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Movement analysis in the diagnosis and management of Parkinson's disease

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Challenges in the diagnosis and treatment of Parkinson's disease: Parkinson's disease (PD) is an increasingly prevalent neurodegenerative disease, at first sight primarily characterized by motor symptoms, although non-motor symptoms also constitute a major part of the overall phenotype. Clinically, this disease cannot be diagnosed reliably until a large part of the vulnerable dopaminergic neurons has been irretrievably lost, and the disease progresses inexorably. New biological criteria for PD have been proposed recently and might eventually improve early diagnosis, but they require further validation, and their use will initially be restricted to a research environment (Darweesh et al., 2024). Today, the clinical diagnosis of PD is based primarily on subjective criteria and is impeded by high intra- and interindividual variability. In early disease stages, the differentiation from other diseases can be challenging, hampering the timely selection of the best treatment options. While some of the cardinal motor symptoms associated with PD can be treated effectively in the early stages, disease-modifying interventions and treatments for debilitating non-motor symptoms remain elusive. The many new (primarily pharmacological) strategies currently evaluated for PD are often optimizations of existing approaches (e.g., variations of treatments with dopamine precursors or dopamine receptor agonists) or belong to the class of the highly debated anti-protein aggregation treatments. Breakthrough strategies to reliably halt or slow down PD progression might be just around the corner but the history of unsuccessful translations of promising novel preclinical treatments for PD during the last decades warrants a certain amount of skepticism.

New promises of movement analysis: On the bright side, PD biomarker development, including movement analysis using digital technologies, progresses fast, as recently reviewed (Burtscher et al., 2023). Great technological advancements, such as wearable and non-wearable smart measuring devices and increasingly powerful machine learning analyses, allow for the collection and meaningful interpretation of objective continuous data from real-life situations and pave the way for clinical applications. A few very recent developments are summarized below to highlight the progress in the field related to movement analysis in PD. These examples demonstrate the potential of such approaches to refine PD diagnosis and to monitor symptoms, responses to medication, and disease progression.

First, the recently Food and Drug Administration cleared (for adults > 45 years with mild to moderate PD) Motor fluctuations Monitor for PD (MM4PD) is an example of an ambulatory monitoring system of movements and medication responses based on inertial sensors (accelerometers and gyroscopes) integrated into a smartwatch (Bloem et al., 2023). MM4PD enables continuous tracking of fluctuations in resting tremor and dyskinesia (particularly dopamine-induced hyperkinetic movement), based on algorithms validated in PD patients and healthy controls, but also records various other parameters, such as daily step counts, step length, heart rate, and heart rate variability. Second, a recent multicenter study evaluated movement analysis for diagnostic and disease progression monitoring, using data from accelerometers attached to the lower back of 587 people with PD and 68 healthy controls (Mirelman et al., 2023). These data were analyzed using a machine learning approach, which revealed a moderate association of the digital mobility measures with Movement Disorder Society-Unified Parkinson's Disease Rating Scale scores. Importantly, the digital mobility data efficiently differentiated early PD from healthy controls and described disease progression more sensitively than the Movement Disorder Society-Unified Parkinson's Disease Rating Scale assessment. Third, in a UK Biobank study, accelerometer measurements of sleep and physical activity from wrist-worn devices were analyzed using machine-learning models (Schalkamp et al., 2023). Measuring and analyzing single (not serial) mean acceleration data allowed the detection of PD-related symptoms before diagnosis and thus potentially the identification of prodromal signs that may enable an earlier PD diagnosis in the future and thus more efficient treatments (Schalkamp et al., 2023). Examples of non-wearable devices to monitor movement in people with PD are wall-mounted installations that allow the measurement of gait characteristics (including speed) using radio waves (Liu et al., 2022). Continuous machine-learning-assisted movement analysis of these data provides promising insights into responses to medications and assessments of disease progression as well (Liu et al., 2022). Moreover, open-source platforms increasingly allow detailed and automatized biomechanical analyses from videos, without the necessity of specialized hard- and software. An example of this development is "OpenCap" which employs algorithms to categorize movements and deduce musculoskeletal processes, and deep learning to calculate three-dimensional kinematics (Uhlrich et al., 2023). Taken together, when movement analysis approaches are shown to sensitively detect motor fluctuations relating to treatment over time, they could ultimately assist in the adaptation of treatment strategies and evaluation thereof. They might also pave the way for more objective, reliable, and earlier PD diagnosis and monitoring of disease progression. However, since age- or disease-related motor abnormalities are common and due to the large symptomatic variation in PD, digital movement data do not just yet sufficiently discriminate between prodromal PD and other causes of motor dysfunctions.

Monitoring exercise interventions: The emerging techniques for recording and analyzing continuous real-life digital movement data are not only valuable tools to assist urgently needed improvements of PD diagnosis, monitoring of symptoms and responses to medication, and clinical rating – which might eventually allow earlier and more efficient interventions. They also provide additional information on the efficacy and optimization opportunities of powerful non-pharmacological interventions, including exercise. The better characterization of specific functional PD subtypes, such as akinetic-rigid and tremor-dominant types, will allow important improvements in the generation of customized training consultations (Burtscher et al., 2023). This is crucial because PD patients greatly differ in their motor capacities: patients with akinetic-rigid PD subtypes are usually more severely impaired in adjusting their posture, which is relevant for important functional factors, e.g., their walking capacity. Exercise can attenuate the general age-related decline of cardiovascular, respiratory, and metabolic functions. Together with beneficial effects on mood and cognitive function, it thereby enhances functional independence and quality of life of older people in general and in PD (Burtscher et al., 2023). Moreover, exercise improves some PD motor symptoms specifically and may even slow down disease progression by strengthening neuroplasticity, synaptic function, and general cellular resilience (Burtscher et al., 2023). Regular exercise also enhances mitochondrial efficiency, antioxidant and anti-inflammatory capacities, and reduces proteotoxicity, thereby likely mitigating PD-pathology formation (Burtscher et al., 2023). A major problem in selecting efficient exercise interventions is the determination of the optimal type and "dose" of exercise. This includes the design of tailored personalized training plans with an appropriate exercise type composition (i.e., endurance, resistance, and balance/coordination), intensity, volume, and session frequency ["extrinsic" factors (Noone et al., 2024)]. Efficient personalized training plan prescriptions are furthermore optimized for ["intrinsic" (individual characteristics) factors (Noone et al., 2024)], which include the specific capacities and limitations of PD patients. Complicating such optimization further, efficient exercise interventions rely on progressive increases in training load, which also necessitates identification of the pace and timing of load changes (Peyré-Tartaruga et al., 2022). The collection of digital movement data allows a more objective evaluation of the efficiency of personalized training plans, documentation of their effects on PD progression, adaptation according to the exercise outcomes, and analysis of interaction effects with medications. Insufficient personalization of exercise interventions to individual predispositions, motor learning capacities, and responsiveness (Noone et al., 2024) currently is a major obstacle that limits the prescription of exercise as medicine in PD. But it can likely be overcome by the new digital monitoring and analysis possibilities, enabling the tailoring of training plans to personal needs, disease stage, and exercise progress. Another central limitation of therapeutic applications of exercise is the need to maintain motivation, compliance, and adherence to training plans (Noone et al., 2024), especially for people with impaired motor functions. Mobile motivational apps, e.g., in combination with wearables, have the potential to improve this factor by providing positive feedback and reinforcement (Schootemeijer et al., 2023).

The emergence of devices to monitor other relevant joint aspects of PD and exercise opens up new opportunities to combine various monitoring approaches for optimal application. Such devices include those for non-invasively tracking multiple physiological and metabolic parameters, such as blood glucose levels and volumetric tissue-specific changes in blood or blood oxygenation using photoplethysmography or electrocardiography (Keshet et al., 2023). Exciting clinical applications of these monitoring possibilities are closed-loop systems, in which the detection of abnormalities is directly coupled to the induction of a regulatory mechanism. Interesting examples are glucose-level monitoring and adjustive insulin administration in diabetes (Keshet et al., 2023) or accelerometer-based monitoring of body position and electrical spinal cord stimulation to delay orthostatic hypotension in a patient with multiple system atrophy (Squair et al., 2022). Closed-loop systems that monitor the occurrence of symptoms in PD and induce corrective inputs (e.g., pharmacological or brain stimulation) are feasible as well, particularly in people with implantations for deep brain

stimulation but possibly also based on movement analysis (Burtscher et al., 2023). Decoding brain signatures of specific locomotor states, such as freezing of gait, via deep brain stimulation-recorded local field potentials automated analysis, could spur the implementation of closed-loop systems in movement disorders like PD (Burtscher et al., 2023). Digital movement data together with continuously assessed physiological (e.g., cardiovascular and respiratory parameters) and metabolic data are about to importantly complement traditional biomarkers (e.g., from body fluids or brain imaging) of PD (Burtscher et al., 2023). The increasing integration of multiplexed biosensing in wearable devices (Keshet et al., 2023) and significant advances in molecular biomarker development for PD (e.g., for alpha-synuclein pathology) render combined approaches ever more promising. Thus, finding optimal combinations with other biomarkers is an important avenue for future research on movement analysis in PD, as well as for personalized adjustments and optimization of training plans (Burtscher et al., 2023).

Conclusions: Recent advances in wearable and non-wearable digital monitoring technologies combined with machine-learning models potentially have considerable value for PD patients. These digital solutions might specifically improve (1) the diagnosis of PD and monitoring of disease progression, (2) tracking physical exercise adaptations, (3) investigating impaired metabolic stress phenomena in PD and (4) the optimization of training plans and other intervention strategies for PD patients (**Figure 1**).

State-of-the-art artificial intelligence applications enable the management of the immense amount of data obtained from multiple continuous recordings, the integration of different assessments, and the extraction of the most sensitive diagnostic factors. These analytical approaches could eventually allow the identification of patterns of movements, metabolic, respiratory or cardiovascular, and other parameters to reliably assess PD subtypes and disease stages and contribute to the validation of the recently suggested biological criteria for PD (Darweesh et al., 2024). They can facilitate tailored exercise prescriptions (Peyré-Tartaruga et al., 2022; Noone et al., 2024) and improve adherence to regular exercise (e.g., for telerehabilitation) (Burtscher et al., 2023). However, the accuracy and capacity to discriminate between PD sub-types, disease stages, and prodromal versus normal age-related motor abnormalities of digital movement analysis by itself is not (yet) sufficient for robust clinical applications. Therefore, the development of suitable and reliable combinations of monitoring approaches, their validation, optimization, and implementation for clinical applications related to PD remain major challenges, but the promises are great.

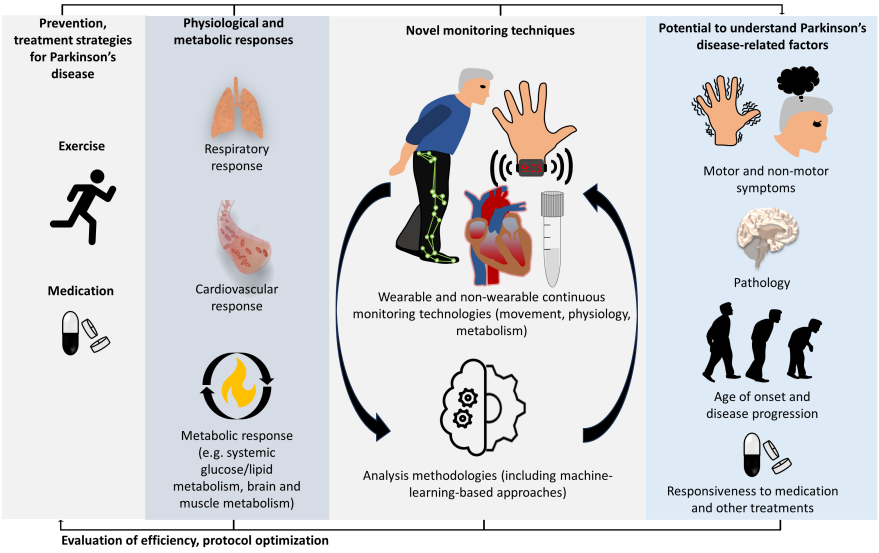

Figure 1 | **The emerging role of digital monitoring techniques in Parkinson's disease research and treatment.** Created with Microsoft PowerPoint.

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