as well as a quality of life assessment are gathered. Information processing is evaluated using the Processing Speed Test (PST) (29–31) adapted from the Symbol Digit Modalities Test (32). The Visual Memory Test (VMT) evaluates episodic memory and delayed memory (31). The Quality of Life in Neurological Disorders (Neuro-QoL) is assessed as a patient-reported quality of life metric for adults with neurological disease (33). Based on our experience with implementation of the MSPT application (34), an important aspect of engaging patients in using technology for the collection of objective and quantitative data by completing assessments they are likely unfamiliar with is that the technology must serve their immediate needs as well. To address this need, patients are asked one open text response question in the MyHealth module: "*What is most important item(s) you want to discuss with your care team today?*" The response to this question is automatically populated at the top of the patient's chart within the EHR and it is the first information shown to the clinician. Querying the patient about their most important concern has facilitated a more focused clinical visit for the patient and allows the provider to quickly see which patients

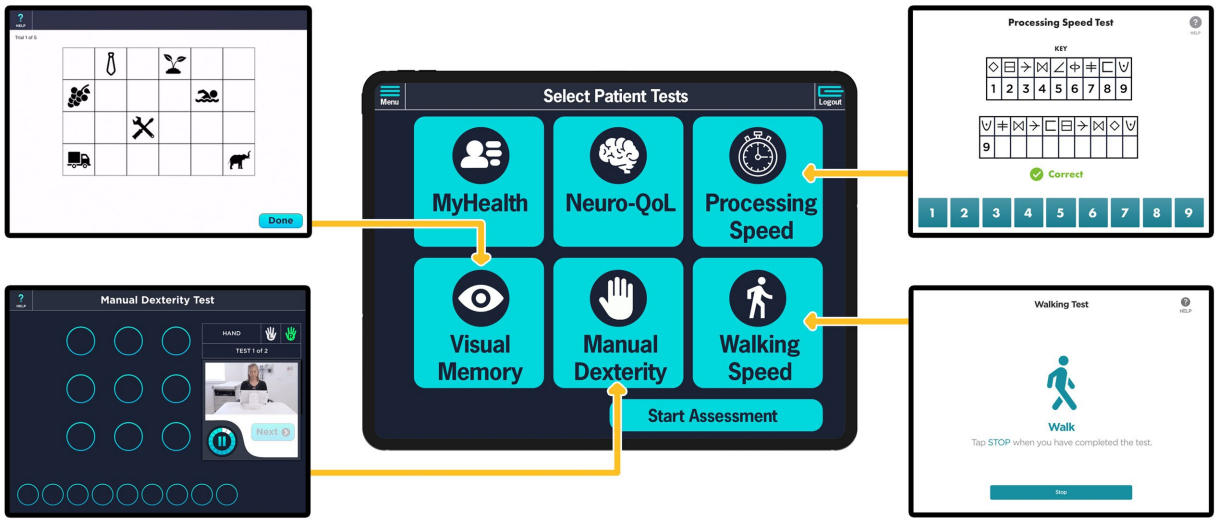


FIGURE 3
PD-Optimize modules presented to PD patients in the Parkinson's disease – Waiting Room of the Future (PD-WROTF). The middle column illustrates the home page initially presented to the patient showing the modules that will be completed. The modules are self-administered at the patient's own pace with the ability to repeat instructions to ensure understanding. The Medical Assistant has the option to de-select a given module if a patient would not be able to complete (e.g., a patient who is non-ambulatory may not complete the Walking Speed module). Screenshots of the Visual Memory Test, Manual Dexterity Test, Processing Speed Test, and the Walking Speed Test are displayed in the left and right columns. The MyHealth questionnaire asks the question "What is most important item(s) you want to discuss with your care team today?" The Neuro-QoL is a patient-reported quality of life metric for adults with neurological disease.

on their schedule may have additional needs and make preparations in advance such as allocating more time to an encounter or further investigation into the patient's chart and data prior to the encounter. Having providers engage patients around this question often facilitates a transition to a discussion about the objective data gathered. As we have demonstrated in MS-PATHS, these data bring the patient and provider together as patient's report they are now both "speaking the same language" (22, 34).

## 4. Patient and data workflow

As illustrated in Figure 4, when a patient arrives to the CNR, they check in at the front desk like a typical appointment. A medical assistant (MA) escorts the patient to the PD-WROTF. Following standard vital sign collection, the MA selects the patient from the schedule on the iPad and gives the iPad to the patient for them to complete the assessment modules. The MyHealth demographics questionnaire confirms identify from the patient, gathers demographics and instructs the patient on how to complete each assessment and ensures the patient can perform basic tasks on the iPad. The patient then completes the four cognitive and motor assessments, quality of life and demographic modules and returns the iPad to the MA. The patient is then taken to an exam room and proceeds with the medical appointment. Results from PD-Optimize are immediately available to the provider in the EHR for review, discussion with the patient and automatically populate clinical notes.

In addition to the PD-Optimize application on the iPad, two servers support the application. The cloud structure and data flow are shown in Figure 5. The architecture was discussed and agreed upon between the development team, cybersecurity and enterprise IT early in the development process. While these initial meetings seemed premature, they were critical in informing the security features that the application had to adhere to and the approach to encrypting the data when transmitting to the cloud and EHR. Briefly, the cloud-based PD-Optimize server, within the Amazon Web Services (AWS) environment stores all incoming data and outgoing assessment results. The iPad application communicates directly with the PD-Optimize server to retrieve information such as the CNR's daily schedule and patient demographics, and to send assessment results to the PD-Optimize server to be stored and sent to the EHR. The second server, the Gateway, communicates bidirectionally with Cleveland Clinic's EHR.

The PD-Optimize server communicates with the iPad to display the CNR's daily schedule to the MA so they can select the correct patient before giving the iPad to the patient. To retrieve data from the EHR, the PD-Optimize server requests data from the Gateway, which in turn requests data from EHR's Interconnect platform through an HTTPS web service. Interconnect uses a custom protocol to securely communicate directly with the primary EHR database. Next, the data from the EHR is transformed into a JSON file and returns the data in response to the gateway's web service call. The gateway then returns the data to the PD-Optimize server. When an iPad requests the schedule from the PD-Optimize server, it returns the most recent EHR data from the gateway server.

When a patient completes the assessment modules, the PD-Optimize application immediately uploads the results as JSON to a URL on the PD-Optimize server. The PD-Optimize application stores the assessment results to a secure research database to make the data easily available and preserved. The PD-Optimize server also sends the data to the gateway server, which sends the data to the EHR for storage in the EHR database as flowsheet data. Because the assessment results are stored in the EHR in real-time, providers can view the results in the EHR during the visit, compare with past results, and include the most recent results in their notes.

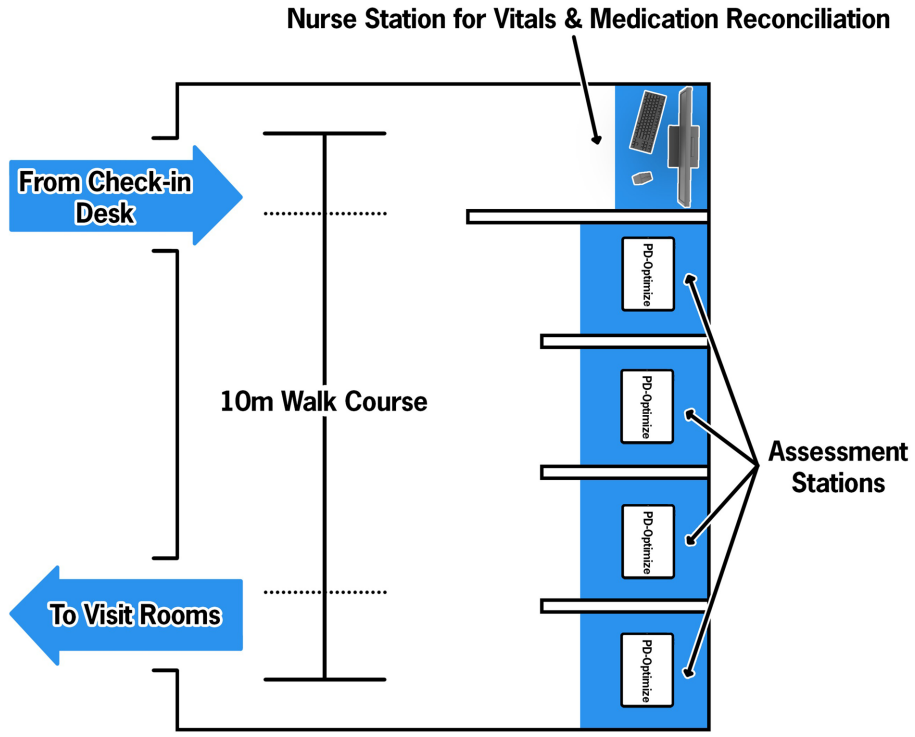


FIGURE 4
Parkinson's disease-Waiting Room of the Future (PD-WROTF) at the Cleveland Clinic Center for Neurological Restoration. Following check-in at the front desk, the patient immediately enters the WROTF where they are greeted by a Medical Assistant (MA). The MA performs a standard vital sign assessment and medication reconciliation. The patient then proceeds to one of four assessment stations where an ITD-managed iPad is housed. The MA selects the patient's name from the daily list and ensures the volume is appropriate via disposable headphones. Through the use of auditory and visual instructions, the patient progresses through each module of PD-Optimize. The modules are all self-administered and the single MA oversees the entire room, including the vitals station. Following completion of PD-Optimize, all data are automatically uploaded to the electronic health record (EHR) and the patient is escorted to their exam room.

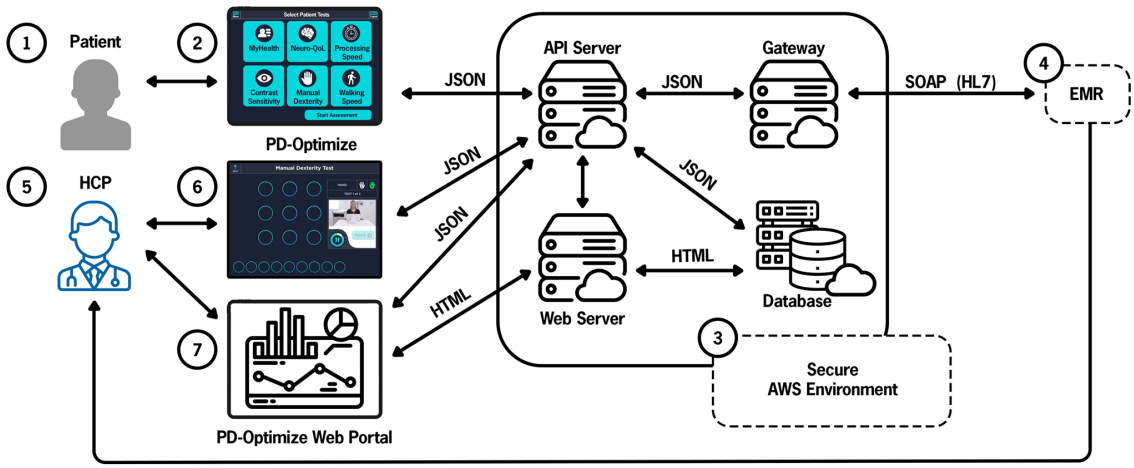


FIGURE 5
PD-Optimize cloud structure and data flow. Patient (1) inputs data using PD-Optimize application (2) and files are instantaneously uploaded to the PD-Optimize cloud, a HIPAA compliant, secure AWS environment (3). Files are transferred in JavaScript Object Notation (JSON) format. Files can be transferred to a web server, a cloud-based database or exported via a gateway to allow integration into the medical record (4). Outside of the medical record, the health care professional (5) can access patient data via the PD-Optimize application (6) or a secure web portal (7). API application programming interface, EMR electronic medical record, AWS Amazon Web Services, HCP health care professional, HIPAA Health Insurance Portability and Accountability Act, HL7 Health Level-7, SOAP Simple Object Access Protocol.

As of January 1, 2023 more than 2,000 unique patients have completed the PD-Optimize application within the WROTF. Nearly 300 patients have completed PD-Optimize at two or more clinical visits. On average, 20 min is required to complete the assessments, including demographics confirmation.

We are currently assessing the response of dopaminergic therapy on bradyphrenia by comparing PST before and after a change in medication. Considering the PD WROTF is still in its nascence, much of its potential in better understanding PD and the development of a biomechanical biomarker will emerge as more patients complete the assessments over repeated clinical visits. Nevertheless, from data collected to date we have surmised that PD results in specific cognitive issues. Specifically, deficits in processing speed and executive function have been observed at rates greater than clinicians anticipated and have led clinicians to question if cognitive deficits observed in the PD-Optimize application map onto difficulties performing instrumental activities of daily living (IADL) in a 'real-world' environment. Fundamentally, these initial insights in cognitive functioning have served as a technology trigger in terms of better understanding how the PD-Optimize outcomes map onto PD patients' performance of IADLs. These discussions between clinicians and researchers have cascaded a *New Technology Trigger* (Figure 2) that aims to leverage the capabilities of virtual reality (VR) to evaluate IADL performance in PD.

## 5. Peak of inflated expectations? Cleveland Clinic virtual reality shopping platform

Patients, providers, hospitals and regulatory bodies are increasingly interested in outcome measures that quantify the effects of PD motor and cognitive symptoms in meaningful daily actions (13, 35–37). Technological advances, like PD-Optimize, provide the opportunity to measure motor and cognitive symptoms for more precise and meaningful measures of PD symptoms. The assessment of IADLs are necessary to systematically evaluate the overall effectiveness of an intervention in a salient environment or determine the potential of an intervention to slow disease progression.

Cooking, crossing a busy street, getting groceries and driving a car (38) are common IADLs that may be compromised in PD patients. IADLs are necessary for independent living and community integration (39), and frequently require the simultaneous performance of two attention-demanding tasks (e.g., motor-cognitive, motor-motor or cognitive-cognitive) (40). It is not realistic to avoid dual-task conditions, as they are necessary to complete the vast majority of daily household and community activities (41, 42). Although dual-task declines associated with PD clearly impact IADL performance, traditional clinical motor evaluations (43–45) and neuropsychological tests (46, 47) are insufficient to evaluate IADLs as they parse cognitive and motor function into distinct components or constructs without consideration of their interplay. Innovative virtual reality technology provides a method of delivering ecologically valid digital content for the patient to interact with and quantifying those interactions using rigorous biomechanical measures.

Based on feedback from providers utilizing the PD-WROTF technology, we identified a gap in the efficient, systematic and quantitative approach to quantifying PD IADL performance. We assembled a team of biomedical engineers, software developers, physical therapists, occupational therapists, and neurologists to create a virtual reality shopping task that had all of the key aspects of motor, cognitive and cognitive-motor components to understand how PD patients perform IADLs. As detailed previously (48), state of the art VR technology was combined with an omnidirectional treadmill which allowed PD patients to physically navigate a virtual grocery store. The Cleveland Clinic Virtual Reality Shopping (CC-VRS), shown in Figure 6, aims to objectively quantify the performance of IADLs in PD patients. The CC-VRS platform addresses the clinical gap by providing a standardized, systematic, objective and quantitative approach to characterizing IADL capabilities in older adults and those with neurological disease. Briefly, the participants complete a 3-min tutorial to ensure understanding of walking on an omnidirectional treadmill and hand trackers (used to display the list and retrieve objects), and to expose the participant to the VR grocery store environment. In order to advance to the CC-VRS assessment, participants must demonstrate proficiency (automatically and objectively measured by the application) in walking, viewing the grocery list, and selecting the item on the list in the tutorial. Once deemed proficient, the patient is progressed to two different CC-VRS scenarios. The Basic CC-VRS requires the patient to ambulate through a grocery store and select 3–5 items from their list. The Complex CC-VRS has the same requirements as the Basic and additionally the patient encounters motor challenges such as narrowed aisles and other shoppers along the path as well as cognitive challenges such as identifying the more cost-effective sale item. Based on preliminary usability testing and data, the Basic and Complex CC-VRS Scenarios can be completed in approximately 12–20 min total.

The CC-VRS is currently being used in two research projects aimed at: (1) identifying the neural signature underlying freezing of gait in advanced PD patients with deep brain stimulation systems and (2) validating performance on the CC-VRS in a group of young adults, older adults, and individuals with PD. These research projects have been critical in supporting the development of the VR technology and validation of outcomes relative to overground walking. We are currently evaluating the clinical viability of deploying this technology by conducting an initial pre-deployment study in a regional family health center. As part of this validation project, 400 healthy older adults will complete the CC-VRS as part of their annual Medicare Wellness Assessment. The outcomes of this project will provide valuable clinical experience and normative healthy older control data that can be used in better understanding the precise effects of PD and will inform whether the CC-VRS will be employed to all CNR PD patients or if a subset of the population would be more appropriate, such as those under consideration for deep brain stimulation as the CC-VRS provides and ecological assessment of dual-task functioning, which is known to be affected by deep brain stimulation (49).

## 6. Moving through the hype cycle

Technology continues to be developed at a dizzying pace, and health care settings continue to be slow to adopt and adapt this

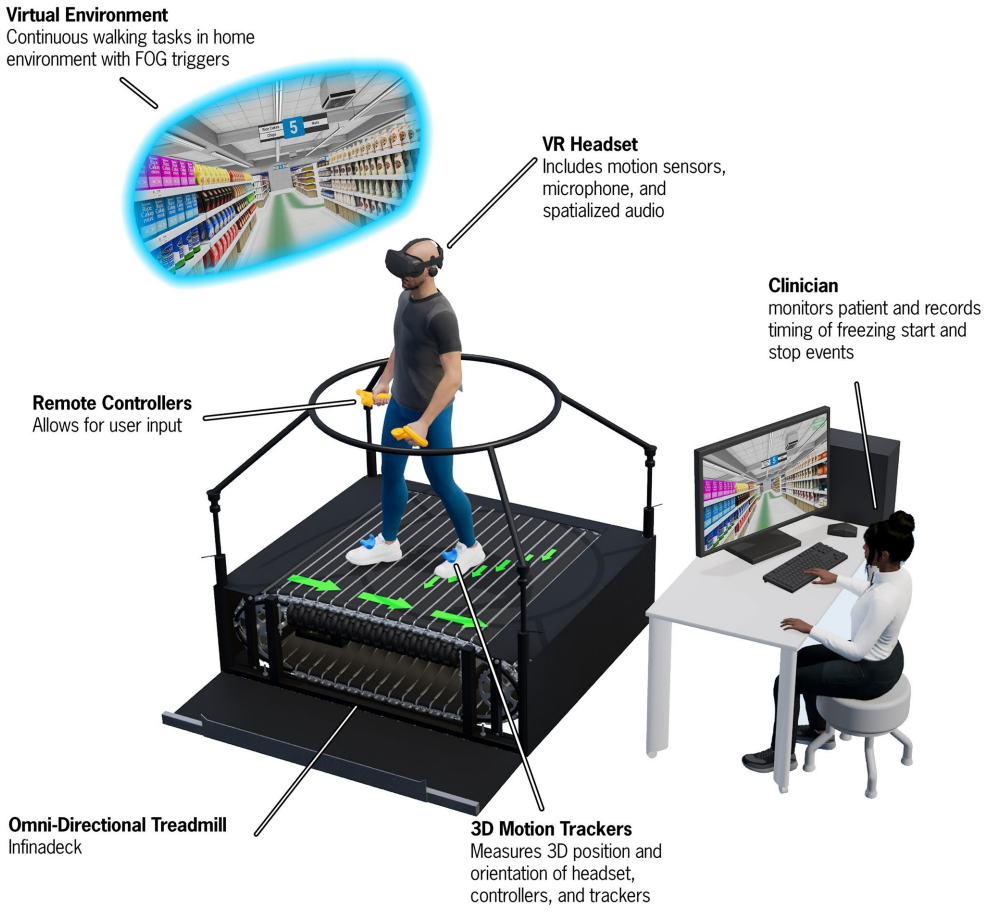


FIGURE 6
A depiction of the Cleveland Clinic-Virtual Reality Shopping (CC-VRS) platform. The patient wears a VR headset and physically walks on an omnidirectional treadmill to navigate through a virtual grocery store. The patient follows a green path and is required to gather five items along this path. Various obstacles (e.g., narrowing of aisles and avoiding spills) and other shoppers must be avoided while performing the CC-VRS. Biomechanical data are derived from position data provide by the 3D motion trackers on the feet and Remote Controllers to characterize gait and upper extremity prehension. A first-person view of the user is provided to the experimenter via the Control Computer and Monitor.

technology to better serve patients during routine clinical care. The DCI model outlines a potential path for technology development that is scalable and adaptable. Developing technology for clinical integration may at times feel like trying to untie a Gordian knot. Unfortunately, the DCI model does not have a secret Alexander the Great sword, however, the model should assist in the time, personnel, expense, outreach, and other resources necessary for meaningful technology development and integration. The DCI model is not a formula, rather it is intended to serve as a roadmap to work through the fluid process of integrating technology into clinical workflows. While the specifics may look different depending on factors such as patient population, healthcare system, and resources, the overarching principles are applicable to many sectors across the healthcare system. It should be acknowledged by all stakeholders that not all technologies will progress to clinical integration using the DCI model; some technologies will not be able to progress out of the peak of inflated expectations or the trough of disillusionment. This is expected, and even encouraged, to ensure the technologies that do advance to clinical integration have been rigorously evaluated and truly enhance the provider and patient experience.

There have been trials and tribulations in the implementation of the PD-WROTF. The group ownership of the project within the DCI model provided a strong sense of ownership in which the failures and success of the project were mourned and celebrated by the entire team. We have now reached a point where the technology has addressed a clinical problem and the patient-provider relationship has been strengthened.

## Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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## Conflict of interest

JA and DS have authored IP related to the PD-Optimize modules; JA and AR have authored IP related to the CC-VRS modules.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Deb R, An S, Bhat G, Shill H, Ogras UY. A systematic survey of research trends in technology usage for Parkinson's disease. *Sensors (Basel)*. (2022) 22:5491. doi: 10.3390/s22155491

2. Saunders JB, Inman VT, Eberhart HD. The major determinants in normal and pathological gait. *J Bone Joint Surg Am*. (1953) 35:543–58. doi: 10.2106/00004623-195335030-00003

3. Morris JR. Accelerometry--a technique for the measurement of human body movements. *J Biomech*. (1973) 6:729–36. doi: 10.1016/0021-9290(73)90029-8

4. Stelmach GE, Worringham CJ, Strand EA. Movement preparation in Parkinson's disease. The use of advance information. *Brain Commun*. (1986) 109:1179–94. doi: 10.1093/brain/109.6.1179

5. Montgomery EB, Nuessen J, Gorman DS. Reaction time and movement velocity abnormalities in Parkinson's disease under different task conditions. *Neurology*. (1991) 41:1476–81. doi: 10.1212/wnl.41.9.1476

6. Fahn S, Elton RLThe UPDRS Development Committee. Unified Parkinson's disease rating Sale In: S Fahn, CD Marsden, M Goldstein and DB Calne, editors. *Recent developments in Parkinson's disease*, vol. *2*. London: Macmillan Healthcare Information (1987). 153–63.

7. Lu M, Poston K, Pfefferbaum A, Sullivan EV, Fei-Fei L, Pohl KM, et al. Vision-based estimation of MDS-UPDRS gait scores for assessing Parkinson's disease motor severity. *Medical Image Comput Assist Intervent*. (2020) 12263:637–47. doi: 10.1007/978-3-030-59716-0_61

8. Hobert MA, Nussbaum S, Heger T, Berg D, Maetzler W, Heinzel S. Progressive gait deficits in Parkinson's disease: a wearable-based biannual 5-year prospective study. *Front Aging Neurosci*. (2019) 11:22. doi: 10.3389/fnagi.2019.00022

9. Thorp JE, Adamczyk PG, Ploeg HL, Pickett KA. Monitoring motor symptoms during activities of daily living in individuals with Parkinson's disease. *Front Neurol*. (2018) 9:1036. doi: 10.3389/fneur.2018.01036

10. Shawen N, O'Brien MK, Venkatesan S, Lonini L, Simuni T, Hamilton JL, et al. Role of data measurement characteristics in the accurate detection of Parkinson's disease symptoms using wearable sensors. *J Neuroeng Rehabil*. (2020) 17:52. doi: 10.1186/s12984-020-00684-4

11. Lu R, Xu Y, Li X, Fan Y, Zeng W, Tan Y, et al. Evaluation of wearable sensor devices in Parkinson's disease: a review of current status and future prospects. *Parkinsons Dis*. (2020) 2020:4693019. doi: 10.1155/2020/4693019

12. Sánchez-Ferro Á, Elshehabi M, Godinho C, Salkovic D, Hobert MA, Domingos J, et al. New methods for the assessment of Parkinson's disease (2005 to 2015): a systematic review. *Mov Disord*. (2016) 31:1283–92. doi: 10.1002/mds.26723

13. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's disease: challenges and opportunities. *Mov Disord*. (2016) 31:1272–82. doi: 10.1002/mds.26642

14. Lingaiah A, Mohanty D, Marchbank J, Jacob AE, Castellanos RL, Holiday V, et al. Improving anxiety in Parkinson's disease: a cautionary tale about mobile health technologies. *Parkinsonism Relat Disord*. (2020) 73:50–1. doi: 10.1016/j.parkreldis.2020.03.010

15. di Biase L, Summa S, Tosi J, Taffoni F, Marano M, Cascio Rizzo A, et al. Quantitative analysis of bradykinesia and rigidity in Parkinson's disease. *Front Neurol*. (2018) 9:121. doi: 10.3389/fneur.2018.00121

16. Rudick RA, Miller D, Bethoux F, Rao SM, Lee JC, Stough D, et al. The multiple sclerosis performance test (MSPT): an iPad-based disability assessment tool. *J Vis Exp*. (2014) 88:e51318. doi: 10.3791/51318

17. Mowry EM, Bermel RA, Williams JR, Benzinger TLS, de Moor C, Fisher E, et al. Harnessing real-world data to inform decision-making: multiple sclerosis partners advancing technology and health solutions (MS PATHS). *Front Neurol*. (2020) 11:632. doi: 10.3389/fneur.2020.00632

18. Hersh CM, Kieseier B, de Moor C, Miller DM, Campagnolo D, Williams JR, et al. Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: Results from MS PATHS. *Mult Scler J Exp Transl Clin*. (2021) 7:205521732110046. doi: 10.1177/20552173211004634

19. Macaron G, Baldassari LE, Nakamura K, Rao SM, McGinley MP, Moss BP, et al. Cognitive processing speed in multiple sclerosis clinical practice: association with patient-reported outcomes, employment and magnetic resonance imaging metrics. *Eur J Neurol*. (2020) 27:1238–49. doi: 10.1111/ene.14239

20. Conway DS, Bermel RA, Planchon SM. The relationship between cognition, education, and employment in multiple sclerosis patients. *Mult Scler J Exp Transl Clin*. (2022) 8:20552173221118309. doi: 10.1177/20552173221118309

21. Abbatemarco JR, Ontaneda D, Nakamura K, Husak S, Wang Z, Alshehri E, et al. Comorbidity effect on processing speed test and MRI measures in multiple sclerosis patients. *Mult Scler Relat Disord*. (2020) 46:102593. doi: 10.1016/j.msard.2020.102593

22. Macaron G, Moss BP, Li H, Baldassari LE, Rao SM, Schindler D, et al. Technology-enabled assessments to enhance multiple sclerosis clinical care and research. *Neurol Clin Pract*. (2020) 10:222–31. doi: 10.1212/CPJ.0000000000000710

23. Maetzler W, Rochester L, Bhidayasiri R, Espay AJ, Sanchez-Ferro A, van Uem JMT. Modernizing daily function assessment in Parkinson's disease using capacity, perception, and performance measures. *Mov Disord*. (2021) 36:76–82. doi: 10.1002/mds.28377

24. Recinos PF, Dunphy CJ, Thompson N, Schuschu J, Urchek JL 3rd, Katzan IL. Patient satisfaction with collection of patient-reported outcome measures in routine care. *Adv Ther*. (2017) 34:452–65. doi: 10.1007/s12325-016-0463-x

25. Rhodes JK, Schindler D, Rao SM, Venegas F, Bruzik ET, Gabel W, et al. Multiple sclerosis performance test: technical development and usability. *Adv Ther*. (2019) 36:1741–55. doi: 10.1007/s12325-019-00958-x

26. Earhart GM, Cavanaugh JT, Ellis T, Ford MP, Foreman KB, Dibble L. The 9-hole PEG test of upper extremity function: average values, test-retest reliability, and factors contributing to performance in people with Parkinson disease. *J Neurol Phys Ther*. (2011) 35:157–63. doi: 10.1097/NPT.0b013e318235da08

27. Feys P, Lamers I, Francis G, Benedict R, Phillips G, LaRocca N, et al. The nine-hole peg test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler*. (2017) 23:711–20. doi: 10.1177/1352458517690824

28. Moore JL, Potter K, Blankshain K, Kaplan SL, O'Dwyer LC, Sullivan JE. A Core set of outcome measures for adults with neurologic conditions undergoing rehabilitation: a clinical practice guideline. *J Neurol Phys Ther*. (2018) 42:174–220. doi: 10.1097/NPT.0000000000000229

29. Rao SM, Losinski G, Mourany L, Schindler D, Mamone B, Reece C, et al. Processing speed test: validation of a self-administered, iPad((R))-based tool for screening cognitive dysfunction in a clinic setting. *Mult Scler*. (2017) 23:1929–37. doi: 10.1177/1352458516688955

30. Gorodeski EZ, Rosenfeldt AB, Fang K, Kubu C, Rao SM, Jansen EA, et al. An iPad-based measure of processing speed in older adults hospitalized for heart failure. *J Cardiovasc Nurs*. (2019) 34:E9–E13. doi: 10.1097/JCN.0000000000000568

31. Rao SM, Galioto R, Sokolowski M, Pierce M, Penn L, Sturtevant A, et al. Cleveland Clinic cognitive battery (C3B): normative, reliability, and validation studies of a self-

administered computerized tool for screening cognitive dysfunction in primary care. *J Alzheimers Dis*. (2023) 92:1051–66. doi: 10.3233/JAD-220929

32. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RH. Screening for cognitive impairment in multiple sclerosis using the symbol digit modalities test. *Mult Scler*. (2007) 13:52–7. doi: 10.1177/1352458506070750

33. Gershon RC, Lai JS, Bode R, Choi S, Moy C, Bleck T, et al. Neuro-QOL: quality of life item banks for adults with neurological disorders: item development and calibrations based upon clinical and general population testing. *Qual Life Res*. (2012) 21:475–86. doi: 10.1007/s11136-011-9958-8

34. Miller DM, Moss B, Rose S, Li H, Schindler D, Weber M, et al. Obtaining patient priorities in a multiple sclerosis comprehensive care center: beyond patient-reported outcomes. *J Patient Exp*. (2020) 7:541–8. doi: 10.1177/2374373519864011

35. Sieber BA, Landis S, Koroshetz W, Bateman R, Siderowf A, Galpern WR, et al. Prioritized research recommendations from the National Institute of Neurological Disorders and Stroke Parkinson's disease 2014 conference. *Ann Neurol*. (2014) 76:469–72. doi: 10.1002/ana.24261

36. van Uem JM, Marinus J, Canning C, van Lummel R, Dodel R, Liepelt-Scarfone I, et al. Health-related quality of life in patients with Parkinson's disease--a systematic review based on the ICF model. *Biobehav Rev*. (2016) 61:26–34. doi: 10.1016/j.neubiorev.2015.11.014

37. Papadopoulos E, Buracchio T. *Drug Development Tool (DDT) COA #000142*, vol. *13*. Silver Spring, MD: US Food & Drug Administration (2021).

38. Uc EY, Rizzo M, Anderson SW, Sparks JD, Rodnitzky RL, Dawson JD. Impaired navigation in drivers with Parkinson's disease. *Brain*. (2007) 130:2433–40. doi: 10.1093/brain/awm178

39. The Commission on Practice. Occupational Therapy Practice Framework: Domain and Process-Fourth Edition. *Am J Occup Ther*. (2020) 74:7412410010p1–7412410010p87. doi: 10.5014/ajot.2020.74S2001

40. MacPherson SE. Definition: dual-tasking and multitasking. *Cortex*. (2018) 106:313–4. doi: 10.1016/j.cortex.2018.06.009

41. O'Shea S, Morris ME, Iansek R. Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Phys Ther*. (2002) 82:888–97. doi: 10.1093/ptj/82.9.888

42. Romero-Ayuso D, Castillero-Perea A, González P, Navarro E, Molina-Massó JP, Funes MJ, et al. Assessment of cognitive instrumental activities of daily living: a systematic review. *Disabil Rehabil*. (2019) 43:1342–58. doi: 10.1080/09638288.2019.1665720

43. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. (2008) 23:2129–70. doi: 10.1002/mds.22340

44. Perlmutter JS. Assessment of Parkinson disease manifestations. *Curr Protoc Neurosci*. (2009) 10:1382–7. doi: 10.1002/0471142301.ns1001s49

45. Palmer JL, Coats MA, Roe CM, Hanko SM, Xiong C, Morris JC. Unified Parkinson's disease rating scale-motor exam: inter-rater reliability of advanced practice nurse and neurologist assessments. *J Adv Nurs*. (2010) 66:1382–7. doi: 10.1111/j.1365-2648.2010.05313.x

46. Neisser U. On "social knowing". *Personal Soc Psychol Bull*. (1980) 6:601–5. doi: 10.1177/014616728064012

47. Neisser U. *Memory observed: Remembering in natural contexts*. Duffield: Worth (1982).

48. Alberts JL, McGrath M, Miller Koop M, Waltz C, Scelina L, Scelina K, et al. The immersive Cleveland Clinic virtual reality shopping platform for the assessment of instrumental activities of daily living. *J Vis Exp*. (2022) 185. doi: 10.3791/63978

49. Alberts JL, Voelcker-Rehage C, Hallahan K, Vitek M, Bamzai R, Vitek JL. Bilateral subthalamic stimulation impairs cognitive-motor performance in Parkinson's disease patients. *Brain*. (2008) 131:3348–60. doi: 10.1093/brain/awn238

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# Digital gait markers to potentially distinguish fragile X-associated tremor/ataxia syndrome, Parkinson's disease, and essential tremor

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**Background:** Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disease that affects carriers of a 55-200 CGG repeat expansion in the *fragile X messenger ribonucleoprotein 1* (*FMR1*) gene, may be given an incorrect initial diagnosis of Parkinson's disease (PD) or essential tremor (ET) due to overlapping motor symptoms. It is critical to characterize distinct phenotypes in FXTAS compared to PD and ET to improve diagnostic accuracy. Fast as possible (FP) speed and dual-task (DT) paradigms have the potential to distinguish differences in gait performance between the three movement disorders. Therefore, we sought to compare FXTAS, PD, and ET patients using quantitative measures of functional mobility and gait under self-selected (SS) speed, FP, and DT conditions.

**Methods:** Participants with FXTAS ($n = 22$), PD ($n = 23$), ET ($n = 20$), and controls ($n = 20$) underwent gait testing with an inertial sensor system (APDM™). An instrumented Timed Up and Go test (i-TUG) was used to measure movement transitions, and a 2-min walk test (2MWT) was used to measure gait and turn variables under SS, FP, and DT conditions, and dual-task costs (DTC) were calculated. ANOVA and multinomial logistic regression analyses were performed.

**Results:** PD participants had reduced stride lengths compared to FXTAS and ET participants under SS and DT conditions, longer turn duration than ET participants during the FP task, and less arm symmetry than ET participants in SS gait. They also had greater DTC for stride length and velocity compared to FXTAS participants. On the i-TUG, PD participants had reduced sit-to-stand peak velocity compared to FXTAS and ET participants. Stride length and arm symmetry index during the DT 2MWT was able to distinguish FXTAS and ET from PD, such that participants with shorter stride lengths were more likely to have a diagnosis of PD and those with greater arm asymmetry were more likely to be diagnosed with PD. No gait or i-TUG parameters distinguished FXTAS from ET participants in the regression model.

**Conclusion:** This is the first quantitative study demonstrating distinct gait and functional mobility profiles in FXTAS, PD, and ET which may assist in more accurate and timely diagnosis.

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KEYWORDS

fragile X-associated tremor/ataxia syndrome, Parkinson's disease, essential tremor, gait, dual-task cognitive motor paradigms

# Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disease that affects carriers of a 'premutation' size (55–200) CGG repeat expansion in the *fragile X messenger ribonucleoprotein 1* (*FMR1*) gene (1). Although the characteristic motor features are intention tremor and cerebellar gait ataxia, there is high phenotypic variability with some carriers also demonstrating parkinsonism, neuropathy, psychiatric symptoms, and/or executive function deficits and dementia (1–5). Because FXTAS was first described relatively recently (1) and has high phenotypic variability and overlap of symptoms with other more well-known movement disorders, patients are frequently given an incorrect initial diagnosis (6). This is especially the case when patients are seen by a primary care physician or general neurologist, or at a non-Fragile X clinic where FXTAS may not be readily recognized. At onset, FXTAS is most commonly diagnosed as Parkinson's disease (PD) or essential tremor (ET), due to overlapping motor symptom profiles and lack of physician awareness of the disorder (6). Inaccurate diagnosis delays the initiation of targeted treatments and the provision of genetic counseling, negatively impacting health outcomes for patients and their families. Distinguishing the FXTAS disease profile, in terms of gait and functional mobility, from those of PD and ET may be critical in assisting with the differential diagnosis. We previously reported that tremorography using an inertial sensor system was able to distinguish between these three movement disorders, where higher kinetic tremor was found in FXTAS compared to PD patients and more bradykinesia was found in FXTAS compared to ET patients (7). Thus, quantitative measures of the prominent motor features of FXTAS, namely kinetic tremor and cerebellar gait ataxia, captured via wearable sensor technologies are likely to be beneficial in assisting clinicians with diagnostic accuracy.

Gait impairments are a common feature in FXTAS that can lead to significant disability. Our group first characterized the gait deficits in a small cohort of FXTAS participants during self-selected (SS) speed walking using an instrumented Timed Up and Go test (i-TUG) and found deficits in gait speed, rhythm, cycle phase, and variability as well as movement transitions compared to healthy controls (8). PD participants have shown similar gait deficits during SS walking using the i-TUG (9–15) and GAITRite® walkway (16), with the addition of abnormalities in the domain of gait asymmetry in arm swing range of motion and stride length (9). Reduced stride velocity and cadence and increased double support time and gait asymmetry have been found in ET participants compared to controls during standard walking on the GAITRite® walkway (17–19). Our group recently used an instrumented 2MWT under SS, fast as possible (FP) speeds, and with the addition of a cognitive dual task (DT) in FXTAS and found reduced stride length and velocity, swing time, and peak turn velocity and greater double limb support time and number of steps to turn as compared to controls under all three conditions. During the FP condition, stride length variability was increased, and cadence was reduced in FXTAS participants. Additionally, stride velocity variability under FP gait was significantly associated with the number of self-reported falls in the last year (20). Studies investigating FP walking in PD report reduced stride length and stride velocity and increased double support time compared to controls (21–23). No studies to date have examined gait under fast speed walking conditions in ET. DT cognitive and motor paradigms have been used previously to explore the interplay between cognition and gait in PD (24), ET (18), and FXTAS (20). PD participants have shown decreased gait velocity, stride length and swing phase time, and increased gait variability during DT gait testing (25–27), and similar interference effects have been seen in ET (28). We previously found greater dual task costs (DTC) of a verbal fluency task on peak turn velocity in men with FXTAS compared to women with FXTAS and controls (20). However, the gait profiles of FXTAS, PD, and ET patients have never been directly compared. This information is critical to inform clinicians of the distinct phenotypes in FXTAS compared to PD and ET, and aid in accurate diagnosis. Therefore, the objective of this study was to compare the gait profiles in FXTAS, PD, and ET using quantitative measures of gait during SS and FP speeds, and a DT cognitive-motor condition to determine whether these measures may be sensitive for distinguishing FXTAS from PD and ET.

# Methods

## Participants

FXTAS, PD, and ET participants were recruited through the Parkinson Disease and Movement Disorders Clinic at Rush University Medical Center (RUMC). Inclusion criteria for participants with movement disorders were: (1) A diagnosis of only one of these disorders made by a movement disorders neurologist at RUMC, (2) a *FMR1* gene test showing one allele with 55–200 CGG repeats for FXTAS participants and < 55 repeats on both alleles for PD and ET participants, (3) symptom onset at ≥ age 50, (4) mild to severe tremor, and (5) mild to moderate parkinsonism for PD participants with Hoehn & Yahr staging of PD score ≤ 3 (29). Exclusion criteria were: (1) A prior history of stroke with focal neurological deficit or any other neurological or muscular disease, (2) seizure disorder or past head trauma resulting in structural brain damage, (3) deep brain stimulation surgery, (4) presence of dyskinesia on neurological exam, and (5) clinical diagnosis of dementia as determined by the neurologist and/or neuropsychologist. Twenty healthy control subjects were recruited from RUMC or from the community. Inclusion criteria were: (1) a normal neurological examination, and (2) a *FMR1* gene test showing both alleles with <55 CGG repeats. Exclusion criteria were the same as for the FXTAS, PD, and ET participants, but also included a significant history of tremor, balance problems, falls, or dizziness. All participants were required to be between 50 and 90 years of age; this range was chosen because FXTAS typically develops after

age 50. This study was approved by the RUMC Institutional Review Board, and all participants gave written informed consent.

## Gait assessments

Quantitative gait analysis was performed during a 25-meter instrumented 2-min walk test (2MWT) using the APDM Mobility Lab™ six inertial sensor system (APDM™; Oregon; version 1) under three conditions: (1) self-selected speed (SS), (2) fast as possible speed (FP), and (3) dual-task (DT). The DT condition involved the participant performing a verbal fluency task (Animal Naming) during the SS 2MWT. FP and DT conditions were used to create gait "stress" conditions that might amplify differences between the three movement disorders under study. Variables were selected from the five key gait domains thought to reflect independent features of neural locomotor control in older adults (30, 31), including (1) gait pace (stride length and velocity), (2) rhythm (cadence), (3) gait variability (stride length, stride velocity, and cadence variabilities), (4) gait cycle phase (percentage of gait cycle spent in double limb support and swing phases), and (5) gait asymmetry [stride length asymmetry and arm symbolic symmetry index (32)]. Stride length asymmetry was calculated as a percentage via the following formula: $\left|\frac{\left(\text{stride length}_{\text{left}} - \text{stride length}_{\text{right}}\right)}{\max\left(\text{stride length}_{\text{left}}, \text{stride length}_{\text{right}}\right)}\right| \times 100$. Higher values of both gait asymmetry variables indicate greater asymmetry. Intra-individual gait variability was determined by the coefficient of variation $\left(\frac{\text{standard deviation}}{\text{mean}} \times 100\right)$ for each gait parameter. A movement transition domain consisting of turn duration, and number of steps to turn was also created as previously described (8) to ascertain whether these were different among the three movement disorders. The level of interference of the cognitive DT on gait performance, or the dual-task cost (DTC), was calculated as $\frac{\text{DT} - \text{SS}}{\text{SS}} \times 100$. In addition, a validated and reliable instrumented Timed Up and Go (i-TUG) was performed six times as previously described (8) and the mean values for sit-to-stand and turn-to-sit measures were calculated.

## Cognitive assessments

Four measures of executive function were administered: the Behavioral Dyscontrol Scale II (BDS-II), the Controlled Oral Word Association Test (COWAT), the Animal Naming test, and the Symbol Digit Modalities Test (SDMT). The BDS-II is a measure of attention and inhibitory control of voluntary motor behavior (33) and the COWAT and Animal Naming tests are measures of verbal fluency (34, 35). The SDMT is a measure of attention and information processing speed (36); the oral version was used so that test results were not altered by the participants' motor symptoms. The Wechsler Abbreviated Scale of Intelligence 3rd edition (WASI-III) was used to obtain a full intelligence quotient (Full IQ), verbal IQ (VIQ) and performance IQ (PIQ) (37). These executive function and intelligence scales were administered because there are known executive function deficits in FXTAS, PD, and ET and lower cognitive function negatively impacts gait and functional mobility in these disorders and therefore could be included as potential confounders in our statistical analysis plan. For example, lower executive function correlates with worse deficits in stride length, speed, variability and asymmetry in PD (26, 38–40), and greater impairments in velocity, cadence, stride length, and double limb support time were also associated with lower cognitive scores in ET (18). We previously found that lower information processing speed was associated with shorter stride lengths and lower response inhibition was associated with slower turn-to-sit times on the i-TUG in FXTAS (41).

## Neuropathy testing

Participants were also administered the Total Neuropathy Score (TNS), modified to exclude nerve conduction velocity testing, from a neurologist (42). Testing for neuropathy is important given that it is prevalent in FXTAS (43) and PD (44) and may negatively affect performance on spatiotemporal measures of gait (45).

## FXTAS rating scale

Participants were videotaped performing the FXTAS Rating Scale (FXTAS-RS), a 44-item scale that rates tremor, postural sway, gait, parkinsonism, coordination, dystonia, speech, and oculomotor deficits to determine the presence and severity of FXTAS symptoms (46). The scale was created using items from the Unified Parkinson's Disease Rating Scale (UPDRS) (47), the Clinical Rating Scale for Tremor (CRST) (48), the International Cooperative Ataxia Rating Scale (ICARS) (49), and a tandem item from the Unified Huntington's Disease Rating Scale (50). The leg agility and pouring items were not collected for all participants, therefore, only forty-two items were included in the scale. Videotapes were acquired for 16 control, 16 FXTAS, 14 PD, and 10 ET participants, which were rated by a movement disorders neurologist who was blinded to genotype.

## Molecular analysis

Blood samples or buccal swabs from all participants were sent to the Rush University Molecular Diagnostic Laboratory (Dr. Berry-Kravis lab) for *FMR1* genotype testing. QIAGEN Blood and Tissue DNA isolation kits were used to isolate DNA from buccal swabs or peripheral blood leukocytes. Allele-specific CGG repeat lengths were determined using the Asuragen Amplidex *FMR1* mPCR kit (Asuragen Inc. Austin, TX) as previously described (51).

## Statistical analysis

All measures were first compared univariately between the four participant groups with one-way ANOVA and Tukey's *post hoc* pairwise comparisons (for normally distributed measures) or the Kruskal-Wallis test followed by pairwise comparisons with Dunn's test for multiple comparisons (for non-normal measures). Significant gait measures from univariate comparisons were then included in a

penalized multinomial logistic regression model to determine which gait measures were best able to distinguish between the groups. Sex differences were first examined within each group to determine if sex should be included as a covariate in the regression model. Age, SDMT scores, and TNS were controlled for in the final regression analysis, as some were significantly different between the groups and thought to be potentially confounding factors. There were a few sex differences in the gait and i-TUG variables within the FXTAS group, but none of these variables were significantly different between groups in the univariate comparisons and therefore sex was not included as a covariate in the final regression model. For significant logistic regression results, ROC analyses were performed and area under the curve (AUC) was computed with 95% confidence intervals for significant between group differences. Sensitivity and specificity were then calculated using the Youden index.

Spearman's rank correlation coefficient (*rho*) was used to assess the relationship between the gait and i-TUG parameters and FXTAS-RS scores in the three movement disorder groups and between CGG repeat size in the FXTAS group. CGG repeat size did not correlate with any gait or i-TUG measures under any condition; therefore, these were not examined as potential predictors of the gait and i-TUG measures in a separate regression model in the FXTAS group. A $p \leq 0.05$ was considered significant. Statistical analyses were performed with SAS (SAS Institute Inc., Cary NC, USA), GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA), and 'pmlr' package in R (R Core Team 2016). For the modified FXTAS-RS, missing values were imputed using the Hot Deck technique.

# Results

## Participant characteristics

Demographic and clinical characteristics are summarized in Table 1. The study included 22 participants with FXTAS, 23 with PD, 20 with ET, and 20 controls. In the FXTAS group, six had a diagnosis of possible FXTAS, eight had probable FXTAS, and eight had definite FXTAS. The three movement disorder groups did not differ in age, although the control group was significantly younger than the PD and ET groups ($p = 0.006$ and 0.04, respectively). As expected, FXTAS participants had significantly greater CGG repeat sizes than all other groups ($p < 0.0001$) and all were in the premutation range. FXTAS and PD participants also had significantly higher TNS scores than controls ($p = 0.0002$ and 0.02, respectively) but there were no significant differences in TNS scores among the 3 movement disorders. ET participants had significantly longer disease duration compared to FXTAS and PD participants ($p = 0.004$ and 0.001, respectively). CGG repeat size did not correlate with any gait or i-TUG measures under

TABLE 1 Participant demographic characteristics.

| Variable | Controls (*n* = 20) | FXTAS (*n* = 22) | PD (*n* = 23) | ET (*n* = 20) |
|---|---|---|---|---|
| Age | 62.65 ± 8.52 (50–83) | 69.14 ± 8.12 (55–86) | 71.26 ± 7.87 (56–87)**a**** | 69.80 ± 8.85 (53–85)**a*** |
| Men, n (%) | 11 (55.0) | 12 (54.5) | 15 (65.2) | 10 (50.0) |
| Ethnicity, n | 19 White/Non-Hispanic, 1 White/Hispanic | 22 White/Non-Hispanic | 20 White/Non-Hispanic, 1 White/Hispanic, 1 Asian, 1 African American | 19 White/Non-Hispanic, 1 African American |
| BMI | 27.07 ± 3.44 (20.6–35.3) | 25.63 ± 4.82 (16.9–34.7) | 25.94 ± 3.62 (19.5–33.8) | 26.93 ± 5.39 (19.6–42.0) |
| Disease duration (years) | N/A | 6.59 ± 4.22 (1–16) | 5.74 ± 3.74 (1–15) | 13.29 ± 9.97 (2–33)**b****,**c**** |
| History of diabetes, n (%) | 2 (10.0) | 3 (13.6) | 0 (0.0) | 2 (10.0) |
| CGG repeat | 31.39 ± 5.42 (23–48) | 85.33 ± 12.33 (60–104)**a***** | 29.64 ± 5.02 (20–42)**b***** | 29.10 ± 6.17 (20–44)**b***** |
| FXTAS Dx | N/A | 6 Possible, 8 Probable, 8 Definite | N/A | N/A |
| FXTAS-RS | 13.6 ± 7.9 (3–26) | 46.4 ± 17.6 (24–78)**a***** | 41.7 ± 13.1 (21–65)**a***** | 46.1 ± 19.6 (24–73)**a***** |
| H&Y stage | N/A | N/A | 2.09 ± 0.29 (2–3) | N/A |
| TNS | 0.59 ± 1.12 (0–4) | 3.67 ± 3.02 (0–14)**a**** | 2.95 ± 3.43 (0–13)**a*** | 2.62 ± 2.99 (0–8) |
| Education | 17.50 ± 2.61 (12–24) | 15.95 ± 3.11 (9–20) | 16.61 ± 2.69 (12–22) | 15.75 ± 2.40 (12–20) |
| WASI full IQ | 127.35 ± 9.98 (108–142) | 118.13 ± 13.00 (84–135) | 117.70 ± 15.24 (86–149) | 116.85 ± 15.17 (84–136) |
| WASI VIQ | 124.50 ± 8.57 (106–136) | 118.07 ± 10.33 (88–129) | 120.17 ± 13.45 (91–140) | 117.55 ± 12.93 (86–136) |
| WASI PIQ | 124.00 ± 11.53 (99–141) | 113.53 ± 14.54 (83–141) | 111.56 ± 16.69 (84–141)**a*** | 111.65 ± 15.94 (86–134) |
| BDS-II | 25.45 ± 1.10 (24–27) | 23.33 ± 2.99 (16–27) | 24.22 ± 1.93 (19–27) | 24.20 ± 1.61 (21–27) |
| COWAT | 108.20 ± 19.76 (82–142) | 96.86 ± 24.98 (54–152) | 101.35 ± 23.84 (74–160) | 99.25 ± 23.42 (66–154) |
| SDMT | 106.89 ± 10.05 (94–128) | 89.56 ± 13.20 (67–118)**a***** | 88.87 ± 12.84 (61–107)**a***** | 88.95 ± 10.75 (72–103)**a***** |
| Animal naming | 36.20 ± 9.56 (22–55) | 28.71 ± 11.34 (11–53) | 28.73 ± 8.93 (9–42) | 27.40 ± 10.30 (13–48)**a*** |

All values are mean ± SD with range in brackets unless indicated otherwise. **a, significantly different from controls; b, significantly different from FXTAS; c, significantly different from PD**; *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$. Age, disease duration, CGG repeat, modified FXTAS Rating Scale score (FXTAS-RS), Hoen & Yahr (H&Y) Stage, Body Mass Index (BMI), Total Neuropathy Score (TNS), Education, Wechsler Abbreviated Scale of Intelligence (WASI) Full Intelligence Quotient (Full IQ), Verbal IQ (VIQ) and Performance IQ (PIQ), Behavioral Dyscontrol Scale II (BDS-II), Controlled Oral Word Association Test (COWAT), Symbol Digit Modalities Test (SDMT) and Animal Naming test were compared between controls, FXTAS, PD and ET. The COWAT and SDMT were scaled for age and years of education.

any condition; therefore, these were not examined as predictors of gait and i-TUG measures in a separate regression model in the FXTAS group. All movement disorder groups had significantly worse FXTAS-RS scores compared to controls ($p < 0.0001$) but were not different from each other. There were no significant differences in BMI, education level, WASI Full IQ or VIQ between any of the groups. PD participants had significantly lower PIQ compared to controls ($p = 0.04$). Roughly 48, 87 and 65% of FXTAS, PD and ET participants, respectively, were on medication for motor symptoms at the time of testing (Supplementary Table S1).

## Cognitive assessments

A summary of between group differences in cognitive function is also shown in Table 1. FXTAS, PD and ET participants all scored lower than controls on the SDMT ($p = 0.0002$ to $<0.0001$). On Animal Naming, ET subjects scored significantly lower than controls ($p = 0.04$). No significant differences were found among any of the movement disorder groups on any of the cognitive measures.

## Gait parameters

### 2MWT

Summaries of between group comparisons of gait parameters for the three walking conditions (SS, FP, and DT) are shown in Table 2. Under the SS condition, FXTAS participants demonstrated significantly increased stride velocity variability and cadence variability compared to PD participants ($p = 0.048$ and 0.04, respectively) (Figures 1A,B). PD participants had significantly shorter stride lengths compared to FXTAS ($p = 0.007$), ET ($p = 0.002$), and control participants ($p = <0.0001$) (Figure 1C), and slower stride velocity compared to controls ($p = 0.003$). They also had significantly greater arm asymmetry than ET and control participants ($p = 0.02$ and 0.004, respectively) (Figure 1D). Lastly, PD participants took significantly longer to complete turns ($p = 0.006$), more steps to turn ($p = 0.03$), and slower peak turn velocity than control participants ($p = 0.04$). Under the FP condition, FXTAS participants had significantly slower stride velocity ($p = 0.003$), increased stride velocity variability ($p = 0.03$), increased stride length asymmetry ($p = 0.02$), and increased turn duration ($p = 0.02$) compared to controls. PD participants had significantly shorter stride lengths ($p = 0.002$ and $< 0.0001$, respectively) and longer turn duration ($p = 0.03$ and 0.0003, respectively) compared to ET and control participants (Figure 2). They also had slower stride velocity ($p = 0.0002$), greater arm asymmetry ($p = 0.0005$), and reduced peak turn velocity ($p = 0.002$) compared to controls. In the DT condition, FXTAS participants took significantly longer to complete turns ($p = 0.03$) and had slower peak turn velocity ($p = 0.03$) compared to controls. PD participants had significantly shorter stride lengths ($p = 0.03$, 0.02, and $< 0.0001$, respectively) and greater arm asymmetry ($p = < 0.0001$, 0.0002, and $< 0.0001$, respectively) compared to FXTAS, ET, and control participants. They also had significantly slower stride velocity ($p < 0.0001$), longer turn duration ($p < 0.0001$), slower peak turn velocity ($p = 0.0001$), and took more steps to turn ($p = 0.009$) compared to controls.

### Dual-task interference

Dual-task costs (DTC) on 2MWT parameters are summarized in Table 3. Compared to FXTAS participants and controls, PD participants had greater DTC for stride length ($p = 0.02$ and 0.004 respectively) and stride velocity ($p = 0.03$ and 0.0006, respectively) (Figure 3). They also had greater DTC for cadence ($p = 0.009$), turn duration ($p = 0.02$), and peak turn velocity ($p = 0.02$) compared to controls. ET participants had greater DTC for peak turn velocity ($p = 0.04$) compared to controls.

### i-TUG

Summaries of between group comparisons of i-TUG parameters are summarized in Table 4. PD participants had significantly reduced sit-to-stand peak velocity compared to FXTAS ($p = 0.002$), ET ($p = 0.009$) and control participants ($p = 0.007$) (Figure 4), and reduced turn-to-sit peak turn velocity compared to controls ($p = 0.006$).

### Regression analysis

In the multinomial logistic regressions controlling for age, SDMT, and TNS, stride length on the DT 2MWT was able to distinguish PD from FXTAS (OR = 0.88, 95% CI = 0.77–0.996, $p = 0.04$) and ET (OR = 1.16, 95% CI = 1.02–1.33, $p = 0.02$), such that participants with shorter stride length were more likely to have a diagnosis of PD (Figure 5A). Arm symmetry index during the DT 2MWT was also able to distinguish between PD from FXTAS (OR = 1.1, 95% CI = 1.01–1.19, $p = 0.03$) and ET (OR = 0.92, 95% CI = 0.85–1.00, $p = 0.05$), such that participants with greater arm asymmetry were more likely to be diagnosed with PD (Figure 5B). No gait or i-TUG variables were found to distinguish FXTAS from ET. Given the relatively low group sample sizes in this study, a multivariable ROC analysis was performed accounting for age, TNS, SDMT scores, stride length during DT gait, and arm symmetry index during DT gait. The ROC analysis comparing FXTAS and PD groups had an AUC of 0.85 (95% CI: 0.73–0.97) with a sensitivity of 0.83 and specificity of 0.71 based on the Youden index. The comparison between PD and ET resulted in an AUC of 0.87 (95% CI: 0.76–0.98) with a sensitivity of 0.81 and specificity of 0.81.

### Correlations

Spearman's correlations between FXTAS-RS scores and gait parameters are summarized in Supplementary Tables S2–S5. Under the SS condition, worse (higher) FXTAS-RS scores were associated with reduced stride length ($p = 0.03$), stride velocity ($p = 0.003$), and peak turn velocity ($p = 0.006$), as well as increased arm asymmetry ($p = 0.03$), turn duration ($p = 0.003$), and number of steps to turn ($p = 0.03$) in FXTAS. On the FP 2MWT, higher FXTAS-RS scores were associated with reduced stride velocity ($p = 0.005$), cadence ($p = 0.048$) and peak turn velocity ($p = 0.02$), as well as increased turn duration ($p = 0.005$) in FXTAS, and lower steps to turn in controls ($p = 0.03$). During the DT 2MWT, worse FXTAS-RS scores were associated with greater stride length asymmetry ($p = 0.04$) and turn duration ($p = 0.047$), as well as reduced stride length ($p = 0.04$), stride velocity ($p = 0.002$), and peak turn velocity ($p = 0.02$) in FXTAS. No significant correlations were found between FXTAS-RS and spatiotemporal variables of gait and turning in PD or ET during SS, FP, or DT walking. On the

TABLE 2 Gait and turning parameters during self-selected (SS), fast as possible (FP), and dual task (DT) two-minute walk test (2MWT).

| i-WALK domain parameters | Controls ($n$ = 20) | FXTAS ($n$ = 22) | PD ($n$ = 23) | ET ($n$ = 20) |
|---|---|---|---|---|
| Self-selected (SS) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Stride length (%stature) | 86.21 (3.48) | 81.93 (8.00) | 75.34 (7.51)**a******,**b**** | 83.06 (6.43)**c**** |
| Stride velocity (%stature/s) | 81.77 (7.09) | 75.77 (8.28) | 72.17 (9.27)**a**** | 76.61 (9.84) |
| Cadence (steps/min) | 113.62 (8.91) | 110.93 (9.24) | 114.97 (9.45) | 110.63 (11.89) |
| Double limb support (%) | 20.22 (3.26) | 22.99 (4.90) | 21.67 (4.87) | 23.12 (4.96) |
| Trunk frontal ROM (degrees) CoV | 0.35 (0.26) | 0.44 (0.33) | 0.24 (0.16) | 0.32 (0.32) |
| Stride length (%stature) CoV | 0.04 (0.03) | 0.05 (0.02) | 0.04 (0.02) | 0.04 (0.02) |
| Stride velocity (%stature/s) CoV | 0.06 (0.04) | 0.08 (0.05) | 0.05 (0.02)**b*** | 0.06 (0.04) |
| Cadence (steps/min) CoV | 0.04 (0.03) | 0.06 (0.04) | 0.03 (0.01)**b*** | 0.04 (0.03) |
| Stride length asymmetry (%) | 1.42 (0.66) | 1.83 (0.71) | 1.60 (0.56) | 1.47 (0.60) |
| Arm symmetry index (%) | 18.20 (5.27) | 21.90 (6.78) | 31.89 (15.89)**a**** | 20.81 (11.02)**c*** |
| Turn duration (s) | 2.06 (0.37) | 2.43 (0.53) | 2.71 (0.61)**a**** | 2.26 (0.63) |
| Number of steps to turn | 4.33 (0.71) | 4.93 (0.97) | 5.44 (1.39)**a*** | 4.48 (0.86) |
| Peak turn velocity | 169.70 (37.50) | 150.96 (26.92) | 137.54 (31.43)**a*** | 166.97 (46.79) |
| Fast as possible (FP) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Stride length (%stature) | 88.52 (4.22) | 83.23 (7.81) | 77.03 (6.99)**a****** | 85.64 (6.39)**c**** |
| Stride velocity (%stature/s) | 96.77 (9.35) | 84.71 (9.90)**a**** | 82.02 (10.54)**a***** | 88.97 (13.27) |
| Cadence (steps/min) | 131.12 (12.39) | 122.05 (12.95) | 127.85 (12.86) | 124.53 (16.43) |
| Double limb support (%) | 16.75 (3.25) | 19.46 (5.49) | 18.69 (4.69) | 19.50 (5.15) |
| Trunk frontal ROM (degrees) CoV | 0.36 (0.28) | 0.47 (0.43) | 0.27 (0.18) | 0.32 (0.25) |
| Stride length (%stature) CoV | 0.04 (0.03) | 0.06 (0.03) | 0.04 (0.02) | 0.05 (0.03) |
| Stride velocity (%stature/s) CoV | 0.06 (0.05) | 0.09 (0.05)**a*** | 0.05 (0.03) | 0.07 (0.04) |
| Cadence (steps/min) CoV | 0.04 (0.03) | 0.06 (0.04) | 0.04 (0.02) | 0.05 (0.03) |
| Stride length asymmetry (%) | 1.34 (0.41) | 1.98 (0.83)**a*** | 1.61 (0.73) | 1.57 (0.67) |
| Arm symmetry index (%) | 14.00 (6.05) | 17.61 (4.42) | 29.59 (17.33)**a***** | 21.35 (11.03) |
| Turn duration (s) | 1.81 (0.32) | 2.27 (0.51)**a*** | 2.45 (0.52)**a***** | 2.04 (0.55)**c*** |
| Number of steps to turn | 4.63 (0.67) | 5.00 (0.74) | 5.52 (1.26) | 4.71 (0.85) |
| Peak turn velocity | 199.34 (41.69) | 167.90 (34.68) | 154.06 (31.86)**a**** | 184.33 (50.59) |
| Dual-task (DT) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Stride length (%stature) | 86.92 (4.50) | 80.88 (9.38) | 73.22 (8.78)**a******,**b*** | 82.23 (6.86)**c*** |
| Stride velocity (%stature/s) | 85.72 (11.99) | 74.75 (11.11) | 68.52 (10.25)**a****** | 75.06 (10.91) |
| Cadence (steps/min) | 117.95 (13.41) | 110.68 (11.64) | 112.52 (12.31) | 109.31 (12.66) |
| Double limb support (%) | 20.17 (3.66) | 23.43 (5.91) | 22.03 (4.44) | 23.95 (4.73) |
| Trunk frontal ROM (degrees) CoV | 0.38 (0.25) | 0.45 (0.37) | 0.27 (0.15) | 0.36 (0.30) |
| Stride length (%stature) CoV | 0.03 (0.02) | 0.05 (0.03) | 0.04 (0.02) | 0.04 (0.03) |
| Stride velocity (%stature/s) CoV | 0.06 (0.04) | 0.08 (0.05) | 0.05 (0.02) | 0.07 (0.04) |
| Cadence (steps/min) CoV | 0.04 (0.03) | 0.06 (0.04) | 0.03 (0.02) | 0.05 (0.03) |
| Stride length asymmetry (%) | 1.40 (0.53) | 1.98 (0.86) | 1.76 (0.66) | 1.54 (0.55) |
| Arm symmetry index (%) | 18.08 (5.59) | 19.48 (5.63) | 35.70 (19.69)**a******,**b****** | 20.03 (6.84)**c***** |
| Turn duration (s) | 1.88 (0.39) | 2.51 (0.86)**a*** | 2.80 (0.69)**a****** | 2.26 (0.66) |
| Number of steps to turn | 4.16 (0.72) | 4.98 (1.36) | 5.49 (1.38)**a**** | 4.45 (0.99) |
| Peak turn velocity | 191.37 (42.21) | 156.46 (38.28)**a*** | 136.85 (34.44)**a***** | 166.54 (42.53) |

Gait and movement transition domain variables for between group comparisons among FXTAS, PD, ET, and controls. $\mathrm{CoV}(\text{coefficient of variation}) = \frac{\mathrm{SD}}{\text{mean}} \times 100$. **a, significantly different from controls; b, significantly different from FXTAS; c, significantly different from PD**; *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

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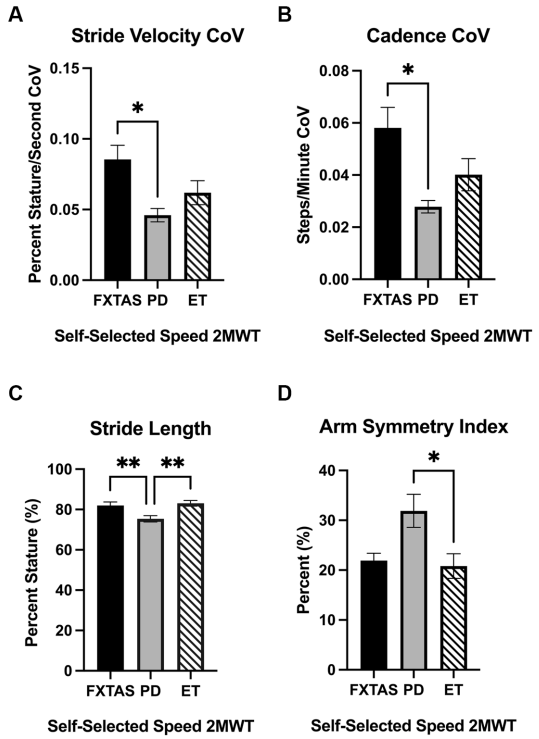


FIGURE 1
Gait parameters under self-selected (SS) speed two-minute walk test (2MWT). Significantly different gait parameters among FXTAS, PD, and ET participants: **(A)** stride velocity variability, **(B)** cadence variability, **(C)** stride length, and **(D)** arm symmetry index. $\mathrm{CoV}(\text{coefficient of variation}) = \frac{\mathrm{SD}}{\text{mean}} \times 100$. All data reported as mean ± SEM. *$p \leq 0.05$, **$p \leq 0.01$.

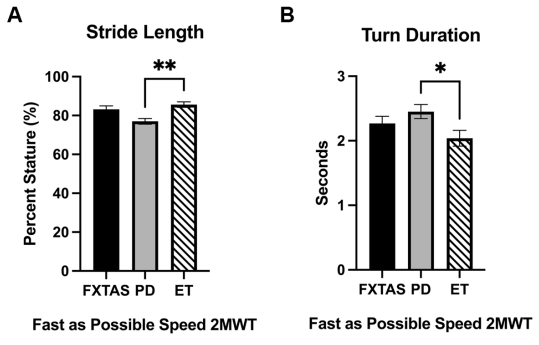


FIGURE 2
Gait parameters under fast as possible (FP) two-minute walk test (2MWT). Significantly different gait and movement transition parameters among FXTAS, PD, and ET participants: **(A)** stride length, and **(B)** turn duration. All data reported as mean ± SEM. *$p \leq 0.05$, **$p \leq 0.01$.

i-TUG, higher FXTAS-RS scores were correlated with increased total duration in PD ($p = 0.01$) and increased turn-to-sit duration in both PD ($p = 0.02$) and ET ($p = 0.02$). In FXTAS participants, no significant correlations were found between CGG repeat size and gait or i-TUG variables.

## Discussion

This is the first study to directly compare gait characteristics in FXTAS, PD, and ET using quantitative gait analysis and gait stress tests including FP and DT paradigms. These results show that gait analysis was able to distinguish between-group differences in gait parameters during SS, FP, and DT conditions. We also identified differences in DTC in the domains of gait pace (stride length and velocity) where PD had significant DTC compared to FXTAS participants. FXTAS participants had significantly slower stride velocity and stride velocity variability, increased stride length asymmetry, and increased turn duration compared to controls during FP walking. Importantly, this condition revealed a greater number of impairments in FXTAS than in ET compared to controls, suggesting that this particular test may be helpful for distinguishing FXTAS from ET in the clinic. It is known that at fast speeds of locomotion, it is more difficult to maintain stability due to signaling delays between the musculoskeletal system and higher-level neural control centers (52). It is possible that this coordination of neural signaling and muscular responses was more stressed by fast walking in the FXTAS participants, requiring them to slow down their strides and turns in order to maintain stability more so than the ET participants. In a previous study, our group characterized the gait deficits using a 7 m i-TUG in a smaller cohort of FXTAS participants and found abnormalities similar to those found in this study, including reduced stride velocity and longer turn duration (8); however, these deficits were seen with SS walking speeds, whereas the current study did not find any gait deficits in FXTAS compared to controls at these speeds. Our present inclusion criteria required that participants had to be able to walk unassisted for 2 min; therefore, the group had milder gait symptoms that might not be detectable at SS speeds. In addition, our prior study only included those with definite cerebellar gait ataxia on neurological exam, whereas the current study included a more heterogeneous group of FXTAS participants with both tremor and ataxia dominant forms of the disease.

Other groups have investigated gait under fast walking speeds in other cerebellar ataxias and reported increased stride length and speed variability in Friedreich ataxia, spinocerebellar ataxia, and idiopathic cerebellar patients using the GAITRite® walkway (53–55). Increased stride velocity variability was seen in FXTAS during FP walking in the current study, which we reported in our prior FP gait study in FXTAS to be significantly associated with increased falls (20). Furthermore, Schniepp et al. found FP walking to be the most strongly correlated to clinical severity of ataxia compared to other walking speeds and concluded that it may be a useful measure in the clinical evaluation of patients with cerebellar ataxia (55). Given that we found the most gait deficits in FXTAS under FP walking in the present study, this test may be useful for evaluating FXTAS patients in the clinic.

PD participants had significantly reduced stride length compared to FXTAS and ET participants on the SS and DT gait conditions, as well as slower stride velocity and reduced stride length compared to controls on all three conditions. They also took significantly longer to turn with lower peak turn velocity and increased turn duration on all three gait conditions, and more steps to turn under SS and DT walking compared to controls. In the FP condition, PD participants were slower to turn than the ET group. Typical PD patients display a slow, shuffling gait pattern, as well as bradykinesia, which is consistent with

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TABLE 3 Dual-task costs for gait and turning parameters.

| i-WALK domain parameters | Controls ($n = 20$) | FXTAS ($n = 22$) | PD ($n = 23$) | ET ($n = 20$) |
|---|---|---|---|---|
| Dual-task cost (DTC) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Stride length (%stature) | 0.81 (2.77) | −1.16 (7.34) | −2.98 (3.76)**a****,**b*** | −1.03 (2.14) |
| Stride velocity (%stature/s) | 4.69 (9.68) | −1.20 (10.59) | −5.15 (5.98)**a*****,**b*** | −2.02 (6.51) |
| Cadence (steps/min) | 3.75 (7.43) | −0.26 (5.38) | −2.23 (4.72)**a**** | −1.13 (5.10) |
| Double limb support (%) | −0.07 (10.16) | 1.98 (13.63) | 2.60 (8.96) | 4.29 (9.85) |
| Trunk frontal ROM (degrees) CoV | 24.66 (47.14) | 4.07 (31.88) | 18.10 (34.02) | 22.04 (32.84) |
| Stride length (%stature) CoV | 3.28 (50.80) | 3.58 (38.33) | 8.15 (33.95) | 3.62 (28.48) |
| Stride velocity (%stature/s) CoV | 11.68 (55.87) | 7.97 (37.26) | 15.20 (36.37) | 19.94 (44.09) |
| Cadence (steps/min) CoV | 31.75 (70.57) | 16.33 (51.26) | 25.47 (35.78) | 30.96 (56.67) |
| Stride length asymmetry (%) | 5.84 (37.59) | 15.58 (58.73) | 11.49 (24.48) | 7.56 (22.96) |
| Arm symmetry index (%) | 2.40 (34.04) | −7.26 (25.27) | 17.06 (59.66) | 7.28 (37.98) |
| Turn duration (s) | −7.84 (13.04) | 3.99 (32.21) | 3.74 (12.17)**a*** | 0.64 (12.43) |
| Number of steps to turn | −2.73 (14.55) | 1.94 (23.55) | 1.52 (10.83) | −0.49 (11.34) |
| Peak turn velocity | 13.19 (13.19) | 3.77 (17.93) | 0.04 (14.79)**a*** | 0.88 (10.64)**a*** |

Dual-task costs (DTC) for gait variables for between group comparisons among FXTAS, PD, ET, and controls. DTC was calculated using the formula $\frac{DT-SS}{SS}\times 100$. $\mathrm{CoV}\left(\text{coefficient of variation}\right)=\frac{SD}{mean}\times 100$. **a, significantly different from controls; b, significantly different from FXTAS**; $^{*}p\leq 0.05$, $^{**}p\leq 0.01$, $^{***}p\leq 0.001$, $^{****}p\leq 0.0001$.

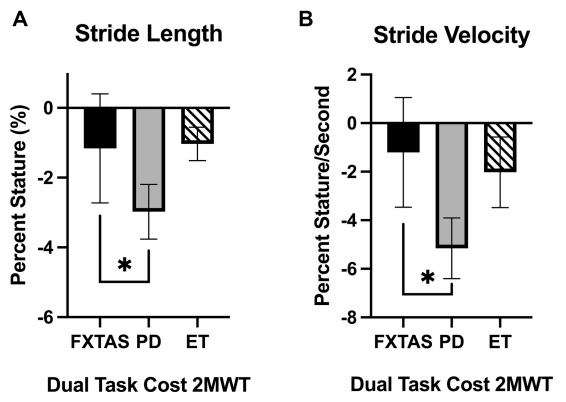


FIGURE 3
Dual task costs for gait parameters. Significantly different gait parameters among FXTAS, PD, and ET participants: **(A)** stride length, and **(B)** stride velocity. DTC was calculated using the formula $\frac{DT-SS}{SS}\times 100$. All data reported as mean ± SEM. $^{*}p\leq 0.05$.

our findings of slower, shorter strides and slower turns. This contrast with the wide-based, ataxic gait pattern typically seen in FXTAS patients, and the mild ataxia seen in roughly half of ET patients (56–60). PD participants also had significantly greater arm asymmetry than ET participants and controls at SS speeds, and than FXTAS, ET, and control participants under DT gait. DT during gait apparently stressed the neuromotor system in PD exacerbating arm asymmetry. These results are consistent with the common asymmetric PD gait pattern. PD symptoms typically present asymmetrically and many patients exhibit a reduced or absent reciprocal arm swing (61).

ET participants were not abnormal on any gait parameters for any of the test conditions, likely because regular bipedal gait in ET patients tends to be normal (58). However, mild gait and postural stability deficits have been found in ET, including difficulties with tandem gait (56–60). It may be that the present study conditions were not challenging enough to extract gait deficits in the ET group, or that the pool of selected ET participants did not have cerebellar gait ataxia.

Compared to FXTAS participants and controls, PD participants had significantly greater DTC for the gait pace domain including stride velocity and stride length parameters. Previous DT studies in PD have shown similar findings. Plotnik et al. found that gait speed and stride length were both impaired by DT using a serial subtraction cognitive interference task (26). Yogev-Seligmann et al. and Fuller et al. also found reduced gait speed under DT in PD using a verbal fluency interference task similar to the current study (27, 62). However, we did not find differences for DTC between movement disorder groups in any of the other gait domains. None of the groups performed worse on the cognitive task during the DT condition, indicating that they were not prioritizing the gait task over the cognitive task. It is possible that the DT verbal fluency test did not provide a sufficient cognitive load to reveal other impairments. Therefore, future studies could utilize a more difficult task that might cause greater cognitive interference. Our results do suggest that PD patients may be more sensitive to cognitive interference, potentially having lower cognitive reserve than those with FXTAS.

The i-TUG was used to evaluate functional movement transitions important in daily living. PD participants had significantly slower speed when transitioning from sit-to-stand compared to FXTAS, ET, and control participants, as well as slower speed when turning to sit compared to controls. Given that bradykinesia is a cardinal symptom of PD, it was expected that the PD group would be slower at completing these movement transitions. These results suggest that the sit-to-stand measure may be helpful for assisting with diagnosis, such that patients with reduced velocities on this parameter may be more likely to have PD. Furthermore, Herman et al. found that i-TUG parameters were able to distinguish between the postural instability and gait disorder and tremor dominant subtypes of PD (10). It has been proposed that there may be two subtypes of FXTAS as well, including tremor and ataxia predominant phenotypes (63). As a follow-up study, it would be interesting to compare these subtypes of

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TABLE 4 Movement transition parameters during the Instrumented Timed Up and Go test (i-TUG).

| i-TUG parameters | Controls ($n = 20$) | FXTAS ($n = 22$) | PD ($n = 23$) | ET ($n = 20$) |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Total duration (s) | 17.71 (2.28) | 20.54 (5.47) | 20.02 (2.64) | 18.95 (3.69) |
| Sit-to-stand duration (s) | 2.28 (0.30) | 2.34 (0.26) | 2.49 (0.23) | 2.35 (0.32) |
| Sit-to-stand peak velocity (deg/s) | 99.29 (47.45) | 98.91 (33.63) | 68.26 (14.90)**a****,b**** | 90.95 (23.46)**c**** |
| Turn-to-sit peak turn velocity (deg/s) | 173.98 (39.34) | 151.89 (36.32) | 135.15 (36.34)**a**** | 160.50 (38.74) |
| Turn-to-sit duration (s) | 4.21 (0.65) | 4.57 (1.03) | 4.56 (0.98) | 4.26 (0.82) |

i-TUG variables for between group comparisons among FXTAS, PD, ET, and controls. **a, significantly different from controls; b, significantly different from FXTAS; c, significantly different from PD**; *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

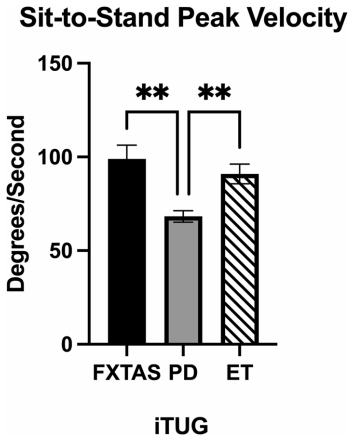


FIGURE 4
Movement transition parameters in the Instrumented Timed Up and Go test (i-TUG). Significantly different parameter among FXTAS, PD, and ET participants: sit-to-stand peak velocity. All data reported as mean ± SEM. *$p \leq 0.05$, **$p \leq 0.01$.

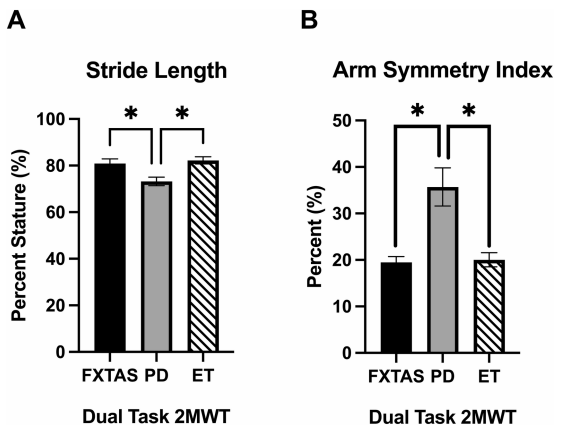


FIGURE 5
Significant multinomial regression results. Significantly different gait parameters among FXTAS, PD, and ET participants during the dual task (DT) condition: **(A)** stride length, and **(B)** arm symmetry index. All data reported as mean ± SEM. *$p \leq 0.05$.

FXTAS to see if i-TUG, FP, and DT gait testing are able to distinguish them; treatment plans could then be tailored based on individual phenotypes.

Multinomial logistic regression analysis showed that on the DT condition, stride lengths was able to distinguish PD from FXTAS and ET, such that participants with shorter stride length were more likely to have PD. Shortening of steps when walking is a common feature in PD, particularly under a stressful condition such as walking while performing a cognitive task where PD patients may be triggered to festinate or take involuntarily short steps (64, 65). Furthermore, in the current study we found that PD participants had a significant DTC for stride length whereas FXTAS participants did not. Thus, it is logical that the measure of stride length would be able to make this distinction. Arm symmetry index during the DT condition was also able to distinguish between FXTAS and PD, and ET and PD, such that participants with greater arm asymmetry were more likely to have PD. This appears logical given that reduction in reciprocal arm swing range of motion and its asymmetry is a hallmark feature in PD (61), while arm asymmetry in FXTAS or ET has not been reported. Our findings of greater arm asymmetry in PD compared to ET are similar to those in a recent report using inertial sensors during performance of the i-TUG and a machine learning approach to distinguish early-stage PD from ET (66). We also have unpublished data in larger cohorts indicating that arm asymmetry and arm range of motion are not different from controls in FXTAS.

As expected, the FXTAS, PD, and ET groups all had significantly worse FXTAS-RS scores compared to healthy controls. However, no differences in rating scale scores were found among the disorders, suggesting that the gait and functional movement transition measures were more sensitive for distinguishing between them than the scale. FXTAS-RS scores were associated with multiple gait measures in FXTAS under all three gait conditions, and number of steps to turn in controls during FP walking. FXTAS-RS scores were also associated with total duration in PD and turn-to-sit duration in PD and ET during the i-TUG. This finding was not unexpected given that FXTAS and PD patients tend to have greater gait impairments than ET patients (67).

Strengths of this study include objective gait measurement using highly sensitive quantitative analysis that has been validated in PD in previous studies, and the use of DT cognitive-motor interference paradigms similar to those used in previous studies of PD, FXTAS, and ET. SS, FP, and DT gait testing was able to distinguish differences between FXTAS and PD and ET and PD. It may be cost effective to add these tests to a clinical evaluation to aid in accurate diagnosis given that each walking condition takes only 2 min to complete. These quantitative measures may improve characterization of these disorders and serve as outcome measures to evaluate treatment responses in future studies.

Limitations of this pilot study include a relatively small sample size; increasing the sample size in future studies will help to

strengthen and corroborate these findings. Another limitation is that there were no significant differences between controls and FXTAS participants on any gait or turn variables in the self-selected (SS) speed condition, suggesting that our FXTAS group was minimally impaired in gait and only showed impairments at fast speeds (FP) and while dual tasking (DT). Future studies could only include those with probable and definite FXTAS with definite cerebellar gait ataxia on clinical exam. The control group was significantly younger than the PD and ET groups, but there were no differences in age between the three movement disorder groups. Additionally, we controlled for age in the regression model, which only compared FXTAS, PD and ET groups, so we do not believe age is a relevant problem with the study. Another potential limitation was that, due to logistical and feasibility issues, all medicated study participants were on their medications at time of testing, which did not allow their gait to be measured in its most natural and debilitating state. In future studies, it would be ideal if participants could be tested both on and off their medication to obtain a more accurate measurement of gait in these disorders.

These findings demonstrate that patients with FXTAS and ET exhibit distinct gait profiles from those with PD. The DT condition was sensitive for distinguishing FXTAS and ET from PD in arm asymmetry and stride length. Significant DT cognitive interference (i.e., DTC) for gait and turn variables were only seen in the PD group. On the i-TUG, FXTAS and ET participants were significantly faster at transitioning from sitting to standing than PD participants. These results suggest that DT walking paradigms and assessment of movement transitions may be useful for diagnosing FXTAS patients in the clinic.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Rush University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

ER-D: Writing – original draft, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing. ET: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Visualization. GP: Writing – review & editing, Data curation, Methodology. BO: Writing – review & editing, Formal analysis. YL: Writing – review & editing, Formal analysis. EB-K: Writing – review & editing, Conceptualization. DH: Writing – review & editing, Conceptualization, Investigation, Methodology, Supervision. JO'K: Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision.

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## Conflict of interest

EB-K has received funding from Acadia, Alcobra, AMO, Asuragen, Avexis, Biogen, BioMarin, Cydan, Engrail, Erydel, Fulcrum, GeneTx, GW, Healx, Ionis, Jaguar, Kisbee, Lumos, Marinus, Moment Biosciences, Neuren, Neurogene, Neurotrope, Novartis, Orphazyme/Kempharm, Ovid, PTC Therapeutics, Retrophin, Roche, Seaside Therapeutics, Taysha, Tetra, Ultragenyx, Yamo, Zynerba, and Vtesse/Sucampo/Mallinckrodt Pharmaceuticals, to consult on trial design or run clinical or lab validation trials in genetic neurodevelopmental or neurodegenerative disorders, all of which is directed to RUMC in support of rare disease programs; EB-K receives no personal funds and RUMC has no relevant financial interest in any of the commercial entities listed. EB-K has also had research support from NICHD, NINDS, NIMH, CDC, NCATS and the John Merck Fund. DH receives research support from the NIH (R01NS125294, U01NS11385, U01NS100610, and R01AG059417), the CHDI Foundation, Lundbeck, Neurocrine, and Regeneron Pharmaceuticals. JO'K received or is receiving research support from the NIH (K01 HD088762, U01NS113851). She also receives research support from the Huntington's Disease Society of America, Regeneron Pharmaceuticals, and a pilot grant from the Rush University Imaging Research Core.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1308698/full#supplementary-material

# References


1. Hagerman RJ, Leehey MA, Heinrichs WL, Tassone F, Wilson RL, Hills J, et al. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology*. (2001) 57:127–30. doi: 10.1212/wnl.57.1.127

2. Grigsby J, Cornish K, Hocking DR, Kraan C, Olichney J, Rivera SM, et al. The cognitive neuropsychological phenotype of carriers of the FMR1 premutation. *J Neurodev Disord*. (2014) 6:28. doi: 10.1186/1866-1955-6-28

3. Seritan AL, Nguyen DV, Farias SET, Hinton WL, Grigsby J, Bourgeois JA, et al. Dementia in fragile X-associated tremor/ataxia syndrome (FXTAS): comparison with Alzheimer's disease. *Am J Med Genet*. (2008) 147B:1138–44. doi: 10.1002/ajmg.b.30732

4. Berry-Kravis E, Abrams L, Coffey S, Hall DA, Greco C, Gane LW, et al. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. *Mov Disord*. (2007) 22:2018–30. doi: 10.1002/mds.21493

5. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *J Investig Med*. (2009) 57:830–6. doi: 10.2310/jim.0b013e3181af59c4

6. Hall DA, Berry-Kravis E, Jacquemont S, Rice C, Cogswell JB, Zhang L, et al. Initial diagnoses given to persons with the fragile X associated tremor/ataxia syndrome (FXTAS). *Neurology*. (2005) 65:299–301. doi: 10.1212/01.wnl.0000168900.86323.9c

7. Robertson E, Hall DA, Pal G, Ouyang B, Liu Y, Joyce J, et al. Tremorography in fragile X-associated tremor/ataxia syndrome, Parkinson's disease and essential tremor. *Clin Parkinsonism Relat Disord*. (2020) 3:100040. doi: 10.1016/j.prdoa.2020.100040

8. O'Keefe JA, Robertson-Dick E, Hall DA, Berry-Kravis E. GAIT and functional mobility deficits in fragile X-associated tremor/ataxia syndrome. *Cerebellum*. (2015) 15:475–82. doi: 10.1007/s12311-015-0714-4

9. Dewey DC, Miocinovic S, Bernstein IH, Khemani P, Dewey RB, Querry RG, et al. Automated gait and balance parameters diagnose and correlate with severity in Parkinson disease. *J Neurol Sci*. (2014) 345:131–8. doi: 10.1016/j.jns.2014.07.026

10. Herman T, Rosenberg-Katz K, Jacob Y, Giladi N, Hausdorff JM. Gray matter atrophy and freezing of gait in Parkinson's disease: is the evidence black-on-white? *Mov Disord*. (2013) 29:134–9. doi: 10.1002/mds.25697

11. Van Uem JMT, Walgaard S, Ainsworth E, Hasmann SE, Heger T, Nussbaum S, et al. Quantitative timed-up-and-go parameters in relation to cognitive parameters and health-related quality of life in mild-to-moderate Parkinson's disease. *PLoS One*. (2016) 11:e0151997. doi: 10.1371/journal.pone.0151997

12. King LA, Mancini M, Priest KC, Salarian A, Rodrigues-De-Paula F, Horak FB. Do clinical scales of balance reflect turning abnormalities in people with Parkinson's disease? *J Neurol Phys Ther*. (2012) 36:25–31. doi: 10.1097/npt.0b013e31824620d1

13. Zampieri C, Salarian A, Carlson-Kuhta P, Aminian K, Nutt JG, Horak FB. The instrumented timed up and go test: potential outcome measure for disease modifying therapies in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. (2009) 81:171–6. doi: 10.1136/jnnp.2009.173740

14. Salarian A, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Aminian K. ITUG, a sensitive and reliable measure of mobility. *IEEE Trans Neural Syst Rehabil Eng*. (2010) 18:303–10. doi: 10.1109/tnsre.2010.2047606

15. Zampieri C, Salarian A, Carlson-Kuhta P, Nutt JG, Horak FB. Assessing mobility at home in people with early Parkinson's disease using an instrumented timed up and go test. *Parkinsonism Relat Disord*. (2011) 17:277–80. doi: 10.1016/j.parkreldis.2010.08.001

16. Nelson AJ, Zwick D, Brody S, Doran C, Pulver L, Rooz G, et al. The validity of the GaitRite and the functional ambulation performance scoring system in the analysis of Parkinson gait1. *NeuroRehabilitation*. (2002) 17:255–62. doi: 10.3233/nre-2002-17312

17. Rao AK, Gillman AE, Louis ED. Quantitative gait analysis in essential tremor reveals impairments that are maintained into advanced age. *Gait Posture*. (2011) 34:65–70. doi: 10.1016/j.gaitpost.2011.03.013

18. Rao AK, Uddin J, Gillman AE, Louis ED. Cognitive motor interference during dual-task gait in essential tremor. *Gait Posture*. (2013) 38:403–9. doi: 10.1016/j.gaitpost.2013.01.006

19. Louis ED, Galecki M, Rao AK. Four essential tremor cases with moderately impaired gait: how impaired can gait be in this disease? *Tremor Other Hyperkinet Mov*. (2013) 3:tre-03-200-4597-1. doi: 10.7916/D8QV3K7G

20. O'Keefe JA, Guan J, Robertson E, Biskis A, Joyce J, Ouyang B, et al. The effects of dual task cognitive interference and fast-paced walking on gait, turns, and falls in men and women with FXTAS. *Cerebellum*. (2020) 20:212–21. doi: 10.1007/s12311-020-01199-3

21. Morris ME, Iansek R, Matyas TA, Summers JJ. Ability to modulate walking cadence remains intact in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. (1994) 57:1532–4. doi: 10.1136/jnnp.57.12.1532

22. Bayle N, Patel A, Crisan D, Guo LJ, Hutin E, Weisz DJ, et al. Contribution of step length to increase walking and turning speed as a marker of Parkinson's disease progression. *PLoS One*. (2016) 11:e0152469. doi: 10.1371/journal.pone.0152469

23. Peterson DS, Mancini M, Fino PC, Horak FB, Smulders K. Speeding up gait in Parkinson's disease. *J Parkinsons Dis*. (2020) 10:245–53. doi: 10.3233/jpd-191682

24. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. *J Neurol Neurosurg Psychiatry*. (2009) 80:347–50. doi: 10.1136/jnnp.2008.157362

25. Vervoort G, Heremans E, Bengevoord A, Strouwen C, Nackaerts E, Vandenberghe W, et al. Dual-task-related neural connectivity changes in patients with Parkinson' disease. *Neuroscience*. (2016) 317:36–46. doi: 10.1016/j.neuroscience.2015.12.056

26. Plotnik M, Dagan Y, Gurevich T, Giladi N, Hausdorff JM. Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations. *Exp Brain Res*. (2010) 208:169–79. doi: 10.1007/s00221-010-2469-y

27. Yogev-Seligmann G, Hausdorff JM, Giladi N. Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Mov Disord*. (2012) 27:765–70. doi: 10.1002/mds.24963

28. Bove M, Marinelli L, Avanzino L, Marchese R, Abbruzzese G. Posturographic analysis of balance control in patients with essential tremor. *Mov Disord*. (2006) 21:192–8. doi: 10.1002/mds.20696

29. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology*. (1967) 17:427. doi: 10.1212/wnl.17.5.427

30. Hollman JH, McDade E, Petersen RC. Normative spatiotemporal gait parameters in older adults. *Gait Posture*. (2011) 34:111–8. doi: 10.1016/j.gaitpost.2011.03.024

31. Lord S, Galna B, Rochester L. Moving forward on gait measurement: toward a more refined approach. *Mov Disord*. (2013) 28:1534–43. doi: 10.1002/mds.2554

32. Sant'anna AP, Salarian A, Wickström N. A new measure of movement symmetry in early Parkinson's disease patients using symbolic processing of inertial sensor data. *IEEE Trans Biomed Eng*. (2011) 58:2127–35. doi: 10.1109/tbme.2011.2149521

33. Luria AR. *The problem of localization of functions in the cerebral cortex*. Boston, MA: Springer. (1966). p. 5–38.

34. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia*. (1967) 5:135–40. doi: 10.1016/0028-3932(67)90015-2

35. Goodglass H, Kaplan E. The assessment of aphasia and related disorders. (1972). Available at:https://ci.nii.ac.jp/ncid/BA24232886

36. Smith A. Symbol Digit Modalities test. *PsycTESTS Dataset*. (1973). doi: 10.1037/t27513-000

37. Wechsler D. Wechsler abbreviated scale of intelligence. *PsycTESTS Dataset*. (1999). doi: 10.1037/t15170-000

38. Stegemöller EL, Nocera J, Malaty IA, Shelley M, Okun MS, Hass CJ. Timed up and go, cognitive, and quality-of-life correlates in Parkinson's disease. *Arch Phys Med Rehabil*. (2014) 95:649–55. doi: 10.1016/j.apmr.2013.10.031

39. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci*. (2005) 22:1248–56. doi: 10.1111/j.1460-9568.2005.04298.x

40. Rochester L, Nieuwboer A, Baker K, Hetherington V, Willems AM, Kwakkel G, et al. Walking speed during single and dual tasks in Parkinson's disease: which characteristics are important? *Mov Disord*. (2008) 23:2312–8. doi: 10.1002/mds.22219

41. O'Keefe JA, Robertson E, Ouyang B, Carns D, McAsey A, Liu Y, et al. Cognitive function impacts gait, functional mobility and falls in fragile X-associated tremor/ataxia syndrome. *Gait Posture*. (2018) 66:288–93. doi: 10.1016/j.gaitpost.2018.09.005

42. Cornblath DR, Chaudhry V, Carter K, Lee D, Seysedadr M, Miernicki M, et al. Total neuropathy score: validation and reliability study. *Neurology*. (1999) 53:1660. doi: 10.1212/wnl.53.8.1660

43. Soontarapornchai K, Maselli RA, Fenton-Farrell G, Tassone F, Hagerman PJ, Hessl D, et al. Abnormal nerve conduction features in fragile X premutation carriers. *Arch Neurol*. (2008) 65:495–8. doi: 10.1001/archneur.65.4.495

44. Zis P, Grünewald RA, Chaudhuri R, Hadjivassiliou M. Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review. *J Neurol Sci*. (2017) 378:204–9. doi: 10.1016/j.jns.2017.05.023

45. De Camargo MR, Barela JA, Nozabieli AJL, Mantovani AM, Martinelli A, Fregonesi CEPT. Balance and ankle muscle strength predict spatiotemporal gait parameters in individuals with diabetic peripheral neuropathy. *Diabetes Metab Syndr*. (2015) 9:79–84. doi: 10.1016/j.dsx.2015.02.004

46. Leehey MA, Berry-Kravis E, Goetz CG, Zhang L, Hall DA, Li L, et al. FMR1 CGG repeat length predicts motor dysfunction in premutation carriers. *Neurology*. (2007) 70:1397–402. doi: 10.1212/01.wnl.0000281692.98200.f5

47. Fahn S. Members of the UPDRS development committee. Unified Parkinson's disease rating scale. *Recent Dev Parkinson's Dis*. (1987) 2:293–304.

48. Fahn S, Tolosa E, Marin C, Jankovic J. Clinical rating scale for tremor In: J Jankovic and E Tolosa, editors. *Parkinson's disease and movement disorders*. Baltimore, MD: Williams & Wilkins (1993). 271–80.

49. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, et al. International cooperative ataxia rating scale for pharmacological assessment of

cerebellar syndrome. *J Neurol Sci*. (1997) 145:205–11. doi: 10.1016/s0022-510x(96)00231-6

50. Kieburtz K, Penney JB, Corno P, Ranen NG, Shoulson I, Feigin A, et al. Unified Huntington's disease rating scale: reliability and consistency. *Mov Disord*. (1996) 11:136–42. doi: 10.1002/mds.870110204

51. Chen L, Hadd AG, Sah S, Houghton JD, Filipovic-Sadic S, Zhang W, et al. High-resolution methylation polymerase chain reaction for fragile X analysis: evidence for novel FMR1 methylation patterns undetected in southern blot analyses. *Genet Med*. (2011) 13:528–38. doi: 10.1097/gim.0b013e31820a780f

52. Nordin AD, Rymer WZ, Biewener AA, Schwartz AB, Chen D, Horak FB. Biomechanics and neural control of movement, 20 years later: what have we learned and what has changed? *J Neuroeng Rehabil*. (2017) 14:91. doi: 10.1186/s12984-017-0298-y

53. Stephenson JL, Zesiewicz TA, Gooch CL, Wecker L, Sullivan KL, Jahan I, et al. Gait and balance in adults with Friedreich's ataxia. *Gait Posture*. (2015) 41:603–7. doi: 10.1016/j.gaitpost.2015.01.002

54. Schniepp R, Wuehr M, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. *Mov Disord*. (2011) 27:125–31. doi: 10.1002/mds.23978

55. Schniepp R, Strupp M, Wuehr M, Jahn K, Dieterich M, Brandt T, et al. Acetyl-DL-leucine improves gait variability in patients with cerebellar ataxia—a case series. *Cerebellum Ataxias*. (2016) 3:8. doi: 10.1186/s40673-016-0046-2

56. Singer C, Sanchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. *Mov Disord*. (2004) 9:193–6. doi: 10.1002/mds.870090212

57. Hubble J, Busenbark K, Pahwa R, Lyons KE, Koller WC. Clinical expression of essential tremor: effects of gender and age. *Mov Disord*. (1997) 12:969–72. doi: 10.1002/mds.870120620

58. Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G. The gait disorder of advanced essential tremor. *Brain*. (2001) 124:2278–86. doi: 10.1093/brain/124.11.2278

59. Kronenbuerger M, Konczak J, Ziegler W, Buderath P, Frank B, Coenen VA, et al. Balance and motor speech impairment in essential tremor. *Cerebellum*. (2009) 8:389–98. doi: 10.1007/s12311-009-0111-y

60. Hoskovcová M, Ulmanová O, Šprdlík O, Sieger T, Novakova J, Jech R, et al. Disorders of balance and gait in essential tremor are associated with midline tremor and age. *Cerebellum*. (2012) 12:27–34. doi: 10.1007/s12311-012-0384-4

61. Nieuwboer A, De Weerdt W, Dom R, Lesaffre E. A frequency and correlation analysis of motor deficits in Parkinson patients. *Disabil Rehabil*. (1998) 20:142–50. doi: 10.3109/09638289809166074

62. Fuller R, Van Winkle EP, Anderson KE, Gruber-Baldini AL, Hill T, Zampieri C, et al. Dual task performance in Parkinson's disease: a sensitive predictor of impairment and disability. *Parkinsonism Relat Disord*. (2013) 19:325–8. doi: 10.1016/j.parkreldis.2012.11.011

63. Juncos JL, Lazarus J, Graves-Allen E, Shubeck L, Rusin M, Novak G, et al. New clinical findings in the fragile X-associated tremor ataxia syndrome (FXTAS). *Neurogenetics*. (2011) 12:123–35. doi: 10.1007/s10048-010-0270-5

64. O'Shea SD, Morris ME, Iansek R. Dual task interference during GAIT in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Phys Ther*. (2002) 82:888–97. doi: 10.1093/ptj/82.9.888

65. Rochester L, Hetherington V, Jones D, Nieuwboer A, Willems A, Kwakkel G, et al. Attending to the task: interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Arch Phys Med Rehabil*. (2004) 85:1578–85. doi: 10.1016/j.apmr.2004.01.025

66. Lin S, Gao C, Li H, Huang P, Ling Y, Chen Z, et al. Wearable sensor-based gait analysis to discriminate early Parkinson's disease from essential tremor. *J Neurol*. (2023) 270:2283–301. doi: 10.1007/s00415-023-11577-6

67. Robertson E, Hall DA, McAsey A, O'Keefe JA. Fragile X-associated tremor/ataxia syndrome: phenotypic comparisons with other movement disorders. *Clin Neuropsychol*. (2016) 30:849–900. doi: 10.1080/13854046.2016.1202239

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# Paradigm shift in Parkinson's disease: using continuous telemonitoring to improve symptoms control. Results from a 2-years journey

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**Introduction:** Conventional care in Parkinson's disease (PD) faces limitations due to the significant time and location commitments needed for regular assessments, lacking quantitative measurements. Telemonitoring offers clinicians an opportunity to evaluate patient symptomatology throughout the day during activities of daily living.

**Methods:** The progression of PD symptoms over a two-year period was investigated in patients undergoing traditional evaluation, supplemented by insights from ambulatory measurements. Physicians integrated a telemonitoring device, the PDMonitor®, into daily practice, using it for informed medication adjustments.

**Results:** Statistical analyses examining intra-subject changes for 17 subjects revealed a significant relative decrease of −43.9% in the device-reported percentage of time spent in "OFF" state (from 36.2 to 20.3%). Following the 24-month period, the majority of the subjects improved or exhibited stable symptom manifestation. In addition to positively impacting motor symptom control, telemonitoring was found to enhance patient satisfaction about their condition, medication effectiveness, and communication with physicians.

**Discussion:** Considering that motor function is significantly worsened over time in patients with PD, these findings suggest a positive impact of objective telemonitoring on symptoms control. Patient satisfaction regarding disease management through telemonitoring can potentially improve adherence to treatment plans. In conclusion, remote continuous monitoring paves the way for a paradigm shift in PD, focusing on actively managing and potentially improve symptoms control.

KEYWORDS

**telemonitoring, real-world data, objective motor assessment, longitudinal analysis, patient satisfaction**

# 1 Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, characterized by a progressive deficiency of dopamine in the brain (1). While the clinical phenotype of PD encompasses various non-motor symptoms like cognitive decline, impulsive behavior, depression, and autonomic nervous system disorders, the primary focus in diagnosing PD revolves around the presence of core motor symptoms, including bradykinesia, muscle stiffness, and tremor (2). Currently, the process of diagnosing and making treatment decisions is conducted through clinical examinations, scales, and patient-reported outcomes (3). To date, therapeutic interventions primarily rely on dopamine replacement drugs, with levodopa being particularly effective in the initial phases of the disease (4).

Nevertheless, disease progression differs from patient to patient and advances at different rates. Conventional care faces limitations due to the significant time and location commitments needed for regular assessments, and it depends on the expertise of physicians, lacking quantitative measurements (5). The accuracy of disease assessment may also be impeded by recall bias and difficulties in patients effectively conveying their symptoms (6). Moreover, the management of PD presents a complex interplay between symptom control and disease progression. Currently, there are no therapies available that can affect the progression of PD. The primary emphasis of medical care is to control the motor symptoms through the use of drugs (7). However, prolonged use of medication leads to significant motor complications, such as limited mobility during the "OFF" period, wearing-off and end-of-dose phenomena, necessitating further treatment modifications (8). To address this unmet need, the utilization of wearable devices, which have become instrumental in telemonitoring, has facilitated the continuous objective measurement of PD symptoms (9).

Telemonitoring offers clinicians an opportunity to evaluate patient symptomatology throughout the day during activities of daily living, to assess response to therapy during long periods of months and years, and to improve follow-up care (10). The concept of continuous telemonitoring for symptoms aligns with the existing standard of care and is not a novel concept in the context of PD (11). Such transformative approaches for PD management pave the way for a paradigm shift aimed at actively managing and potentially improving symptoms control. In this study, the progression of PD symptoms over a two-year observation period in patients undergoing traditional evaluation, combined with insights derived from objective ambulatory measurements is investigated. To the authors' knowledge, this marks the first study involving longitudinal objective real-world data collected at non-clinical settings.

# 2 Materials and methods

## 2.1 Telemonitoring system

The PDMonitor® ecosystem, manufactured by PD Neurotechnology Ltd., is a class IIa medical device for continuous home monitoring of Parkinson's disease patients. It comprises a base (or SmartBox), monitoring devices, mounting accessories, a mobile app, a physician online dashboard, and a cloud service provide an environment for long-term remote PD monitoring. The system includes five wearable sensing devices with motion sensors and accessories for attachment to particular body regions, as well as a SmartBox for collecting and uploading data. For a more in-depth exploration of the ecosystem, the interested reader is directed to (12).

To measure everyday activities and device reported outcomes (DROs) associated with PD, the system uses digital signal processing and machine learning to assess raw movement signals. The system automatically detects waist and limb device positioning throughout waking hours. System output includes heatmaps of symptom severity for a 30-min interval and plots of average symptom intensity for any time of day. The DROs include the percentage of time in "OFF" state (OFF), the percentage of time with dyskinesia (DYS), and the percentage of time in "ON" state (ON), that is defined as 100-OFF-DYS. Moreover, the system provides DROs associated with the unified Parkinson's disease rating scale (UPDRS). As it was suggested by NICE in 2023 (13), the system presents a novel way to remote PD monitoring, giving useful information associated with the antiparkinsonian therapy.

TABLE 1 Demographic data of the participants[a].

| | |
|---|---|
| Sex | 10 females, seven males |
| Age | 64.3 (10.4) years |
| Years with disease | 8.9 (6.6) years |
| LEDD (baseline) | 799.6 (451.2) mg |
| LEDD (2-years) | 1,055.2 (453.8) mg |

LEDD, L-dopa equivalent daily dose. [a]Total values are presented as "mean (standard deviation)".

## 2.2 Dataset

A cohort of 20 patients who utilized the telemonitoring device in Greece for 2 years formed the basis of this study. These individuals worn the wearable sensors over multiple days, allowing averaged symptom data extraction. To guarantee the inclusion of high-quality data, DROs corresponding to single-day recordings were excluded, leading to the final cohort comprising 17 subjects. The demographic data of the participants are provided in Table 1. Consistent with applicable privacy laws across the world, no identifiable protected health information (PHI) was extracted, accessed, or used during the course of the study. Pursuant to the USA Health Insurance Portability and Accountability Act (HIPAA) of 1996 with updated provisions (14), the EU General Data Protection Regulation (GDPDR) of 2018 (15), our study used de-identified or anonymous data and therefore does not require institutional review board (IRB) approval or waiver of authorization. Physicians incorporated DROs into their daily practices, relying on this tool to make informed decisions about medication adjustments. Notably, patients with advanced therapies such as Deep Brain Stimulation (DBS) and infusion pumps were excluded from this specific analysis on medication management.

## 2.3 Statistical analysis

In this study evaluating the progression of motor core symptoms in PD, a paired *t*-test was employed to assess changes between baseline (0 months) and the end of the study (24 months) for each participant individually. This analysis focused on within-subject differences, providing insights into the efficacy of the intervention over the study period. Additionally, a linear mixed-effects model was employed to analyze the longitudinal data, incorporating random slopes and random intercepts to account for variations among subjects. The model allowed for the examination of individual trajectories over time while considering both fixed effects, such as time points, and random effects, capturing subject-specific deviations from the overall trend. This comprehensive statistical approach facilitated the exploration of both within-subject changes and inter-subject variability, providing a robust analysis of the impact of the intervention on motor core PD symptoms over the 24-month study duration. In this study, the significance threshold was set to $p < 0.05$.

Questionnaires, employing Likert scales and qualitative inquiries, were also administered to provide valuable insights into the multifaceted clinical benefits of the telemonitoring approach, encompassing patient satisfaction, medication efficacy, patient-physician interactions, and the overall perceived advantages of remote monitoring in the management of PD. Questionnaires were administrated before, during, and after the use of telemonitoring system, allowing for multiple responses from each subject.

# 3 Results

Figure 1 illustrates the findings of the statistical analyses for various DROs. As depicted in Figure 1A, a statistically significant decrease in the percentage of OFF (−15.9, or −43.9%) was observed at the end of the study compared to baseline. The intra-subject differences between 0 months and 24 months indicate that telemonitoring contributes significantly to OFF improvement. While there is also a discernible ascending trend of ON outcome (Figure 1D), the statistical significance was not attained. This can be attributed both to the small sample size and the increase of dyskinesia in some patients (Figure 1G). No statistical differences were found for device-reported UPDRS, highlighting the stability of motor core symptoms (Figure 1J).

Results from linear mixed-effects models depict the influence of telemonitoring on the motor core PD symptoms throughout the 24-month study period. Among various DROs, the temporal factor exhibited a statistically significant effect on OFF (mean slope = −0.48, $p < 0.05$), as illustrated in Figure 1B. Although the effect of time was not significant concerning other DROs, subject-specific slopes suggest a notable increase in ON (Figure 1F), while UPDRS either decreased or remained relatively constant across the majority of the subjects (Figure 1L). Only a limited number of participants exhibited exacerbation in terms of dyskinesia (Figure 1I).

The findings underscore the utility of telemonitoring in comprehensively evaluating and understanding the dynamic changes in PD symptoms over an extended observational timeframe. Following a 24-month period utilizing the telemonitoring system, the majority of the subjects improved or exhibited consistent symptom manifestation, and a reduction in the number of patients lacking proper control of their motor symptoms was achieved. The considerable significance of time as a determinant in the progression of PD symptoms when employing the telemonitoring system in patients with PD undergoing traditional evaluation, proves the efficacy of the intervention.

Figure 2 depicts an example of OFF evolution for a patient. The patient, a 71-year-old female diagnosed with PD a decade ago and treated with levodopa and rotigotine patches for the last 5 years, had OFF phenomena lasting more than 3 h in the last months of 2020. At the beginning of 2021, the patient was recommended to use the telemonitoring system to evaluate symptom fluctuation during the day and the intensity and duration of wearing OFF phenomena. Adjustments in dosing intervals of levodopa (daily dose 475 mg) and dietary habits resulted in a reduction in reported OFF periods and an enhancement in ON periods after three months. These improvements were sustained for more than 6 months without increasing the daily dose. However, escalation in daytime OFF periods led to a decision by the physician to change the treatment regimen by increasing the daily dose from 475 mg of levodopa to 750 mg. The improvement was sustained for 9 months, after which deterioration in gait occurred again. As this was corroborated by the physician during the subsequent visit, further adjustments to the treatment regimen were implemented. Firstly, the discontinuation of the rotigotine patch was decided due to the observed onset of impulse control disorder. Additionally, guided by the insights provided by the DROs, the dosage of levodopa was increased from 750 to 1,250 mg. The efficacy of the treatment was reassessed in the subsequent months using the telemonitoring device, confirming that the patient's condition was adequately managed.

Table 2 presents the results from questionnaires regarding the satisfaction levels of patients. There is a notable increase in the percentage of satisfied patients, rising from 26.9 to 38.5%, regarding the effectiveness of the medication both before and after the utilization of telemonitoring, respectively. Furthermore, the proportion of very satisfied patients experienced a substantial surge, escalating from 7.7 to 23.1%. In contrast, the dissatisfied group exhibited a decline, decreasing from 46.2 to 34.6%. Moreover, upon analyzing the responses from patients concerning the perceived advantages of remote monitoring, a significant majority, constituting 81.5%, acknowledged the beneficial impact of telemonitoring (Table 3). Additionally, 44.4% of respondents reported an improvement in their condition attributable to telemonitoring, while 37.0% indicated that their condition remained unchanged (Table 4). Notably, a substantial proportion of participants (81.5%) conveyed that telemonitoring enhanced communication with their physicians (Table 5). Improved patient-physician interactions and enhanced perceived effectiveness of the medication underscore the positive impact of telemonitoring in the context of PD management.

# 4 Discussion

In this study, the control of motor symptoms in patients with PD was examined over a two-year observation period. The

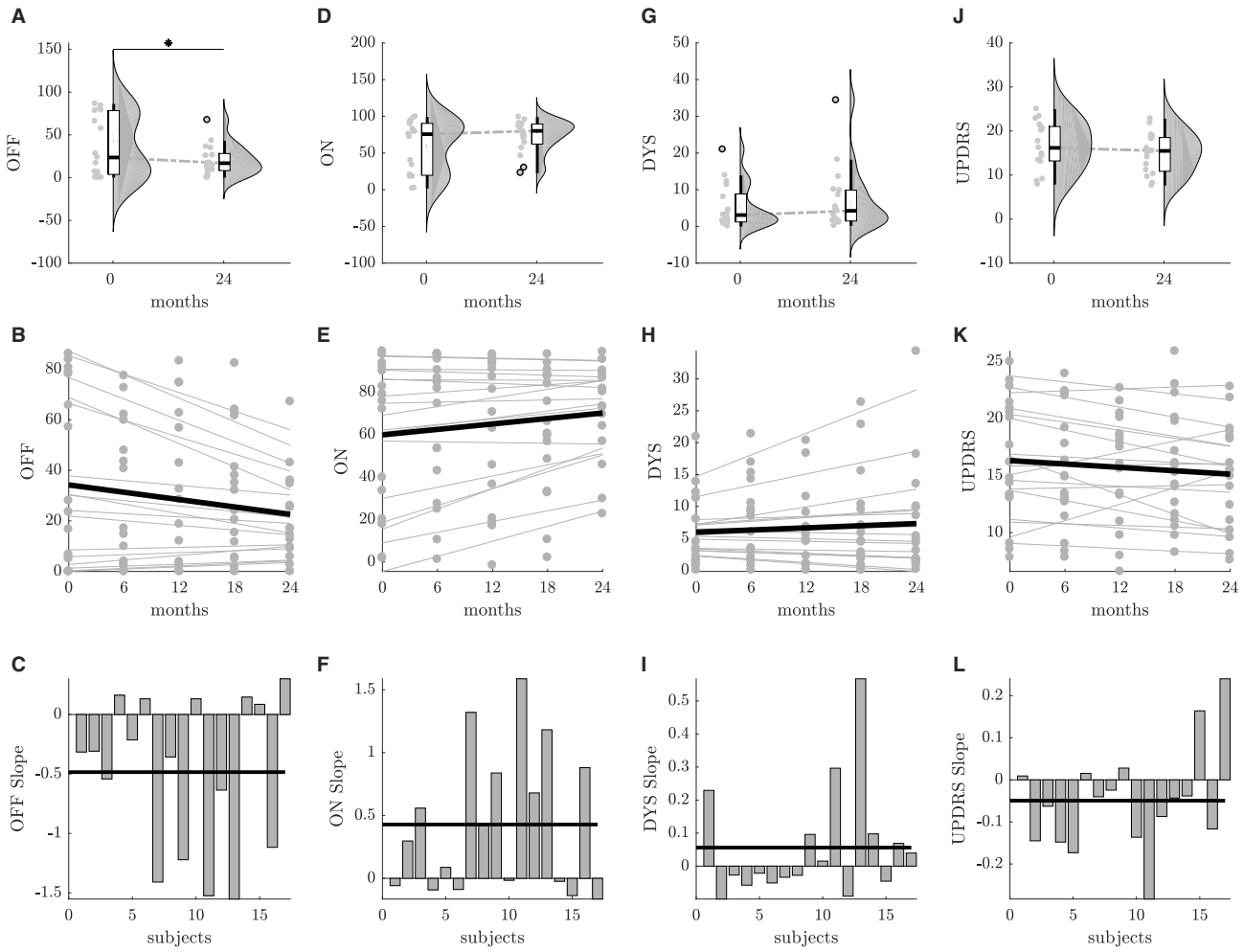


FIGURE 1
Findings from statistical analyses concerning different DROs. **(A–C)** OFF, **(D–F)** ON, **(G–I)** DYS, **(J–L)** UPDRS. The first row displays a combination of boxplots, scatter plots and violin plots for data collected at both 0 and 24 months. Statistically significant differences between groups are marked with an asterisk. The second row shows plots with individually fitted lines for longitudinal data. The average of these individual thick lines is represented by a heavy black line. The third row illustrates barplots with the slope values across all subjects. The mean slope is indicated with a heavy black line.

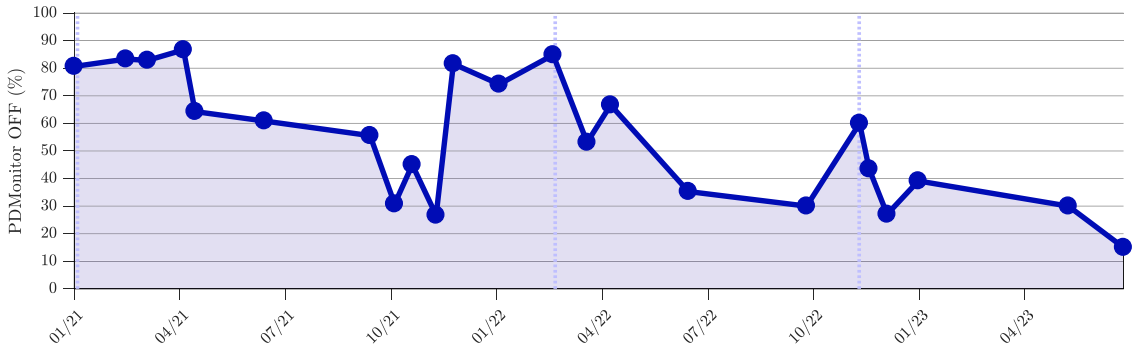


FIGURE 2
An example of device-reported OFF evolution for a patient. Vertical dashed lines indicate adjustments of treatment regimen.

investigation centered on patients who underwent traditional medical examination combined with a comprehensive analysis of objective ambulatory measurements collected at non-clinical settings. The impact of telemonitoring for continuous home monitoring on the management of PD was evaluated.

TABLE 2 Q1:"How satisfied are you with the effectiveness of your medication prior to using the PDMonitor®?" Q2:"How satisfied are you with the effectiveness of your medication after using the PDMonitor®?"

| Choices | Q1 (%) | Q2 (%) |
|---|---|---|
| Very satisfied | 7.7 | 23.1 |
| Satisfied | 26.9 | 38.5 |
| Neither | 46.2 | 34.6 |
| Dissatisfied | 15.4 | 3.8 |
| Very dissatisfied | 3.8 | 0 |
| Didn't answer | 0 | 0 |

TABLE 3 "To what degree do you agree that the use of PDMonitor® has helped you up to this point?"

| Choices | Answers (%) |
|---|---|
| Strongly agree | 59.3 |
| Agree | 22.2 |
| Undecided | 7.4 |
| Disagree | 11.1 |
| Strongly disagree | 0 |
| Didn't answer | 0 |

TABLE 4 "Since you started using PDMonitor®, do you consider that your condition has improved, worsened, or remained unchanged?"

| Choices | Answers (%) |
|---|---|
| Significantly improved | 11.1 |
| Improved | 33.3 |
| Remained unchanged | 37.0 |
| Worsened | 14.8 |
| Significantly worsened | 3.7 |
| Didn't answer | 0 |

TABLE 5 "To what degree do you agree that the use of PDMonitor® has improved the communication with your physician?"

| Choices | Answers (%) |
|---|---|
| Strongly agree | 63.0 |
| Agree | 18.5 |
| Undecided | 3.7 |
| Disagree | 14.8 |
| Strongly disagree | 0 |
| Didn't answer | 0 |

Real-world evidence of this new treatment paradigm showed a significant improvement in the percentage of OFF time over the 24-month study period (Figure 1A). The observed decrease in OFF, accompanied by a trend of increasing ON time (Figure 1E), suggests a positive influence of telemonitoring on motor symptom control. Increasing the number of patients with improved or stable symptom manifestation, as reflected by the absence of statistical differences and significant trends in device-reported UPDRS and DYS scores (Figures 1G, J), further emphasizes the reliability of the telemonitoring approach in PD management. Further investigations are warranted to explore limited exacerbation in dyskinesia and UPDRS, as indicated by only a subset of participants (Figures 1I, L). In cases where patients experience worsening symptoms, the referral to advanced therapies, such as DBS, should be considered (16).

The clinical significance of these findings is enhanced when considering that the motor function is usually worsened significantly with time in patients with PD. Previous studies suggest that annual rates of progression of the total UPDRS score range from 7.8 to 14 points, and of the UPDRS III (motor) score from 5.2 to 8.9 points (17, 18). Moreover, the worsening is faster during the first years of disease and the increase over time is independent of sex and age (19, 20). The late stages of Parkinson's disease are marked by a progressive decline in both physical and cognitive function, leading to a substantial reduction in quality of life for individuals affected by the condition (21) and placing significant strain on caregivers and healthcare systems (22, 23). Minimizing "OFF" time and maximizing "ON" time leads to an improved quality of life for patients, with optimum cognitive and mental health (24). Improved motor function and reduced motor fluctuations are the key considerations to be taken into account in PD treatment to minimize potential side effects such as postural abnormalities and freezing episodes, which are associated with an increased risk of falls (25, 26). Telemonitoring emerges as a valuable tool for healthcare professionals, facilitating the optimization of medication management and enabling timely adjustments to the treatment plan (27). When symptoms are effectively controlled, the necessity for follow-up consultations can be diminished, thereby achieving treatment waning (13).

The frequency of therapy adjustments and the subsequent increase in dopaminergic burden underscore a critical consideration in treatment approaches. In this study, the average change in treatment was minimal, resulting in an LEDD of 255.6 mg (from 799.6 to 1,055.2 mg) (Table 1). Although there are periods lasting up to several years in which pharmacological treatment could extremely efficiently control symptoms, the majority of PD patients will experience ineffective symptom management during disease course (28). For instance, the patient illustrated at Figure 2 shows improved symptoms control, which, however, was accompanied with an increased L-Dopa of about 800 mg during the 2 year follow-up period. This highlights that there is an ongoing challenge in maintaining optimal symptom control without increasing dopaminergic burden. While effective symptom management is a desirable outcome in PD management, healthcare practitioners should balance the therapeutic benefits of dopaminergic medications with the potential risks of increased burden and side effects (29). This emphasizes the importance of continually reassessing treatment strategies through the use of telemonitoring to address evolving patient needs and disease dynamics.

The findings of this study also demonstrated that telemonitoring not only aids in objective symptom assessment but also contributes to a positive subjective experience for

patients, potentially influencing adherence to treatment plans. It should be noted that the prevalence of significant medication non-compliance in PD is high and it is linked to reduced quality of life and heightened severity of both motor and non-motor complications (30, 31). Therefore, the reported improvement in the perceived medication effectiveness underscores the potential of telemonitoring in optimizing treatment strategies by improving treatment adherence and satisfaction of patients about their disease status (Table 2). The questionnaire-based assessment of patient satisfaction revealed a notable increase in the percentage of satisfied and very satisfied patients following telemonitoring (Tables 3, 4). Perceived advantages of remote monitoring, as reported by a significant majority of participants, also include improved communication with physicians (Table 5), highlighting an improved, patient-centered approach to care. In accordance with findings in the literature, considerable interest of employing telemonitoring is observed for patients as well as healthcare professionals, with noteworthy levels of satisfaction reported by both parties (32). The quality of care administered to PD patients through telemedicine is deemed comparable to that of in-person care, albeit a preference for a hybrid approach combining telemonitoring and in-person visits has been expressed by patients (33).

Despite the promising findings, this study has several limitations. The small sample size may limit the generalizability of the results, and further research with larger cohorts is warranted to validate the observed trends. Additionally, the exclusion of patients with advanced therapies such as DBS and infusion pumps may limit the applicability of the findings to this specific subgroup. Future studies, considering factors such as device adherence, should explore the long-term sustainability of telemonitoring benefits. This study relied on device-reported outcomes to assess symptoms, which does not allow a direct comparison with previous studies that used standard clinical scales (e.g., UPDRS). Future research comparing telemonitoring with traditional in-person care approaches and assessing the cost-effectiveness of telemonitoring interventions would provide additional insights into its broader implications. Additional studies are required to quantify the net effect of telemonitoring on symptoms control. Controlled longitudinal evaluation for longer observation period could assess whether a different symptoms trajectory exists between patients undergoing traditional practice and people undergoing telemonitoring.

In conclusion, implementing telemonitoring could lead to more efficient use of healthcare resources. By reducing the need for frequent in-person visits, clinicians can allocate their time more effectively, focusing on patients who require immediate attention while remotely monitoring others. The study indicates that this paradigm shift in PD improved patient satisfaction with their treatment and communication with healthcare providers. This enhanced engagement can lead to better adherence to treatment plans and more active participation in managing the disease, ultimately improving outcomes. Additionally telemonitoring facilitates better disease management and potentially reduces the frequency and severity of symptom exacerbations, which in turn can alleviate the burden on caregivers. Consequently, this may result in an improved quality of life for both patients and their families.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the datasets generated for this study are available on request to the corresponding author. Requests to access these datasets should be directed to g.rigas@pdneurotechnology.com.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

SKoni: Writing – original draft, Writing – review & editing, Methodology, Conceptualization, Investigation, Supervision. AA: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. PZ: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. CS: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. GT: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. GX: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. KT: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. NK: Formal analysis, Software, Visualization, Investigation, Methodology, Writing – original draft, Writing – review & editing, Data curation. FK: Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. AN: Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. SKont: Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing, Validation. GR: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

NK, FK, AN, Skont, and GR were employed by PD Neurotechnology Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Publisher's note



## References

1. Hayes MT. Parkinson's disease and parkinsonism. *Am J Med*. (2019) 132:802–7. doi: 10.1016/j.amjmed.2019.03.001

2. World Health Organization. *Parkinson's Disease*. WHO (2023) Available online at: https://www.who.int/news-room/fact-sheets/detail/parkinson-disease (accessed April 10, 2024).

3. Monje MH, Foffani G, Obeso J, Sánchez-Ferro Á. New sensor and wearable technologies to aid in the diagnosis and treatment monitoring of Parkinson's disease. *Annu Rev Biomed Eng*. (2019) 21:111–43. doi: 10.1146/annurev-bioeng-062117-121036

4. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA*. (2020) 323:548–60. doi: 10.1001/jama.2019.22360

5. Maetzler W, Klucken J, Horne M. A clinical view on the development of technology-based tools in managing Parkinson's disease. *Mov Disord*. (2016) 31:1263–71. doi: 10.1002/mds.26673

6. Papapetropoulos S. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Ther*. (2012) 18:380–7. doi: 10.1111/j.1755-5949.2011.00253.x

7. Lee TK, Yankee EL. A review on Parkinson's disease treatment. *Neuroimmunol Neuroinflamm*. (2021) 8:222–44. doi: 10.20517/2347-8659.2020.58

8. Váradi C. Clinical features of Parkinson's disease: the evolution of critical symptoms. *Biology*. (2020) 9:103. doi: 10.3390/biology9050103

9. Ossig C, Antonini A, Buhmann C, Classen J, Csoti I, Falkenburger B, et al. Wearable sensor-based objective assessment of motor symptoms in Parkinson's disease. *J Neural Transm*. (2016) 123:57–64. doi: 10.1007/s00702-015-1439-8

10. Ryu S. History of telemedicine: evolution, context, and transformation. *Healthc Inform Res*. (2010) 16:65–6. doi: 10.4258/hir.2010.16.1.65

11. Tsamis KI, Odin P, Antonini A, Reichmann H, Konitsiotis S. A paradigm shift in the management of patients with Parkinson's disease. *Neurodegener Dis*. (2023) 23:13–9. doi: 10.1159/000533798

12. Antonini A, Reichmann H, Gentile G, Garon M, Tedesco C, Frank A, et al. Toward objective monitoring of Parkinson's disease motor symptoms using a wearable device: wearability and performance evaluation of PDMonitor®. *Front Neurol*. (2023) 14:1080752. doi: 10.3389/fneur.2023.1080752

13. National Institute for Health and Care Excellence. *Devices for Remote Continuous Monitoring of People With Parkinson's Disease (NICE Guideline DG51)*. (2023) Available online at: https://www.nice.org.uk/guidance/dg51/ (accessed April 10, 2024).

14. Centers for Medicare and Medicaid Services. *CFR-Title 45-Chapter A-Subchapter C-Part 164-Subpart E-Section 164.*502, *Subsection (d) Standard Uses and Disclosures of De-identified Protected Health Information*. 45 *CFR 164.*502(*d), and 164.*514(a)-(c) (2002). Available online at: https://www.law.cornell.edu/cfr/text/45/164.502 (accessed May 16, 2024).

15. European Union. *EU General Data Protection Regulation. Recital 26*. (2018). Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN (accessed May 16, 2024).

16. National Institute for Health and Care Excellence. *Parkinson's Disease in Adults (NICE Guideline NG71)*. (2017). Available online at: https://eur-lex.europa.eu/eli/reg/2016/679/oj

17. Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Progression of motor impairment and disability in Parkinson disease: a population-based study. *Neurology*. (2005) 65:1436–41. doi: 10.1212/01.wnl.0000183359.50822.f2

18. Maetzler W, Liepelt I, Berg D. Progression of Parkinson's disease in the clinical phase: potential markers. *Lancet Neurol*. (2009) 8:1158–71. doi: 10.1016/S1474-4422(09)70291-1

19. Holden SK, Finseth T, Sillau SH, Berman BD. Progression of MDS-UPDRS scores over five years in de novo Parkinson disease from the Parkinson's progression markers initiative cohort. *Mov Disord Clin Pract*. (2018) 5:47–53. doi: 10.1002/mdc3.12553

20. Poonja S, Miyasaki J, Fu X, Camicioli R, Sang T, Yuan Y, et al. The trajectory of motor deterioration to death in Parkinson's disease. *Front Neurol*. (2021) 12:670567. doi: 10.3389/fneur.2021.670567

21. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers*. (2021) 7:1–21. doi: 10.1038/s41572-021-00280-3

22. Schrag A, Hommel A, Lorenzl S, Meissner W, Odin P, Coelho M, et al. The late stage of Parkinson's-results of a large multinational study on motor and non-motor complications. *Parkinsonism Relat Disord*. (2020) 75:91–6. doi: 10.1016/j.parkreldis.2020.05.016

23. Martinez-Martin P, Skorvanek M, Henriksen T, Lindvall S, Domingos J, Alobaidi A, et al. Impact of advanced Parkinson's disease on caregivers: an international real-world study. *J Neurol*. (2023) 270:2162–73. doi: 10.1007/s00415-022-11546-5

24. Santos García D, de Deus Fonticoba T, Cores C, Muñoz G, Paz González JM, Martínez Miró C, et al. Predictors of clinically significant quality of life impairment in Parkinson's disease. *NPJ Parkinsons Dis*. (2021) 7:118. doi: 10.1038/s41531-021-00256-w

25. Thanvi B, Lo T. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J*. (2004) 80:452–8. doi: 10.1136/pgmj.2003.013912

26. Okuma Y. Freezing of gait and falls in Parkinson's disease. *J Parkinsons Dis*. (2014) 4:255–60. doi: 10.3233/JPD-130282

27. Cubo E, Delgado-López PD. Telemedicine in the management of Parkinson's disease: achievements, challenges, and future perspectives. *Brain Sci*. (2022) 12:1735. doi: 10.3390/brainsci12121735

28. Alonso-Canovas A, Voeten J, Gifford L, Thomas O, Lees AJ, Bloem BR. The early treatment phase in Parkinson's disease: not a honeymoon for all, not a honeymoon at all? *J. Parkinsons Dis*. (2023) 13:323–8. doi: 10.3233/JPD-225064

29. Zahoor I, Shafi A, Haq E. Pharmacological treatment of Parkinson's disease. *Exon Publ*. (2018) 129–144. doi: 10.15586/codonpublications.parkinsonsdisease.2018.ch7

30. Malek N, Grosset DG. Medication adherence in patients with Parkinson's disease. *CNS Drugs*. (2015) 29:47–53. doi: 10.1007/s40263-014-0220-0

31. Straka I, Minár M, Škorvánek M, Grofik M, Danterová K, Benetin J, et al. Adherence to pharmacotherapy in patients with Parkinson's disease taking three and more daily doses of medication. *Front Neurol*. (2019) 10:799. doi: 10.3389/fneur.2019.00799

32. Eisenberg JL, Hou JG, Barbour PJ. Current perspectives on the role of telemedicine in the management of Parkinson's disease. *Smart Homecare Technol TeleHealth*. (2018) 1–12. doi: 10.2147/SHTT.S152018

33. Qiang JK, Marras C. Telemedicine in Parkinson's disease: a patient perspective at a tertiary care centre. *Parkinsonism Relat Disord*. (2015) 21:525–8. doi: 10.1016/j.parkreldis.2015.02.018

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# Gait analysis in the early stage of Parkinson's disease with a machine learning approach

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**Background:** Gait disorder is a prominent motor symptom in Parkinson's disease (PD), objective and quantitative assessment of gait is essential for diagnosing and treating PD, particularly in its early stage.

**Methods:** This study utilized a non-contact gait assessment system to investigate gait characteristics between individuals with PD and healthy controls, with a focus on early-stage PD. Additionally, we trained two machine learning models to differentiate early-stage PD patients from controls and to predict MDS-UPDRS III score.

**Results:** Early-stage PD patients demonstrated reduced stride length, decreased gait speed, slower stride and swing speeds, extended turning time, and reduced cadence compared to controls. Our model, after an integrated analysis of gait parameters, accurately identified early-stage PD patients. Moreover, the model indicated that gait parameters could predict the MDS-UPDRS III score using a machine learning regression approach.

**Conclusion:** The non-contact gait assessment system facilitates the objective and quantitative evaluation of gait disorder in PD patients, effectively distinguishing those in the early stage from healthy individuals. The system holds significant potential for the early detection of PD. It also harnesses gait parameters for a reasoned prediction of the MDS-UPDRS III score, thereby quantifying disease severity. Overall, gait assessment is a valuable method for the early identification and ongoing monitoring of PD.

KEYWORDS

**Parkinson's disease, gait analysis, early-stage diagnosis, MDS-UPDRS III score, non-contact assessment, machine learning**

## 1 Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases, affecting approximately 1% of the population over 60 years of age (1). The typical motor symptoms of PD include resting tremor, bradykinesia, rigidity, postural and gait disorders. Among these, gait disorder is one of the principal symptoms in PD patients. Patients exhibit characteristic gait patterns such as reduced turning agility, short and slow steps, festinating, and freezing of gait (2, 3). Given the strong correlation between gait disorders and diminished quality of life, precise gait assessment is vital (4, 5). However, it is challenging for neurologists to assess gait

in the early stage of PD (6). Early gait disorders are very subtle, and some patients even exhibit motor symptoms without conscious gait complaints (7); Additionally, the presence of short and slow steps is a common trait in the aging population (8, 9), complicating the differentiation of PD-induced gait changes from age-related alterations. Consequently, precise identification and surveillance of gait anomalies are essential for the effective treatment and prognosis of PD, particularly in its early stage.

Currently, the clinical assessments of gait in PD patients rely on traditional scales, such as the Section III of the modified movement disorder society version of the unified Parkinson's disease rating scale (MDS-UPDRS III), the Timed-Up and Go test, and the Freezing of Gait Questionnaire, and so on (10). However, these scales depend on the subjective assessments of clinical physicians and have the limitations of being semi-quantitative, time-consuming, and potentially leading to inconsistent and imprecise results. In recent years, along with the rapid advancement of science and technology, a variety of objective and quantitative gait assessment techniques have gradually matured, propelling PD gait research into a new stage (11), such as multi-camera motion capture systems, wearable sensors, and pressure-sensitive insoles. However, the existing methods also have various shortcomings. For instance, multi-camera motion capture systems offer the highest capture accuracy and are considered as the golden standard in clinical gait analysis (11), yet they are costly and demand a large space, making them difficult to popularize currently. Wearable sensors, while portable, still face several challenges, such as discomfort during wear, data synchronization, and noise contamination. In summary, although new technologies show great potential in gait assessment in PD, they still need further improvement and optimization in terms of popularization and clinical application (12). In order to provide more refined and convenient gait monitoring methods for PD patients, future research should focus on enhancing the universality of the technology, reducing costs, improving user experience, and maintaining the accuracy and reliability of the data in the same time.

Based on the current challenges faced by PD gait assessments, we have utilized a non-contact gait assessment system (ReadyGo, Beijing CAS-Ruiyi Information Technology Co., Ltd.) (13), in order to overcome the limitations of traditional evaluation methods. With its non-invasive characteristic, real-time data collection capability, cost-effectiveness, and unique ability to capture rich 3D skeletal information, ReadyGo has quickly became an ideal choice for gait assessment in both clinical and scientific research. Through implicit monitoring, this technology not only reduced the discomfort of patients but also captured the most authentic gait data in a natural state, providing a solid foundation for precision medicine and personalized treatment.

Despite the increasing number of objective and quantitative assessments of gait disorder in PD patients in recent years, there is a relative lack of research focusing on the gait characteristics in the early stage of the disease. Our study aimed to deep explore the gait disorder characteristics of PD patients, especially those in the early stage, and to explore whether gait assessment can effectively identify differences between early-stage PD patients and healthy elderly individuals.

By conducting a detailed comparative analysis of gait parameters between early-stage PD patients and healthy controls (HC), we hoped to reveal the unique gait patterns of early-stage PD patients. This would not only help improve the accuracy and timeliness of early diagnosis but also provide key information for predicting PD progression and optimizing intervention strategies. Our research was expected to bring advancements to the early diagnosis and management of PD, especially in the aspects of identification and monitoring of gait disorder, opening up new methods for improving the quality of life for patients.

# 2 Materials and methods

## 2.1 Participants

In this study, 63 patients with primary PD were encompassed, with 27 being male and 36 being female. The inclusion criteria were as follows: (1) Meeting the 2015 Movement Disorder Society (MDS) diagnostic criteria for primary PD (14); (2) Hoehn and Yahr (H&Y) stages between stage 1 and 3; (3) The Mini-Mental State Examination (MMSE) score of 24 or above. Additionally, 65 gender- and age-matched healthy participants were selected as the healthy control group, including 35 males and 30 females. The ages of participants ranged from 46 to 85 years old, and all of them were able to complete the tests without any assistance from others. Exclusion criteria included: (1) Atypical Parkinsonism; (2) Severe systemic diseases (such as musculoskeletal, cardiovascular, cerebrovascular and respiratory) and other neurological diseases; (3) Uncorrected visual impairments, or diseases that could alter gait patterns. This study was approved by the Ethics Committee of Central Hospital of Dalian University of Technology (Reference No. YN2022-039-57). Each participant signed the informed consent before participating in this study. The study was performed according to the guidelines of the declaration of Helsinki.

## 2.2 Clinical assessment

Demographic information was collected, including age, gender, height (cm), weight (kg), and disease duration. All patients were assessed by two experienced neurologists in movement disorders. The severity of the disease were evaluated using the H&Y staging scale (15) which score ranged from 0 (no symptoms) to 5 (wheelchair bound or bedridden unless aided) and the MDS-UPDRS III (16) which consisted of 33 items with a score ranged from 0 (no symptoms) to 132 (severe motor symptoms). Cognitive was evaluated using the MMSE which score ranged from 0 to 30, with higher score indicating better cognitive function (17).

## 2.3 Gait assessment

Gait parameters were assessed using ReadyGo. Unlike the traditional multi-camera system, ReadyGo system innovatively utilizes a set of integrated cameras, including one RGB (red/green/blue) camera and a single depth camera, to capture and analyze three-dimensional (3D) motion data. The main advantage of this system lies in its unique skeletal tracking technology, which uses deep learning algorithms for precise positioning of skeletal points without requiring participants to wear any additional sensors, greatly enhancing the experience of the participants and the convenience of data collection

(Figure 1). By meticulously analyzing the gait of PD patients, the system can automatically extract and quantify up to 19 key gait parameters, covering many aspects of the gait cycle, including gait speed, cadence, stride length, swing and stance phases, and so on, providing numerous details for a comprehensive understanding of gait disorder in PD patients. The accuracy and sensitivity of the ReadyGo system have been validated in previous studies (13), showing high reliability in capturing key gait parameters such as stride length and gait speed.

## 2.4 Procedure

1 Scale assessment: MDS-UPDRS III and H&Y staging scale were performed by two experienced neurologists in movement disorders, and then gait assessment was carried out. PD patients underwent all of the above, and healthy controls only underwent gait assessment but without clinical scale assessments.
2 Gait assessment: the gait assessment device was placed in the equipment placement area which was 1.5 meters away from the endline. Participants stood at the starting line which was 4.5 meters directly in front of the device. During the test, participants were asked to walk at their self-selected comfortable pace without using any assistant device, start from the starting line, walk to the end line, turn around, and return to the starting line, repeat this process three times before ending the recording (Figure 2). Each participant should undergo a practice trial before the test to ensure that they understood the instructions clearly.

The gait data was achieved through a non-contact method, 19 gait parameters were extracted based on the images of gait and depth information, including stride length (left, right), step height (left, right), step width, gait speed, stride speed (left, right), swing speed (left, right), turning time, cadence (left, right), swing phase (left, right), stance phase (left, right), double support phase (left, right). The specific definitions were shown in Table 1 and the gait cycle was shown in Figure 3.

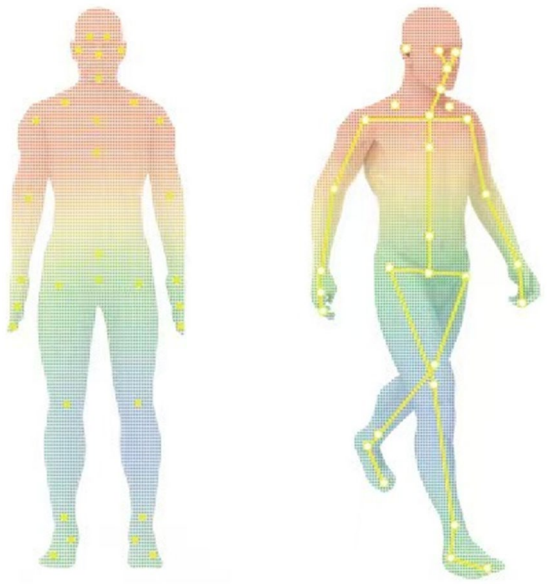

FIGURE 1
Human skeletal point tracking and motion recognition (the yellow markers indicate the key skeletal points tracked by the ReadyGo system).

## 2.5 Modeling

In this study, we defined patients in the H&Y 1 and 2 as early-stage PD and constructed a classification model using gait parameters of early-stage PD and healthy controls. The classification model was constructed to distinguish early-stage PD from healthy controls using gait parameters. Ten gait parameters with a statistical significance level of $p < 0.001$ were selected as input features. The dataset was split into a training set (70%) and a test set (30%) to evaluate the model's performance. We utilized the LightGBM algorithm to build the classifier. The model was trained and validated using the training set, and its predictive performance was evaluated on the test set.

The Receiver Operating Characteristic (ROC) curve was performed as an important tool to evaluate the performance of the model, exploring whether gait parameters can identify early-stage PD from healthy controls. The ROC curve showed the relationship between the true positive rate (sensitivity) and the false positive rate (1-specificity), visually presented the classification capability of the model at different thresholds. In this study, we paid particular attention to the Area Under the Curve (AUC) of the ROC, the closer the value is to 1, indicated the better classification performance of the model, i.e., the stronger ability of gait parameters to identify early-stage PD.

By comprehensively analyzing the ROC curve and AUC value of the model, we hoped to validate the feasibility of gait parameters as early diagnostic biomarkers for PD, to provide a new perspective and basis for the early detection, intervention, and management of PD. This research would also lay a theoretical foundation for the subsequent development of more precise and personalized early screening tools for PD, promoting continuous advancement in clinical practice.

In the process of deepening our research, we adopted a more refined analytical strategy, using the Random Forest algorithm to train a machine learning regression model, which used all the 19 gait parameters as input features and MDS-UPDRS III score as output labels. This methodological shift aimed to explore how gait parameters quantitatively correlate with the severity of PD. By training a Random Forest regression model, we could predict the MDS-UPDRS III score of PD patients. To evaluate the performance of the model, we utilized the Leave-One-Out Cross Validation (LOOCV) method. In LOOCV, each instance of the dataset is used once as a test set while the remaining instances form the training set. This iterative process ensures that every data point is used for both training and validation, providing a robust assessment of the model's generalization capability and predictive accuracy.

We could comprehensively evaluate the performance of the regression model by using these metrics: R-squared ($R^2$), Mean Absolute Error (MAE), Mean Absolute Percentage Error (MAPE). $R^2$ measured how well the model fitted the data, ranging from 0 to 1, the closer the value was to 1, indicated a better fit of the model. MAE

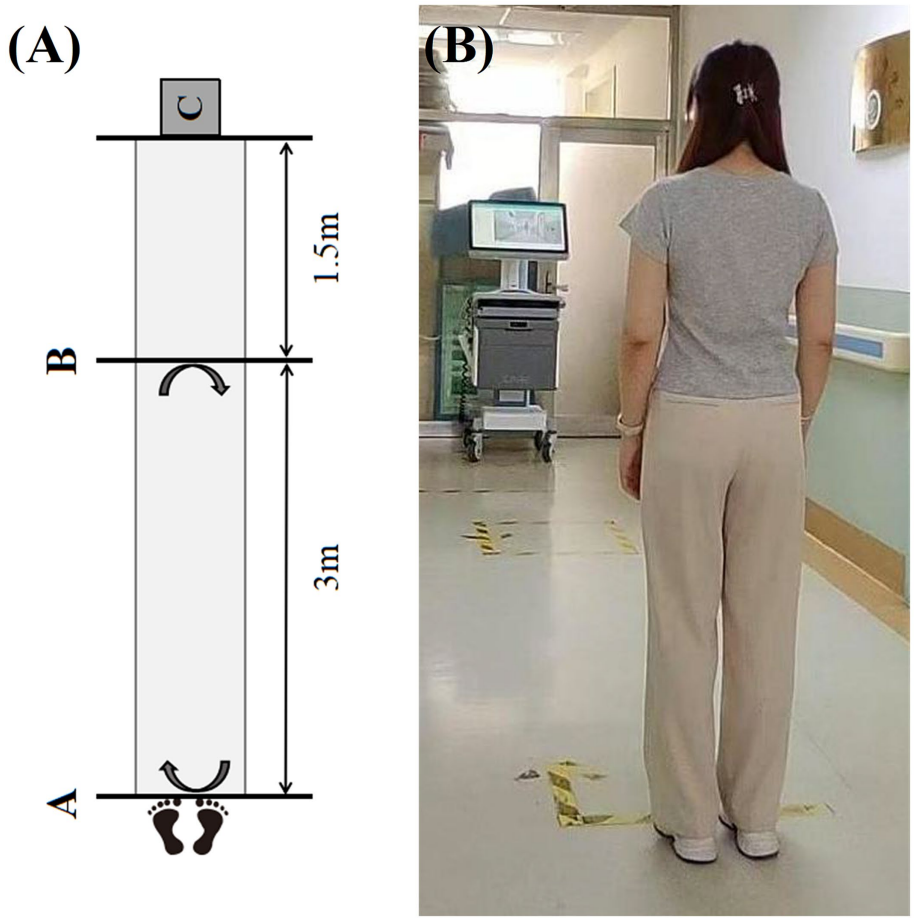


FIGURE 2
The procedure of gait assessment. **(A)** The schematic diagram of gait assessment (Line A is the starting line which is the departure point for the gait assessment; Line B is the end line which is the turning point for the gait assessment; C represents the area where the gait assessment device is placed). **(B)** The photograph of the actual procedure of gait assessment.

quantified the average absolute difference between the predicted value and true value, the smaller value suggested higher predictive accuracy of the model. MAPE was the average absolute percentage error expressed as a percentage, which was better for assessing the relative error between predicted value and true value, which was often used to understand the prediction accuracy of a model over different ranges.

## 2.6 Statistical analysis

The statistical analysis in this study was analyzed using SPSS 26.0 (IBM Corp., Armonk, NY). Continuous variables with normal distribution were presented as mean ± standard deviation ($\overline{x} \pm s$), the comparisons between two groups were made using the Independent Samples *t*-Test, the comparisons among multiple groups with homogeneous variances were made using one-way ANOVA followed by Bonferroni post-hoc test, the comparisons among multiple groups with non-homogeneous variances were made using the Welch test followed by Games-Howell (A) post-hoc test. Continuous variables with non-normal distribution were presented as median and interquartile distances [$M$ ($P_{25}$, $P_{75}$)], and comparisons between two groups were made using the Mann–Whitney $U$ test, while comparisons among multiple groups were made using the Kruskal-Wallis test followed by post-hoc test. Categorical variables were described by frequency, and group comparisons were made using the Pearson Chi-square test. The statistically significant difference was considered $p < 0.05$ in two-tailed tests. In this study, scikit-learn data analysis library of Python 3.8 was used to train and verify the classification and regression models. Meanwhile, drawing libraries such as matplotlib and seaborn were used to visually display the distribution characteristics of data and prediction effects of the models.

# 3 Results

## 3.1 Demographic and clinical characteristics

The demographic data between PD patients and the healthy controls were comparable (the first four lines in Table 2), there were no significant statistical differences in gender, age, height, and weight between the two groups ($p > 0.05$).

The disease duration of PD patients ranged from 1 to 10 years, the MMSE score ranged from 24 to 30 points, the median MDS-UPDRS

III score was 25.5 points, and H&Y stages ranged from 1 to 3, including 13 individuals in stage of H&Y 1, 38 individuals in stage of H&Y 2, and 12 individuals in stage of H&Y 3.

## 3.2 Comparison of gait parameters between PD patients and healthy controls

There were statistically significant differences in gait parameters between PD patients and healthy controls except for step width and right step height. The PD patients exhibited shorter stride length, slower gait speed, slower stride speed, slower swing speed, longer turning time, slower cadence, longer percentage of stance phase, shorter percentage of swing phase, and longer percentage of double support phase (Table 3). These results confirmed the "short and slow" gait characteristics of PD patients.

TABLE 1 Specific definitions of gait parameters in this study.

| Gait parameter | Definition |
|---|---|
| Stride length-L/R (m) | The distance between two landings of the left/right foot. |
| Step height-L/R (m) | The highest distance from the ground during the swing of the left/right foot. |
| Step width (m) | The average of the width of the left and right feet in each image frame. |
| Gait speed (m/s) | Average speed during straight travel (not including the turning time). |
| Stride speed-L/R (m/s) | Average speed during a left/right stride. |
| Swing speed-L/R (m/s) | Average speed during a left/right swing. |
| Turning time (s) | The time from turning start to turning end. |
| Cadence-L/R (steps/min) | Frequency of left/right footstep. |
| Swing phase-L/R (%) | Percentage of left/right swing phase time in the left/right stride time. |
| Stance phase-L/R (%) | Percentage of left/right stance phase time in the left/right stride time. |
| Double support-L/R (%) | Percentage of double support phase time in the left/right stride time. |

L, left; R, right.

## 3.3 Comparison of gait parameters among H&Y 1, H&Y 2, and H&Y 3

PD patients were divided into three groups according to the H&Y stages: H&Y 1, H&Y 2, and H&Y 3. We found that there were statistically significant differences in stride length, step height, gait speed, stride speed, swing speed, and percentage of double support phase among the three groups. Post-hoc test showed that these differences occurred between H&Y 1 and H&Y 3, and between H&Y 2 and H&Y 3, but there was no statistically significant difference when comparing H&Y 1 with H&Y 2. That was to say, compared with H&Y 1 and H&Y 2, H&Y 3 exhibited shorter stride length, lower step height, slower gait speed, slower stride speed, slower swing speed, and a longer percentage of time with both feet on the ground (Table 4; Figure 4).

## 3.4 Comparison of gait parameters between early-stage PD and healthy controls

From Table 4, we could find that there was no statistically significant difference in gait parameters between H&Y 1 and H&Y 2. Therefore, we defined H&Y 1 and H&Y 2 as early stage and compared them with the healthy controls. We found that early-stage PD patients had shorter stride length (left, right), slower gait speed, slower stride speed (left, right), slower swing speed (left, right), slower cadence (left, right), and longer turning time. This indicated that the gait parameters such as stride length, gait speed, stride speed, swing speed, turning time, and cadence were the first to be affected in the early stage of PD.

## 3.5 ROC analysis

From Table 5, we selected 10 gait parameters with a statistical significance level of $p < 0.001$ when comparing early-stage PD with healthy controls, including stride length (left, right), gait speed, stride speed (left, right), swing speed (left, right), turning time, and cadence (left, right). We performed ROC analysis on the combined gait parameters mentioned above, and evaluated the ability of gait

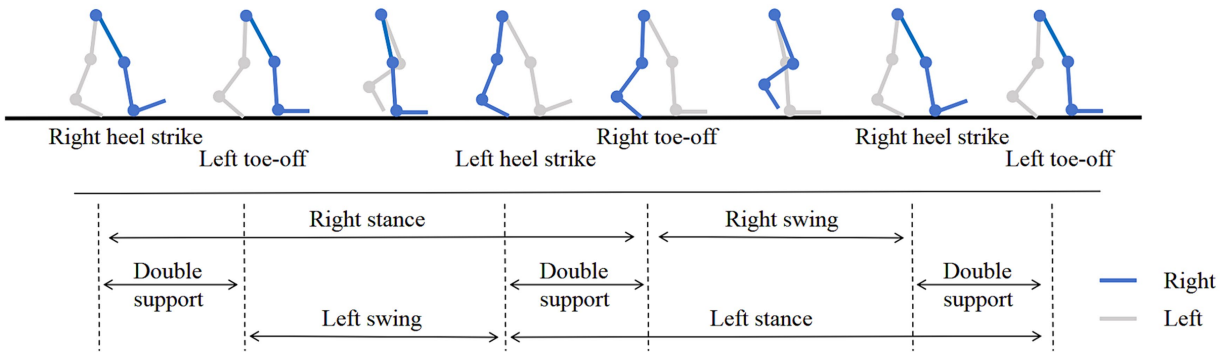


FIGURE 3
Gait cycle.

TABLE 2 Demographic and clinical characteristics.

| Variable | PD ($n$ = 63) | HC ($n$ = 65) | $p$ value |
|---|---|---|---|
| Gender (male/female) | 27/36 | 35/30 | 0.214 |
| Age (years) | 66.90 ± 8.43 | 67.40 ± 7.17 | 0.721 |
| Height (cm) | 165.10 ± 7.98 | 165.46 ± 7.96 | 0.795 |
| Weight (kg) | 67.83 ± 12.38 | 66.92 ± 11.37 | 0.665 |
| Disease duration (years) | 1–10 | NA | NA |
| MMSE (score) | 24–30 | NA | NA |
| H&Y stage | | NA | NA |
| 1 | 13 | | |
| 2 | 38 | | |
| 3 | 12 | | |
| MDS-UPDRS III (score)–overall | 25.50 (17.00, 39.00) | NA | NA |
| MDS-UPDRS III (score)–H&Y 1 | 13.15 ± 4.30 | NA | NA |
| MDS-UPDRS III (score)–H&Y 2 | 25.50 (21.00, 35.25) | NA | NA |
| MDS-UPDRS III (score)–H&Y 3 | 48.83 ± 11.89 | NA | NA |

PD, Parkinson's disease; HC, healthy controls; MMSE, Mini-Mental State Examination; H&Y, Hoehn and Yahr; MDS-UPDRS III, section III of the modified movement disorder society version of the unified Parkinson's disease rating scale; NA, not applicable.

TABLE 3 Comparison of gait parameters between PD patients and healthy controls.

| Gait parameter | PD ($n$ = 63) | HC ($n$ = 65) | $p$ value |
|---|---|---|---|
| Stride length-L (m) | 0.89 ± 0.23 | 1.10 ± 0.15 | < **0.001** |
| Stride length-R (m) | 0.89 ± 0.24 | 1.09 ± 0.15 | < **0.001** |
| Step height-L (m) | 0.10 ± 0.03 | 0.12 ± 0.02 | **0.004** |
| Step height-R (m) | 0.10 ± 0.03 | 0.10 (0.09, 0.12) | 0.127 |
| Step width (m) | 0.14 (0.12, 0.15) | 0.13 ± 0.02 | 0.091 |
| Gait speed (m/s) | 0.72 ± 0.23 | 1.10 (1.01, 1.21) | < **0.001** |
| Stride speed-L (m/s) | 0.80 ± 0.24 | 1.20 ± 0.21 | < **0.001** |
| Stride speed-R (m/s) | 0.80 ± 0.24 | 1.20 ± 0.22 | < **0.001** |
| Swing speed-L (m/s) | 1.93 ± 0.45 | 2.74 ± 0.36 | < **0.001** |
| Swing speed-R (m/s) | 1.94 ± 0.47 | 2.75 ± 0.41 | < **0.001** |
| Turning time (s) | 1.60 (1.21, 2.06) | 1.03 (0.89, 1.31) | < **0.001** |
| Cadence-L (steps/min) | 112.49 (100.00, 119.99) | 128.57 (120.00, 138.46) | < **0.001** |
| Cadence-R (steps/min) | 105.88 (100.00, 112.50) | 128.57 (120.00, 141.76) | < **0.001** |
| Swing phase-L (%) | 31.17 ± 3.17 | 32.39 ± 2.69 | **0.021** |
| Swing phase-R (%) | 31.09 ± 3.50 | 33.33 (31.43, 34.62) | < **0.001** |
| Stance phase-L (%) | 68.82 ± 3.17 | 67.61 ± 2.69 | **0.022** |
| Stance phase-R (%) | 68.90 ± 3.50 | 66.67 (65.39, 68.57) | < **0.001** |
| Double support-L (%) | 38.14 ± 6.34 | 34.62 (33.33, 36.85) | < **0.001** |
| Double support-R (%) | 37.43 ± 6.21 | 34.62 (33.33, 36.85) | **0.004** |

L, left; R, right. $p$ values in bold indicate statistical significance ($p < 0.05$).

parameters to distinguish early-stage PD from healthy controls. The accuracy was 91.43%, the sensitivity was 93.33%, the specificity was 90.0%, and the area under the curve (AUC) was 0.99, indicating that the gait parameters could correctly distinguish 91.43% early-stage PD from healthy controls. We further analyzed the feature contribution of the included 10 gait parameters, feature contribution was evaluated using the SHAP (SHapley Additive exPlanations) method, which quantifies each parameter's contribution to the model's predictions. The contribution degree was in the following order: cadence (right), gait speed, turning time, cadence (left), swing speed (right), stride length (left), stride speed (left), stride length (right), swing speed (left), and stride speed (right). Cadence, gait speed, and turning time had the greatest influence of the gait parameters for distinguishing between early-stage PD and the healthy controls, while stride length, stride speed, and swing speed had a secondary influence (Figure 5).

## 3.6 Predicting MDS-UPDRS III score

To explore whether gait parameters could predict MDS-UPDRS III score, we trained a machine learning regression model using all the 19 gait parameters as input features and MDS-UPDRS III score as the output label. The scatter plot indicated that the model had a strong explanatory power for MDS-UPDRS III score ($R^2 = 0.897$), with MAE of 4.015 and MAPE of 0.198 (Figure 6). The scatter plot showed the relationship between the predicted value and the true value of the regression model. It could be visually seen from the figure that the model performance for predicting MDS-UPDRS III score was good.

# 4 Discussion

Our study used a non-contact gait assessment system to assess and quantify gait parameters in patients with PD. Our findings confirmed that there were significant differences in gait parameters between PD patients and healthy controls. PD patients had slower gait speed and shorter stride length, which was consistent with the existing research. Gait is a very important motor function in daily life, gait disorder is closely associated with the quality of life (18). Therefore, early recognition and monitoring of gait is crucial for the diagnosis, treatment, and prognosis of PD patients. It is challenging to identify gait abnormalities in the early stage of PD, even to detect gait abnormalities without the complaint of gait disorder. Previous studies defined the early stage as H&Y stage below 2.5 (19, 20).

We divided PD patients into three groups according to H&Y stages and found that compared with H&Y 1–2, H&Y 3 had shorter stride length, lower step height, slower gait speed, slower stride speed, slower swing speed, and a longer percentage of time with both feet on the ground. But there was no statistically significant difference between H&Y 1 and H&Y 2. To explore gait abnormalities in the early stage of PD, we defined H&Y 1 and H&Y 2 as early stage, and compared them with healthy controls. We found that early-stage PD had shorter stride length, slower gait speed, slower stride speed, slower

TABLE 4 Comparison of gait parameters among H&Y 1, H&Y 2, and H&Y 3.

| Gait Parameter | H&Y stage | | | *p* value | | | |
|---|---|---|---|---|---|---|---|
| | H&Y 1 (*n* = 13) | H&Y 2 (*n* = 38) | H&Y 3 (*n* = 12) | Overall | 1 *vs* 2 | 1 *vs* 3 | 2 *vs* 3 |
| Stride length-L (m) | 1.03 ± 0.13 | 0.91 ± 0.22 | 0.66 ± 0.22 | **<0.001** | 0.060 | **<0.001** | **0.007** |
| Stride length-R (m) | 1.02 ± 0.17 | 0.91 ± 0.22 | 0.66 ± 0.23 | **<0.001** | 0.383 | **< 0.001** | **0.001** |
| Step height-L (m) | 0.11 ± 0.02 | 0.11 ± 0.03 | 0.07 ± 0.02 | **<0.001** | 1.000 | **0.001** | **0.001** |
| Step height-R (m) | 0.11 ± 0.03 | 0.11 ± 0.03 | 0.08 ± 0.02 | **0.025** | 1.000 | 0.068 | **0.029** |
| Step width (m) | 0.13 ± 0.02 | 0.13 ± 0.02 | 0.14 (0.13, 0.15) | 0.706 | - | - | - |
| Gait speed (m/s) | 0.82 ± 0.16 | 0.75 ± 0.21 | 0.54 ± 0.24 | **0.003** | 0.855 | **0.004** | **0.011** |
| Stride speed-L (m/s) | 0.92 ± 0.19 | 0.82 ± 0.22 | 0.60 ± 0.23 | **0.002** | 0.420 | **0.002** | **0.012** |
| Stride speed-R (m/s) | 0.90 ± 0.22 | 0.83 ± 0.22 | 0.61 ± 0.24 | **0.004** | 0.984 | **0.005** | **0.011** |
| Swing speed-L (m/s) | 2.07 ± 0.32 | 1.99 ± 0.44 | 1.56 ± 0.44 | **0.006** | 1.000 | **0.012** | **0.009** |
| Swing speed-R (m/s) | 2.15 ± 0.42 | 1.97 ± 0.47 | 1.61 ± 0.40 | **0.011** | 0.686 | **0.011** | **0.049** |
| Turning time (s) | 1.36 ± 0.39 | 1.68 (1.26, 2.17) | 1.95 ± 1.00 | 0.105 | - | - | - |
| Cadence-L (steps/min) | 107.28 ± 12.05 | 110.50 ± 13.05 | 114.74 ± 20.39 | 0.441 | - | - | - |
| Cadence-R (steps/min) | 106.83 ± 12.48 | 105.88 (99.34, 112.50) | 107.87 ± 16.93 | 0.948 | - | - | - |
| Swing phase-L (%) | 32.31 ± 4.29 | 31.29 ± 2.57 | 29.55 ± 3.12 | 0.156 | - | - | - |
| Swing phase-R (%) | 33.19 ± 3.93 | 31.34 (29.91, 33.85) | 28.51 ± 3.49 | **0.005** | 0.866 | **0.006** | **0.021** |
| Stance phase-L (%) | 67.68 ± 4.29 | 68.70 ± 2.57 | 70.45 ± 3.12 | 0.156 | - | - | - |
| Stance phase-R (%) | 66.80 ± 3.93 | 68.66 (66.14, 70.09) | 71.49 ± 3.49 | **0.005** | 0.866 | **0.006** | **0.021** |
| Double support-L (%) | 34.96 ± 8.35 | 36.78 (34.24, 40.81) | 43.10 ± 6.09 | **0.012** | 1.000 | **0.018** | **0.027** |
| Double support-R (%) | 34.91 ± 8.39 | 36.14 (33.33, 39.97) | 41.79 ± 5.76 | **0.014** | 1.000 | **0.018** | **0.037** |

L, left; R, right. *p* values in bold indicate statistical significance ($p < 0.05$).

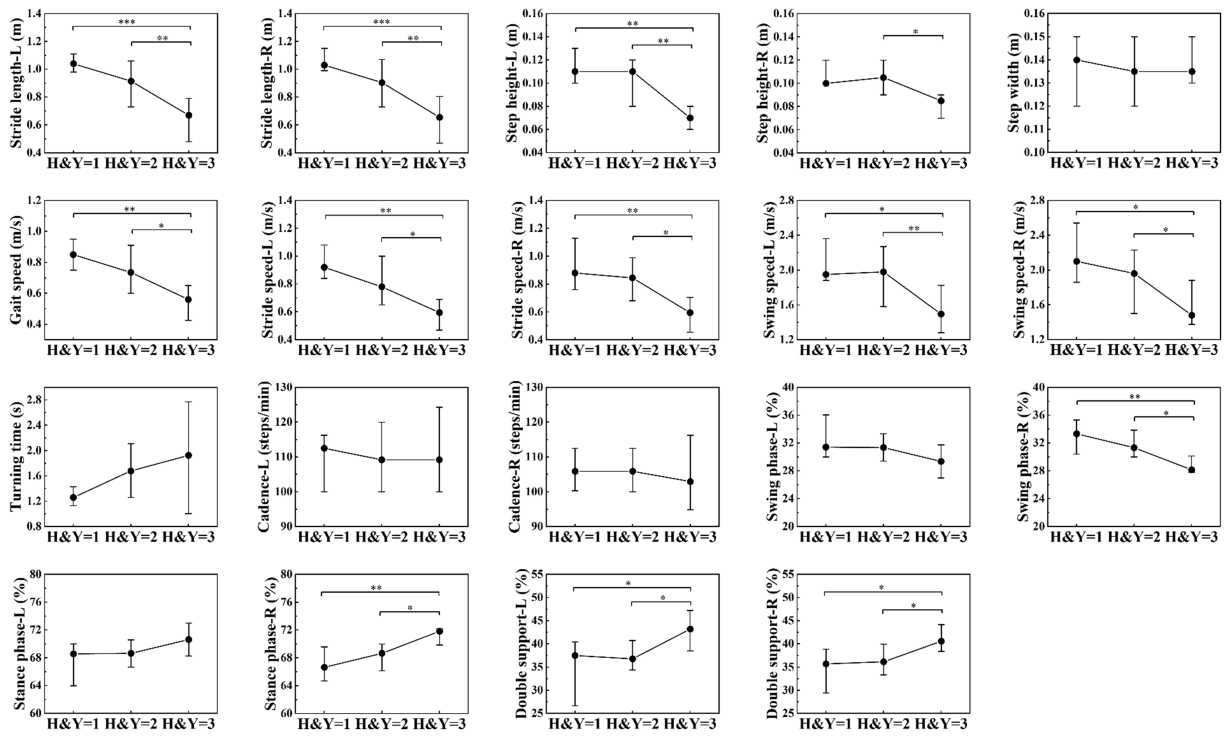


FIGURE 4
Comparison of gait parameters among H&Y 1, H&Y 2 and H&Y 3. The filled circles represent the median, lower and upper lines represent the 25th and 75th percentile, respectively. *represents $p < 0.05$, **represents $p < 0.01$, ***represents $p < 0.001$.

TABLE 5 Comparison of gait parameters between early-stage PD and healthy controls.

| Gait Parameter | Early-stage PD ($n$ = 51) | HC ($n$ = 65) | $p$ value |
|---|---|---|---|
| Stride length-L (m) | 0.94 ± 0.20 | 1.10 ± 0.15 | **< 0.001** |
| Stride length-R (m) | 0.94 ± 0.21 | 1.09 ± 0.15 | **< 0.001** |
| Step height-L (m) | 0.11 ± 0.03 | 0.12 ± 0.02 | 0.175 |
| Step height-R (m) | 0.11 ± 0.03 | 0.10 (0.09, 0.12) | 0.781 |
| Step width (m) | 0.13 ± 0.02 | 0.13 ± 0.02 | 0.156 |
| Gait speed (m/s) | 0.76 ± 0.20 | 1.10 (1.01, 1.21) | **< 0.001** |
| Stride speed-L (m/s) | 0.84 ± 0.22 | 1.20 ± 0.21 | **< 0.001** |
| Stride speed-R (m/s) | 0.85 ± 0.22 | 1.20 ± 0.22 | **< 0.001** |
| Swing speed-L (m/s) | 2.01 ± 0.41 | 2.74 ± 0.36 | **< 0.001** |
| Swing speed-R (m/s) | 2.02 ± 0.46 | 2.75 ± 0.41 | **< 0.001** |
| Turning time (s) | 1.56 (1.23, 2.05) | 1.03 (0.89, 1.31) | **< 0.001** |
| Cadence-L (steps/min) | 109.68 ± 12.77 | 128.57 (120.00, 138.46) | **< 0.001** |
| Cadence-R (steps/min) | 105.88 (100.00, 112.50) | 128.57 (120.00, 141.76) | **< 0.001** |
| Swing phase-L (%) | 31.55 ± 3.08 | 32.39 ± 2.69 | 0.123 |
| Swing phase-R (%) | 31.42 (30.00, 33.97) | 33.33 (31.43, 34.62) | **0.001** |
| Stance phase-L (%) | 68.44 ± 3.08 | 67.61 ± 2.69 | 0.127 |
| Stance phase-R (%) | 68.57 (66.02, 70.00) | 66.67 (65.39, 68.57) | **0.003** |
| Double support-L (%) | 36.97 ± 5.86 | 34.62 (33.33, 36.85) | **0.008** |
| Double support-R (%) | 36.41 ± 5.90 | 34.62 (33.33, 36.85) | 0.086 |

L, left; R, right. $p$ values in bold indicate statistical significance ($p < 0.05$).

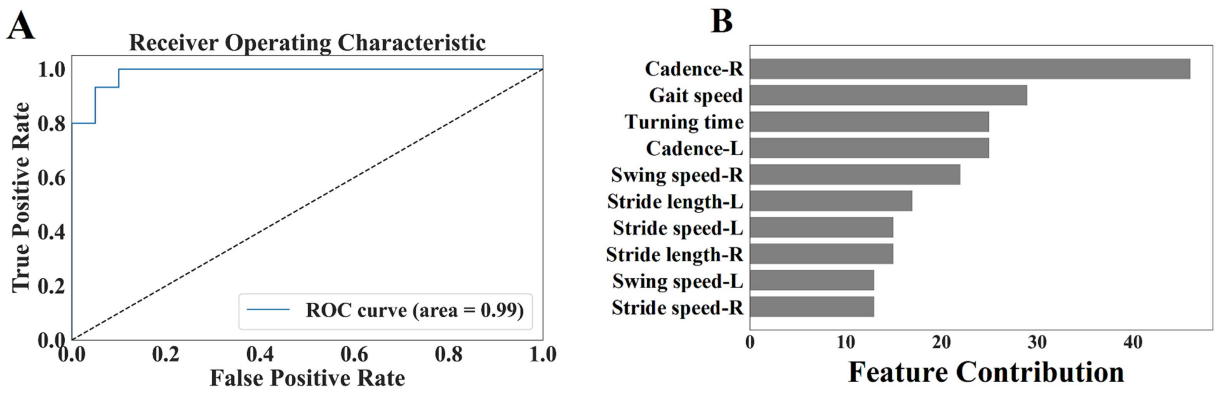


FIGURE 5
**(A)** Shows the ROC curve of the selected gait parameters in early-stage PD. **(B)** Shows the feature contribution of the selected gait parameters.

swing speed, slower turning time, and slower cadence. This indicated that in the early stage of PD, stride length, gait speed, stride speed, swing speed, turning time, and cadence were the first to be affected, suggested that they could be used to detect gait abnormalities in the early stage. In the progressive stage of the disease, step height, gait speed, stride speed, and swing speed decrease further, and the percentage of time with both feet on the ground was prolonged, indicated that these parameters could be used to monitor the progression of the disease.

We innovatively proposed an auxiliary diagnostic method based on fine-grained gait feature analysis, aimed to identify signs of PD in the early stage, we paid a particular attention to the potential value of gait parameters in the early diagnosis of PD. By using the machine learning model, we conducted an in-depth exploration of the selected ten gait parameters, including stride length (left, right), gait speed, stride speed (left, right), swing speed (left, right), turning time, and cadence (left, right). The results showed that these gait parameters could effectively distinguish early-stage PD from healthy controls. The model showed an encouraging classification performance, with an accuracy of up to 91%, the sensitivity of 93%, and the specificity also maintained at a high level of 90%. This strongly proved the practicality and reliability of the constructed model in the auxiliary diagnosis of early-stage PD.

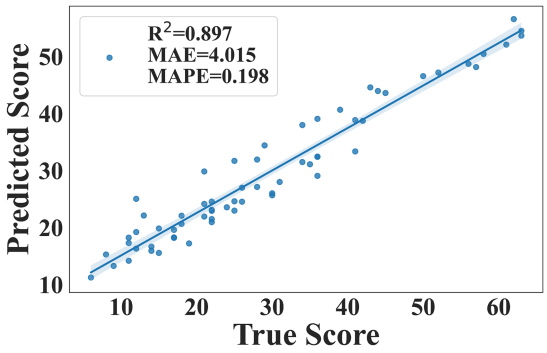


FIGURE 6
The scatter plot of the relationship between the predicted value and true value of the regression model (the horizontal axis of the scatter plot represents the true value of the MDS-UPDRS III score and the vertical axis represents the predicted value of the MDS-UPDRS III score).

To more comprehensively evaluate the potential of gait parameters in quantifying disease severity, we further explored their association with MDS-UPDRS III score. We constructed a predictive model using all the 19 gait parameters as input features and MDS-UPDRS III score as output label. The model showed excellent explanatory power and predictive accuracy: a high $R^2$ value indicated that the model could effectively explain most of the score variations; a low MAE value indicated good consistency between the predicted value and true value of the model; and a low MAPE value highlighted the high precision of the model in predicting MDS-UPDRS III score. In summary, our research not only confirmed the importance of gait parameters in the early diagnosis of PD but also demonstrated their great potential in quantifying disease progression. This provided a new perspective and tool for the future clinical management and personalized treatment of PD.

While our study has revealed the potential of gait parameters in the auxiliary diagnosis of early-stage PD, there were still some limitations that should be acknowledged. The primary challenge lied in the limitation of sample size, that was, the relatively small number of participants. A small sample size might affect the power of statistical analysis and potentially constrain the generalizability and stability of the results. Additionally, the current study focused only on spatiotemporal parameters, such as stride length and gait speed, without involving more detailed kinematic parameters like joint angles. In light of these limitations, we plan to expand the sample size in future research and include more gait parameters, such as kinematic parameters, in order to build a more comprehensive and accurate diagnostic model.

## 5 Conclusion

In summary, the non-contact gait assessment system we used was capable of objectively and quantitatively evaluating gait disorder in PD patients, providing clinicians with a valuable tool for predicting MDS-UPDRS III score. Our machine learning models could accurately distinguish early-stage PD from healthy controls by integrating analysis of gait parameters such as stride length, gait speed, stride and swing speed, turning time, and cadence, and the model could also make reasonable prediction of MDS-UPDRS III score. This achievement reinforced the role of gait analysis in the early diagnosis of PD and paved the way for the development of early intervention and personalized treatment strategies for PD.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Central Hospital of Dalian University of Technology (Reference No. YN2022-039-57). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

WY: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. WZ: Formal analysis, Methodology, Writing – review & editing. HG: Writing – review & editing. XN: Data curation, Writing – review & editing. CS: Data curation, Writing – review & editing. XF: Writing – review & editing. CW: Methodology, Resources, Supervision, Writing – review & editing.

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## Conflict of interest

Xiangmin Fan is an editorial board member of Frontiers. This has no impact on the peer review process and the final decision. Wencheng Zhu is an employee of Beijing CAS-Ruiyi Information Technology Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

# References


1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm*. (2017) 124:901–5. doi: 10.1007/s00702-017-1686-y

2. Mirelman A, Bonato P, Camicioli R, Ellis TD, Giladi N, Hamilton JL, et al. Gait impairments in Parkinson's disease. *Lancet Neurol*. (2019) 18:697–708. doi: 10.1016/S1474-4422(19)30044-4

3. Mermelstein S, Barbosa P, Kaski D. Neurological gait assessment. *Pract Neurol*. (2024) 24:11–21. doi: 10.1136/pn-2023-003917

4. Creaby MW, Cole MH. Gait characteristics and falls in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord*. (2018) 57:1–8. doi: 10.1016/j.parkreldis.2018.07.008

5. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry*. (2000) 69:308–12. doi: 10.1136/jnnp.69.3.308

6. Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease. *Neurology*. (2016) 86:566–76. doi: 10.1212/WNL.0000000000002350

7. Fereshtehnejad SM, Romenets SR, Anang JBM, Latreille V, Gagnon JF, Postuma RB. New clinical subtypes of Parkinson disease and their longitudinal progression. *JAMA Neurol*. (2015) 72:863–73. doi: 10.1001/jamaneurol.2015.0703

8. Aboutorabi A, Arazpour M, Bahramizadeh M, Hutchins SW, Fadayevatan R. The effect of aging on gait parameters in able-bodied older subjects: a literature review. *Aging Clin Exp Res*. (2016) 28:393–405. doi: 10.1007/s40520-015-0420-6

9. Melzer I, Oddsson LIE. The effect of a cognitive task on voluntary step execution in healthy elderly and young individuals. *J Am Geriatr Soc*. (2004) 52:1255–62. doi: 10.1111/j.1532-5415.2004.52353.x

10. Opara JA, Malecki A, Malecka E, Socha T. Motor assessment in Parkinson's disease. *AAEM*. (2017) 24:411–5. doi: 10.5604/12321966.1232774

11. Guo Y, Yang JX, Liu YX, Chen X, Yang GZ. Detection and assessment of Parkinson's disease based on gait analysis: a survey. *Front Aging Neurosci*. (2022) 14:916971. doi: 10.3389/fnagi.2022.916971

12. Bonato P, Feipel V, Corniani G, Arin-Bal G, Leardini A. Position paper on how technology for human motion analysis and relevant clinical applications have evolved over the past decades: striking a balance between accuracy and convenience. *Gait Posture*. (2024) 113:191–203. doi: 10.1016/j.gaitpost.2024.06.007

13. Jing Y, Qin PN, Fan XM, Qiang W, Wencheng Z, Sun W, et al. Deep learning-assisted gait parameter assessment for neurodegenerative diseases: model development and validation. *J Med Internet Res*. (2023) 25:e46427. doi: 10.2196/46427

14. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disord*. (2015) 30:1591–601. doi: 10.1002/mds.26424

15. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. *Neurology*. (1967) 17:427–42. doi: 10.1212/WNL.17.5.427

16. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. (2008) 23:2129–70. doi: 10.1002/mds.22340

17. Tombaugh TN, Mcintyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. (1992) 40:922–35. doi: 10.1111/j.1532-5415.1992.tb01992.x

18. Ellis T, Cavanaugh JT, Earhart GM, Ford MP, Foreman KB, Dibble LE. Which measures of physical function and motor impairment best predict quality of life in Parkinson's disease? *Parkinsonism Relat Disord*. (2011) 17:693–7. doi: 10.1016/j.parkreldis.2011.07.004

19. Nair P, Shojaei Baghini M, Pendharkar G, Chung HM. Detecting early-stage Parkinson's disease from gait data. *Proc Inst Mech Eng H*. (2023) 237:1287–96. doi: 10.1177/09544119231197090

20. Pistacchi M, Gioulis M, Sanson F, de Giovannini E, Filippi G, Rossetto F, et al. Gait analysis and clinical correlations in early Parkinson's disease. *Funct Neurol*. (2017) 32:28–34. doi: 10.11138/FNeur/2017.32.1.028

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# Lower-limb muscle synergies in musician's dystonia: a case study of a drummer

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Musician's dystonia (MD) is a movement disorder characterized by involuntary muscle contractions specifically triggered by playing an instrument. This condition often leads to a loss of fine motor control, threatening the careers of affected musicians. While MD is commonly associated with the hands, it can also affect the lower limbs, particularly in drummers. Understanding the muscle coordination involved in MD is crucial for comprehending its neurological mechanisms, yet the muscle coordination of lower-limb dystonia has not been thoroughly explored. This study aimed to investigate the differences in lower-limb muscle synergies in a drummer with MD, utilizing non-negative matrix factorization (NMF) to analyze coordinated muscle activity patterns during drumming tasks. A 36-year-old male professional drummer with lower-limb MD was instructed to play a drum set in time with a metronome set at 80 beats per minute. The task involved striking the bass drum pedal in time with the downbeat. Electromyographic (EMG) data were collected from 10 muscles in the right lower limb. The data were analyzed using NMF to extract muscle synergies and compare the number of synergies, spatial modules, and temporal modules between the data with and without dystonia symptoms. The number of muscle synergies did not differ significantly between the data with and without symptoms. Notably, changes were observed in both the spatial and temporal modules of muscle synergies. Spatial modules revealed the appearance of dystonia-specific muscle synergy, which is considered related to compensatory movement. Temporal modules showed significant earlier overactivation in timing, which is considered the direct manifestation of dystonia symptoms. These findings indicate that lower-limb dystonia in drummers affects the spatial and temporal profiles of muscle synergies. This study underscores the importance of considering both spatial and temporal modules of muscle synergy in understanding and treating lower-limb dystonia in drummers. Further research is needed to validate these findings and apply muscle synergy analysis for the clinical assessment of lower-limb dystonia in drummers.

KEYWORDS

**dystonia, drummer, muscle synergy, lower limb, coordination**

# 1 Introduction

Focal task-specific dystonia (FTSD) is an involuntary movement disorder affecting some musicians due to maladaptive neuroplasticity (1–4). When this disorder manifests in musicians, it is referred to as musician's dystonia (MD). It primarily induces involuntary movements specific to playing an instrument, presenting symptoms as a loss of fine motor control. This often leads to musicians abandoning their performance careers (5), making it a critical disorder for musicians.

While MD is most commonly reported in the hands, it also affects the lower limbs of drummers (6–8). In a case study of a drummer with lower limb MD, abnormal co-contraction in the thigh of the affected side during drum pedaling actions was noted (9). This drummer could alternately contract the plantar flexor and dorsiflexor muscles of the ankle on both affected and unaffected sides at a slow tempo. However, at increased tempos, he exhibited co-contraction of thigh muscles and was unable to maintain consistent performance at a fast tempo (9). In another case study of a drummer with lower limb MD, particularly in the right lower leg, it was revealed that the onset of symptoms led to increased activity in the ankle dorsiflexor muscles and partial thigh muscles, accompanied by a decrease in the activity of some toe extensor muscles (10). As a result, the amplitude of the played notes decreased, and synchronization errors increased (10). While these previous studies revealed symptom-specific activities in the individual lower limb muscles, how the symptom affected the coordination among the multiple muscles remains unclear.

By using a computational decomposition technique, such as non-negative matrix factorization (NMF), it is possible to extract a small number of synchronized activation groups of muscles, referred to as muscle synergies, from the activities of multiple muscles (11–14). Previous studies have demonstrated that the activities of multiple muscles in cyclic movements, like locomotion, can be decomposed into several sets of weighting coefficients assigned to individual muscles, i.e., spatial modules, and activation coefficients related to the phase of movement, i.e., temporal modules (15–18). From the perspective of muscle synergies, there are at least three potential ways that muscle coordination could be altered when dystonia symptoms manifest. First, the number of muscle synergies could differ. A reduction or increment in the number of muscle synergies suggests affecting the number of motor modules that can be independently recruited (19, 20). Second, the spatial modules of muscle synergy could differ. Changes in the spatial modules would indicate that dystonia primarily affects the extent to which each muscle participates in movement. Third, the temporal modules of muscle synergy could vary. Changes in temporal modules would show that the dystonia impacts the time-dependent profiles of when and how strongly each muscle synergy is activated to perform the movement. Together, investigating how dystonia symptoms influence (1) the number of synergies, (2) spatial modules, and (3) temporal modules is crucial. Clarifying these aspects would contribute to understanding how FTSD affects muscle coordination and elucidate clinical outcomes and neural underpinnings.

A central question of this study is how muscle synergies differ when dystonic symptoms occur in a drummer with lower limb dystonia. The previous research on pianists with MD revealed that while the number of muscle synergies remained unchanged, partial changes were observed in the coordination structures (spatial modules) between the affected and unaffected hands, as well as in comparison to the hands of healthy pianists (21). Moreover, these changes were identified as either directly related to the dystonic symptoms or as compensatory, based on their association with performance accuracy (21). This suggests that occurrence of dystonia symptoms affects the spatial modules without changes in the number of synergies. Another previous research in childhood dystonia reported the differences in the temporal modules while the number of synergies remained unchanged (22). This suggests that occurrence of dystonia symptoms affects the temporal modules without changes in the number of synergies. Taken together, the previous studies on muscle synergies in FTSD suggest changes in either spatial or temporal modules, but not in the number of synergies. Considering these previous studies on muscle synergies in FTSD, we hypothesized the following: (1) the drummer with lower-limb dystonia would show no significant change in the number of muscle synergies, while there would be changes in (2) the spatial modules, and/or (3) the temporal modules. The aim of this study was to investigate how the number of muscle synergies and the spatial and temporal modules would differ when dystonic symptoms occur in a drummer with lower-limb dystonia and to test the hypotheses in a drummer with right lower-limb dystonia while performing a drum pattern.

# 2 Methods

## 2.1 Participant

The same participant as Honda et al. participated in this study (10). The participant was a 36-year-old male professional rock drummer. He began playing drums at age 14 and was diagnosed by a neurologist with focal task-specific dystonia in his right lower limb at age 29. He first experienced symptoms at the age of 24 while on a national tour. He complained that the right lower leg involuntarily contracted during drum playing. At times when his symptoms were most severe, he felt discomfort in his right foot during activities that resembled drum pedaling motions, such as ascending stairs and driving a vehicle. To mitigate these symptoms, he utilized sensory tricks, such as adjusting the height of his shoes and chair, which provided only temporary relief. Eventually, the progression of focal task-specific dystonia impaired his ability to play the drums, leading to his withdrawal from public performances. Given the task-specific nature of his dystonia, which was triggered exclusively by drumming-related motions, and the temporary relief provided by sensory tricks, his diagnosis of FTSD was confirmed after ruling out other neurological conditions, including multiple sclerosis, minor spasticity (latent cerebral palsy), and rare ion-channel disorders such as stiff-man syndrome, based on the specific characteristics of his symptoms. The cumulative practice time from when he began playing the drum until he first experienced dystonia symptoms at the age of 24 was 6,760 h, and by the time he was diagnosed with FTSD at age 29, his total practice time had reached 9,360 h. His family history revealed no neurological disorders. His gait was normal, and he had no other neurological diseases. He was prescribed no medication for at least the past 3 years. He had no history of other neuropsychiatric disorders or neurosurgery. Ethical approval for this study was obtained from the Communication Science Laboratories Research Ethics Committee at Nippon Telegraph and Telephone Corporation

(Approval Number: H30-009). The experiment was conducted according to principles originating in the Declaration of Helsinki. Written informed consent was obtained from the participant in this study.

## 2.2 Experimental task

The participant was instructed to play an eight-beat drum pattern on a drum set in time with a metronome sound set at a constant tempo of 80 beats per minute (bpm). This tempo was chosen because it was the speed at which the participant most frequently experienced dystonic symptoms. The score of the drum pattern is depicted in Figure 1. The drumming pattern consisted of a single chunk of four metronome sounds that indicated the beat position in the pattern (see the vertical arrows in Figure 1), defined as 1 bar. Each trial consisted of 60 bars, and the participant completed a total of four trials. The affected right lower limb was used to play the bass drum, striking the drum pedal on the downbeat of the first beat and the syncopated upbeat of the third beat. The downbeat corresponds to the beginning of a beat, while the upbeat is situated between consecutive downbeats, such as when the participant played between the third and fourth beats. At the beginning of each trial, the participant started playing after hearing a 1 kHz pure tone and four metronome tones, which served as a cue for the start of the trial and to signal the tempo. The cue signal mimicked the standard practice in live performances, where a four-beat count-in is used. The participant was allowed a rest period of at least 1 min between trials. During the drum pattern, the participant verbally reported the occurrence of symptoms whenever he felt an abnormality in his movements.

## 2.3 Data collection

Electromyographic (EMG) activities were measured using active bipolar Ag/AgCl surface electrodes with a Trigno Wireless EMG system (DELSYS Corp., Boston, MA, United States). The EMG activities were recorded from 10 muscles in the right lower extremity: rectus femoris (RF), lateral head of biceps femoris (BF), vastus lateralis (VL), vastus medialis (VM), tibialis anterior (TA), extensor digitorum longus (EDL), gastrocnemius (GAS), soleus (SOL), peroneus longus (PL), and extensor digitorum brevis (EDB), at a sampling rate of 1,111 Hz. The interelectrode distance was 10 mm to prevent cross-talk between neighboring muscles. A trigger signal from the EMG system was sent to an audio interface (Fireface UCX: RME Corp., Germany), and the metronome sounds were recorded synchronously with the EMG signals at a sampling rate of 48,000 Hz.

## 2.4 Data preprocessing

Of the four trials, the first trial was excluded due to the failure of EMG recording, and the fourth trial was excluded from the analysis because the participant self-reported that he intentionally changed his drumming movements compared to the other trials. Consequently, we analyzed the data from the second and third trials to investigate muscle synergy. Since each of the trial consisted of 60 bars, there were 120 bars of the data in the second and third trials. During the second trial, the participant verbally reported 11 occurrences of symptoms on the downbeat of the first beat and 2 occurrences on the upbeat of the third beat. In the third trial, the participant reported 9 occurrences of symptoms on the downbeat of the first beat but no occurrences of symptoms on the upbeat of the third beat. Taken together, the participant reported 20 occurrences of symptoms on the downbeat of the first beat and 2 occurrences on the upbeat of the third beat in the second and third trials. Because the participants reported the symptoms mostly on the downbeat of the first beat, we decided to analyze the right lower-limb EMG data of playing the bass drum for the first beat. In total, there were 20 beats of data with dystonia and 100 beats of data without dystonia. Since three of the EMG data without dystonia included artifacts caused by intense electrode vibration during body movement, we excluded these data from the analysis. Thus, we used 20 beats of EMG data with dystonia and 97 beats of EMG data without dystonia for muscle synergy analysis.

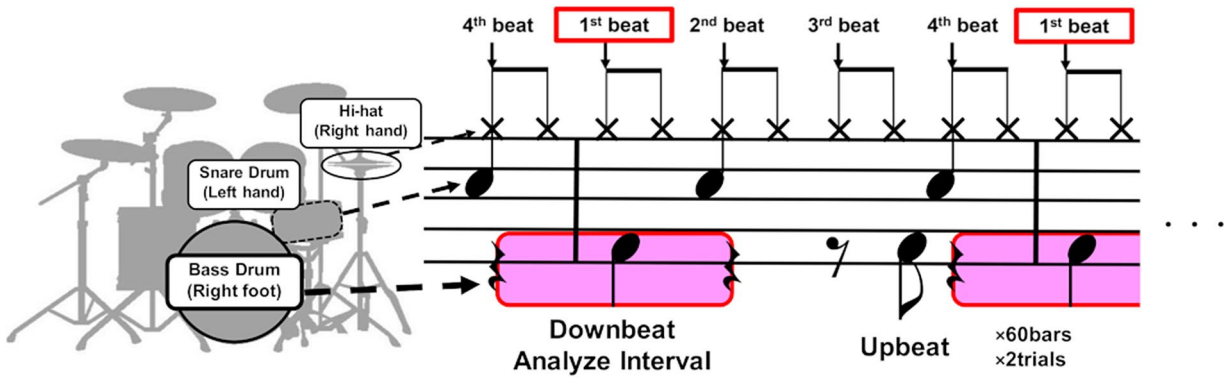


FIGURE 1
The score of the drum pattern used in the experiment. The participant was instructed to play an eight-beat drum pattern on a drum set in time with a metronome consisting of a single chunk of four metronome sounds that indicated the beat position in the pattern (see the vertical black arrows). The drumming pattern involved playing the bass drum with the right foot, the snare drum with the left hand, and the hi-hat cymbals with the right hand. The participant mostly exhibited dystonia symptoms in the right lower limb when playing the downbeat of the first beat (see the areas highlighted in pink). We therefore analyzed the muscle synergy of the right lower limb before and after the downbeat timings.

The EMG signals were demeaned, full-wave rectified, and low-pass filtered using the 4th order Butterworth filter with a cutoff of 20 Hz. The metronome sound signals were rectified, and the envelope was calculated to detect the peak timings, which were used as reference timings. We extracted the EMG signals 0.75 s before and after the reference timings. The interval of 0.75 s was selected because the metronome tempo was set at a constant tempo of 80 bpm, resulting in intervals of approximately 0.75 s between the reference timings (i.e., 60 s/80 beats = 0.75 s/beat). Each of the extracted EMG data within this interval included the lifting and lowering of lower-limb movements to kick the bass drum in synchronization with the metronome sounds.

Each of the extracted EMG data over the 1.50 s, termed as one cycle of EMG data, was resampled into 151 time points. Since we recorded the EMG from 10 muscles, we formed an EMG data matrix consisting of 10 muscles × 20 cycles for the data with dystonia, and an EMG data matrix consisting of 10 muscles × 97 cycles for the data without dystonia. The minimum and maximum values across the cycles were calculated for each of the 10 muscles and normalization was performed for each muscle vector by subtracting the minimum value and dividing it by the maximum value. Thus, each muscle vector in the EMG data matrix was divided by standard deviation of each muscle vector, $\sigma$, to have unit variance, ensuring that the activity of each muscle was equally weighted (15).

## 2.5 Overview of muscle synergy analysis

Muscle synergy analyses were performed in two steps to examine the commonalities and differences between the EMG activities with and without dystonia symptoms. In the first step, muscle synergies were extracted for each of the EMG activities with and without dystonia. This first step aimed to determine the number of muscle synergies in each of the dataset. In the second step, we pooled the EMG data with and without dystonia, and muscle synergies were simultaneously extracted from the pooled dataset. The second step aimed to identify the shared and specific muscle synergies (23). Specifically, we aimed to extract the commonalities and differences in the muscle synergy due to the presence or absence of dystonia symptoms.

## 2.6 Muscle synergy analysis for each of the EMG data with and without symptoms

Muscle synergies were extracted for each of the EMG data matrices with and without dystonia symptoms using NMF (11, 14, 24). NMF assumes that a given muscle activation pattern $M$ at each point in time is composed of a linear combination of several muscle weight vectors $W_i$, each recruited by activation coefficients $C_i$ (11, 14, 24). Therefore, a specific muscle activation pattern $M$ can be expressed as follows:

$$M = \sum_{i=1}^{N} W_i C_i + \varepsilon \left( W_i \geq 0, C_i \geq 0 \right)$$

where $i$ represents the relative contribution of muscles involved in the synergy, $N$ denotes the number of synergies, and $\varepsilon$ represents the residual. To compare muscle weight vectors of synergies between the data with and without symptoms with the same scaling as the measured EMG activity, a unit variance scaling was reverted by multiplying each weight of the $i$th muscle by $\sigma_i$ for all muscle synergies. The muscle weight and activation coefficient matrices were normalized so that each weight vector became a unit vector.

We first tested whether the number of muscle synergies was similar between the data with and without dystonia. For the EMG dataset with dystonia, the data across 20 cycles were randomly split into an 80% training set (i.e., 16 cycles) and a 20% test set (i.e., 4 cycles) for cross validation (25, 26). The test EMG datasets were reconstructed by muscle-weighting matrices derived from 1 to 10 muscle synergies extracted from the training EMG datasets. This cross-validation procedure was repeated 20 times. Then, the goodness-of-fit of the data reconstruction was quantified for each number of muscle synergies by the average value of the variance accounted for (VAF), which was defined as a 100 × the uncentered Pearson correlation coefficient (27, 28). For the EMG dataset without dystonia, 20 cycles of data were randomly selected from the 97 cycles. The cross-validation procedure was the same as for the data with dystonia but repeated 1,000 times to estimate the 95% bootstrapping confidence interval (95% CI) of the VAF value. This series of procedures aimed to confirm whether the VAF value from the EMG dataset with symptoms fell within the range of inter-cycle variability of the EMG dataset without dystonia. To determine the number of muscle synergies, a least squares method was used to fit a line to the portion of the VAF curve, identifying the point at which the VAF curve linearly plateaued as the number of muscle synergies where the mean squared error (MSE) falls below $10^{-5}$ (26).

For the EMG dataset without symptoms, to estimate the 95% CI of the muscle weighting vectors and activation coefficients of muscle synergies, the sets of muscle synergies were extracted 1,000 times across randomly selected EMG datasets each consisting of 20 cycles. Using k-means clustering, the entire set of muscle synergies were classified into clusters based on the cosine of the angle between pair of muscle weight vectors (15). K-means clustering was applied with pairwise constraints, preventing muscle synergies calculated in any of the 1,000 iterations from being classified into the same cluster (15, 29). The number of clusters was defined as the same determined based on the VAF curve as described above.

## 2.7 Shared and specific muscle synergy analysis

The EMG dataset with symptoms (20 cycles) and the EMG dataset without dystonia (97 cycles) were combined into a single EMG data matrix to extract muscle synergies that explain the entire EMG data matrix (i.e., shared synergies) and each of the datasets with and without dystonia (i.e., specific synergies) (23). First, the total number of muscle synergies to be extracted was set to the sum of the number of muscle synergies determined for each of the datasets with and without dystonia, assuming that there was no muscle synergies shared between the datasets with and without dystonia. Consequently, the activation coefficients specific to the dataset with dystonia were set to zero for the muscle synergies without dystonia, and vice versa. The total number of extracted muscle synergies was then reduced one by one in each extraction procedure, and the number of shared and

specific muscle synergies was adjusted. The number of shared and specific muscle synergies was determined as the minimum number of muscle synergies required to exceed the VAF value extracted in the analyses for each of the data with and without dystonia.

# 3 Results

## 3.1 The number of muscle synergies

The VAF curves linearly plateaued as the number of muscle synergies for each of the datasets with and without dystonia symptoms (see red and blue lines, respectively, in Figure 2). For the data with symptoms (red), the minimum number of muscle synergies for which the MSE calculated from the VAF curve was below $10^{-5}$ was 6 ($MSE = 7.22 \times 10^{-6}$). The 6 muscle synergies explained 96.46% of the original EMG data variance with dystonia. For the data without dystonia (blue), the minimum number of muscle synergies for which the MSE calculated from the VAF curve was below $10^{-5}$ was also 6 ($MSE = 6.79 \times 10^{-6}$). The 6 muscle synergies explained 92.36–96.99% (lower and upper limits of 95% CIs) of the original EMG data variance without dystonia. The VAF values with 1 to 7 muscle synergies to account for the EMG data with dystonia were within the 95% CI range for those without dystonia, indicating that the number of synergies was the same to account for both the data with and without dystonia.

## 3.2 Muscle synergies for each of the data with and without dystonia

The 6 muscle synergies extracted for each of the datasets with and without dystonia symptoms are shown in Figure 3. The spatial modules of muscle synergy, or the extracted muscle-weight vectors, are shown in the left panels of Figure 3, while the temporal modules of muscle synergy, or the extracted time-dependent profiles of when and how strongly each muscle synergy was activated, are shown in the right panels of Figure 3.

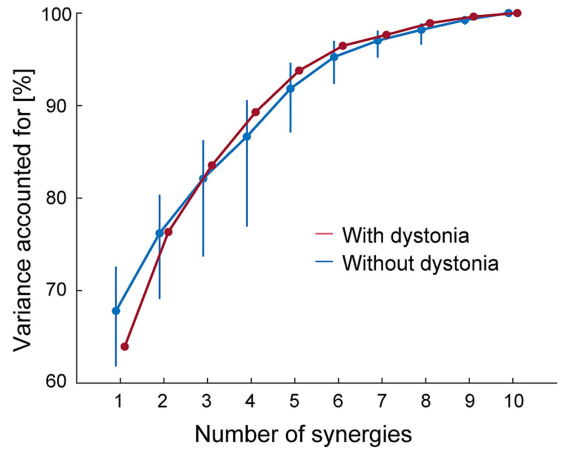


FIGURE 2
The variance accounted for (VAF) as a function of the number of muscle synergies. The VAF for the EMG data with dystonia symptoms is shown in red, and that for the data without dystonia symptoms is shown in blue. The blue bars represent the upper and lower limits of the 95% bootstrapping confidence intervals (CIs) of the VAF for each number of muscle synergies in the data without dystonia symptoms.

The first spatial module, or the extracted muscle-weight vector ($W_1$), showed a high weighting for the RF muscle, which is responsible for hip flexion. The cosine similarity demonstrated the commonality in the use of this spatial module between the data with and without symptoms ($r = 0.992$). The time-dependent profiles (i.e., temporal modules) of this muscle synergy showed peak values at approximately 338 milliseconds (ms) and 318 ms before the metronome sound for the data with and without dystonia, respectively. The peak values were 0.40 [arbitrary units (a.u.)] and 0.37 (a.u.) for the data with and without dystonia, respectively. Both the spatial and temporal modules of this muscle synergy were similar between the data with and without dystonia, indicating that $W_1$ for hip flexion to lift the thigh in preparation for the kicking movement was used in a similar manner, irrespective of the presence or absence of symptoms.

The second spatial module ($W_2$) showed high weightings for the TA and EDL muscles, which are responsible for ankle dorsiflexion. The cosine similarity demonstrated the commonality in the use of this spatial module between the data with and without dystonia ($r = 0.984$). However, the temporal modules of this muscle synergy differed between the data with and without dystonia. Specifically, the temporal module shifted earlier and was more activated in the data with symptoms compared to those without dystonia: the peak values were observed at approximately 318 ms and 219 ms before the metronome sound for the data with and without dystonia, respectively. The peak values were 0.58 (a.u.) and 0.20 (a.u.) for the data with and without dystonia, respectively. Thus, while the spatial modules were similar, the temporal modules differed between the data with and without dystonia, indicating that the temporal module of ankle dorsiflexion muscle synergy to prepare for the kicking movement occurred earlier and over-activated when the symptoms occurred.

The third spatial module ($W_3$) showed a relatively high weighting for the EDB muscle, which is responsible for toe extension, and relatively low weightings for the other muscles (RF, VL, BF, TA, EDL, GAS, and PL). The cosine similarity of $W_3$ demonstrated relatively lower values compared to the other spatial modules ($r = 0.868$). The temporal modules of this muscle synergy also differed between the data with and without dystonia. Specifically, the temporal module shifted earlier and was less activated in the data with dystonia compared to those without dystonia: the peak values were observed at approximately 248 ms and 179 ms before the metronome sound for the data with and without dystonia, respectively. The peak values were 0.05 (a.u.) and 0.11 (a.u.) for the data with and without dystonia, respectively. Thus, both the spatial and temporal modules differed between the data with and without dystonia.

The fourth spatial module ($W_4$) showed a high weighting for the VL muscle, which is responsible for stabilizing the hip joint. The cosine similarity demonstrated the commonality in the use of this spatial module between the data with and without dystonia ($r = 0.997$). The temporal modules of this muscle synergy showed peak values at approximately 60 ms before the metronome sound for both the data with and without dystonia. The peak values were 0.20 (a.u.) and 0.26 (a.u.) for the data with and without dystonia, respectively. Nevertheless, the temporal modules of this muscle

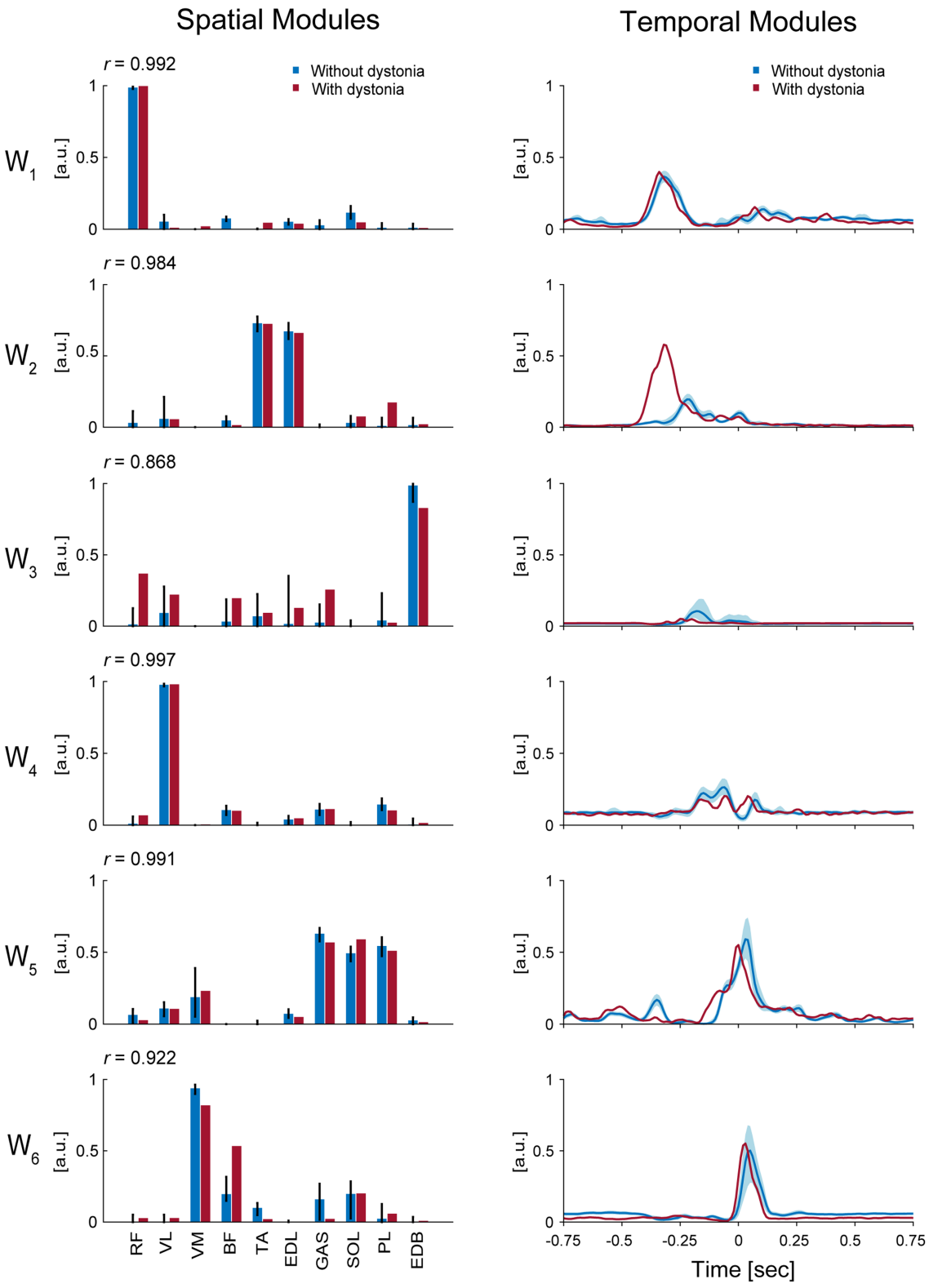


FIGURE 3
Muscle synergies for each of the data with and without dystonia. The spatial and temporal modules of muscle synergies are shown in the left and right panels, respectively. The red bars and lines indicate the spatial and temporal modules extracted from the data with dystonia, while the blue bars and lines indicate those from the data without dystonia. In the left panels, the bars represent muscle weights of rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA), extensor digitorum longus (EDL), soleus (SOL), gastrocnemius (GAS), peroneus longus (PL), and extensor digitorum brevis (EDB), respectively, extracted from the non-negative matrix factorization (NMF). The error bars represent the 95% CI in the data without dystonia. The *r* value indicates the cosine similarity between the muscle-weight vectors with and without dystonia. In the right panels, the activation coefficients in the NMF, or the temporal modules of muscle synergy, are shown 0.75 s before and after the metronome sound. The order of the muscle synergies ($W_1$–$W_6$) was sorted by the time of peak activation of the temporal modules.

synergy were slightly different between the data with and without dystonia.

The fifth spatial module ($W_5$) showed high weightings for the GAS, SOL, and PL muscles, which are responsible for plantar flexion. The cosine similarity demonstrated the commonality in the use of this spatial module between the data with and without dystonia ($r = 0.991$). The temporal modules of this muscle synergy showed peak values around the metronome sound for the data with symptoms and approximately 30 ms after the metronome sound for the data without dystonia. The peak values were 0.55 (a.u.) and 0.59 (a.u.) for the data with and without dystonia, respectively. The shape of the temporal modules of this muscle synergy was overall similar but appeared slightly shifted earlier in the data with dystonia compared to those without dystonia.

The sixth spatial module ($W_6$) showed relatively high weightings for the VM and BF muscles, which are responsible for stabilizing the knee and hip joints. The cosine similarity of $W_6$ was $r = 0.922$, which was relatively lower compared to the other spatial modules. Specifically, the weighting for the VM was lower, but the weighting for the BF was higher in the data with dystonia. The temporal modules of this muscle synergy showed peak values at approximately 30 ms and 50 ms after the metronome sound for the data with and without dystonia, respectively. The peak values were 0.55 (a.u.) and 0.50 (a.u.) for the data with and without dystonia, respectively. The shape of the temporal modules of this muscle synergy was overall similar but appeared slightly shifted earlier in the data with dystonia compared to those without dystonia.

## 3.3 Shared and specific muscle synergies

The shared and specific muscle synergy analysis showed a VAF of 95.79% for the combined dataset, a VAF of 95.45% for the data with dystonia, and a VAF of 94.96% for the data without dystonia. The analysis revealed that there were 5 shared muscle synergies between the data with and without dystonia symptoms, while there were 2 specific muscle synergies each for the data with and without dystonia symptoms (Figure 4).

The first shared spatial module ($SH_1$) showed a high weighting for the RF muscle, which is responsible for hip flexion. The time-dependent profiles (i.e., temporal modules) of this muscle synergy were similar between the data with and without dystonia, indicating that $SH_1$ for hip flexion to lift the thigh in preparation for the kicking movement was shared between the data with and without dystonia symptoms.

The second shared spatial module ($SH_2$) showed high weightings for the TA and EDL muscles, which are responsible for ankle dorsiflexion. The temporal modules of this muscle synergy clearly differed between the data with and without dystonia. Specifically, the temporal module shifted earlier and was more activated in the data with dystonia compared to those without symptoms. Thus, this shared spatial module was activated more and earlier when symptoms occurred.

The without-dystonia-specific synergy (WODSP) showed a high weighting for the EDB muscle, which is responsible for toe extension (see blue in Figure 4). This muscle synergy appeared specifically in the data without dystonia, indicating that the muscle synergy for toe extension during the preparation movement was observed when dystonia symptoms did not occur.

The third shared spatial module ($SH_3$) showed a high weighting for the VL muscle, which is responsible for stabilizing the hip joint. The shape of the temporal modules of this muscle synergy was overall similar between the data with and without dystonia but appeared slightly shifted earlier in the data with dystonia compared to those without dystonia.

The fourth shared spatial module ($SH_4$) showed high weightings for the GAS, SOL, and PL muscles, which are responsible for plantar flexion. The shape of the temporal modules of this muscle synergy was overall similar between the data with and without dystonia but appeared slightly shifted earlier in the data with dystonia compared to those without dystonia.

The with-dystonia-specific synergy (WDSP) showed relatively high weightings for the BF and VM muscles, and relatively low weightings for the RF, VL, EDL, SOL, PL, and EDB muscles. The temporal module showed activation shortly after the metronome sound, indicating that this muscle synergy was contributing to stabilizing the kick movement after pedaling specifically when the dystonia symptoms occurred.

The fifth shared spatial module ($SH_5$) showed a high weighting for the VM muscle. The shape of the temporal modules of this muscle synergy was overall similar between the data with and without dystonia but appeared slightly shifted earlier in the data with dystonia compared to those without dystonia.

# 4 Discussion

By utilizing NMF to extract the spatial modules (i.e., muscle-weight vectors) and the temporal modules (i.e., activation coefficients), we aimed to investigate how the number of muscle synergies and the spatial and temporal modules would differ when dystonic symptoms occur in a drummer with lower-limb dystonia. Specifically, we tested whether (1) the drummer with lower-limb dystonia would show no significant change in the number of muscle synergies, while there would be changes in (2) the spatial modules, and/or (3) the temporal modules when the dystonia symptoms occurred. Our results showed that, while the number of muscle synergies was the same in accounting for both the data with and without dystonia, the spatial and temporal modules of the muscle synergies changed when the dystonia symptoms occurred.

## 4.1 Number of synergies

Our first hypothesis was that the drummer with lower-limb dystonia would show no significant change in the number of muscle synergies when the dystonia symptoms occurred. Our results showed that 6 muscle synergies explained 96.46% and 92.36–96.99% of the original EMG data variance in the data with and without dystonia, respectively (Figure 2). These results indicate that six muscle synergies account for both the data with and without symptoms, and the number of synergies was the same regardless of the occurrence of symptoms. Thus, our results support the first hypothesis and align with previous studies on MD pianists (21) and dystonia in children (22), suggesting that the number of synergies or motor modules that

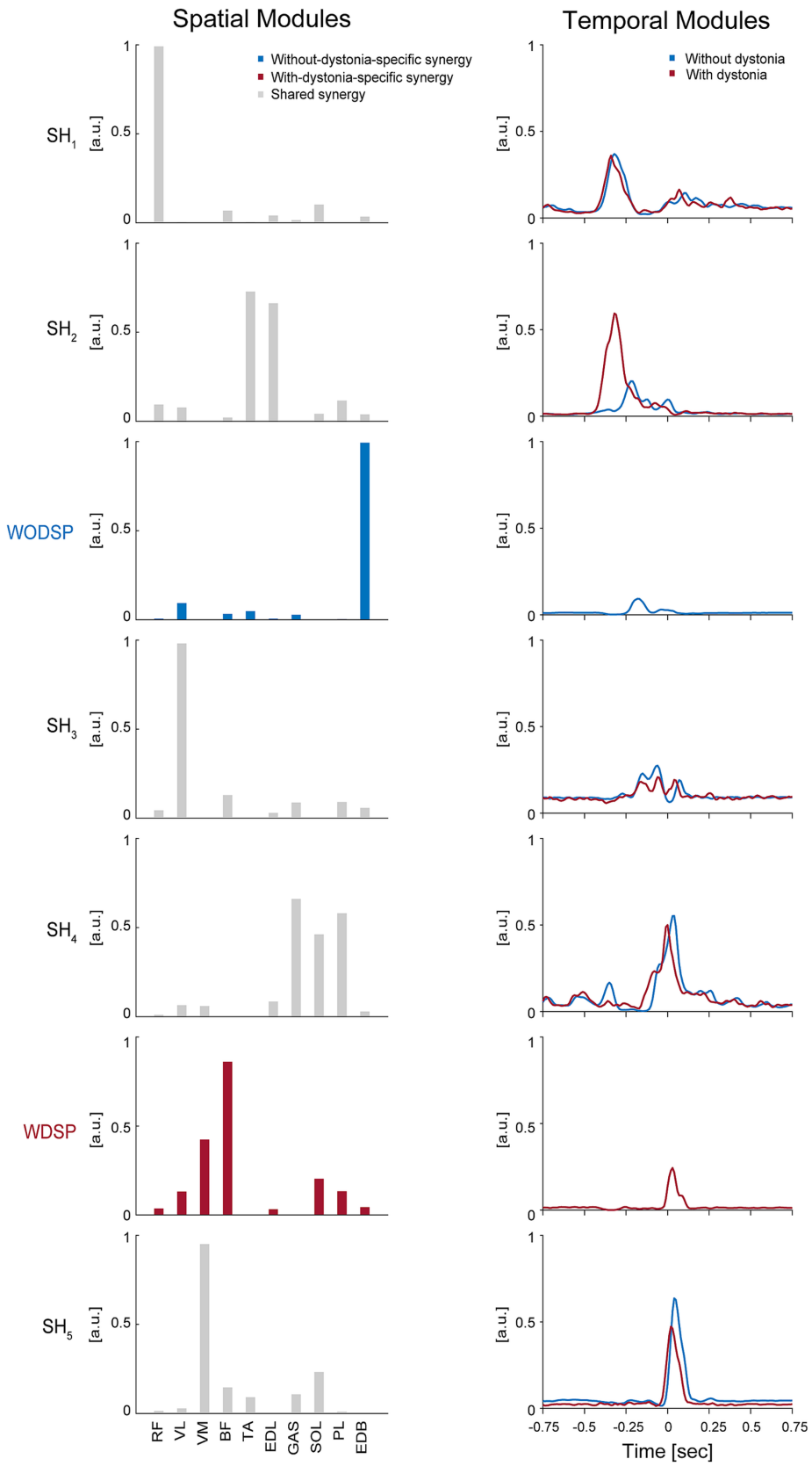


FIGURE 4
Shared muscle synergies between the data with and without dystonia and specific muscle synergies for each dataset. The spatial and temporal modules of shared and specific muscle synergies are shown in the left and right panels, respectively. In the left panels, the bars represent muscle weights of rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA), extensor digitorum longus (EDL),

(Continued)

FIGURE 4 (Continued)
soleus (SOL), gastrocnemius (GAS), peroneus longus (PL), and extensor digitorum brevis (EDB), respectively, extracted from the non-negative matrix factorization (NMF). The grey bars represent the shared spatial modules between the data with and without dystonia ($SH_{1-5}$). The blue bars represent the without-dystonia-specific synergy (WODSP). The red bars represent the with-dystonia-specific synergy (WDSP). In the right panels, the activation coefficients in the NMF, or the temporal modules of muscle synergy, are shown 0.75 s before and after the metronome sound. The red lines indicate the temporal modules for the data with dystonia, while the blue lines indicate those for the data without dystonia.

can be independently recruited remains unchanged when dystonia symptoms occur.

Nevertheless, it is worth mentioning that previous studies on patients with stroke (19, 30), cerebral palsy (31), spinal cord injury (32), and Parkinson's disease (33) have shown changes in the number of muscle synergies. Specifically, these studies reported a reduction in the number of muscle synergies due to these neurological disorders. The reduced number of synergies indicates that motor commands become simplified and less complex when these neurological disorders occur. In contrast, we did not observe a reduction in the number of synergies, suggesting a specific nature of FTSD compared to other neurological conditions such as stroke, cerebral palsy, spinal cord injury, and Parkinson's disease. Our results suggest that the lower-limb dystonia in the drummer cannot be explained by simplified motor commands or a reduced number of muscle synergies.

## 4.2 Spatial modules

Our second hypothesis was that there would be changes in the spatial modules of muscle synergies when the dystonia symptoms occurred. Our results showed that the structure of the spatial modules differed when the dystonia symptoms occurred. Specifically, the shared and specific muscle synergy analyses revealed that there were 5 shared muscle synergies between the data with and without dystonia symptoms, while there were 1 specific muscle synergies each for the data with and without dystonia symptoms (Figure 4). These results support the second hypothesis, indicating that the spatial modules of muscle synergies change when symptoms occur in the drummer with lower-limb dystonia.

It is noteworthy that we observed the without-dystonia-specific synergy (WODSP), which had a high weighting for the EDB muscle (blue in Figure 4). Since this muscle synergy was activated before the kicking movement and the EDB muscle contributes to toe extension, this synergy seemed to contribute to the fine control of toe extension in preparation for the kicking movement when the dystonia symptoms did not occur. In contrast, when the dystonia symptoms occurred, we observed the with-dystonia-specific synergy (WDSP), which had high weightings for the BF and VM muscles (red in Figure 4). Since this muscle synergy was activated after the metronome sound, it appeared to contribute to stabilize the lower limb after the kicking movement. Thus, although the number of synergies was the same—six (5 shared plus 1 specific synergy)—between the data with and without dystonia, we found a different structure of the spatial modules depending on the absence or occurrence of the symptoms.

The previous study on pianists with MD showed changes in the spatial modules of muscle synergies between the affected and unaffected hands, as well as in comparison to the hands of healthy pianists (21). These changes in the spatial modules were identified as either directly related to the dystonic symptoms or as compensatory (21). We suggest that the with-dystonia-specific synergy (WDSP) observed in this study may be interpreted as compensatory rather than as a direct manifestation of dystonic symptoms. This interpretation is based on the fact that the WDSP was observed relatively late in the kicking movement. The spatial module specific to dystonia symptoms in this study may therefore be understood as a muscle synergy that compensates for the movement after the direct manifestation of dystonic symptoms. Interestingly, a previous study by Lee and Altenmüller (9) reported abnormal co-contraction in the thigh muscles of the affected side during drum pedaling actions in a drummer with FTSD. Specifically, they reported the co-contraction of the quadriceps and BF muscles. In this study, we measured the BF and three of the quadriceps muscles (RF, VL, and VM). It is noteworthy that our muscle synergy analysis showed that the WDSP had relatively high weightings for the BF and VM muscles, and relatively low weightings for the RF and VL muscles (Figure 4). These results suggest that the WDSP observed in this study is similar to the co-contraction in the thigh muscles of the affected side reported in the previous study (9). Compensatory activity of the thigh muscles may be a common feature of drummers with lower-limb dystonia.

## 4.3 Temporal modules

What kind of muscle synergy would reflect the direct manifestation of symptoms in the drummer with lower-limb dystonia? Based on the results of the temporal modules in this study, we propose that a change in the temporal module of muscle synergy reflects the direct manifestation of dystonic symptoms in the drummer. Specifically, we found that the temporal modules of the second shared spatial module ($SH_2$), which had high weightings for the TA and EDL muscles, clearly differed between the data with and without symptoms: the temporal module shifted earlier and was more activated in the data with dystonia compared to those without dystonia (Figure 4). This synergy was activated at almost the same timing as the first shared spatial module ($SH_1$), suggesting that the temporal module intended to activate $SH_1$ may have contaminated the other muscle synergy and driven $SH_2$ when the symptoms occurred.

What could be the neural mechanisms related to the earlier-shifted overactivity of the muscle synergy ($SH_2$) observed in this study? We suggest that abnormal inhibition and/or excitation of motor commands driving the muscle synergy may be one of the mechanisms. Previous neuroimaging studies have shown abnormal overactivity of the primary motor cortex (M1) in patients with FTSD (34, 35). Transcranial magnetic stimulation (TMS) studies have also shown a loss of inhibition in M1 in patients with FTSD (36–38). Moreover, a recent study on pianists with FTSD showed reduced inhibition and elevated facilitation in M1 compared to healthy controls (39). Considering these previous studies,

we assume that the overactivity or loss of inhibition in M1 might be related to the earlier-shifted overactivity of the muscle synergy $SH_2$. It might be possible that the motor commands driving the muscle synergy for hip flexion ($SH_1$) contaminated the muscle synergy for ankle dorsiflexion ($SH_2$) due to the overactivity or loss of inhibition in M1.

We suggest that the occurrence of the earlier-shifted overactivity of the muscle synergy $SH_2$ concealed the without-dystonia-specific synergy (WODSP) and induced slight shifts in the temporal-module activities of $SH_3$, $SH_4$, and $SH_5$. This, in turn, might have resulted in the appearance of the with-dystonia-specific synergy (WDSP) to compensate for the movement. Specifically, the enhanced dorsiflexion movement due to the earlier-shifted overactivity of the muscle synergy $SH_2$ during the pedaling preparation phase might lead to a decrease in the force applied to the pedal. To compensate for this reduced force, the with-dystonia-specific synergy (WDSP) might appear to provide the necessary force for pedaling despite the disrupted motor control caused by the dystonia symptoms.

In a previous study of lower-limb dystonia in drummers by Honda et al. (10), it was reported that the appearance of dystonia symptoms resulted in the earlier timing of bass drum performance. We suggest that the earlier shift of temporal-module activity of $SH_2$, together with the slight shifts in those of $SH_3$, $SH_4$, and $SH_5$, caused the earlier timing of bass drum performance. The without-dystonia-specific synergy (WODSP) is considered to contribute to the fine control of toe extension in preparation for the kicking movement. This might help achieve a "whip-like motion" or the sequential proximal-to-distal motion in preparation for the kicking movement. Similar preparatory movements have been reported in skilled pianists, where a lifting of the upper limb from the proximal to the distal end precedes the keystroke (40), suggesting a common motor strategy among musicians to facilitate skilled performance. We suggest that the earlier-shifted overactivity of the muscle synergy $SH_2$ hindered the "whip-like" preparation for the kicking movement and resulted in compensatory movement caused by the with-dystonia-specific synergy (WDSP). Taken together, we propose that the change in the temporal module of muscle synergy reflects the direct manifestation of dystonic symptoms in the drummer with lower-limb dystonia, and this supports our third hypothesis.

### 4.4 Clinical implications and limitations

As far as we know, this is the first case study to apply NMF to investigate the muscle synergy of the lower limb in a drummer with FTSD. So far, there have been a limited number of studies on drummers with FTSD (6–10). Therefore, formal assessments and clinical interventions for lower limb dystonia in drummers have not been fully explored. Based on the results of this study, we suggest that NMF and muscle synergy analysis may be useful tools for assessing the symptoms of lower-limb dystonia. As shown in this study, muscle synergy analysis allows for the quantitative identification of the combination of muscles that activate simultaneously and the timing of activation, based on EMG data obtained from multiple muscles across multiple repetitions of movements. In clinical settings, dystonia symptoms can vary from person to person, and quantitatively identifying the symptoms from multiple muscles and repetitions of movements for each individual becomes challenging. We suggest that muscle synergy analysis offers the advantage of organizing such complex data and capturing the statistical properties of symptoms.

However, given the limited research on drummer's dystonia, more studies are needed before clinical applications can be developed. One of the limitations of this study is that our data is based on a single case, and the muscle synergy patterns identified in this study may vary considerably in other drummers with lower-limb dystonia. For instance, future research should expand the sample size of MD drummers and compare them to healthy drummers to validate the findings from this study. Longitudinal studies tracking changes in muscle synergies over time with various interventions would also be valuable in understanding the progression and potential recovery mechanisms of dystonia in musicians. Furthermore, it would also be interesting to compare lower-limb muscle synergies between the affected and unaffected sides of the legs at different tempi using a mirror-symmetrical task. These future studies will provide further insights into lower-limb dystonia in drummers with FTSD.

## 5 Conclusion

By applying NMF to 10 lower-limb muscles in a drummer with FTSD, we found that the number of muscle synergies did not differ between the data with and without dystonia; however, changes were observed in both the spatial and temporal modules of muscle synergies due to the appearance of symptoms. Spatial modules revealed the appearance of dystonia-specific muscle synergy, which is considered related to compensatory movement. Temporal modules showed significant earlier overactivation in timing, which is considered the direct manifestation of dystonia symptoms. These findings indicate that lower-limb dystonia in drummers affects the spatial and temporal profiles of muscle synergies, and NMF and muscle synergy analysis may be useful tools for assessing the symptoms of a drummer's lower-limb dystonia.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Communication Science Laboratories Research Ethics Committee of Nippon Telegraph and Telephone Corporation. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable data included in this article.

## Author contributions

SS: Writing – original draft, Writing – review & editing, Data curation, Validation, Visualization, Formal analysis, Funding

acquisition, Methodology, Investigation. KH: Data curation, Formal analysis, Methodology, Software, Writing – review & editing. SY: Resources, Writing – review & editing. MiK: Writing – review & editing, Data curation. SK: Methodology, Writing – review & editing. MaK: Resources, Writing – review & editing. SH: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Investigation. SF: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

KH and MK are employed by the NTT Communication Science Laboratories, Nippon Telegraph and Telephone Corporation, Japan.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Lim VK, Altenmüller E, Bradshaw JL. Focal dystonia: current theories. *Hum Mov Sci*. (2001) 20:875–914. doi: 10.1016/S0167-9457(01)00076-8

2. Altenmüller E, Jabusch H-C. Focal hand dystonia in musicians: phenomenology, etiology, and psychological trigger factors. *J Hand Ther*. (2009) 22:144–55; quiz 155. doi: 10.1016/j.jht.2008.11.007

3. Altenmüller E, Baur V, Hofmann A, Lim VK, Jabusch H-C. Musician's cramp as manifestation of maladaptive brain plasticity: arguments from instrumental differences. *Ann N Y Acad Sci*. (2012) 1252:259–65. doi: 10.1111/j.1749-6632.2012.06456.x

4. Furuya S, Hanakawa T. The curse of motor expertise: use-dependent focal dystonia as a manifestation of maladaptive changes in body representation. *Neurosci Res*. (2016) 104:112–9. doi: 10.1016/j.neures.2015.12.001

5. Lee A, Eich C, Ioannou CI, Altenmüller E. Life satisfaction of musicians with focal dystonia. *Occup Med*. (2015) 65:380–5. doi: 10.1093/occmed/kqv038

6. Ray S, Pal PK. Dystonia in performing artists: beyond focal hand dystonia. *Can J Neurol Sci*. (2022) 49:29–37. doi: 10.1017/cjn.2021.41

7. Rosset-Llobet J, Fàbregas-Molas S, Pascual-Leone A. Drummer's lower limb dystonia. *J Neurol*. (2012) 259:1236–7. doi: 10.1007/s00415-011-6324-2

8. Katz M, Byl NN, San Luciano M, Ostrem JL. Focal task-specific lower extremity dystonia associated with intense repetitive exercise: a case series. *Parkinsonism Relat Disord*. (2013) 19:1033–8. doi: 10.1016/j.parkreldis.2013.07.013

9. Lee A, Altenmüller E. Heavy metal curse: a task-specific dystonia in the proximal lower limb of a professional percussionist. *Med Probl Perform Art*. (2014) 29:174–6. doi: 10.21091/mppa.2014.3035

10. Honda K, Sata S, Komine M, Yamaguchi S, Kim S, Kashino M, et al. Drumming performance and underlying muscle activities in a professional rock drummer with lower-limb dystonia: a case study. *Front Neurol*. (2024) 15:1398476. doi: 10.3389/fneur.2024.1398476

11. Hagio S, Kouzaki M. The flexible recruitment of muscle synergies depends on the required force-generating capability. *J Neurophysiol*. (2014) 112:316–27. doi: 10.1152/jn.00109.2014

12. Ting LH, Chiel HJ, Trumbower RD, Allen JL, McKay JL, Hackney ME, et al. Neuromechanical principles underlying movement modularity and their implications for rehabilitation. *Neuron*. (2015) 86:38–54. doi: 10.1016/j.neuron.2015.02.042

13. Bizzi E, Cheung VCK, d'Avella A, Saltiel P, Tresch M. Combining modules for movement. *Brain Res Rev*. (2008) 57:125–33. doi: 10.1016/j.brainresrev.2007.08.004

14. Tresch MC, Saltiel P, Bizzi E. The construction of movement by the spinal cord. *Nat Neurosci*. (1999) 2:162–7. doi: 10.1038/5721

15. Hagio S, Nakazato M, Kouzaki M. Modulation of spatial and temporal modules in lower limb muscle activations during walking with simulated reduced gravity. *Sci Rep*. (2021) 11:14749. doi: 10.1038/s41598-021-94201-9

16. Dominici N, Ivanenko YP, Cappellini G, d'Avella A, Mondì V, Cicchese M, et al. Locomotor primitives in newborn babies and their development. *Science*. (2011) 334:997–9. doi: 10.1126/science.1210617

17. Sylos-Labini F, La Scaleia V, Cappellini G, Fabiano A, Picone S, Keshishian ES, et al. Distinct locomotor precursors in newborn babies. *Proc Natl Acad Sci USA*. (2020) 117:9604–12. doi: 10.1073/pnas.1920984117

18. Cheung VCK, Cheung BMF, Zhang JH, Chan ZYS, Ha SCW, Chen C-Y, et al. Plasticity of muscle synergies through fractionation and merging during development and training of human runners. *Nat Commun*. (2020) 11:4356. doi: 10.1038/s41467-020-18210-4

19. Cheung VCK, Turolla A, Agostini M, Silvoni S, Bennis C, Kasi P, et al. Muscle synergy patterns as physiological markers of motor cortical damage. *Proc Natl Acad Sci USA*. (2012) 109:14652–6. doi: 10.1073/pnas.1212056109

20. Safavynia SA, Torres-Oviedo G, Ting LH. Muscle synergies: implications for clinical evaluation and rehabilitation of movement. *Top Spinal Cord Inj Rehabil*. (2011) 17:16–24. doi: 10.1310/sci1701-16

21. Oku T, Furuya S. Neuromuscular incoordination in musician's dystonia. *Parkinsonism Relat Disord*. (2019) 65:97–104. doi: 10.1016/j.parkreldis.2019.05.011

22. Lunardini F, Casellato C, Bertucco M, Sanger TD, Pedrocchi A. Children with and without dystonia share common muscle synergies while performing writing tasks. *Ann Biomed Eng*. (2017) 45:1949–62. doi: 10.1007/s10439-017-1838-0

23. Sawers A, Allen JL, Ting LH. Long-term training modifies the modular structure and organization of walking balance control. *J Neurophysiol*. (2015) 114:3359–73. doi: 10.1152/jn.00758.2015

24. Lee DD, Seung HS. Learning the parts of objects by non-negative matrix factorization. *Nature*. (1999) 401:788–91. doi: 10.1038/44565

25. Hagio S, Ishihara A, Terada M, Tanabe H, Kibushi B, Higashibata A, et al. Muscle synergies of multidirectional postural control in astronauts on earth after a long-term stay in space. *J Neurophysiol*. (2022) 127:1230–9. doi: 10.1152/jn.00232.2021

26. Cheung VCK, d'Avella A, Tresch MC, Bizzi E. Central and sensory contributions to the activation and organization of muscle synergies during natural motor behaviors. *J Neurosci*. (2005) 25:6419–34. doi: 10.1523/JNEUROSCI.4904-04.2005

27. Zajac FE. Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control. *Crit Rev Biomed Eng*. (1989) 17:359–411.

28. Torres-Oviedo G, Macpherson JM, Ting LH. Muscle synergy organization is robust across a variety of postural perturbations. *J Neurophysiol*. (2006) 96:1530–46. doi: 10.1152/jn.00810.2005

29. Wagstaff K, Cardie C, Rogers S, Schroedl S. (2001). Constrained K-means clustering with background knowledge. Proceedings of the Eighteenth International Conference on Machine Learning. 577–584.

30. Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA. Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *J Neurophysiol*. (2010) 103:844–57. doi: 10.1152/jn.00825.2009

31. Steele KM, Rozumalski A, Schwartz MH. Muscle synergies and complexity of neuromuscular control during gait in cerebral palsy. *Dev Med Child Neurol*. (2015) 57:1176–82. doi: 10.1111/dmcn.12826

32. Hayes HB, Chvatal SA, French MA, Ting LH, Trumbower RD. Neuromuscular constraints on muscle coordination during overground walking in persons with chronic incomplete spinal cord injury. *Clin Neurophysiol*. (2014) 125:2024–35. doi: 10.1016/j.clinph.2014.02.001

33. Rodriguez KL, Roemmich RT, Cam B, Fregly BJ, Hass CJ. Persons with Parkinson's disease exhibit decreased neuromuscular complexity during gait. *Clin Neurophysiol*. (2013) 124:1390–7. doi: 10.1016/j.clinph.2013.02.006

34. Pujol J, Roset-Llobet J, Rosinés-Cubells D, Deus J, Narberhaus B, Valls-Solé J, et al. Brain cortical activation during guitar-induced hand dystonia studied by functional MRI. *NeuroImage*. (2000) 12:257–67. doi: 10.1006/nimg.2000.0615

35. Haslinger B, Altenmüller E, Castrop F, Zimmer C, Dresel C. Sensorimotor overactivity as a pathophysiologic trait of embouchure dystonia. *Neurology*. (2010) 74:1790–7. doi: 10.1212/WNL.0b013e3181e0f784

36. Sohn YH, Hallett M. Disturbed surround inhibition in focal hand dystonia. *Ann Neurol*. (2004) 56:595–9. doi: 10.1002/ana.20270

37. Stinear CM, Byblow WD. Impaired modulation of intracortical inhibition in focal hand dystonia. *Cereb Cortex*. (2004) 14:555–61. doi: 10.1093/cercor/bhh017

38. Beck S, Richardson SP, Shamim EA, Dang N, Schubert M, Hallett M. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. *J Neurosci*. (2008) 28:10363–9. doi: 10.1523/JNEUROSCI.3564-08.2008

39. Furuya S, Uehara K, Sakamoto T, Hanakawa T. Aberrant cortical excitability reflects the loss of hand dexterity in musician's dystonia. *J Physiol*. (2018) 596:2397–411. doi: 10.1113/JP275813

40. Furuya S, Kinoshita H. Organization of the upper limb movement for piano key-depression differs between expert pianists and novice players. *Exp Brain Res*. (2008) 185:581–93. doi: 10.1007/s00221-007-1184-9

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# Evaluation of motor fluctuations in Parkinson's disease: electronic vs. conventional paper diaries

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**Background:** Paper symptom diaries are a common tool for assessing motor fluctuations in Parkinson's disease (PD) patients, but there are concerns about inaccuracies in the assessment of motor fluctuation due to recall bias and poor compliance. We, therefore, developed an electronic diary with reminder and real-time recording functions.

**Objectives and methods:** To evaluate the effectiveness of the electronic diary, we compared compliance and motor fluctuation assessment with a paper diary. Nineteen PD patients were recruited and recorded paper diaries every 30 min from 8 am to 8 pm for 7 days, followed by 7 days of electronic diary recording using a smartphone and smartwatch. Prior to the recording period, the Parkinson's Disease Questionnaire (PDQ)-39 and the Movement Disorders Society-sponsored Unified Parkinson's Disease Rating Scale-Revised (MDS-UPDRS) 1, 2, 3, 4 were measured. Patients completed a patient questionnaire on the usability of the diaries after the recording period.

**Results:** Total reported time was significantly longer in paper diaries, but there was no significant difference in the number of entries (paper 115 [71–147] vs. electronic 109 [93–116], $p = 0.77$). There was a significant correlation between paper and electronic diaries with respect to motor status. ON time rate recorded in the electronic diary was significantly correlated with PDQ-39, MDS-UPDRS 1, 2, and 4, while MDS-UPDRS 1 was only correlated with ON time rate in the paper diary. The usability of our electronic diary was found to be satisfactory based on the results of patient questionnaire.

**Conclusion:** Electronic diaries are useful tools that more accurately reflect PD motor fluctuations.

KEYWORDS

**Parkinson's disease, motor symptom diary, motor fluctuations, electric device, patient reported outcome measures**

# Introduction

As Parkinson's disease (PD) progresses, fluctuations in motor and non-motor symptoms can significantly affect quality of life (1). Therefore, PD symptom diaries are widely used in clinical research and medication reconciliation as an important tool to monitor patients' symptom fluctuations. Prior studies have examined the reliability of paper symptom diaries and have demonstrated the reliability of the patient- or caregiver-reported symptom outcome (2–4). However, current symptom diaries have also raised issues such as low record rates and inaccuracy due to recall bias (5, 6). Therefore, an electronic symptom diary has been developed to record symptoms more accurately and in a real-time manner (7, 8).

A previous study compared the motor status of patients recorded in paper and electronic symptom diaries. It showed no significant differences in ON–OFF status or number of entries between electronic and paper diaries, indicating no advantage of electronic symptom diaries over paper diaries (9).

We focused on recall bias and developed an electronic symptom diary that allows only real-time recording. The purpose of this study is to compare the symptom variability in PD patients recorded by our electronic symptom diaries and by traditional paper symptom diaries and to evaluate the effectiveness of our electronic diary that allowed only real-time recording.

# Materials and methods

## Study protocol approvals and patient consent

The protocol conformed to Helsinki Declaration principles and was approved by the Osaka University review board (approval number: 22311). All participants received written informed consent.

## Participants

This observational study was conducted from May to November 2023. Participants were recruited from PD patients attending the outpatient department of neurology at Osaka University, Japan. The inclusion criteria were as follows: a diagnosis of clinically established or probable PD on the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease, age 20 years or older, ability to understand and consent to the study, and a history of smartphone use. Exclusion criteria were Mini Mental State Examination (MMSE) score of 26 or less and the inability to use a smartphone.

## Procedures

The procedures are summarized in Figure 1.

**Visit 1:** Patients were introduced to the electronic symptom diary, with a demonstration to ensure they could operate it effectively. The paper symptom diary was also explained, and patients were asked if they felt confident in filling it as instructed. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 1, 2, 3, 4, and The Parkinson's Disease Questionnaire (PDQ)-39 were investigated.

**Training period:** To allow adequate time for participants, those who already use smartphones, to become familiar with this electronic diary, patients were asked to use both the electronic and paper symptom diaries at home for 1 month for both diaries. There were no restrictions on the frequency of assessments, and patients freely entered their symptoms into either the paper or digital diaries. During this time, they received phone support as needed for any questions or technical issues. This one-month period was deemed sufficient to become familiar with this application.

**Visit 2:** During the training period, we verified that the equipment was used correctly and moved to the recording period.

**Recording period (i)** Paper diary record: A paper symptom diary record was conducted for 7 consecutive days. Patients recorded symptoms every 30 min for 12 h from 8:00 am to 8:00 pm. Patients were allowed to look back and describe their symptoms in accordance with the conventional paper symptom diary recording method.

**Recording period (ii)** Electronic diary record: The patient was subsequently recorded in an electronic symptom diary for seven consecutive days after 7 days paper diary record. Recording was done every 30 min for 12 h from 8:00 a.m. to 8:00 p.m. Every 30 min, an alert with vibration was displayed to prompt recording. Patients were only allowed to record in real-time and were not allowed to look back on past symptoms (Supplementary Figure 1).

Patients completed a patient questionnaire on the usability of the diaries after the recording period (7). The questions in the questionnaire were as follows.

Responses given to the usability questionnaire (%). **Q1**: "The paper diary interfered with my normal activities." Responses: 1 – Strongly Agree, 2 – Agree, 3 – Sometimes Agree, 4 – Occasionally Agree, 5 – Strongly Disagree. **Q2**: "Using the paper diary system on a daily basis was easy." Responses: 1 – Strongly Disagree, 2 – Occasionally Agree, 3 – Sometimes Agree, 4 – Agree, 5 – Strongly Agree. **Q3**: "If your doctor wants to use paper diary to monitor your symptoms and adjust your medications, how long would you be willing to record your symptoms?" Responses: 1 – A few days, 2 – 1 week, 3 – 2–3 weeks, 4 – More than 1 month. **Q4**: "The electronic diary interfered with my normal activities." Responses: 1 – Strongly Agree, 2 – Agree, 3 – Sometimes Agree, 4 – Occasionally Agree, 5 – Strongly Disagree. **Q5**: "Using the electronic diary system on a daily basis was easy." Responses: 1 – Strongly Disagree, 2 – Occasionally Agree, 3 – Sometimes Agree, 4 – Agree, 5 – Strongly Agree. **Q6**: "If your doctor wants to use electronic diary to monitor your symptoms and adjust your medications, how long would you be willing to record your symptoms?" Responses: 1 – A few days, 2 – 1 week, 3 – 2–3 weeks, 4 – More than 1 month. **Q7**: "I felt comfortable wearing the smartwatch." Responses: 1 – Strongly Disagree, 2 – Occasionally Agree, 3 – Sometimes Agree, 4 – Agree, 5 – Strongly Agree. **Q8**: "The smartwatch was easy to put on/take off." Responses: 1 – Strongly Disagree, 2 – Occasionally Agree, 3 – Sometimes Agree, 4 – Agree, 5 – Strongly Agree. **Q9**: "I felt embarrassed wearing the smartwatch." Responses: 1 – Strongly Agree, 2 – Agree, 3 – Sometimes Agree, 4 – Occasionally Agree, 5 – Strongly Disagree. **Q10**: I experienced technical problems with the electronic diary. Responses: 1 – Strongly Agree, 2 – Agree, 3 – Sometimes Agree, 4 – Occasionally Agree, 5 – Strongly Disagree. Color code from green (score = 1 for least favorable response) to orange (score = 5 for most favorable response).

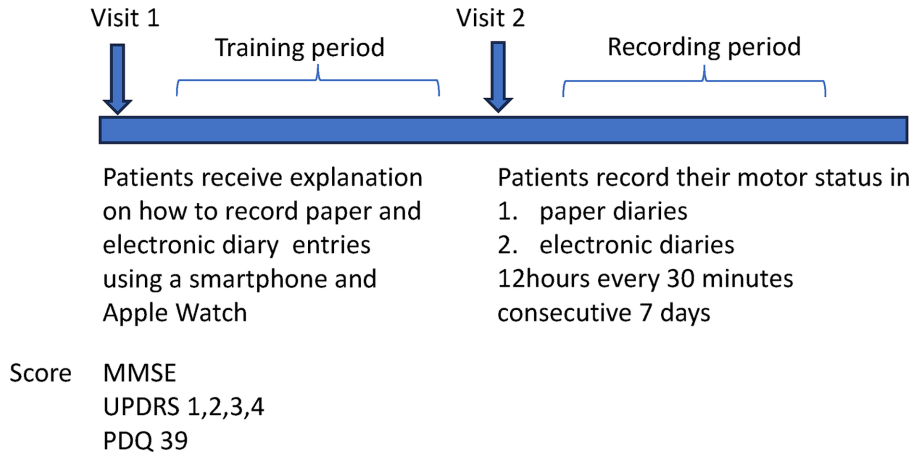


FIGURE 1
The study protocol. Participants conducted 1 week of recording in each diary after the one-month training period.

## About the symptom diary

The paper symptom diary used was Parkinson's Disease Home Diary (10). Participants were then asked every half-hour time period to indicate their predominant symptom status using the categories of On without dyskinesia, On with non-troublesome dyskinesia, On with troublesome dyskinesia, and Off for seven consecutive days.

In both paper and electronic diary, On with non-troublesome dyskinesia and On without dyskinesia were defined as ON-status. Off was defined as OFF-status. Troublesome dyskinesia was defined as Troublesome dyskinesia-status. Number of entries was defined as the number of times the patient actually recorded the symptom diary. For example, in the paper symptom diary, if the patient described his/her motor status for the last 2 h at once, the number of entries was counted as 1 and the recording time was counted as 2 h. The electronic symptom diary did not permit retrospective entries, so the recording time was 30 min per entry count (Supplementary Figure 2).

We defined "Missing time" as no recordings within 30 min and "Duplicate time" as multiple motor status recordings within 30 min. Both "Missing time" and "Duplicate time" were treated as missing data. "Reporting time" is the number of hours minus "Missing time" and "Duplicate time." The proportion of motor status was calculated as the percentage of time recorded as troublesome dyskinesia status/ON status/OFF status out of the total input time, excluding missing data (Missing + Duplicate time).

## Outcomes and statistics

The primary outcome was the number of entries in the electronic diary compared to the paper symptom diary. The secondary outcome was the potential association/s between motor fluctuation recorded in each diary and patient-reported outcomes (MDS-UPDRS 1,2,3,4 and PDQ-39). While not all the measures are matched in their recorded time period, this correlational analyses can explore whether they are related measures. Moreover, we evaluated whether the diary type (either paper diary or electronic diary) and number of days were associated with changes in the number of entries recorded. Additionally, we surveyed the patients' usability questionnaire.

All data are presented as median and interquartile ranges (IQR) or counts and percentages.

Values were compared using the Mann–Whitney U-test for continuous variables and the chi-square test for categorical variables. Spearman correlation coefficient was used to correlate motor fluctuation rates between paper and electronic diaries. Spearman correlation coefficient was also used to compare the MDS-UPDRS 1, 2, 3, 4, PDQ-39 and the motor symptoms recorded on paper and electronic diaries, respectively, to examine the validity of the recorded symptoms. To evaluate whether the diary type and number of days were associated with changes in the number of entries recorded, an analysis of covariance (ANCOVA) was performed. The ANCOVA model included the diary type (either paper diary or electronic diary) and the number of days as independent variables, with the number of entries as the dependent variable. Statistical analysis was performed using the R software.[1] The level of significance was set at $p < 0.05$.

# Results

The number of participants was 19. A total of 17 participants were analyzed, excluding one who entered the data only once during the 7-day paper and digital diary recording period, respectively, and one whose paper symptom diary was illegible. The median age was 61 years (IQR 48–64) and 10 (59%) were male. Detailed basic characteristics are shown in Table 1.

Table 2 shows the entry status of the paper and electronic symptom diaries. No significant difference in the number of entries was found between paper and electronic symptom diaries (paper 115 [71–147] vs. electronic 109 [93–116], $p = 0.77$). Reporting time was significantly higher in the paper symptom diary, and "Missing time" was significantly higher in the electronic symptom diary.

1 https://cran.r-project.org/

TABLE 1 Baseline characteristics of patients with Parkinson's disease.

| | Patients ($n = 17$) |
|---|---|
| Age, years (IQR) | 61 (48–64) |
| Sex, *n* (%) | |
| Male | 10 (59) |
| Female | 7 (41) |
| Duration, year (IQR) | 8 (6–10) |
| Hoehn and Yahr, *n* (%) | |
| 2 | 13 (77) |
| 3 | 3 (18) |
| 4 | 1 (6) |
| LEDD, mg (IQR) | 1,050 (600–1,510) |
| MMSE, *n* (%) | |
| 27 | 2 (12) |
| 28 | 1 (6) |
| 29 | 3 (18) |
| 30 | 11 (65) |
| MDS-UPDRS 1 (IQR) | 7 (4–14) |
| MDS-UPDRS 2 (IQR) | 9 (6–14) |
| MDS-UDPRS3 3 (IQR) | 16 (11–18) |
| MDS-UPDRS 4 (IQR) | 4 (0–11) |
| PDQ-39 (IQR) | 32 (15–54) |

IQR, interquartile range; LEDD, levodopa equivalent daily dose; MMSE, mini mental state examination; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PDQ-39, The Parkinson's disease questionnaire-39.

TABLE 2 Comparison of recording time for each status in paper and electronic diaries.

| | Paper-D. | Electronic-D. | *p* |
|---|---|---|---|
| Total entries, (IQR) | 115 (71–147) | 107 (93–116) | 0.77 |
| Total reported time, h (IQR) | 69 (61–80) | 48 (33–57) | 0.001 |
| Troublesome dyskinesia time, h (IQR) | 0 (0–1.5) | 0 (0–0.5) | 0.63 |
| Troublesome dyskinesia rate, % (IQR) | 0 (0.0–0.2) | 0 (0–0) | 0.81 |
| Total ON time, h (IQR) | 49.5 (28.5–56) | 33 (24.5–50) | 0.12 |
| ON time rate, % (IQR) | 67 (62–81) | 80 (64–98) | 0.44 |
| Total OFF time, h (IQR) | 16 (8–28) | 5 (0.5–9.5) | 0.01 |
| OFF time rate, % (IQR) | 25 (13–36) | 14 (1–27) | 0.34 |
| Total duplicate time, h (IQR) | 0 (0–0.5) | 0.5 (0.5–2.0) | 0.14 |
| Total Missing time, h (IQR) | 12.5 (4.5–20) | 37.5 (33.5–51.5) | < 0.001 |

IQR, interquartile range.

Next, we compared the motor fluctuation rate (ON-time rate, OFF-time rate, and Troublesome dyskinesia rate) evaluated by paper and electronic diaries (Figure 2). Significant correlations were found between paper and electronic diaries for ON-time rate, OFF-time rate, and troublesome dyskinesia time rate ($r = 0.61$ [$p < 0.05$], $r = 0.76$ [$p < 0.05$], and $r = 0.57$ [$p < 0$ 05], respectively). Then, we analyzed the correlation between the status of the motor symptoms captured in each symptom diary and the Parkinson's disease clinical scales, MDS-UPDRS part 1–4 and PDQ-39 (Table 3). Interestingly, the electronic diary-based ON time rate was significantly correlated with several clinical scales, including MDS-UPDRS part 1, 2, 4, and PDQ-39. The electronic diary-based OFF time rate was also significantly correlated with MDS-UPDRS part 1 and 2. On the other hand, the paper diary-based ON time rate was only significantly correlated with UPDRS part 1 and 4, and the paper diary-based OFF time rate was not significantly correlated with any of the scores.

Additionally, we analyzed whether the diary type and number of days were associated with changes in the number of entries recorded (Figure 3). The number of days was associated with a decrease in the

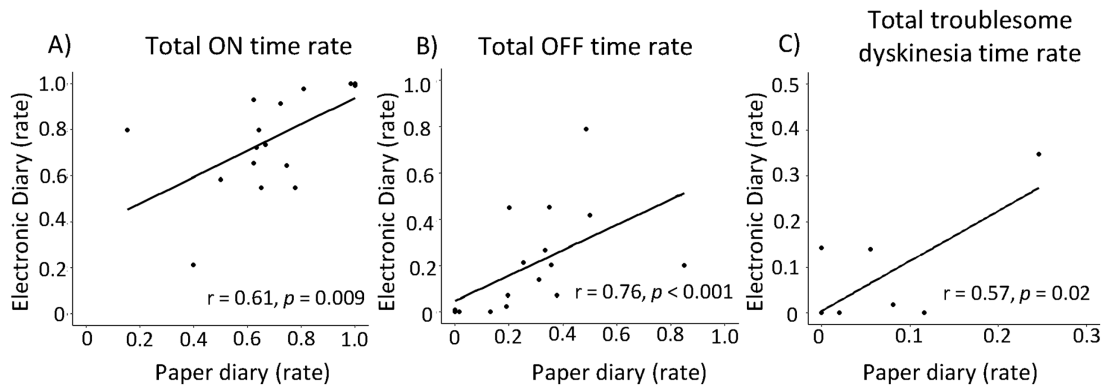


FIGURE 2
Correlations between electronic diary and paper diary. Correlations between electronic diary and paper diary based on motor status: Total ON time rate (A), total OFF time rate (B), Total troublesome dyskinesia rate (C). There were significant correlations between the proportion of motor status each group.

TABLE 3 Correlations between symptom diaries and scales.

| | Electronic-D. ON time-rate | Electronic-D. OFF time-rate | Paper-D. ON time-rate | Paper-D. OFF time-rate |
|---|---|---|---|---|
| MDS-UPDRS part 1 | −0.69** | 0.51* | −0.48* | 0.38 |
| MDS-UPDRS part 2 | −0.58* | 0.49* | −0.07 | 0.10 |
| MDS-UPDRS part 3 | 0.07 | −0.28 | 0.23 | −0.35 |
| MDS-UPDRS part 4 | −0.70** | 0.47 | −0.56* | 0.42 |
| PDQ-39 | −0.58** | 0.40 | 0.24 | 0.21 |

Spearman correlation: $^{**}p < 0.01$, $^{*}p < 0.05$.
MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PDQ-39, The Parkinson's disease questionnaire-39.

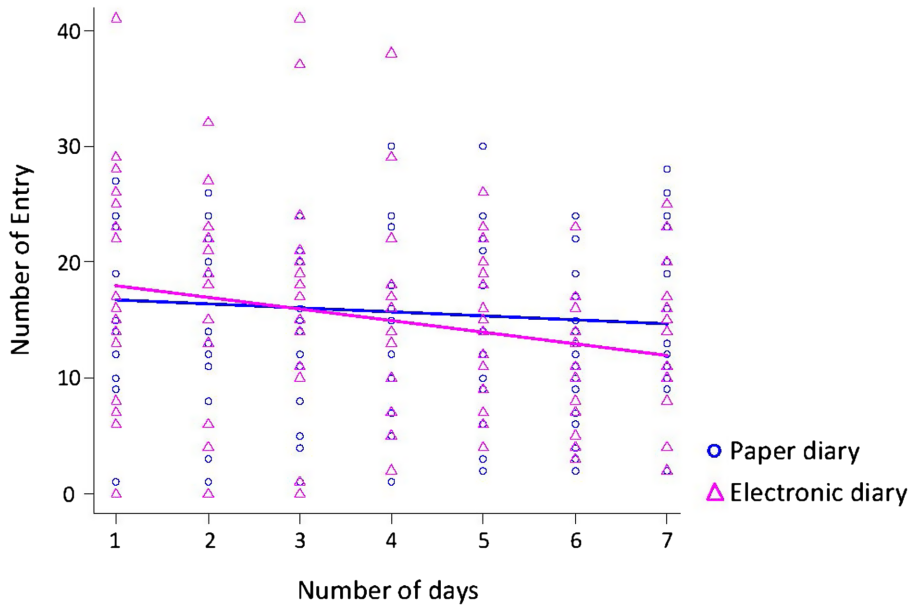


FIGURE 3
Relationship between the number of entries and the number of days. The number of days was associated with a decrease in the number of entries. Diary type was not significantly associated with a decrease in the number of entries.

number of entries ($F_{1,235} = 6.83$, $p = 0.01$). Diary type was not significantly associated with a decrease in the number of entries ($F_{1,235} = 0.48$, $p = 0.49$).

Finally, the results of the patient survey about usability are shown in Figure 4. Regarding daily life interruptions due to the use of the symptom diary, about half of the patients reported that the paper

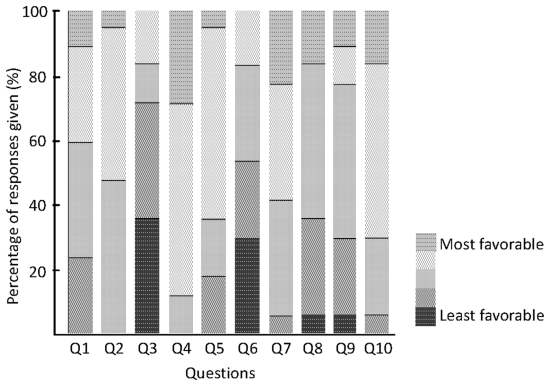


FIGURE 4
Patients questionnaire. Responses given to the usability questionnaire (%). Color code from green (score = 1 for least favorable response) to orange (score = 5 for most favorable response).

version sometimes or frequently interfered with their daily life (Q1). In contrast, no patient reported that the electronic diary interfered frequently and only 12% of the patients reported that it sometimes interfered with their daily life (Q4). None of the participants found the recording method difficult on paper (Q2). Even with the electronic diary, 80% of patients rated it as operable (Q5).

## Discussion

We developed an electronic diary in Japanese. There was no significant difference in the number of entries between the paper and electronic diaries, maintaining compliance. However, the reported time was significantly shorter for the electronic symptom diaries. This suggests that the paper diary involves recording symptoms retrospectively. Our results showed that about one-fourth of the time recorded in the paper diary was done retrospectively, highlighting the issue of recall bias, which has been identified as a problem with paper symptom diaries. In this study, we showed that the status of the motor symptoms, such as ON time rate, OFF time rate, and Troublesome dyskinesia rate, was significantly correlated between paper and electronic symptom diaries, which is consistent with previous studies. Interestingly, however, when comparing the recorded status of the motor symptoms to other patient-reported outcomes such as MDS-UPDRS part 1, 2, 4 and PDQ-39, the electronic symptom diary showed significant correlations with a wider range of items than the paper symptom diary. PDQ-39 and MDS-UPDRS part 4 have been reported to correlate with motor fluctuations in PD patients (11, 12). MDS-UPDRS part 1 and 2 have been reported to relate to quality of life in PD patients (13). Therefore, the electronic symptom diary may more accurately reflect the patient's symptoms and quality of life. Our electronic diary, which allowed only real-time entries, may have eliminated recall bias, thereby reflecting the patient's symptoms more accurately. The reason why MDS-UPDRS par 3 did not correlate with both paper and electronic diary may be due to the fact that MDS-UPDRS part 3 was only evaluated at the time of the outpatient visit, which does not correctly reflect the patient's motor fluctuation and general status at home. The symptom diary, which records continuous symptoms, is crucial in managing patients with Parkinson's disease. Our electronic diary offers the advantage of also being able to record and evaluate patient-reported outcomes such as MDS-UPDRS part 1, 2, 4 and PDQ-39.

The usability of our electronic diary was found to be satisfactory based on the results of patients` questionnaire.

The present study also suggests that real-time input is difficult. Missing time in the electronic symptom diary averaged 37.5 h, or 45% of the total time. The devices had reminders to remind them every 30 min with vibration, but patients said that they often did not notice the vibration in their daily life and work, and even when they did notice it, they could not respond immediately, resulting in missed entries. In addition, the electronic symptom diary was sometimes unavailable for a certain period of time due to equipment failure or battery problems with the device. Improvement of the reminding function should be considered in the future. Furthermore, regardless of the type of symptom diary (paper or electronic), the number of entries tended to decrease as the number of days passed, suggesting user fatigue. Despite the reduced recording time, the correlations between exercise symptoms recorded in the electronic diary and patient-reported outcomes such as MDS-UPDRS part 1, 2, 4 and PDQ-39 were strong, suggesting that the recording frequency need not be as frequent as every 30 min. Determining the appropriate recording frequency is a subject for future study.

In addition, this study has several other limitations. The study design included a small sample size and was not a crossover. Conducting the paper diary first, followed by the electronic diary, also introduces potential bias. We acknowledge the need for a larger crossover study in the future. Another limitation is that the study did not implement the paper and app-based symptom diaries simultaneously, so it was not possible to examine concordance between the two methods for identical epochs. However, since there were no medication changes for Parkinson's disease during this period and the assessments were conducted within a similar timeframe, we believe that the two methods likely reflect comparable motor fluctuations. Furthermore, the doctor's evaluation was not conducted simultaneously with the patient reports, so no supervised data were available. In future studies, it would be beneficial to incorporate objective data collection methods, such as accelerometers, to compare against patient-oriented diaries. As previously noted, the correlational analyses were not based on exactly matching time periods, making it difficult to determine whether the reported motor fluctuations are accurate when compared to the patient questionnaire data (MDS-UPDRS and PDQ-39).

In conclusion, our electronic diary is a useful tool that more accurately reflects the patient's motor symptoms and quality of life compared to the paper symptom diary. In the future, we hope that the use of such digital instruments to assess drug efficacy and DAT responsiveness will enhance more data-driven Parkinson's disease treatment and ultimately lead to improved patient quality of life.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by the Osaka University review board (approval number: 22311). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

KA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. ES: Data curation, Formal analysis, Methodology, Writing – review & editing. KIw: Data curation, Formal analysis, Software, Writing – review & editing. HN: Data curation, Formal analysis, Methodology, Software, Writing – review & editing. YKa: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. ST: Conceptualization, Formal analysis, Supervision, Writing – review & editing. LG: Methodology, Supervision, Writing – review & editing. KK: Data curation, Supervision, Writing – review & editing. YKi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. TM: Investigation, Methodology, Project administration, Software, Supervision, Writing – review & editing. HU: Conceptualization, Data curation, Software, Supervision, Writing – review & editing. KIk: Conceptualization, Formal analysis, Investigation, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. HM: Investigation, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1476708/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Examples of each symptom diary. (A) Paper diary. In this case, the diary showed eight entries, and the reported time was 8 h. (B) Electronic dairy. In this case, the diary showed eight entries, and the reported time was 4 h.

SUPPLEMENTARY FIGURE 2
Data protocol. Patients use a smartphone or smartwatch application to record their motor status. The data is transmitted to a server/database and can be shared with doctors through a web application. A reminder function is available on both the smartphone and smartwatch, which sends a push notification if no symptom entries are recorded within a 30-min period.

# References


1. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord*. (2005) 20:224–30. doi: 10.1002/mds.20279

2. Hauser RA, Deckers F, Lehert P. Parkinson's disease home diary: further validation and implications for clinical trials. *Mov Disord*. (2004) 19:1409–13. doi: 10.1002/mds.20248

3. Timpka J, Löhle M, Bremer A, Christiansson S, Gandor F, Ebersbach G, et al. Objective observer vs. patient motor state assessments using the PD home diary in advanced Parkinson's disease. *Front Neurol*. (2022) 13:e935664. doi: 10.3389/fneur.2022.935664

4. Papapetropoulos SS. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Ther*. (2012) 18:380–7. doi: 10.1111/j.1755-5949.2011.00253.x

5. Antonini A, Martinez-Martin P, Chaudhuri RK, Merello M, Hauser R, Katzenschlager R, et al. Wearing-off scales in Parkinson's disease: critique and recommendations. *Mov Disord Clin Pract*. (2011) 26:2169–75. doi: 10.1002/mds.23875

6. Lyons KE, Pahwa R. Electronic motor function diary for patients with Parkinson's disease: a feasibility study. *Parkinsonism Relat Disord*. (2007) 13:304–7. doi: 10.1016/j.parkreldis.2006.06.008

7. Debelle H, Packer E, Beales E, Bailey HGB, Mc Ardle R, Brown P, et al. Feasibility and usability of a digital health technology system to monitor mobility and assess medication adherence in mild-to-moderate Parkinson's disease. *Front Neurol*. (2023) 14:e1111260. doi: 10.3389/fneur.2023.1111260

8. Vizcarra JA, Sánchez-Ferro Á, Maetzler W, Marsili L, Zavala L, Lang AE, et al. The Parkinson's disease e-diary: developing a clinical and research tool for the digital age. *Mov Disord*. (2019) 34:676–81. doi: 10.1002/mds.27673

9. Terroba-Chambi C, Bruno V, Medina-Escobar A, Nanni F, Cerquetti D, Rossi M, et al. Open-access electronic diary for motor fluctuation and dyskinesia evaluation in Parkinson disease: comparison with paper diary. *Clin Neuropharmacol*. (2018) 41:20–2. doi: 10.1097/WNF.0000000000000264

10. Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. *Clin Neuropharmacol*. (2000) 23:75–81. doi: 10.1097/00002826-200003000-00003

11. Hechtner MC, Vogt T, Zöllner Y, Schröder S, Sauer JB, Binder H, et al. Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries. *Parkinsonism Relat Disord*. (2014) 20:969–74. doi: 10.1016/j.parkreldis.2014.06.001

12. Raciti L, Nicoletti A, Mostile G, Bonomo R, Contrafatto D, Dibilio V, et al. Validation of the UPDRS section IV for detection of motor fluctuations in Parkinson's disease. *Parkinsonism Relat Disord*. (2016) 27:98–101. doi: 10.1016/j.parkreldis.2016.03.008

13. Skorvanek M, Rosenberger J, Minar M, Grofik M, Han V, Groothoff JW, et al. Relationship between the non-motor items of the MDS-UPDRS and quality of life in patients with Parkinson's disease. *J Neurol Sci*. (2015) 353:87–91. doi: 10.1016/j.jns.2015.04.013

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# Patient perspectives on the use of digital medical devices and health data for AI-driven personalised medicine in Parkinson's Disease

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**Introduction:** Parkinson's Disease (PD) affects around 8.5 million people currently with numbers expected to rise to 12 million by 2040. PD is characterized by fluctuating motor and non-motor symptoms demanding accurate monitoring. Recent advancements in digital medical devices (DMDs) like wearables and AI offer promise in addressing these needs. However, the successful implementation of DMDs in healthcare relies on patients' willingness to adopt and engage with these digital tools.

**Methods:** To understand patient perspectives in individuals with PD, a cross-sectional study was conducted as part of the EU-wide DIGIPD project across France, Spain, and Germany. Multidisciplinary teams including neurodegenerative clinics and patient organizations conducted surveys focusing on (i) sociodemographic information, (ii) use of DMDs (iii) acceptance of using health data (iv) preferences for the DMDs use. We used descriptive statistics to understand the use of DMDs and patient preferences and logistic regression models to identify predictors of willingness to use DMDs and to share health data through DMDs.

**Results:** In total 333 individuals with PD participated in the study. Findings revealed a high willingness to use DMDs (90.3%) and share personal health data (97.4%,) however this differed across sociodemographic groups and was more notable among older age groups (under 65 = 17.9% vs. over 75 = 39.29%, $p = 0.001$) and those with higher education levels less willing to accept such use of data (university level = 78.6% vs. 21.43% with secondary level, $p = 0.025$). Providing instruction on the use of DMDs and receiving feedback on the results of the data collection significantly increased the willingness to use DMDs (OR = 3.57, 95% CI = 1.44–8.89) and (OR = 3.77, 95% CI = 1.01–14.12), respectively.

**Conclusion:** The study emphasizes the importance of considering patient perspectives for the effective deployment of digital technologies, especially for older and more advanced disease-stage patients who stand to benefit the most.

KEYWORDS

Parkinson's Disease, patient-centeredness, personalized medicine, acceptance of digital medical devices, patient preferences, use of health data, trust, Adoption of AI

# Introduction

Parkinson's Disease (PD) is a complex neurodegenerative condition affecting approximately 8.5 million people, with the number expected to rise to 12 million by 2040 (1). The condition is characterized by a spectrum of combined motor and non-motor symptoms that fluctuate over the course of the disease, necessitating timely and accurate monitoring of treatment response, disease severity, and progression. Recent advances in Digital Medical Devices (DMDs) and related health technologies, including wearables and sensors, coupled with Artificial Intelligence (AI), hold substantial promise in addressing these requirements in both clinical and clinical research settings (2–4). By capturing precise and reliable longitudinal information regarding the daily functioning of individuals diagnosed with PD, these technologies enable accurate and objective assessments of health trajectories, aid in communication and clinical decision-making, and make it possible to evaluate treatment effectiveness (2, 5). Indeed, current assessment methods predominantly rely on clinical and patient-reported assessments, introducing numerous biases such as the experience of the clinician, patient recall, episodic assessments and inter-rater variability, which pose substantial challenges in measuring the fluctuating nature of PD symptoms (6, 7).

Despite the increasing availability and advantages of DMDs, the successful implementation of these technologies in healthcare and clinical research will depend highly on patient acceptance and engagement (8). Numerous studies in the general population have highlighted that various personal factors such as sociodemographic characteristics, digital literacy or privacy and trust concerns can hinder the use of DMDs (9–12). Regarding the acceptance of AI in healthcare, some of the major reasons behind the lack of trust are found to be the lack of responsibility attribution in terms of error, concerns over individual privacy and 'perceived uniqueness neglect'– AI's inability to adequately capture the unique characteristics and symptoms of individual patients (13, 14).

Studies investigating the acceptance and the use of digital tools and AI by individuals with PD generally suggest that individuals with PD are more accepting DMDs if they are younger, when they perceive their added value, and if technologies are more user-friendly. In general, they would accept DMDs if they facilitate disease management, track functionalities and symptoms, improve interactions with healthcare professionals or provide knowledge and social support (15–17). For instance, Duroseau et al. (18) studied the acceptance of DMD-based communication tools in a sample of 109 individuals with PD and found that willingness to use digital communication tools decreased with age. In addition, individuals with PD are more inclined to utilize DMDs for home care if the technology requires minimal effort, can be seamlessly integrated into their daily routine, and if they receive sufficient support from the study team (19). A study by LaBueno et al. further found that higher digital acceptance rates were associated with higher digital competencies among the users (16).

While these studies explore the factors that could influence patient acceptance of DMDs in general, there has been limited work on the perspective of individuals with PD regarding their willingness to use AI-based DMDs as well as their preferences regarding the sharing of their data for AI-driven personalized care. This lack of focus on patient needs and preferences can have major implications when implementing DMDs and AI in healthcare and clinical research, especially as it concerns complex diseases such as PD. Therefore, this study aims to investigate the determinants of the willingness to use DMDs and the collection of sensitive data for AI processing, as well as to capture patient views, concerns, and preferences related to such use while considering their sociodemographic and the clinical status.

# Materials and methods

## Study design, population and setting

This multicentre cross-sectional study was conducted across Parkinson's patient cohorts in France, Spain, and Germany as part of the EU-wide DIGIPD project (20). The primary objective of the project was to validate the potential of digital biomarkers to support early diagnosis and personalized disease management of patients with PD. The cross-sectional survey, which is the subject of this paper, enrolled participants who had received a clinical diagnosis of Parkinson's and provided informed consent (Review Ethical Committee Code: 22/320-E). Individuals with PD exhibiting significant cognitive impairment, intellectual disability, or other severe psychiatric conditions were excluded from participation.

## Patient recruitment

To recruit participants, a multifaceted approach was conducted, leveraging databases from collaborating organizations, national patient associations, and prominent social media platforms such as Twitter, Facebook, LinkedIn, Google+, in addition to communication channels like partner magazines. The DIGIPD project's social networks, accessible at https://www.digipd.eu/, were also instrumental in reaching potential participants. The recruitment process involved proactive engagement by members of the DIGIPD team who sent invitations to all individuals with PD who expressed interest in being contacted for research projects. Interested participants received project information and reviewed and signed online or paper-based informed consent form. The principal investigator and a trained team member responsible for obtaining informed consent facilitated this process. Those meeting the inclusion criteria were invited to participate within the designated timeframe (January to March 2022) by e-mail or by phone.

## The development of the survey

The development of the questionnaires was informed by the literature on acceptance of digital health technologies (21, 22), as well as by the input of clinicians, researchers, individuals with PD and patient organization. The survey was divided into four main themes: (i) sociodemographic information, (ii) use of DMDs (iii) acceptance of using health data (iv) preferences for the DMDs use. The survey, initially drafted in English, was translated into French, German and Spanish using the EU survey platform's automated translation feature. Subsequently, to ensure linguistic accuracy and cultural relevance, the translations underwent review by personnel affiliated with the project partners: the Clinical Research Centre of the Paris Brain Institute for French, the University Hospital Erlangen for German and the Association Parkinson Madrid for Spanish. This collaborative effort aimed to enhance the quality and precision of the translated survey content, aligning it with the linguistic nuances and context-specific considerations of each target language. Finally, the survey was tested for feasibility in a workshop with three PD patients and researchers. The primary objectives of the workshop were twofold: firstly, to estimate the time required for completion of the survey, and secondly to assess and ensure a comprehensive understanding of the survey content and to make necessary adjustments, ensuring the overall robustness of the survey instrument prior to its wider dissemination. The complete survey can be found in Appendix 1.

## Main study variables

### Sociodemographic and clinical characteristics

The following variables were collected as a part of the sociodemographic characteristics: country of residence (France, Germany, Spain, Other) age categories (under 65, 65 to 75, Over 75), gender (female, male, intersex), educational level (no formal education, primary, secondary, post-secondary, bachelor degree, master degree, doctorate) added as a continuous variable in the regression model, and disease duration since diagnosis (<1 year, 1 to 5 years, 6 to 10 years, 11 to 15 years, 16 to 20 years, over 20 years) grouped across four levels due to small sample size in some categories (newly diagnosed, 1 to 5 years, 6 to 10 years and over 10 years).

### Willingness to use DMDs, sharing health data and confidence in AI for health decision-making

Patients were asked questions about:

- their willingness to use DMDs in the healthcare context: '*Would you use digital devices (i.e., smartphone, tablet, computer, specific wearable device – gait sensor on a shoe) if this would improve the information that your healthcare team has about you*' with response categories (yes, no, not sure), grouped into a binary variable ("yes" or "no/not sure").
- their acceptance of health data collection through digital tools for clinical purposes: '*Would you accept the use of your physical or mental state data, gathered through digital devices (i.e., smartphone, tablet, computer, specific wearable device – gait sensor on a shoe), for your medical treatment and health care purposes?*', with response categories (yes, no and not sure), as well grouped into a binary variable ("yes" or "no/not sure")
- their confidence in the use of AI-based clinical decision and support: '*Would you be confident in a healthcare decision/recommendations based on a computer calculation using formula of your data?*', dichotomized into 'No Confidence AI' (I refuse such use, I am afraid of such use) and 'Confidence in AI' (I accept such use if it helps the physician with the diagnosis, I fully trust it).

### Preferences and concerns

Finally, participants were asked about their preferences related to the use and functionalities of DMDs. This included preferences for particular types of DMDs (smartphones, computers with microphone and webcam, shoe sensors, headset microphone), preferred data collection settings (at home, hospital, both), and duration. Participants were also queried about their perspective on receiving feedback on the obtained measurements, instructions, and motivational messages (yes, no/not sure), and whether those functionalities would encourage their use of DMDs. Moreover, participants were asked about preferences regarding the type of instructions (animation videos, real-person videos, written manuals, pop-up messages). Lastly, participants were asked to share concerns related to the use of DMDs (abilities to handle them, privacy concerns, time-consuming, no concerns).

## Statistical analysis

In the first step, we performed a descriptive analysis of the sample characteristics and main variables concerning the use of DMDs, concerns and preferences. Next, depending on the sample size, for the categorical variables we used chi-squared or Fisher exact tests, to identify significant differences in the use and willingness to use DMDs, concerns with DMDs, trust in AI as well as preferences for data collection across various countries, sociodemographic groups and among participants with various disease durations. Post-hoc analysis was performed to analyze adjusted residuals (person residuals divided by an estimate of their standard error) (23). To ensure the clarity and meaningful interpretation of our analysis, participants categorized under 'Other' in the country variable were excluded from the study. We report only results where we found significant differences between study variables. Finally, we performed a logistic regression analysis to understand which clinical, sociodemographic, and support factors (such as having instructions or receiving personalized feedback) are associated with the willingness to use DMDs (Model 1) and willingness to share health data for AI (Model 2) while controlling for country effects. The predictors were estimated on an odds ratio scale, with a 95% confidence interval. The first aimed to ensure that excluding the 'other' category from the country analysis would not significantly alter the results. The second analysis aimed to confirm that excluding participants who responded 'not sure' from the analysis and grouping them with those who responded 'no' did not yield different results.

# Results

## Patient sociodemographic and clinical characteristics

A total of 333 individuals with PD participated in the study. France accounted for 17%, Germany 8%, Spain 64%, and the remaining 11%

represented other regions. Among these participants, nearly half were below the age of 65, accounting for 49% ($n = 162$). The majority were male, making up 67% ($n = 221$), and a substantial proportion were well-educated, with 75.6% holding a university degree. Additionally, most participants (82%, $n = 270$) had been diagnosed with Parkinson's Disease (PD) within the past 10 years. A more detailed overview of the main participant's characteristics can be found in Table 1.

## Willingness to use DMDs, share health data, and confidence in AI for clinical decision support

Almost half of the participants (47%; $n = 159$) have already used digital devices (i.e., smartphone, tablet, computer, specific wearable device – gait sensor on a shoe) that collect, process, and/or display personal health data, although there were differences between countries. Those living in Germany reported higher use of DMDs than those living in Spain (77.8% vs. 45.5%, $p = 001$) (Figure 1A). The majority of individuals with PD (90.3%, $n = 278$) stated that they are willing to use DMDs if that aids clinical decision-making. However, this strong commitment was lower among the older age groups (6.45% of those under 65 stating they are not willing to use DMDs vs. 17.86% of those aged over 75, $p = 0.046$) (Figure 1B). Most participants (97.4%, $n = 302$) indicated that they would accept sharing their health data collected through DMDs. However, we observed differences across age groups and educational levels, with older age groups less willing to share their health data (under 65 = 17.9% vs. over 75 = 39.29%, $p = 0.001$) (Figure 2A), and those with higher education levels less willing to accept such use of data (78.6% with university level vs. 21.43% with secondary level, $p = 0.025$) (Figure 2B). Regarding confidence in AI for clinical decision support, although most of the respondents expressed confidence in AI, those with higher educational levels (university) tended to be less likely to trust an algorithm for clinical decision support compared to those with lower educational levels (secondary or less) (8% vs. 5.8%, $p = 0.016$) (Figure 3). No other significant differences across socio-demographic groups or disease duration were observed regarding the level of confidence in AI for clinical decision support.

TABLE 1 Characteristics of participants ($N = 333$).

| Variables | N | (%) |
|---|---|---|
| **Gender** | | |
| Male | 221 | 66.77 |
| Female | 110 | 33.23 |
| **Age categories (years)** | | |
| Under 65 | 162 | 48.80 |
| 65–75 | 108 | 32.53 |
| Over 75 | 62 | 18.67 |
| **Country of residence** | | |
| France | 56 | 16.8 |
| Germany | 27 | 8.11 |
| Spain | 214 | 64.26 |
| Other | 36 | 10.81 |
| **Level of education** | | |
| No primary school | 10 | 3.00 |
| Primary school | 19 | 5.71 |
| Secondary school | 52 | 15.62 |
| Bachelor's degree | 109 | 32.73 |
| Master's degree | 103 | 30.93 |
| Doctoral degree | 40 | 12.01 |
| **PD disease duration** | | |
| <1 year | 19 | 5.76 |
| 1–5 years | 142 | 43.03 |
| 6–10 years | 109 | 33.03 |
| Over 10 years | 60 | 18.18 |
| **Already used DMDs** | | |
| Yes | 159 | 47.89 |
| No | 165 | 49.70 |
| I'm not sure | 8 | 2.41 |

DMDs, Digital Medicine Devices.
Due to non-responses in certain demographic categories (e.g., gender, age, PD duration), some categories do not reflect the full sample size. Percentages are calculated based on the number of respondents for each specific category.

## Concerns related to the use of DMDs and preferences

Over half of the respondents with Parkinson's Disease (63%, $n = 210$) stated that they do not have any specific concerns related to the use of DMDs. However, this differed across countries (France = 67.9%, Germany = 44.4% and Spain = 28%, $p = 0.001$). Most of the concerns about using DMDs were related to the time burden of using a device (11%) and the inability to handle the device even with support from others (9%), which was particularly salient among the older respondents (66.7% in those over 75 vs. 13.3% in those under 65, $p = 0.000$) (Figure 4A), and among those with more advanced PD duration ($p = 0.51$) (Figure 4B). Only 5% of the respondents expressed concern about sharing their health data.

When it comes to the choice of DMDs, the majority of respondents (72.37%) preferred using smartphones, 20.42% preferred using a headset microphone, 30.33% expressed a preference for using a computer with a webcam and 45.05% expressed a preference for a shoe-sensor. However, differences in the level of preference for smartphones were found between those who were newly diagnosed (<1 year disease duration) and those with a longer PD disease duration (over 10 years) (94.7% vs. 61.7%, $p = 0.016$), respectively (Figure 5A), and across educational levels (primary = 41.4% and university level = 74.2%, $p = 0.002$) (Figure 5B). In terms of preferences for setting for data collection, 46% of the respondents expressed a preference for daily or monthly data collection at home, in contrast to the 3.3% who favored periodic data collection at the hospital with no statistical differences across sociodemographics or clinical status. Finally, the majority of the participants preferred to receive instructions (83%), with the most frequently preferred type of instructions being real-person

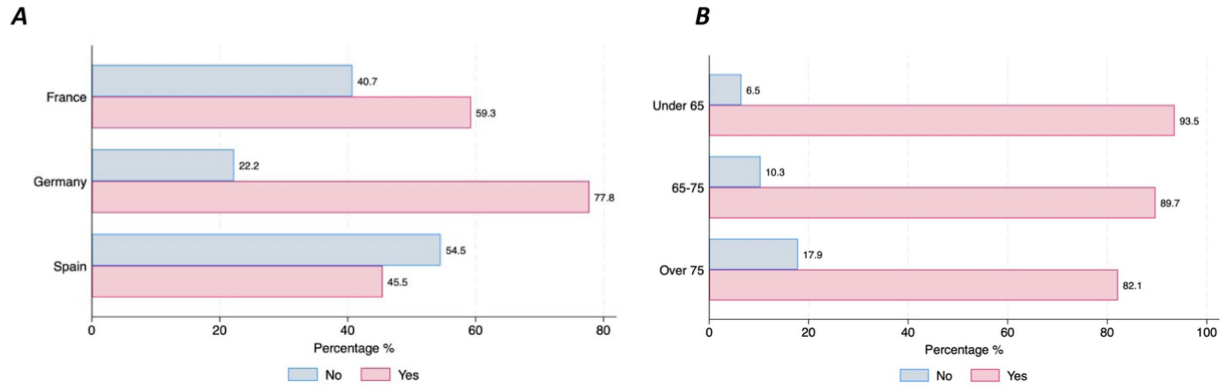


FIGURE 1
Use and Willingness to use DMDs by country and age groups. **(A)** Use of DMDs. **(B)** Willingness to use DMDs.

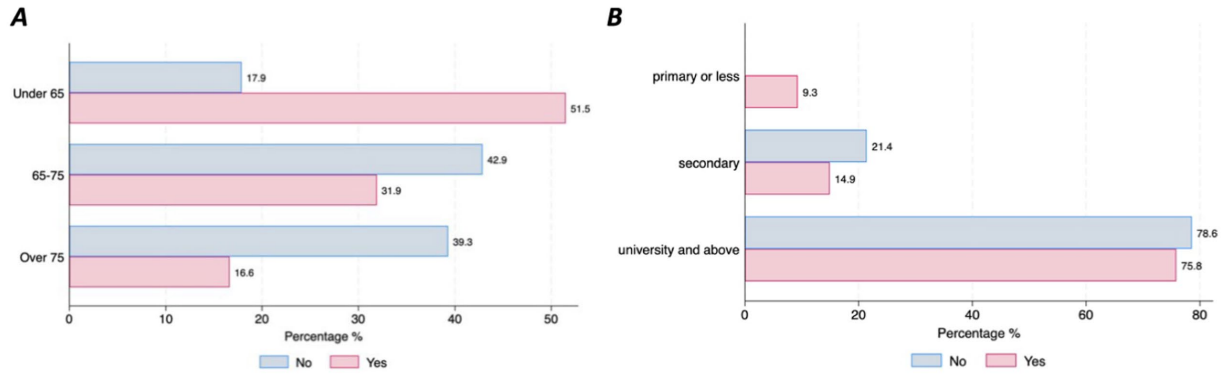


FIGURE 2
Willingness to share personal health data through DMDs for healthcare purposes by age and educational level. **(A)** Willingness to share health data by age. **(B)** Willingness to share health data by educational level.

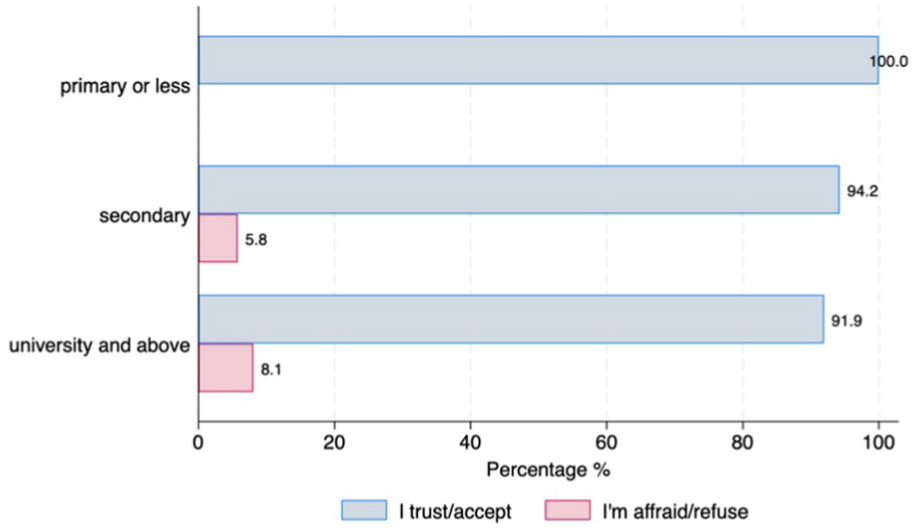


FIGURE 3
Confidence in AI for clinical decision support by educational level.

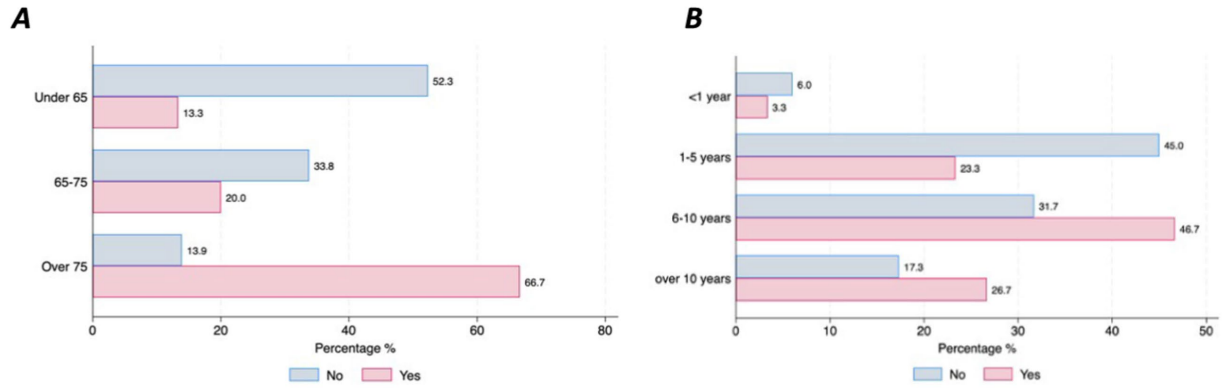


FIGURE 4
Concerns about handling DMDs by age and disease duration. **(A)** Concerns by age. **(B)** Concerns by disease duration.

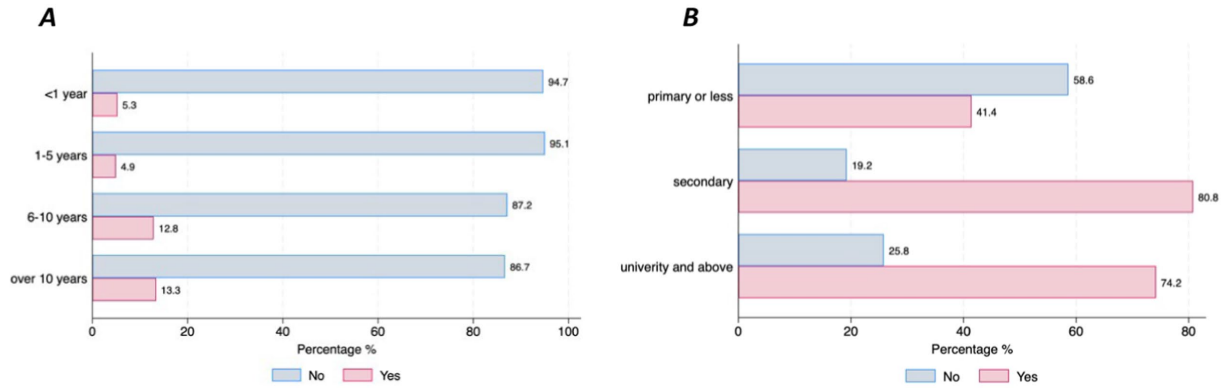


FIGURE 5
Preferences for using smartphones by disease duration and educational level. **(A)** Preferences for smartphones by PD duration. **(B)** Preferences for smartphones by education.

videos (43.2%), followed by animation videos (38.5%). Most of the respondents also expressed preferences for feedback, such as reports on the data that has been collected (94.3%), and the use of motivational messages (68.9%). No differences in preference for instructions, feedback or motivational messages based on sociodemographic characteristics and PD duration were observed.

## Results from the logistic regression

After controlling for country effects, findings from the first logistic regression model (Model 1, Table 2), examining the relationship between willingness to use DMDs for healthcare purposes and the clinical and sociodemographic factors, and support factors, show that age as well as support factors such as having instructions and feedback are strongly associated with the willingness to use DMDs in the context of healthcare. Individuals with PD who are over the age of 75 were less likely to be willing to use DMDs in the healthcare context (OR = 0.31, 95% CI = 0.11–0.83). Having instructions (OR = 3.57, 95% CI = 1.44–8.89) and feedback, such as reports on the results of the data collection (OR = 3.77, 95% CI = 1.01–14.12), increased the willingness to use DMDs almost 4-fold, although with wide confidence intervals mostly due to the sample size.

The results in the second logistic regression model (Model 2, Table 2) that investigated the association between the willingness to share health data through DMDs for healthcare purposes and sociodemographic, clinical and support factors yield similar results to the first model, show that those within the older age categories are less likely to be willing to share their health data for healthcare purposes: (OR = 0.20, 95% CI = 0.06–0.63) for those between the age of 65 and 75, and (OR = 0.11, 95% CI = 0.03–0.38) for those over the age of 75. Receiving instructions (OR = 3.24, 95% CI = 1.19–8.81) and feedback (OR = 4.93, 95% CI = 1.37–17.72) from the data collected was associated with increased odds in the willingness to share data through DMD for healthcare purposes.

# Discussion

Overall, the findings of this study demonstrate a high acceptance of DMDs and trust in AI for the purpose of personalized health, aligning with results from other studies (21, 22, 24). However, our

TABLE 2 Logistic regression models presenting factors associated with the willingness to use AI-based DMDs and share health data in healthcare settings.

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| | Willingness to use DMD in healthcare | | | Willingness to share health data through DMDs for healthcare purposes | | |
| | Odds ratio | [95% Confidence interval] | | Odds ratio | [95% Confidence interval] | |
| **Country of residence (ref: Germany)** | | | | | | |
| France | 0.27 | 0.03 | 2.55 | 0.82 | 0.14 | 4.70 |
| Spain | 0.48 | 0.06 | 4.07 | 1.0 | 0.20 | 4.96 |
| **Age categories (ref: Under 65)** | | | | | | |
| 65–75 | 0.57* | 0.21 | 1.53 | 0.20*** | 0.06 | 0.63 |
| Over 75 | 0.31 | 0.11 | 0.83 | 0.11*** | 0.03 | 0.38 |
| **Gender (ref: female)** | | | | | | |
| Male | 0.93 | 0.39 | 2.23 | 1.06 | 0.43 | 2.61 |
| Educational level | 1.14 | 0.81 | 1.6 | 0.76 | 0.52 | 1.09 |
| **Disease duration (ref: newly diagnosed)** | | | | | | |
| 1–5 years | 0.88 | 0.1 | 7.68 | 1.03 | 0.12 | 9.15 |
| 6–10 years | 0.72 | 0.08 | 6.41 | 0.71 | 0.08 | 6.43 |
| over 10 years | 0.92 | 0.09 | 9.32 | 1.41 | 0.13 | 15.4 |
| **Receiving instruction (ref: no)** | | | | | | |
| Yes | 3.57*** | 1.44 | 8.89 | 3.24** | 1.19 | 8.81 |
| **Receiving feedback (ref: no)** | | | | | | |
| Yes | 3.77** | 1.01 | 14.12 | 4.93** | 1.37 | 17.72 |
| Constant | 3.1 | 0.09 | 16.25 | 11.793 | 0.45 | 30.17 |
| Pseudo r-squared | | | 0.127 | | | 0.171 |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$.
DMDs, Digital Medical Devices; ref, Reference category.

study found that the level of use and the preferences for particular DMDs varied across participants' country of residence as well as clinical and sociodemographic factors.

Based on a sample of individuals with PD across three large European Countries, namely France, Germany, and Spain, we found that those living in Germany were more likely to have used DMDs compared to those living in Spain, which might be due to the country's digital readiness given the implementation of DMDs within the healthcare system. Indeed, Germany is a pioneering country that authorizes healthcare providers to prescribe Digital Health Applications so-called DIGAs (25). Furthermore, our findings indicate that individuals in the older age groups were less willing to adopt technologies. Older individuals with PD voiced higher concerns regarding their ability to manage the DMDs and concerns regarding the time burden of using the device. These results are in line with studies on acceptance of digital health technologies indicating that older adults with chronic diseases and individuals living with PD are less likely to use DMDs and more prone to express concerns related to time burden and difficulties in managing DMDs (10, 21). We also observed differences in the preferences for device technology, as individuals in more advanced disease stages and with lower education levels tended to show lower preferences toward using smartphones. This tendency might be attributed to the levels of digital literacy and challenges experienced by individuals with PD who face both motor symptoms (such as tremors, gait problems, or rigidity) and non-motor symptoms, including cognitive difficulties (26). These challenges might make handling DMDs particularly smartphones, more demanding for this subgroup. Therefore, it is imperative to offer opportunities to increase digital literacy in these populations as well as to design user-friendly DMDs that seamlessly integrate into the daily activities of individuals with PD. Previous research suggests that automating data collection through commonly used devices like watches, shoes, and jewellery could reduce the physical and mental effort of individuals with PD, consequently improving use and engagement (22, 27). In addition, our results show that the majority of the participants expressed preferences to receive instructional videos on how to use the DMDs (predominantly in the form of real-person videos), which was also shown to be strongly associated with the willingness to use DMDs in the logistic regression model. Previous studies on the acceptance of technologies confirm these findings, suggesting that having technical and social support such as instructions, and encouragement from healthcare professionals or caregivers and families are important predictors of the acceptance of digital technologies (10, 28). Furthermore, in our sample, the majority of respondents favored the concept of home monitoring over periodic monitoring and assessments in the hospital. This is expected given that most of the individuals with PD have difficulties with mobility, making it harder for them to travel to a clinic. One intriguing finding lies in the association of lower confidence in healthcare decisions based on AI and a decreased willingness to share personal health data through DMDs for healthcare purposes among those with higher levels of education. However, the relationship between education and willingness to share personal health data diminished in the regression analysis after controlling for other demographic and clinical factors, suggesting that the relationship might be confounded and factors such as age, and receiving feedback and instruction play a more important role.

Advancing efforts toward transparency regarding the use of data collected from digital technologies is a critical step in fostering trust and, consequently, increasing the willingness to share health data for AI processing. Investing in innovative approaches for privacy-perceiving digital infrastructure such as federated health records or the development of synthetic data could address privacy concerns among individuals with PD (29, 30) and allow to leverage the data to improve the health of individuals with PD. Additionally, transparency about how algorithms are developed and deployed, as well as rising awareness about the benefits of AI for clinical decision support among individuals with PD is important to increase their trust and confidence in AI. In the European Union, the General Data Protection Regulation (GDPR) overall aims to ensure lawful, fair, transparent, secure, and accountable handling of personal health information within a concise timeframe. The Regulation mandates, *inter alia*, transparent processing of personal health data, requiring clear and accessible information to be provided to patients, including purposes of

processing, recipients, and data storage duration. Furthermore, patients possess legal rights to access their personal data, request rectification of their inaccuracies, obtain their erasure or processing restriction in some circumstances, and object to their processing based on individual circumstances, unless an exception applies. Importantly, patients also have the right not to be subject to a decision based solely on automated processing which significantly affects them (31).

Finally, in this article, we also show that the perceived benefits of using DMDs were strongly related to the willingness to share health data via DMDs. For instance, participants show high preferences for receiving feedback, such as reports on their health based on the collected data. The insights derived from their personalized health data can offer valuable information for individuals with PD, contributing to their higher patient engagement and empowerment. This is confirmed in previous studies, suggesting that providing feedback on the data obtained from the patients was found to be an important motivator in adherence to digital technologies (17, 32, 33), and therefore should be widely implemented.

## Limitations

Although this study foregrounds the perspectives of individuals with PD across three different European countries (France, Germany and Spain), one of the main limitations is its generalizability across all individuals with PD. In our study, the participants were mainly younger and highly educated which might overestimate the willingness to use these technologies. In addition, the majority of the participants were living in Spain, limiting the scope of country comparisons. Enhancing recruitment engagement strategies to include individuals with lower socioeconomic status necessitates collaborating with peers and community organizations, and disseminating information in simple language. Additionally, targeting locations where these communities reside can facilitate more inclusive participation. Furthermore, incorporating the experiences of healthcare professionals (34) and caregivers is essential to broaden perspectives, particularly for those in more advanced stages of the disease. While our study shows that sociodemographic and clinical characteristics of people with PD are important determinants to consider, other factors, such as the cost of DMD itself, should also be considered, especially if the DMDs are not reimbursed by the healthcare system. Lastly, it is important to note that our findings provide a general perspective rather than direct applicability to specific DMDs. Further studies assessing patient perspectives and acceptance of specific DMDs, such as smartphone apps and wrist-worn or waist-located devices, would offer valuable insights regarding the use and acceptance of specific types of technologies.

# Conclusion

Our study underscores the importance of carefully considering patients' needs and perspectives regarding the development and deployment of DMDs for personalized care. The specific needs of older patients and patients with a more advanced disease stage need to be considered to increase adoption and meaningful engagement with DMDs as those are also the groups that could benefit the most from it. Further research should also take into account the perspective of different migrant/ethnic groups, given the structural inequalities that these groups face in the healthcare system and their specific needs and perspectives. The high enthusiasm revealed by the participants' readiness to use digital health technology to enable better monitoring of their disease and clinical decision-making should be matched with their implementation in healthcare services. Therefore, increased patient involvement and working in partnership with researchers and clinicians is an important step toward the successful and sustainable implementation of DMDs for research and personalized healthcare. Such involvement of patients or their representatives is required by the GDPR (29).

Finally, although this was a study to understand the willingness of individuals with PD to use DMDs and share health information for the purpose of personalized care and decision support, the gap between willingness and actual use should be further explored. Indeed, although some individuals with PD are willing to use digital technologies, understanding the hurdles they face when it comes to real-time use and practical application is crucial.

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

# Ethics statement

The studies involving humans were approved by the Research Ethics Committee of the Hospital Clínico San Carlos de Madrid, with the assigned code 22/320-E. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

# Author contributions

IP: Conceptualization, Formal analysis, Visualization, Writing – original draft. MV: Conceptualization, Writing – review & editing. LM: Writing – review & editing. NB: Conceptualization, Writing – review & editing. AI: Writing – review & editing. JW: Writing – review & editing. MF: Writing – review & editing. SS: Writing – review & editing. FK: Writing – review & editing. J-CC: Writing – review & editing. HF: Funding acquisition, Writing – review & editing. JK: Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note



## References

1. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis*. (2018) 8:S3–8. doi: 10.3233/JPD-181474

2. Klucken J, Krüger R, Schmidt P, Bloem BR. Management of Parkinson's disease 20 years from now: towards digital health pathways. *J Parkinsons Dis*. (2018) 8:S85–94.

3. Eskofier BM, Klucken J. Predictive models for health deterioration: understanding disease pathways for personalized medicine. *Annu Rev Biomed Eng*. (2023) 25:131–56. doi: 10.1146/annurev-bioeng-110220-030247

4. Fröhlich H, Bontridder N, Petrovska-Delacréta D, Glaab E, Kluge F, Yacoubi ME, et al. Leveraging the potential of digital technology for better individualized treatment of Parkinson's disease. *Front Neurol*. (2022) 13:788427. doi: 10.3389/fneur.2022.788427

5. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's disease: challenges and opportunities. *Mov Disord Off J Mov Disord Soc*. (2016) 31:1272–82. doi: 10.1002/mds.26642

6. Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov. Disord. Off. J. Mov. Disord. Soc*. (2019) 34:657–63. doi: 10.1002/mds.27671

7. Post B, Merkus MP, de Bie RMA, de Haan RJ, Speelman JD. Unified Parkinson's disease rating scale motor examination: are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Mov Disord*. (2005) 20:1577–84. doi: 10.1002/mds.20640

8. Paccoud I, Leist AK, Schwaninger I, van Kessel R, Klucken J. Socio-ethical challenges and opportunities for advancing diversity, equity, and inclusion in digital medicine. *Digit Health*. (2024) 10:20552076241277705. doi: 10.1177/20552076241277705

9. Uncovska M, Freitag B, Meister S, Fehring L. Patient acceptance of prescribed and fully reimbursed mHealth apps in Germany: an UTAUT2-based online survey study. *J Med Syst*. (2023) 47:14. doi: 10.1007/s10916-023-01910-x

10. Gordon NP, Crouch E. Digital information technology use and patient preferences for internet-based health education modalities: cross-sectional survey study of middle-aged and older adults with chronic health conditions. *JMIR Aging*. (2019) 2:e12243. doi: 10.2196/12243

11. Marxreiter F, Buttler U, Gassner H, Gandor F, Gladow T, Eskofier B, et al. The use of digital technology and Media in German Parkinson's disease patients. *J Parkinsons Dis*. (2020) 10:717–27. doi: 10.3233/JPD-191698

12. Paccoud I, Baumann M, Le Bihan E, Pétré B, Breinbauer M, Böhme, et al. Socioeconomic and behavioural factors associated with access to and use of patient electronic health records: a cross-sectional analysis of four European countries. *BMC medical informatics and decision making*, (2020) 21, 1–11.

13. Longoni C., Bonezzi A., Morewedge C. Resistance to medical artificial intelligence. (2019). SSRN Scholarly Paper at: https://papers.ssrn.com/abstract=3375716.

14. Juravle G, Boudouraki A, Terziyska M, Rezlescu C. Chapter 14- trust in artificial intelligence for medical diagnoses In: BL Parkin, editor. Progress in brain research, vol. *253*. Amsterdam, Netherlands: Elsevier (2020). 263–82.

15. Ozanne A, Johansson D, Hällgren Graneheim U, Malmgren K, Bergquist F, Alt Murphy M. Wearables in epilepsy and Parkinson's disease-a focus group study. *Acta Neurol Scand*. (2018) 137:188–94. doi: 10.1111/ane.12798

16. LoBuono DL, Shea KS, Tovar A, Leedahl SN, Mahler L, Xu F, et al. Acceptance and perception of digital health for managing nutrition in people with Parkinson's disease and their caregivers and their digital competence in the United States: a mixed-methods study. *Health Sci Rep*. (2021) 4:e412. doi: 10.1002/hsr2.412

17. Riggare S, Stamford J, Hägglund M. A long way to go: patient perspectives on digital health for Parkinson's disease. *J Parkinsons Dis*. (2021) 11:S5–S10. doi: 10.3233/JPD-202408

18. Duroseau N, Abramson T, Pergament K, Chan V, Govindavari JP, Ciraco C, et al. Acceptance of technology-based tools in a sample of Parkinson's patients. *Chronic Illn*. (2017) 13:3–13. doi: 10.1177/1742395316653453

19. Graeber J, Warmerdam E, Aufenberg S, Bull C, Davies K, Dixon J, et al. Technology acceptance of digital devices for home use: qualitative results of a mixed methods study. *Digit Health*. (2023) 9:20552076231181239. doi: 10.1177/20552076231181239

20. Bontridder N, Hähnel T, Valero MM, Marín LC, Corvol JC, El-Yacoubi MA, et al. Leveraging the potential of digital technology for personalised medicine. *Journal of AI Law and Regulation* (2024) 1, 249–53.

21. Helleman J, Johnson B, Holdom C, Hobson E, Murray D, Steyn FJ, et al. Patient perspectives on digital healthcare technology in care and clinical trials for motor neuron disease: an international survey. *J Neurol*. (2022) 269:6003–13. doi: 10.1007/s00415-022-11273-x

22. Godoy Junior CA, Miele F, Mäkitie L, Fiorenzato E, Koivu M, Bakker LJ, et al. Attitudes toward the adoption of remote patient monitoring and artificial intelligence in Parkinson's disease management: perspectives of patients and neurologists. *Patient-Patient-Centered Outcomes Res*. (2024) 17:275–85. doi: 10.1007/s40271-023-00669-0

23. Sharpe D. Your chi-square test is statistically significant: now what? *Pract Assess Res Eval*. (2015) 20:n8. doi: 10.7275/tbfa-x148

24. Boise L, Wild K, Mattek N, Ruhl M, Dodge HH, Kaye J. Willingness of older adults to share data and privacy concerns after exposure to unobtrusive in-home monitoring. *Gerontechnol Int J Fundam Asp Technol Serve Ageing Soc*. (2013) 11:428–35. doi: 10.4017/gt.2013.11.3.001.00

25. Dittrich F, Mielitz A, Pustozerov E, Lawin D, von Jan U, Albrecht UV. Digital health applications from a government-regulated directory of reimbursable health apps in Germany—a systematic review for evidence and bias. *Health*. (2023) 9:35. doi: 10.21037/mhealth-23-17

26. De Vleeschhauwer J, Broeder S, Janssens L, Heremans E, Nieuwboer A, Nackaerts E. Impaired touchscreen skills in Parkinson's disease and effects of medication. *Mov Disord Clin Pract*. (2021) 8:546–54. doi: 10.1002/mdc3.13179

27. Botros A, Schütz N, Camenzind M, Urwyler P, Bolliger D, Vanbellingen T, et al. Long-term home-monitoring sensor technology in patients with Parkinson's disease—acceptance and adherence. *Sensors*. (2019) 19:5169. doi: 10.3390/s19235169

28. Venkatesh V, Morris MG, Davis GB, Davis FD. User acceptance of information technology: toward a unified view. *MIS Q*. (2003) 27:425–78. doi: 10.2307/30036540

29. Raab R, Küderle A, Zakreuskaya A, Stern AD, Klucken J, Kaissis G, et al. Federated electronic health records for the European health data space. *Lancet Digit Health*. (2023) 5:e840–7. doi: 10.1016/S2589-7500(23)00156-5

30. Giuffrè M, Shung DL. Harnessing the power of synthetic data in healthcare: innovation, application, and privacy. *NPJ Digit Med*. (2023) 6:1–8. doi: 10.1038/s41746-023-00927-3

31. Regulation P. Regulation (EU) 2016/679 of the European Parliament and of the council. *Regul Eu*. (2016) 679:2016.

32. Pfaeffli Dale L, Whittaker R, Dixon R, Stewart R, Jiang Y, Carter K, et al. Acceptability of a Mobile health exercise-based cardiac rehabilitation intervention: a RANDOMIZED TRIAL. *J Cardiopulm Rehabil Prev*. (2015) 35:312–9. doi: 10.1097/HCR.0000000000000125

33. van Eijk RP, Beelen A, Kruitwagen ET, Murray D, Radakovic R, Hobson E, et al. A road map for remote digital health technology for motor neuron disease. *J Med Internet Res*. (2021) 23:e28766. doi: 10.2196/28766

34. Virbel-Fleischman C, Rétory Y, Hardy S, Huiban C, Corvol JC, Grabli D. Body-worn sensors for Parkinson's disease: a qualitative approach with patients and healthcare professionals. *PLoS One*. (2022) 17:e0265438. doi: 10.1371/journal.pone.0265438

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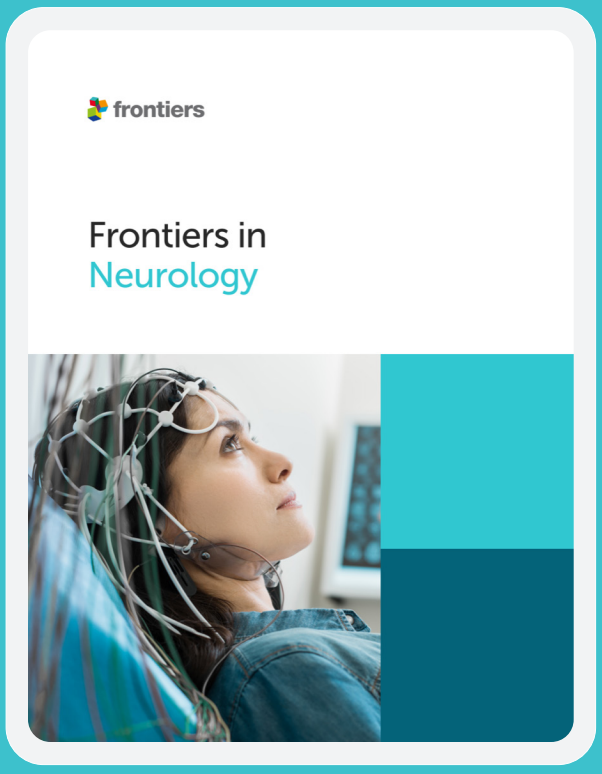


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