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Review article

Exercise and gait/movement analyses in treatment and diagnosis of Parkinson's Disease

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ABSTRACT

Cardinal motor symptoms in Parkinson's disease (PD) include bradykinesia, rest tremor and/or rigidity. This symptomatology can additionally encompass abnormal gait, balance and postural patterns at advanced stages of the disease. Besides pharmacological and surgical therapies, physical exercise represents an important strategy for the management of these advanced impairments. Traditionally, diagnosis and classification of such abnormalities have relied on partially subjective evaluations performed by neurologists during short and temporally scattered hospital appointments. Emerging sports medical methods, including wearable sensor-based movement assessment and computational-statistical analysis, are paving the way for more objective and systematic diagnoses in everyday life conditions. These approaches hold promise to facilitate customizing clinical trials to specific PD groups, as well as personalizing neuromodulation therapies and exercise prescriptions for each individual, remotely and regularly, according to disease progression or specific motor symptoms. We aim to summarize exercise benefits for PD with a specific emphasis on gait and balance deficits, and to provide an overview of recent advances in movement analysis approaches, notably from the sports science community, with value for diagnosis and prognosis. Although such techniques are becoming increasingly available, their standardization and optimization for clinical purposes is critically missing, especially in their translation to complex neurodegenerative disorders such as PD. We highlight the importance of integrating state-of-the-art gait and movement analysis approaches, in combination with other motor, electrophysiological or neural biomarkers, to improve the understanding of the diversity of PD phenotypes, their response to therapies and the dynamics of their disease progression.

1. Background

Parkinson's Disease (PD) had an estimated global prevalence of more than 6 million in 2015 and is considered the neurological disease with the fastest growing prevalence (Dorsey et al., 2018). It is characterized by highly heterogeneous disease manifestations and age of onset (Tolosa et al., 2021). Cardinal symptoms of PD are bradykinesia (slowness of movement and decrement in amplitude or speed), muscular rigidity, resting tremor, later followed by postural control deficits and gait impairments (Mirelman et al., 2019; Postuma et al., 2015). Movement symptoms are highly diverse and individual patients usually suffer from unique combinations (Kalia and Lang, 2015). The symptoms encompass neurological motor deficits, pain, or peripheral symptoms and they may be associated with cognitive and psychiatric derangements. Despite its traditional classification as a motor disease, PD symptomatology includes a broad array of so-called "non-motor symptoms", including sleep problems, dysautonomia, cognitive and mood/psychiatric components, such as anxiety and depression (Kalia and Lang, 2015).

Although several mono-genetic mutations have been identified that can cause PD (and affect age of onset and disease progression (Tolosa et al., 2021)), these familial cases of PD make up only about 10% of patients. Most cases are idiopathic; i.e., without a defined genetic cause,

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with age being the most important risk factor, although genetic and environmental risk factors play important roles too (Hou et al., 2019). No disease-modifying treatment strategies (i.e., that can slow down or stop disease progression instead of the mere control of disease symptoms) are yet available. Early PD diagnosis is critical; especially for the advent of future disease-modifying treatments since these are expected to be most efficient in early disease stages. PD diagnosis traditionally relies predominantly on clinical evaluation containing several subjective criteria. A diagnostic error rate of about 20% has been estimated and did not substantially improve during the last decades (Rizzo et al., 2016).

Physical activity ("any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al., 1985)) and exercise ("planned, structured, and repetitive" physical activity aiming for "improvement or maintenance of physical fitness" (Caspersen et al., 1985)) have emerged as important interventional strategies for PD (Bouça-Machado et al., 2020; Feng et al., 2020; Goodwin et al., 2008). Exercise is an important component of physical therapy, which is defined as a nonpharmacological, holistic and patient-centered therapeutic intervention to improve motor function and movement independence; in PD management it focuses on improving physical fitness, transfers, manual activities, balance and gait (Bouça-Machado et al., 2020). Methods, used primarily in sports sciences to assess exercise and movement, are becoming highly interesting for PD diagnosis. Massive technological advances in motor behavioral analysis represent potent tools for this purpose but are only starting to be systematically employed for clinical assessment of PD.

Recent advances in biomarkers discovery but also in the analysis of movements have paved the way for the development of more objective assessments of PD motor symptoms. This may improve early diagnosis and symptomatic disease staging, contribute to sub-classification of PD-variants and allow calibration of pharmacotherapies and exercise interventions according to current symptoms.

In this narrative review, we evaluate the roles and potential of exercise as a treatment and movement analysis as a diagnostic strategy in PD. We first review the pathogenesis and disease progression of PD, discuss the development of motor and non-motor symptoms, and highlight individual differences of the disease course. Next, we provide an overview of how exercise benefits different aspects of PD and how movement analysis can improve PD diagnosis and the customization of treatment strategies. Finally, we will point out the need for combination of movement analysis with other biomarkers and argue that such interdisciplinary assessments will not only improve (early) diagnosis but will be key for appropriate patient subgroup stratification for clinical trials and personalized medicine approaches. Despite huge advances in the field of movement analysis, its implementation as a diagnostic tool in PD remains slow. Therefore, we aimed to identify possible reasons and present research questions to spur new studies that hopefully will accelerate the adoption of sports science-based movement analysis and precision exercise interventions for PD patients. We conclude that the liaison of neurological and sports science methods is expected to unlock the full potential of therapeutic exercise for PD patients by enabling the selection of the most adequate exercise interventions for each disease stage and each patient.

2. Progression and diversity of Parkinson's Disease

Triggered or facilitated by different genetic predispositions and/or environmental events, molecular alterations in the brain initiate inexorable neurodegenerative processes contributing to PD development and progression. Neurodegeneration of selectively vulnerable neuronal and non-neuronal cell populations drives clinical manifestations in PD. Dopaminergic neurons in the *substantia nigra, pars compacta* are vulnerable cells in PD (Gonzalez-Rodriguez et al., 2020) and their demise leads to deregulation of dopaminergic inputs to motor-centers of the brain, especially the striatum, and the appearance of motor symptoms. Major molecular hallmarks of PD – and important parameters for post-mortem characterization of the disease – are Lewy bodies and Lewy neurites (together referred to as Lewy pathology), intracellular proteinaceous inclusions consisting predominantly of misfolded and aggregated α-synuclein protein and membranous components (Lashuel et al., 2013). Mutations or multiplications of the gene encoding for α-synuclein, *SNCA*, have been unambiguously linked to familial forms of PD (Lashuel et al., 2013).

Deficits in glucose metabolism and oxygen-consuming processes likely constitute cellular vulnerabilities in PD (Burtscher and Millet, 2021; Burtscher et al., 2021a; Burtscher et al., in press) and are linked to further molecular hallmarks of PD, such as oxidative stress, abnormal iron metabolism, neuroinflammation and mitochondrial dysfunction (Greenamyre, 2018).

There are currently no objective tests available for PD diagnosis, and the diagnosis is based primarily on partially subjective clinical criteria and responsiveness to levodopa (Postuma et al., 2015). Despite recent advancements in the development and application of diagnostic biomarkers for PD diagnosis and disease staging, no accurate diagnosis is yet possible for early-stage PD (Tolosa et al., 2021). Genetic testing and brain imaging have become fundamental components of clinical routine diagnostic procedures and much progress is being made on the development of new molecular biomarkers (Tolosa et al., 2021). Among brain imaging approaches, structural and diffusion-weighted magnetic resonance imaging (MRI), dopamine transporter (DAT) scans using single-photon emission computerized tomography (SPECT) with ioflupane I-123, fluorodeoxyglucose-positron emission tomography (PET), and transcranial ultrasound are widely used as ancillary approaches to confirm suspected PD (Tolosa et al., 2021). Numerous radionuclide tracers for PET and SPECT imaging have been suggested or are in development for PD diagnosis (Strafella et al., 2017). While DAT scanning, which detects impaired nigral dopaminergic input to the striatum, is routinely used for clinical PD diagnosis (but does not differentiate from other neurodegenerative parkinsonisms), a focus in biomarker development for PD has been put on α-synuclein. PET tracers, and assessment of α-synuclein tissue or biological fluid levels are expected to detect early disease stage pathology (Magalhães and Lashuel, 2022).

Since several neurological disorders are characterized by overlapping phenotypes and pathologies (Ali and Morris, 2015), which in conjunction with dynamic alterations of symptoms based on the progression of the underlying pathology complicate PD diagnosis, accurate diagnostic tools are still missing but of utmost importance for patient characterization (Tolosa et al., 2021). PD subtypes, determined in part by genetic risk factors or environmental insults, may further be characterized by age of onset, disease progression, differential prognosis, specific symptoms (e.g., tremor-dominant or not), underlying pathology and thus differential amenability for specific treatment strategies (Tolosa et al., 2021).

The failure of most clinical interventional trials to modify PD pathogenesis in the last decades despite myriad promising results of treatment strategies in preclinical PD-models further highlights the need for differential diagnosis; clinical trial participants with heterogeneous clinical manifestations and likely divergent neuropathological features may increase the variability in patient responsiveness and thus lead to negative results for treatments that would be beneficial for specific patient subgroups. The emerging availability of more objective diagnostic tools, including biomarker-based diagnosis and characterization (Tolosa et al., 2021) and in-lab/in-clinic to in-home monitoring of PD patients (Chandrabhatla et al., 2022) has immense potential to improve the diagnosis.

The prodromal phase of the disease can last 20 years or longer (Kalia and Lang, 2015) and is characterized by a combination of subtle non-motor and possibly motor signs in absence of the cardinal motor symptoms and thus represents a hitherto insufficiently exploited opportunity for earlier diagnosis. Common complaints in this period include sleep disturbances – including rapid eye movement (REM)-sleep behavior disorder – loss of smelling (hyposmia), constipation and

urinary dysfunction, anxiety and depression and mild cognitive symptoms (Fig. 1) (Tolosa et al., 2021). Suspected diagnosis due to cardinal motor features is considered "clinically established" when there is a clear dopa-responsiveness of the parkinsonism (Postuma et al., 2015), which, however, still can only be confirmed with certainty by brain autopsy and post-mortem assessment of loss of dopaminergic neurons and of Lewy pathology (Kalia and Lang, 2015).

Gait and balance impairments in PD are associated with reductions in independence and, therefore, quality of life, as well as risk of falls. These symptoms change dynamically during the disease course (Mirelman et al., 2019), likely drive progressive motor disability and are among the earliest functional impairments by many patients, with about 25% of people with UPDRS-scores < 20 reporting subtle walking difficulties (Shulman et al., 2008). Gait impairments in individuals with idiopathic REM-sleep behavior disorder were also observed years before they were diagnosed with parkinsonism (Postuma et al., 2012). Various gait-related parameters, such as slower speed, impaired gait initiation, reduced stride rate, higher stride length variability, arm swing abnormalities, leg dragging, impaired orientation after turning or bent posture are among the most common functional impairments in early PD (Carpinella et al., 2007) and may partially precede diagnosis. While slower walking speed is a common early gait abnormality in people with PD (Del Din et al., 2019), a recent meta-regression analysis indicates that slower walking speed may not be influenced by age, disease duration, or PD stage – as assessed by the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) or Hoehn and Yahr scale – in medicated people with PD (Zanardi et al., 2021). These authors also found that many gait parameters that did not robustly change in age-matched controls (self-select walking speed, stride length, cadence, double support, swing time and sagittal hip angle) changed in PD (Zanardi et al., 2021). Transitional elements of walking, such as turning, are most robustly impaired already at early disease stages and represent promising early diagnostic opportunities for gait analysis. Lower walking economy (increased rate of oxygen consumption during walking) is also observed in early PD but likely is also not correlated with diseases stage (Christiansen et al., 2009; Jeng et al., 2020b). During disease progression, posture and balance impairments as well as freezing of gait (FOG) become more common and are often (especially at later stages) not sufficiently responsive to levodopa and even less to other drugs like dopamine receptor agonists, or to deep brain stimulation (Fasano et al., 2015; Rambold et al., 2011).

3. Exercise as a treatment strategy for Parkinson's Disease and mechanistic considerations

Muscle weakness and other motor deficits strongly impede PD patient engagement in physical activity (Mak et al., 2017; Speelman et al., 2011), resulting in substantially reduced physical activity levels (van Nimwegen et al., 2011) and quality of life. In contrast, physical activity, and especially exercise, can be a highly beneficial intervention strategy for PD. Physical activity has been shown to be inversely correlated with disease severity (van Nimwegen et al., 2011), and to improve motor deficits in PD (Rutz and Benninger, 2020; Speelman et al., 2011). Consequently, reduced physical activity levels and deteriorating physical capacities due to lack of physical activity represent a vicious cycle in PD and possibly account for the reduction of aerobic capacity at later stages of PD (Mak et al., 2017). In addition, exercise can also improve non-motor symptoms (such as anxiety or cognitive impairments) and low quality of life (Speelman et al., 2011); factors that may further predispose PD patients to inactive life-styles (van Nimwegen et al., 2011).

Besides PD-specific motor deficits, exercise is beneficial for many general health aspects, particularly those that deteriorate at older age. Exercise improves cardiorespiratory fitness, metabolic and mental health, cardio-, cerebrovascular and autonomic function; and it counteracts osteoporosis, sarcopenia, chronic inflammation and mitochondrial dysfunction (Ruegsegger and Booth, 2018; Warburton et al., 2006). The decline of these functions and capacities may represent risk factors for PD and can further reduce functional independence, including the capacity to perform physical activities and exercise. Volume, type and intensity of exercise are determinants of beneficial outcomes. High-intensity exercise may be better suited for early stages of PD than

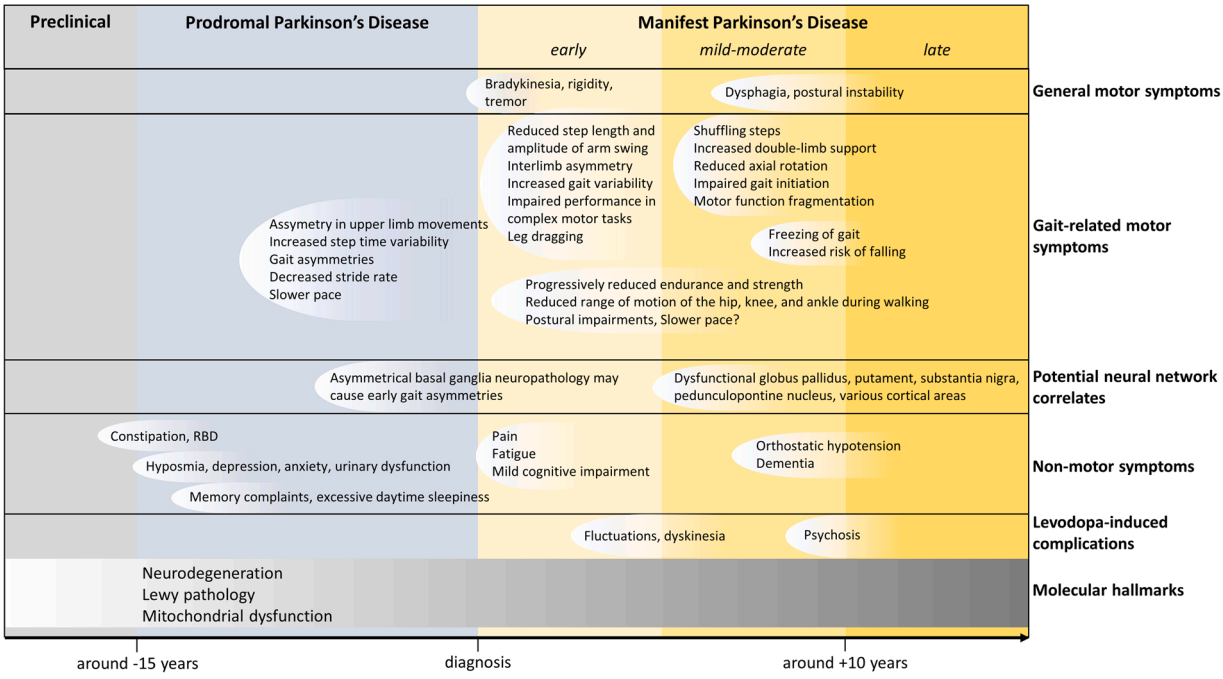

Fig. 1. Simplified overview of Parkinson's disease stages with a focus on gait alterations. Graph style and temporal classification of motor and non-motor symptoms, as well as levodopa-induced complications are based on Kalia and Lang (Kalia and Lang, 2015) and Tolosa et al. (Tolosa et al., 2021). For more information on gait-related symptoms and neural network correlates, see text. Note that disease stages are highly variable and differ from individuum to individuum depending on genetic and environmental conditions but also lifestyle factors, such as physical activity levels. RBD: rapid eye movement sleep behavior disorder.

low-intensity training (Schenkman et al., 2018) and individualized training with motivation and feedback likely further increases exercise benefits for PD patients. Such an individualized exercise intervention ("Lee Silverman Voice training BIG", LSVT-BIG) that focused on high-intensity and large movement amplitudes was more efficient than low-intensity, isolated walking or workouts at home to improve motor symptoms at Hoehn & Yahr stages I–III (mild to moderate PD) (Ebersbach et al., 2010). FOG and gait impairments, which are frequently pharmaco-resistant, have been shown to be more amenable to different exercise types, such as treadmill, aquatic obstacle, or supervised slackline training (Rutz and Benninger, 2020). These are particularly important in the acute post-operative phase after implantation of deep brain stimulation devices (Tassorelli et al., 2009).

Several weeks of gait (at least 4 weeks) or balance (at least 8 weeks) training programs or regular resistance, exercise or dance training interventions induce well-described long-lasting benefits on strength, balance and walking capacities (Mak et al., 2017). Based on the analysis of different exercise interventions, a review from 2016 (Lauzé et al., 2016) concluded that in people with PD general physical (strength, flexibility, motor control and metabolism) and cognitive capacities were consistently improved by exercise, resulting in better functional capacities. Gait efficiency, gait velocity and cadence, and balance/posture/risk of falls were among the features most robustly improved (Lauzé et al., 2016). In contrast, while some specific PD symptoms (gait, posture and rigidity) also profited from exercise, other symptoms, such as bradykinesia, rigidity and tremor benefited less robustly (Lauzé et al., 2016).

Exercise may not only improve motor symptoms and slow down functional decline but also – unlike available pharmacological approaches – could modify disease progression by improving neuroplasticity and synaptic function (Bouça-Machado et al., 2020; Petzinger et al., 2013). Aerobic exercise (e.g., cycling at 50–80% heart rate reserve, 3 times per week for 30–45 min over 6 months) improved the functional connectivity of the anterior putamen with the sensorimotor cortex and preserved the structural integrity of the brain in PD patients with mild-moderate motor symptoms (average baseline MDS-UPDRS-III of 30.2 ± 11.4) (Johansson et al., 2022). A similar exercise intervention (36 sessions of 30–50 min of cycling at 60–80% of maximum aerobic capacity, $\dot{V}O_2max$) improved ventral striatum responses and evoked dopamine release in the caudate nucleus of idiopathic PD-patients at Hoehn & Yahr stages I–III (Sacheli et al., 2019). These findings suggest that exercise not only improves symptoms but has the capacity to re-balance underlying neural circuitries. While the restorative effects of exercise require more investigation in PD, the key role of sensory feedback to boost neural plasticity, circuit reorganization, and motor recovery has been extensively demonstrated in spinal cord injury rehabilitation (Formento et al., 2018; Takeoka et al., 2014). Results from animal models of PD further suggest that endurance exercise and walking training reduce PD-related pathologies at the cellular level, including oxidative stress, neuroinflammation and α-synuclein pathology, while increasing neurotrophic support, together attenuating neurodegeneration and motor-symptoms (Jang et al., 2017; Leem et al., 2023).

In addition, exercise can reduce quality of life-reducing non-motor symptoms in PD; e.g., cognitive decline (Johansson et al., 2022). Furthermore, higher physical activity levels are associated with fewer psychiatric symptoms, such as anxiety and depression, as recently demonstrated in a meta-analysis of systematic reviews investigating various adult healthy and disease populations (Singh et al., 2023). Evidence of potential reduction of psychiatric symptoms by exercise in PD remains, however, conflicting and may depend especially on the type of exercise, with combined training (aerobic exercise combined with strength, balance or flexibility training) being superior to aerobic exercise alone (Singh et al., 2023).

A major limitation currently is the selection of appropriate exercise modalities, volume and intensity individually tailored to people with PD. Recently, the selection of these parameters based on an evaluation battery consisting of functional (10 m walking test; timed up and go test) and clinical (MDS-UPDRS and Hoehn and Yahr score) characterization has been proposed (Peyré-Tartaruga et al., 2022). These authors highlight 3 exercise modalities with specific benefits for PD: exercising in deep water for physically severely impaired patients and Nordic walking and Brazilian dance as strategies to reduce freezing events, protect from falling and improve functional mobility (Dos Santos Delabary et al., 2020; Monteiro et al., 2017).

In summary, while exercise and its motivational social implications (Rodrigues de Paula et al., 2006) can clearly improve gait deficits (Tsukita et al., 2022), and increase physical fitness (Bouça-Machado et al., 2020), strength and balance in people with PD (Goodwin et al., 2008), methodological limitations of the available studies (Mirelman et al., 2019) currently impede full understanding of direct gait- and potentially pathology-improving effects of exercise. These limitations include (i) insufficiently accurate gait analysis, (ii) heterogeneous exercise protocols, and (iii) potential confounding by medication status. Identification of optimal exercise protocols (intensity, duration, frequency, type and combinations of exercise) remain a challenge for future research. The increasing availability of advanced tools for movement assessment and analysis, often originating from sports sciences, offers great support for this goal.

4. Advances and value of movement and gait analysis in Parkinson's disease

Beyond their relevance to tailor physical training protocols, technologies for movement assessment may also represent a key component to improve PD diagnostics. The identification of objective parameters in the detection and monitoring of motor functions – complemented with well-established clinical testing – has the potential to increase diagnosis accuracy and phenotypic PD subtype classification. Earliest-possible diagnosis is necessary to maximize the therapeutic potential of emerging disease-modifying treatments (Poewe et al., 2020), for which movement analysis could play a pivotal role.

Already early "technology-based objective measures" (TOMs) (Espay et al., 2016) analyses indicated the existence of numerous balance and gait abnormalities in PD patients that by themselves did not qualify as specific disease markers (Horak and Mancini, 2013). This is partially based on the substantial overlap of PD motor impairments with age or other disease-related motor impairments. General motor disability is becoming increasingly common after the age of 65 and affects approximately 50% of individuals at the age of 80 (Bennett et al., 1996). These disabilities can include typical mild parkinsonian symptoms such as bradykinesia, and postural and gait deficits in individuals not diagnosed with PD and have been reported to progressively deteriorate (Buchman et al., 2016; Oveisgharan et al., 2021). In addition, they can be associated with PD-like neuropathology in post-mortem brains, including in the substantia nigra (Buchman et al., 2012), and therefore may represent pre- or sub-clinical forms of PD. Hence, a good understanding of PD-independent and comorbidity-related axial and limb impairments on gait parameters in PD are essential to avoid confounding between PD- and comorbidity-associated deficits (Mirelman et al., 2019).

The combined analysis of gait tasks in very specific and complex settings (e.g., dual tasks, specific motor tasks such as turning, timed up and go test, etc.) has special potential to enable highly sensitive gait evaluation (Mirelman et al., 2019), already in individuals with an increased likelihood to develop PD, such as the ones presenting with REM sleep behavior disorder (Ehgoetz Martens et al., 2019). The performance in dual tasks (e.g. walking while performing arithmetic calculations) may for example provide more accurate information on the cognitive state in people with PD than in older adults without PD (Ivaniski-Mello et al., 2023). Among published applications of TOMs of movement with high relevance for PD are the measurement of general

decline of ambulatory activity (Cavanaugh et al., 2012), tracking of movement abnormalities during laboratory testing of various motor tasks (Das et al., 2011) or during unrestrained activity (Roy et al., 2013), postural stability (Ozinga et al., 2015), gait and turning (Mariani et al., 2013), movement and fall occurrence monitoring without training (Weiss et al., 2014) or after balance and gait training (Shen and Mak, 2015), and the effects of medication on motor behavior (Espay et al., 2011) in PD.

The use of different motor tasks for gait and movement analysis is an interesting avenue to explore, with vast amounts of possible variations. Already slightly more complex motor tasks than normal walking at self-selected speed can reveal specific impairments in PD patients; for example, backward walking or turning. Backward walking commonly results in falls in gait-impaired individuals and is known to be more strongly impaired in PD patients than forward walking (Hackney and Earhart, 2009). Axial rigidity, impaired inter-limb coordination, and asymmetric movement patterns may be involved in turning difficulties in PD patients (Boonstra et al., 2008). The assembly of batteries of short and more complex motor testing, such as inadequate obstacle courses or moderately challenging physical coordination tasks, could help to identify more specific deficits in the future.

Recent technological developments rendered movement analysis extremely powerful (di Biase et al., 2020; Dorsey et al., 2020; Espay et al., 2016; Hobert et al., 2014). They are expected to allow objective assessment of motor and non-motor behavior as well as optimization of treatment strategies (individually optimized timing, quantity and quality of medication, and lifestyle recommendations, including exercise) and therefore to profoundly impact on TOMs-based diagnostic applications for PD and other neurological disorders in the future. These developments include wearable and ambulatory systems, as well as advanced data analysis methods, e.g., based on machine-learning algorithms, with clear general and PD-specific clinical value (Bonato, 2010; Maetzler et al., 2013; Shull et al., 2014).

Spatiotemporal gait analysis has been proven useful for clinical assessment in PD patients (Hobert et al., 2014; Salarian et al., 2004) and inertial measurement units (IMU)-based wearable sensors have been repeatedly used to assess gait in PD (Dijkstra et al., 2010; Maetzler et al., 2012; Salarian et al., 2004). They allow quantification, evaluation and fine-tuning of exercise/physical therapy. Moreover, there is an emerging consensus that such approaches can enhance sensitivity and accuracy of PD diagnosis and disease progression monitoring (Espay et al., 2016). For instance, Del Din and colleagues (Del Din et al., 2019) reported the value of several gait parameters, derived from wearable devices, to predict future diagnosis with PD. Among those parameters were notably step time variability and gait asymmetries. In addition, lower pace was associated with increased probability of PD diagnosis 4 years later.

Several reported machine learning algorithms distinguished PD patients from healthy people and early from later disease stages, based on their gait characteristics with up to 90–100% accuracy (di Biase et al., 2020). However, these algorithms may be valid only for the tested populations (overfitting problem) (di Biase et al., 2020). For example, Veeraragavan and colleagues (Veeraragavan et al., 2020) presented an artificial neural network model based on the vertical ground reaction force (VGRF) signal that enabled PD diagnosis at an accuracy of 97%. These authors reported a prediction accuracy of the disease severity according to the Hoehn and Yahr score of 87%. They argued that VGRF data derived from one single short gait test may be sufficient to diagnose and assess progression stages in early PD. Similarly, Mirelman, (Mirelman et al. (2021) reported a machine-learning assisted gait analysis approach using an array of wearables to identify motor disease stages in PD patients with sensitivity values from 72% to 83% and specificity of 69–80%. This study also demonstrates the advantage of using specific sensor locations, with upper limb sensors being especially useful to assess early motor symptoms (i.e., asymmetry measures) and lower limb sensors being most powerful to capture late disease-stage symptoms, such as FOG. Although technologies are rapidly advancing and many studies on movement analysis and specifically gait analysis have been conducted, until now only few studies suggest sufficient accuracy for diagnosis or symptom progression monitoring in PD. Wearables specifically facilitate the assessment of relevant but rare events (e.g., falls), long-term and longitudinal assessment of movements and tracking/fine-tuning of exercise programs. They allow monitoring of PD symptoms during daily life activities, including during behaviors that may differ from clinical and laboratory settings. They, therefore, increase the temporal and spatial resolution of behavioral monitoring and increase ecological validity (Espay et al., 2016).

Importantly, most available evidence related to gait analysis for PD has been restricted to patients in the ON medication condition (Zanardi et al., 2021). The application of the aforementioned technologies will be key in the assessment of both ON and OFF phases [phases during which the medication (e.g., levodopa) is efficient or not], and yield important new insights on the individual impairments both during and outside of efficient medication periods. A wearable system has recently been shown to have 97% sensitivity and 88% specificity to detect OFF-phases in PD-patients (Bayés et al., 2018). Beside the cardinal motor symptoms, levodopa treatment can improve gait speed, step length, turning speed (Curtze et al., 2015) and FOG. Conversely, levodopa seems to be much less efficient against gait instability and can even aggravate postural sway and arm swing range of motion (Curtze et al., 2015). Long-term motor behavior monitoring will allow assessment of individual effects of medication and complementation/coordination with other treatment strategies, e.g., determination of best periods to perform exercise.

Comprehensive movement analysis by wearables results in massive data outputs that are difficult to analyze with traditional statistical approaches, and previously represented a major limitation of these approaches. Emerging machine learning algorithms now facilitate the analysis of such complex, multifactorial datasets (Chandrabhatla et al., 2022; Phinyomark et al., 2018). Novel advanced stages movement analysis approaches (e.g., pd neuro-technology's 'PD monitor', Magnes' Nushu 'sensorised' shoes or 'StrivePD' app from Rune Labs) compared to classical clinical diagnostics can increase objectivity and reliability and enable testing in real-life settings and the quantifiable evaluation of diverse motor activities. The potential of these new techniques to detect even subtle movement abnormalities (Nocera and Hass, 2012) as well as applications outside of laboratory settings (Hobert et al., 2014) (e.g., monitoring of sleep-related disturbances using bed sensors) render them valuable for assessment of disease stages (Fig. 2).

In summary, gait and movement analysis are promising tools for better diagnosis and characterization of PD but require further optimization and standardization (both data acquisition and analysis) for reliable applications in heterogeneous PD-patient populations. Validation, combination and cross-correlation with other disease markers and clinical assessments remain future challenges to enable broad clinical applications. In particular, categorization of PD subtypes according to motor symptoms will strongly profit from advances in gait and movement analysis. Promising results are already available and include the characterization of akinetic-rigid and tremor dominant types of PD, with akinetic-rigid types presenting with greater impairments in postural adjustments specifically during gait initiation and in obstacles negotiation (Casal et al., 2021). Evaluation of such differences becomes increasingly precise with advanced movement analysis and is crucial for the individual optimization of treatment strategies, including neurorehabilitation.

5. The need for integrative diagnosis in Parkinson's Disease: an outlook

Beside the ongoing revolutionary discoveries in the development of imaging and molecular biomarkers for PD, the methodological and technological advancements to analyze motor deficits have emerged as powerful diagnostic tools. Still, few approaches accurate enough for diagnosis or disease progression monitoring are presently available (di

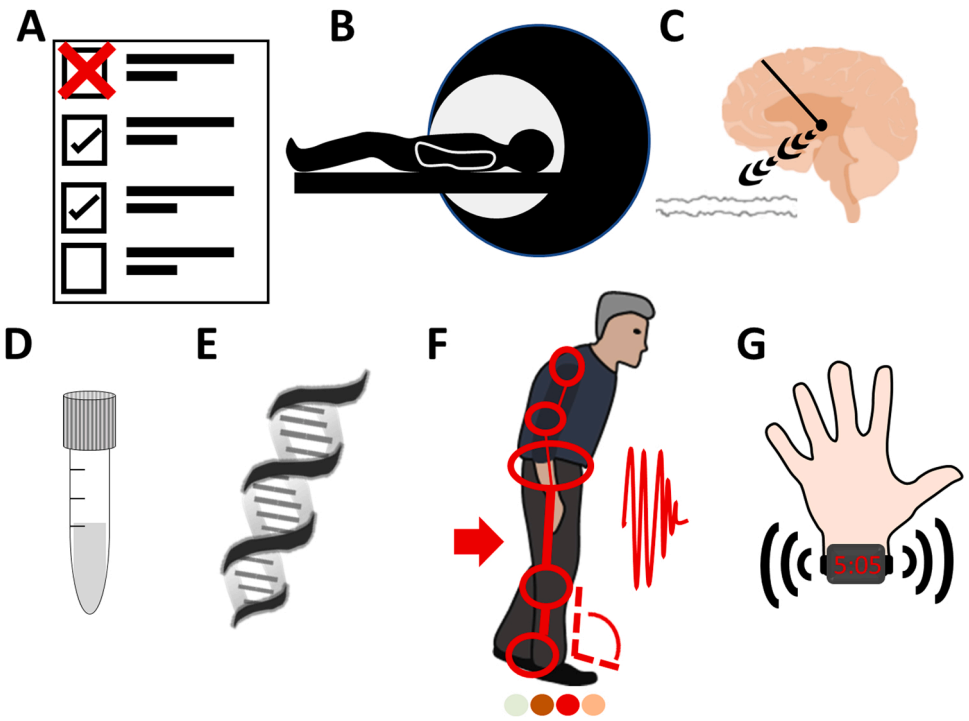

Fig. 2. Diagnostic approaches for Parkinson's Disease. (A) clinical assessment, (B) neuroimaging, (C) electrophysiological assessments like local field potential measurements, (D) fluid and tissue biomarkers, (E) genetic testing, (F) quantitative movement analysis, including gait analysis, and (G) wearables to detect other parameters.

Biase et al., 2020). The huge potential of the increasingly available tools for powerful data analysis further asks for the collaborative development of new testing protocols (e.g., batteries of different and adequately challenging motor tasks) by clinical, physical therapy and sports sciences partners to detect subtle motor impairments in patients. Especially, novel complex movement tests that include challenging coordinative tasks could improve early PD diagnosis, since abnormalities in turning, backward walking, changes in speed, etc. have been more robustly linked to early PD than linear walking (Carpinella et al., 2007). In combination with other diagnostic assessments (Fig. 2), the resulting data can potentially be correlated to specific patient groups and neuropathologies and may enable earlier and more accurate diagnosis. For example, gait analysis can readily be combined with neuroimaging, such as in a recent approach to correlate discrete gait deficits in recently diagnosed PD with alterations in glucose metabolism of brain networks by [^{18} F]− 2-fluoro-2-deoxyglucose PET (Sigurdsson et al., 2022). In this study, metabolic alterations in networks related to regions of the frontal cortex, insula, supplementary motor area, ventrolateral thalamus, cerebellum and cuneus were associated with step velocity and step length, while the metabolism of another neuronal network (increased superior parietal cortex metabolism and decreased metabolism in cerebellum, basal ganglia, insula, hippocampus, red nucleus and mediodorsal thalamus) was related to the variability of swing and step time in PD (Sigurdsson et al., 2022). Future longitudinal studies of at-risk populations could evaluate whether gait abnormalities, together with neural correlates possibly associated with early PD, may predict PD development. Other candidate markers for gait deficits include reduced caudate dopamine and compromised integrity of the pedunculopontine nucleus (Craig et al., 2020) as well as β-amyloid 1–42 (Kim et al., 2019; Rochester et al., 2017) and α-synuclein (Goldman et al., 2018), both measured in cerebrospinal fluid. Similarly, movement assessments may be combined with electrophysiological and neural readouts. In particular, electromyography (EMG) analyses reveal information about muscle coordination, weakness or co-contraction abnormalities, which can guide physical therapy exercises to reinforce specific muscle groups (Islam et al., 2020; Ting et al., 2015). Recent advances in neurotechnology for deep brain stimulation now enable recording brain signals in chronically implanted patients, wirelessly and in real-time. The specific neural biomarkers that underline gait dysfunction (Thenaisie et al., 2022) provide key, online feedback to predict episodic gait manifestations (e.g., FOG), characterize daily fluctuations, and in turn control closed-loop therapies to maximize locomotor performance over time via focused stimulation.

The possibility to comprehensively analyze many different early gait and movement parameters might enable the identification of specific movement impairment patterns as reliable markers for PD subtypes or disease stages. The evaluation of combinations of movement analysis with other biomarkers and clinical assessments is necessary for confirmation and will contribute to a better understanding of PD symptoms and pathogenesis associated with specific PD sub-types. Gait and movement analysis can further contribute to the identification of specific disabling motor deficits, based on which therapeutic approaches can be suggested to facilitate physical activity and exercise. It could also inform how to best integrate regular, intense exercise training in everyday life conditions, for example through telerehabilitation, for which important technological and logistic considerations remain to be addressed to ensure exercise-motivation and adherence over time. Correlating motor deficits with neuronal network activity and specific pathologies will open new avenues for differential diagnosis and possibly new treatment strategies (Mirelman et al., 2019). Movement analysis can further be used to assess the efficiency of specific types of exercise in PD patients or at-risk populations and may be useful for the challenging recommendation of new personalized exercise programs or the modification of existing ones (Fig. 3). In addition, it could help to identify specific limitations of gait-impaired individuals that must be considered for exercise prescription (e.g., reduced a step-rate threshold (Jeng et al., 2020a)). For complex training setups, individual motor learning capacities that may be impaired in PD must also be taken into account (Freidle et al., 2023).

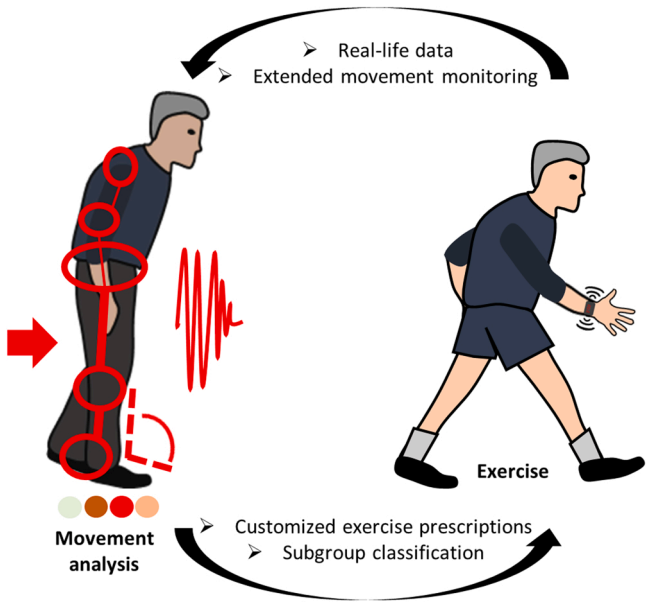

Fig. 3. Combination of movement analysis and exercise in Parkinson's Disease. The benefits of specific exercise protocols can be evaluated by movement analysis in-lab/in-clinic or outside. Such analysis can help to select the most appropriate personalized exercise interventions, identify specific patient characteristics and thereby improve diagnosis and prognosis.

6. Conclusions

In conclusion, molecular and imaging biomarkers are increasingly capable of providing valuable information on pathological alterations in peripheral tissues and the brain. However, as pathology appears not to perfectly correlate with symptomatology, functional parameters, such as motor capacities and non-motor symptoms must be considered to increase diagnosis and individual disease staging reliability and enable efficient personalized medicine. Overall, the powerful combination of new tools for movement data recording and analysis is becoming invaluable for PD research and treatment approaches, particularly exercise. To take full advantage of the possibilities, numerous questions remain to be answered (see open questions box).

7. Open questions

- How do movement parameters correlate with other disease characteristics and biomarkers?
- Can specific movement patterns – maybe in combination with other biomarkers – be used for earlier diagnosis?
- The analysis of which in-lab/in-clinic movement tasks are most useful for diagnosis/prognosis?
- Which in-lab/in-clinic movement tasks are important complements to movement data that can be collected outside the lab/clinic?
- Are distinct exercise interventions differentially effective in specific PD patient groups?
- Which exercise parameters (type, intensity, duration) are most useful for which PD-patient groups and at which stages?
- Can appropriate exercise protocols slow down or even reverse disease progression?
- Which machine-learning models are the most accurate to derive valid and reliable diagnostic information from movement data?

CRediT authorship contribution statement

Johannes Burtscher: Conceptualization, Writing- Original draft preparation, Writing- Reviewing and Editing. **Eduardo Martin Moraud:** Writing- Reviewing and Editing. **Davide Malatesta:** Writing- Reviewing and Editing. **Grégoire P. Millet:** Writing- Reviewing and Editing. **Julien F. Bally:** Writing- Reviewing and Editing. **Aurélien Patoz:** Conceptualization, Writing- Reviewing and Editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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