Gait impairments in Parkinson's disease

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Gait impairments are among the most common and disabling symptoms of Parkinson's disease. Nonetheless, gait is not routinely assessed quantitatively but is described in general terms that are not sensitive to changes ensuing with disease progression. Quantifying multiple gait features (eg, speed, variability, and asymmetry) under natural and more challenging conditions (eg, dual-tasking, turning, and daily living) enhanced sensitivity of gait quantification. Studies of neural connectivity and structural network topology have provided information on the mechanisms of gait impairment. Advances in the understanding of the multifactorial origins of gait changes in patients with Parkinson's disease promoted the development of new intervention strategies, such as neurostimulation and virtual reality, aimed at alleviating gait impairments and enhancing functional mobility. For clinical applicability, it is important to establish clear links between specific gait impairments, their underlying mechanisms, and disease progression to foster the acceptance and usability of quantitative gait measures as outcomes in future disease-modifying clinical trials.

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Introduction

The typical pathological manifestations of Parkinson's disease (bradykinesia, rigidity, and reduced amplitude and automaticity of movement) affect the gait patterns of patients with the disease. Patients have reduced gait speed and step length, increased axial rigidity, and impaired rhythmicity. Gait problems worsen as the disease progresses, which is a major disease burden that markedly affects independence and quality of life (panel).[1,8] Although dopaminergic medications improve certain aspects of walking such as velocity and step length, temporal characteristics and episodic symptoms such as freezing of gait, defined as the sudden inability to continue walking despite the intent to maintain locomotion, have responses that are much more variable.[2,20] Gold-standard dopaminergic treatments also create multiple challenges that can further impair gait, including fluctuations in motor response (so-called wearing off) and dyskinesia.[4] Thus, optimal evaluation and treatment of alterations in gait in patients with Parkinson's disease demands an understanding of the multiple mechanisms and factors that contribute to these problems.

The current understanding of gait impairments in patients with Parkinson's disease is based mainly on cross-sectional studies that do not provide insights into individual gait changes associated with disease progression.[3,7,8] The rare use of quantitative assessment of gait (eg, speed and variability) in the routine clinical examination and poor understanding of the underlying mechanisms limits the use of gait measures as viable outcomes for assessing disease progression and effects of treatment. Advances in wearable technology and imaging techniques have generated knowledge relevant to assessment, understanding of mechanisms, and treatment of gait impairments in patients with Parkinson's disease. Low-cost sensing technology (eg, accelerometers and gyroscopes) is rapidly replacing complex camera-based motion-capture systems, allowing clinicians to quantitatively assess gait not only in the clinic but also during daily living activities in the home and community settings. This method of measurement provides valuable information on habitual function, motor fluctuations, and response to medications. Neuroimaging techniques that record neural activity during walking have advanced the understanding of the mechanisms causing aberrant gait patterns in patients with Parkinson's disease, leading to the design of more effective clinical interventions.[21–26]

This Review evaluates the advances made in three related aspects of gait impairments in patients with Parkinson's disease: assessment, mechanisms, and interventions to improve gait. The Review highlights the gaps in knowledge and provides insights that might lead to new discoveries and innovations to improve clinical decisions and treatments.

Assessment of gait abnormalities

Gait assessment in clinical and research settings

The approach to assessing gait evolved from just a few items on the Unified Parkinson's Disease Rating Scale (UPDRS),[27] the most commonly used rating scale for symptoms of Parkinson's disease, to more detailed observational and quantitative assessments of different aspects of gait associated with functional limitations (table 1). Many observational scales (eg, Dynamic Gait Index)[28] and performance-based tests (eg, Timed Up and Go Test)[28] have been validated and used in the clinic, providing information on gross motor characteristics such as slow and short shuffling steps. However, these tests are suboptimal because they are influenced by instruction and tester bias and measure only relatively simple gait metrics (ie, speed).[28] For example, the Timed Up and Go Test is a performance-based measure of functional mobility that provides information on transitions, gait, and risk of falling. Yet, its clinical use is limited to timed cutoff scores that do not provide information on the pattern or quality of the movement. Although this and other similar clinical scales or tests are more informative than the UPDRS, they are not disease-specific and have low sensitivity, which limits their usefulness in assessing disease progression or response to treatment.[28]

Historically, increasing the sensitivity of assessment required large laboratories dedicated to gait assessment

Panel: Characteristic gait impairments in patients with Parkinson's disease as a function of disease stage

Early stage

In the early stages of Parkinson's disease, the gait of patients slows and step length shortens, compared with those of age-matched healthy adults.[1,2,3] These changes in gait are common in, but not specific to, patients with Parkinson's disease, as many diseases can reduce gait speed. However, reduced amplitude of arm swing and smoothness of locomotion and increased interlimb asymmetry are more specific to Parkinson's disease and often are the first motor symptoms.[3–6] In the early stages of the disease, symptoms are often unilateral, corresponding to asymmetrical basal ganglia neuropathology (video).[3–5] Both interlimb and intralimb movements, such as the timing of swing duration, are also impaired.[7] Range of motion of the hip, knee, and ankle during walking start to diminish, especially during the late-stance phase of the gait cycle.[1,8] Changes in posture and range of motion further affect the magnitude of movement, for example contributing to the reduction of step length. Gait variability is larger than that seen in age-matched healthy controls, and performance on complex locomotor tasks is also impaired (eg, reduced angular velocity of turning).[7] Additionally, as ambulation in this stage becomes less automatic, many gait alterations become apparent or exaggerated when patients are asked to walk and do another task at the same time (ie, dual-tasking).[6]

Mild-to-moderate stage

In general, many of the spatiotemporal features altered in the early stages of the disease progress bilaterally, so that asymmetry might actually decrease, and movement becomes more bradykinetic with disease progression.[1,2] Shuffling steps, increased double-limb support (ie, both feet are on the ground) and increased cadence become common. The magnitude of arm swing is reduced bilaterally with accompanied reduction of axial rotation (video).[5,9] Postural changes, such as stooped posture, might further contribute to the decline in gait by altering gait kinematics.[3] Motor automaticity becomes further impaired, resulting in fragmented motor function, such as defragmentation of turns (ie, turning en block)[10,11] and problems with gait initiation. Freezing of gait and festination might appear and patients have an increased risk of falling in this stage.[12–16]

Advanced stage

The changes in gait worsen. Additionally, blocks in motor function (eg, freezing of gait) become frequent, accompanied by reduced balance and postural control and severe risk of falling.[17–19] Motor fluctuations and dyskinesias are present in most patients and negatively impact gait. Endurance and muscle force further decline, leading to reduced motor capacity and the need for assistance devices or wheelchair use.[17–19]

See Online for video

and expensive equipment, such as motion analysis technology. Using such approaches showed that gait in Parkinson's disease is marked by a reduced range of motion and muscle power at the hip, knee, and ankle.[1,3] Impaired muscle contraction, rigidity, and postural instability all probably contribute to reduced forward limb propulsion, which, in turn, can negatively affect spatiotemporal gait parameters, such as speed and step length.[1,3] However, insufficient access to motion analysis technology and scarcity of expertise to assess these features of gait resulted in incomplete evidence regarding the link between disease pathology, range of motion and force production, the timing of their appearance, and their contribution to impaired gait and reduced function.[8] Thus, treatments were generally one-size-fits-all and not tailored to individual phenotypes or disease states, limiting their usefulness.

Technological advances produced relatively low-cost tools, such as inertial sensors (eg, accelerometers and gyroscopes) and pressure-sensitive carpets suitable for quantifying gait.[24,29] These sensor-based approaches enabled the detection of subtle deviations in gait (such as arm-swing asymmetry) and their changes over time in patients with Parkinson's disease.[5,9] Sensor-based approaches also enable the assessment of more granular measures of gait. For example, increased variability in gait (ie, the magnitude of stride-to-stride fluctuations) reflects increased volitional control, reduced automaticity, and increased gait instability[6,30] that can be detected early in the disease and serve as markers of disease progression.[30] In complex walking situations, such as turning or dual-tasking, when additional cognitive resources are needed for planning and processing of internal and external stimuli, variability increases[30,31] and gait becomes more fragmented (ie, less fluid;[8] panel). Gait changes observed during turning or while dual-tasking have been linked to falls and injuries in patients with Parkinson's disease[10,11] and are exacerbated with disease progression,[32] as seen in patients with freezing of gait.[12,33] Because of the impact of complex walking situations on gait, they can be used to unmask compensatory mechanisms related to higher-level cognitive control of gait in patients with Parkinson's disease[6,30,34–36] and potentially unravel motor impairments.[5]

Although the assessment of variability in gait and turning provides important information that complements more conventional spatiotemporal parameters (eg, rhythmicity and coordination), clinical usefulness, norms, and standard procedures for their measurement need to be established. In fact, besides gait speed and stride length, psychometric and clinometric measures across the disease course are absent.[3,37–39] For instance, although the mechanisms underpinning variability of gait and turning appear to be independent from each other and from gait speed, the causes of these alterations, their changes during the course of the disease, and their contribution to a clinically applicable assessment are not well described.[39]

Research into gait in patients with Parkinson's disease has yet to fully take advantage of the wealth of mathematical techniques available to assess the repeatability and complexity of movement patterns.[37,38] One study[40] used principal component analyses, a tool for dimension reduction, to summarise the plethora of gait parameters by grouping them into domains (eg, pace, rhythm, variability, asymmetry) correlated with participants' demographics and clinical features. This initial attempt at grouping relevant parameters of gait has the potential to improve the clinical interpretation of gait assessments (by identifying a minimal dataset necessary for assessment), enhancing our understanding of underlying mechanisms (by explaining different disease phenotypes) and, consequently, improving the effectiveness of individualised interventions.[40] Nonetheless, questions remain about whether a single composite score can enhance interpretability and be

	Potential indication	Responsiveness to levodopa	Changes with disease progression	Method of assessment	Comments
Clinical use					
Velocity (m/s)*	Bradykinesia, amplitude control	Yes	Yes	Observational and timed analysis, pressure-sensitive walkway, 3D GA, BFS	Not specific to Parkinson's disease, affected by age; unclear if changes are monotonic or differ across the disease stages
Stride length (cm)*	Bradykinesia, amplitude control	Yes	Yes	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), pressure-sensitive walkway, 3D GA, BFS	Unclear if independent from gait velocity and if could be a marker of disease
Initiation (s)*	Planning of gait, force generation, bradykinesia	Yes	Data not available	3D GA, pressure-sensitive walkway	Unclear how it changes with disease progression and is impacted by non-motor symptoms and kinematic changes; unclear impact on quality of life
Turning (time or n of steps)*	Susceptibility to falling, planning of gait, postural stability, disabiltiy	Pilot evidence only	Yes	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), 3D GA, BFS	Clinical usefulness, reference ranges, and response to medication have not been fully established; home-based assessment is needed to investigate turning as a potential marker of disease progression, fall risk, and disability
Timed Up and Go (s)*	Transitions, fall risk, bradykinesia	Evidence for effect on time to completion, data unavailable on effect on task components	Yes	Observational and timed analysis, 3D GA, BFS, smartphones	Clinical usefulness and reference ranges have been established for older adults (≥60 years) and patients with Parkinson's disease; accepted measure of fall risk with ageing, not specific for Parkinson's disease, yet easy to use and provides indication of functional capacity; home-based digital assessment (via smartphone) has been reported; prospective studies are needed to establish change with disease progression and disability
Research use					
Step time (s) and cadence (steps per min)	Timing control	Inconsistent findings	Inconsistent findings	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), pressure-sensitive walkway, 3D GA, BFS, smartphone	Response to medication and disease progression requires further study to explain inconsistent findings; impact of kinematic changes and independence from spatial measures should be studied to understand what contributes to changes in step time
Stance duration (s)	Timing control	Some reports suggest that levodopa worsens stance duration	Inconsistent findings	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), pressure-sensitive walkway, 3D GA, BFS	Response to medication and disease progression and association with kinematic changes are required to explain why and when stance duration changes
Variability in stride length, time, and width (%)	Fall susceptibility, planning and conscious control of gait, postural stability	Stride time is responsive, data unavailable on length or width	Yes	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), pressure-sensitive walkway, BFS	Clinical usefulness, reference ranges, and standardisation for these gait measures have not been established; further research needed to investigate impact of age and disease severity to assess the potential of using these metrics as biomarkers
Double support (s)	Postural stability, proprioceptive sampling	Inconsistent findings	Data not available	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), BFS, pressure-sensitive walkway	Unclear if independent from timing aspects of gait and how it relates to falls, freezing of gait, and disease progression
Limb coordination	Early detection of disease and disease progression	Arm swing and leg range of motion improve	Pilot studies suggest a change with disease progression	Observational and timed analysis (eg, Timed Up and Go, dual-tasking), 3D GA, BFS	Insufficient information on coordination of upper and lower extremities; magnitude of change with disease progression and response to medication should be further studied, as well as the effects of gait speed

3D GA=three-dimensional gait analysis. BFS=body-fixed sensors. *Used in both clinical and research settings.

Table 1: **Commonly used measures of gait performance**

used in the clinical assessment of disease severity. In the absence of such a composite score, gait speed has become the standard gait parameter because it is easy to measure and interpret, normative data are readily available, and gait speed is responsive to dopaminergic treatment.[36,41] Still, reduced gait speed is not disease-specific and might not be suitable to characterise and monitor gait changes across the disease course. Furthermore, it is yet to be determined if the increased granularity in gait measures translates into improvements in clinical decision making and patient outcomes.

Gait assessment in the home and community setting

The assessment of gait during normal daily activities of patients with Parkinson's disease, outside the confines of the clinic or the laboratory is emerging as an alternative approach to traditional gait analysis. Using smartphones, smart watches, and other wearable devices, gait can be

quantified in the home and community settings. These instruments show how patients walk outside of the artificial laboratory setting, where other factors have important roles (eg, the environmental context, dual-tasking, social interactions, or emotional affect).[42,43] Continuous monitoring of daily living can identify alterations in movement quantity (ie, number of steps, scale of activity) and typical patterns of gait (eg, decreased step regularity).[44,45] Changes in gait characteristics can also be evaluated throughout the day and the cycle of medication, and detection of episodic occurrences such as falls and freezing of gait can be achieved.[12,44,46–48] Such information is highly valuable to assess disease severity and quality of life, and to support disease management.

A pilot study investigated the construct validity of an objective score for Parkinson's disease severity derived from structured tests of mobility, such as gait and finger tapping done using smartphones in 23 patients with mild Parkinson's disease (mean age 64·6 [SD 11·5] years, mean score 2·1 [0·7] on the Hoehn and Yahr scale).[43] The study showed that structured, home-based testing could complement standard measures for Parkinson's disease progression by providing frequent, objective, real-world assessments. Such information is extremely valuable as it can potentially be used to assess treatment and disease-modifying effects in clinical trials. However, there are many challenges in the validation of real-world data obtained without the presence of an observer or labelling of specific activities (eg, datasets unannotated with task information). Additionally, the optimal location on the body, number, and type of sensors needs to be determined. For example, from the patient's perspective, devices worn on the wrist might be most acceptable. However, interpretation of data and analysis of gait features might be easier when using sensors placed on the trunk. Moreover, much is unknown regarding the variability of movement during daily activities and how these changes represent disease progression. Further, the issue of compliance with these types of assessments should be considered. For example, the feasibility of implementing wearable technology for passive monitoring was investigated in a trial of 953 patients with Parkinson's disease,[49] where median compliance was only 65%. Furthermore, it is unclear how these quantitative assessments of gait compare with one-off assessments in the clinic and whether they should replace or only augment the current gold-standard measures like the UPDRS.

Influence of non-motor symptoms on gait

Non-motor symptoms (eg, depression, anxiety, apathy, and cognitive decline) are common in patients with Parkinson's disease and highly affect quality of life.[50,51] These symptoms often accompany motor impairments and can exacerbate slow gait, lead to greater gait variability, and trigger freezing of gait.[51,52] For example, greater incidence of cognitive decline is reported in patients with Parkinson's disease who have the postural instability and gait disturbance (PIGD) subtype, compared with those with the tremor-dominant subtype.[50] The interrelationships between gait and cognitive function suggest that the assessment of gait can potentially be used to make quantitative inferences about cognition.[53,54] However, further validation work is needed before such an approach can be applied clinically. Additionally, comorbidities like peripheral neuropathy and osteoarthritis are common in patients with Parkinson's disease and can further impair gait as the primary or secondary gait dysfunction.[55]

There is evidence that treatment of non-motor symptoms (ie, depression and cognitive impairment) can improve gait and reduce motor complications such as freezing of gait.[56,57] Assessing the interaction of comorbidities (eg, peripheral neuropathy and osteoarthritis) and non-motor symptoms with the progression of gait impairments is important to improve disease management and treatment. Thus, by contrast with the current approach to research, which aims to include subgroups with relatively homogeneous disease manifestations, large-scale studies should include patients with additional comorbidities and non-motor symptoms (eg, severe depression) to investigate these potentially multiplicative interactions and to foster generalisability of the findings.

Mechanisms underlying gait impairments

Differences in gait phenotypes

Symptomatic heterogeneity in patients with Parkinson's disease has led to the classification of the disease into subtypes, such as PIGD and tremor-dominant. This classification is based on items from the UPDRS.[58] Compared with patients with the tremor-dominant subtype, those with the PIGD subtype are typically less responsive to levodopa and are more likely to develop motor fluctuations and dyskinesia, non-motor symptoms, and dementia.[53,59,60] Patients with the PIGD subtype have slower gait speed, shorter strides,[61] excessive instability,[17] impaired adaptive walking behaviours,[62] and a high propensity for falls.[17] Conversely, disease progression is slower in patients with the tremor-dominant subtype, despite having a younger age of onset than patients with PIGD.[50] However, with approximately 20% of patients overlapping as part of an intermediate subgroup,[63] this subtyping is unstable, with patients shifting between phenotypic subtypes as the disease progresses,[64] while the severity of individual symptoms is overlooked.

New arguments suggest that phenotypes should not be assessed as discrete subtypes, but rather as a multidimensional continuum that accounts for various modifiers, including non-motor symptoms.[65] Quantitative features of gait, such as variability and regularity,[61] might help with the classification of phenotypes (table 1). Yet classification alone does not elucidate the underlying mechanisms of gait dysfunction. Factors such as responsiveness to levodopa and the contribution of

non-motor symptoms might be important foci of future research to better understand the mechanisms that contribute to the variance of symptomatology across the phenotypic continuum, improve long-term prognosis, and promote personalised medical management.

Freezing of gait

Freezing of gait is one of the most debilitating, yet difficult to assess impairments of gait, as it is episodic and variable by nature.[66] Multiple theories try to explain the underlying mechanisms, with motor, sensory, cognitive, and affective impairments all being implicated.[13–15,67] However, the neural correlates and triggers are less understood.[68] Laboratory protocols including the use of reported behavioural triggers such as turning, traversing narrow passages, cadence manipulations, and obstacle avoidance have provided important insights into the variability in the pathophysiology of freezing.[15,16,31,69] Yet, these protocols are often inefficient, not representative of everyday situations, and have been unable to produce the number of freezing episodes needed for advanced analyses.[33,69] Freezing of gait can be classified as responsive, resistant, or induced by dopaminergic medication, suggesting the existence of subtypes.[68] Assessment in everyday conditions and the development of criteria for the identification of subtypes of freezing of gait might lead to better understanding and treatment of freezing of gait.

Although there is some evidence that freezing of gait can be detected even in the home, at least to some degree,[12,70,71] the multiplicity of triggers and heterogeneity of presentation of this symptom makes its prediction challenging. A clear and objective definition based on measurable motor behaviours as to what constitutes an episode of freezing of gait and how it is related to other motor and non-motor symptoms would facilitate the development of methods to detect and predict these episodes. Objective measures quantifying severity of freezing of gait, using standardised protocols, should be validated to foster comparability and replicability of research and clinical protocols.[12,70] Further, it might be beneficial to identify markers that predict which patients will manifest freezing of gait. However, in the absence of objective measures and an understanding of the problem, therapy and prevention are likely to be suboptimal.

Neural correlates of gait

Understanding the underlying mechanisms of gait impairments is crucial for the development of theoretical frameworks and targeted interventions for patients with Parkinson's disease. As MRI and functional MRI can only provide indirect insight into the neural mechanisms of gait because actual movement inside the scanner is limited, imaging studies often focus on differences between patients and healthy individuals and those with defined gait impairments (eg, patients with PIGD and tremor-dominant Parkinson's disease subtype, and patients with and without freezing of gait).[35,51,72] Compared with healthy individuals, patients with Parkinson's disease who have impaired gait show atrophy in several brain areas with evidence of lateralised changes (figure, appendix). Functional networks in resting-state and task-based functional MRI studies also show altered functional connectivity,[76,77] but increased prefrontal activation during gait imagery tasks in patients with Parkinson's disease[35,78] compared with healthy controls, reflecting the increased cognitive effort, even in the preparation stages of gait.

See Online for appendix

Degeneration of the globus pallidus; reduced putamen volume; decreased dorsolateral, frontal, and medial cortical thickness; and diffusion tensor changes (eg, reduced functional anisotropy and increased diffusivity) in the substantia nigra and pedunculopontine nucleus have been associated with severity of freezing of gait.[72,74,77] Changes in the topology of the structural network and dysfunctional fronto–striato–limbic processes support the relation between freezing of gait and anxiety in patients with Parkinson's disease.[51,68,79] Cortical changes, including reduced volume of the presupplementary and primary motor grey matter, more hyperintensities in white matter, and more severe microstructural changes (eg, increased diffusivity in the globus pallidus) were associated with the loss of gait automaticity in patients with the PIGD subtype.[73,75]

The vast number of structures implicated in gait deficits is an important concern that might be attributed to the variable research methodologies that have been used (eg, whole-brain analysis *vs* regions of interest). The variety of approaches (including motor imagery, virtual reality stimuli, motor tasks, and dual-task paradigms as surrogates of gait function) probably elicit different interactions with multiple networks, and this effect is compounded by small patient cohorts and different analytic approaches controlling for group and medication effects (appendix). Thus, the ability to compare studies and to clearly identify the mechanisms associated with gait impairment in patients with Parkinson's disease and the influence of additional neurotransmitters (ie, noradrenergic or cholinergic) is limited. It is imperative to standardise scanning protocols for these measures to foster reproducibility and generalisability through data aggregation across sites. Future studies should also investigate longitudinal changes with disease progression, the influence of comorbidities (ie, vascular and other neurodegenerative pathologies), and the impact of treatment on the structure and function of gait-related brain areas.

Throughout the past decade, EEG and functional near-infrared spectroscopy have been developed as promising tools to study brain function during walking.[80–83] Motor abnormalities have been linked to reduced power in low-frequency bands, which are also associated with attention and executive function.[81] Changes in β activity have been related to freezing of gait,[83] alterations in γ activity were associated with motor execution and gait,[82] and changes

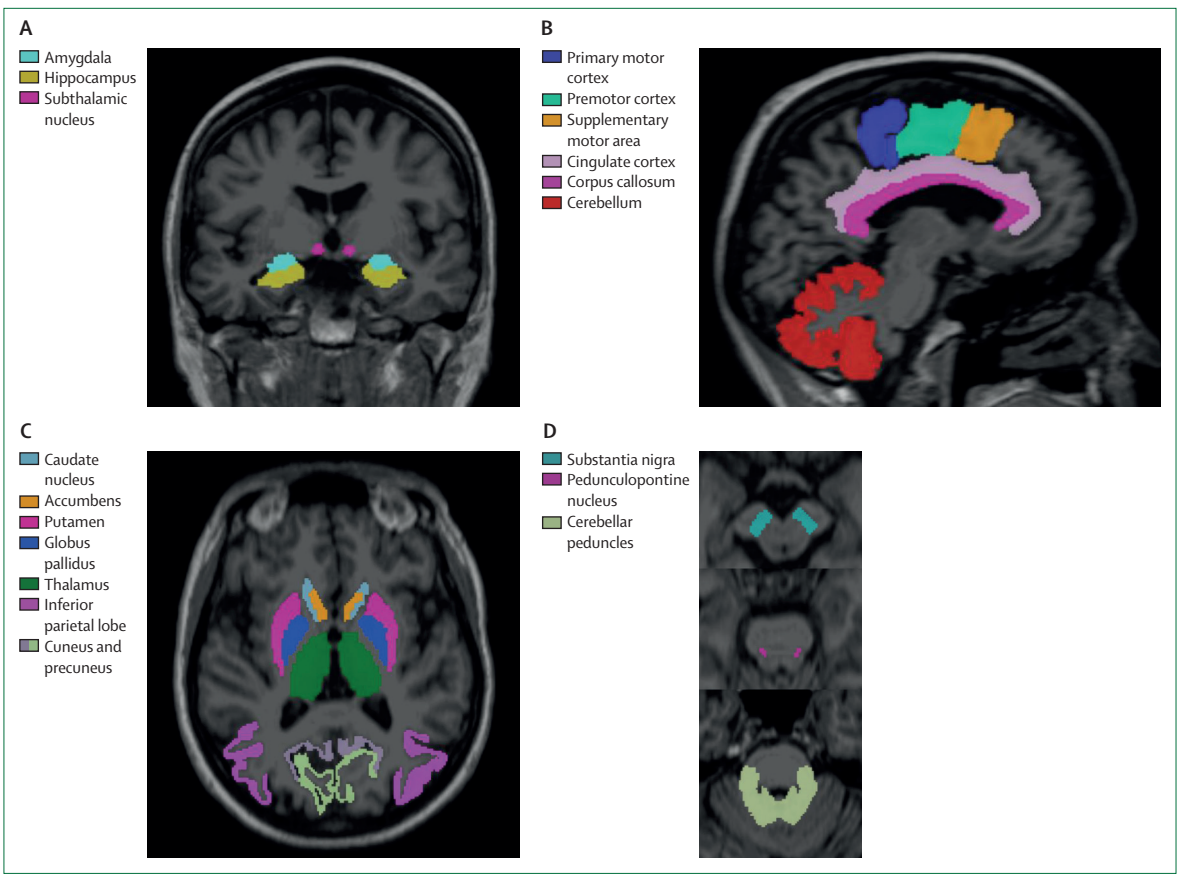

Figure: **Brain regions associated with gait dysfunction in patients with Parkinson's disease**
(A) Coronal, (B) sagittal, and (C) transverse view of the brain. (D) Three transverse brainstem slices of regions related to gait. Coloured areas reflect brain regions where volumetric alterations or changes in white matter integrity have been associated with gait impairments in patients with Parkinson's disease. These areas include regions that have been shown to differ significantly when comparing patients with and without freezing of gait (studies with or without healthy age-matched controls) or motor subtypes (PIGD and tremor-dominant) related to gait, or to be significantly correlated with clinical measures of gait. For example, atrophy was reported in subcortical structures, including the amygdala, hippocampus, and subthalamic nucleus;[72,73] cortical motor areas, including primary motor, premotor, and supplementary motor areas, and the cingulate gyrus;[73,74] cortical non-motor areas, including the inferior parietal lobule, cuneus, and precuneus;[74] and the cerebellum.[73] Diffusion-tensor changes in white matter are reported in the corpus callosum.[74] Brainstem (pedunculopontine nucleus and substantia nigra[75]), basal ganglia (caudate[73] and putamen[72,73]), and thalamic structural changes are also illustrated (appendix). PIGD=postural instability and gait disturbance.

in θ activity have been related to preparation for locomotion.[82,84] Functional near-infrared spectroscopy studies in patients with Parkinson's disease, compared with healthy controls, have shown increased frontal lobe activation even in straight-line, unobstructed walking tasks, reaffirming their need for greater recruitment of cognitive resources when walking.[67,80] These dynamic imaging techniques could aid in better understanding of neural activation during walking and enable the development of patient-specific clinical interventions to improve gait in patients with Parkinson's disease.

Interventions

The most common treatment for motor dysfunction in patients with Parkinson's disease is dopaminergic. However, there is increasing evidence, particularly from the past 5 years, on the efficacy of non-pharmacological interventions to improve motor function and gait and to reduce the risk of falling.

Pharmacological interventions

Speed and amplitude (ie, step length) of gait generally improve with levodopa treatment.[4,20] By contrast, temporal metrics, such as cadence and double support, do not improve.[20] Turning speed seems to also improve with levodopa treatment,[20] as does freezing of gait.[85,86] Long-term use of levodopa typically leads to motor response fluctuations (ie, on-off events, during which the medication is either working or not) and dyskinesia.[18] Both conditions have been related to gait instability.[18] Notably, falls mostly occur while patients are on medication;[18] however, it is not clear if this association reflects just disease severity or if there is a clear mechanistic link between levodopa and gait impairments.

Dopamine agonists improve some aspects of gait, including gait initiation and turning.[87] However, dopamine agonists might lead to sedation, increasing the risk of falling and mildly affecting freezing of gait.[87] There is some evidence[88] that inhibitors of amine oxidase B might

reduce the likelihood of developing freezing of gait. However, this possibility still needs to be investigated using more objective and sensitive measures in the home and community settings.

Altered cholinergic activity has also been implicated in gait impairments in patients with Parkinson's disease.[41] Accordingly, acetylcholinesterase inhibitors have been shown to reduce falling.[29,89] Methylphenidate, which increases dopaminergic stimulation at the postsynaptic receptor level, was reported to improve freezing of gait in patients with advanced Parkinson's disease.[90] However, more specific measures of gait, such as step length and stride time did not improve.[90] Thus, the evidence for treatment remains inconclusive (table 2).

Medications commonly used for non-motor symptoms such as anti-depressive, anti-anxiety, antipsychotic, or sedative drugs, can all affect gait and falling.[19] Increased anticholinergic burden and higher number of prescription medications were positively associated with falls and fractures in patients with Parkinson's disease.[19,91] These findings highlight the importance of evaluating gait in conjunction with treatment of non-motor symptoms (and vice versa).

Non-pharmacological interventions

Exercise can improve gait through various mechanisms, some specific to central aspects of gait control and some indirect via improved fitness, strength, and balance. It is probable that exercise interventions can improve multiple aspects of gait simultaneously. Most forms of exercise have clinical benefits on both spatial and temporal measures (ie, velocity, stride length, and cadence) of the gait of patients with Parkinson's disease (appendix) that can be effectively enhanced by external auditory or visual cues.[21] Such cues also improve various aspects of gait variability (ie, length and time of step), reinforcing the benefits of externally induced pacing to enhance rhythmicity and automaticity of walking.[26] Cue-augmented training was also shown to reduce the duration of turning[23] and freezing of gait.[21] Still, the benefits of cueing were primarily immediate, with decreased long-term consolidation and transfer effects, whereas intermittent cueing did not have a benefit.[22,92] More integrative approaches (ie, motor imagery, action observation)[92–94] that address motor-cognitive interactions (eg, dual-tasking) have shown improvements in gait speed. However, the effects on other spatiotemporal measures of gait (ie, assymetry and variability) are not well studied (appendix). Emerging technology-driven approaches, such as virtual reality, robotics, exergaming (ie, gaming platforms that incorporate physical exercise), and transcranial direct-current stimulation, show some benefit in improving measures of gait, such as velocity, distance walked, step and stride length, and falls (appendix).

Intervening early on, before the onset of severe motor problems such as falls (ie, preventive rehabilitation), has many theoretical advantages. One study found that high-intensity aerobic exercise in the form of brisk walking for patients in early stages of Parkinson's disease (ie, newly diagnosed and not yet on medication) had potentially beneficial disease-modifying effects and could optimise outcomes related to gait[25] (appendix). However, further research is needed to evaluate the potential of exercise interventions for improving symptoms over time.

Methodological limitations of the existing non-pharmacological studies hinder the clinical applicability of their findings (appendix). Most exercise interventions include fairly crude clinical measures of gait (ie, speed), restricting insight into the potential mechanisms that underlie the observed improvements.[26,92] Assessments are typically done at discrete timepoints in a research or clinical environment, reducing their ecological validity and insufficiently representing everyday activities.[26,92] Furthermore, some assessments are done while patients are on medication and others during periods off medication, making comparisons across studies difficult. The dosage (eg, frequency, duration, and intensity) of non-pharmacological approaches differs considerably across studies, potentially contributing to the reported inconsistencies in efficacy. Most studies of exercise typically include patients with mild-to-moderate disability and disease duration of 5–10 years, and exclude comorbidities, such as orthopaedic or cardiovascular problems and peripheral neuropathies. The presentation of symptoms in these disease stages varies considerably (ie, presence *vs* absence of falling or freezing of gait, mild cognitive impairment, or early dementia), making it difficult to generalise across the disease course or identify a subgroup of patients who might benefit most from a particular approach. It is possible that greater precision in tailoring exercises to a particular phenotype might improve outcomes, but additional research is needed.

Neuromodulation interventions

For two decades, neuromodulation techniques have been used to alleviate both the hypokinetic and hyperkinetic symptoms of Parkinson's disease, but their impact on gait is still controversial. A study of 20 patients with Parkinson's disease temporarily reduced the progression of gait and balance instability after deep brain stimulation of the subthalamic nucleus,[95] whereas another study reported long-term beneficial effects of low-frequency stimulation of the subthalamic nucleus on freezing of gait in 11 patients with Parkinson's disease.[96] A meta-analysis of six studies with 31 patients that assessed the effects of deep brain stimulation of the pedunculopontine nucleus showed moderate improvements in the PIGD phenotype, freezing of gait, and falls.[97] The variable effects seen from deep brain stimulation of different brain regions further illustrate the complexity of the neural control of gait in patients with Parkinson's disease.

Based on these observations, a new approach, mid-thoracic spinal cord stimulation, has been examined as a means to ameliorate impairments of gait in patients with

	Potential solutions and future directions
Assessment of gait parameters	
Quantitative evaluation of gait parameters does not yet lead to actionable results	Studies designed to better understand differences among various categories of gait parameters (eg, pace, rhythm, variability, asymmetry) and their responsiveness to different therapies
The impact of comorbidities on gait parameters is poorly understood	Large observational studies that include patients with common comorbidities, such as osteoarthritis or peripheral neuropathy, to understand the impact of these conditions on clinical outcomes of gait impairment and disease symptoms in Parkinson's disease
The impact of non-motor symptoms and medications on gait parameters are poorly understood	Consideration and monitoring of non-motor symptoms and medications to clarify their potentially multilayered interactions and to enhance the potential clinical applicability of assessing gait
Gait parameters that are most sensitive to change over the disease course have not been identified; unclear whether the gait parameters most sensitive to change differ by disease stage	Large, prospective, longitudinal studies to systematically measure changes in well defined gait parameters (including imaging) over time; examination of changes in these parameters in intervention studies to identify modifiable alternative targets, potentially reducing the duration and number of patients needed in clinical trials
The technical and clinical validity of information received from wearable sensors and constant monitoring has not been fully investigated	Studies evaluating gait measures in everyday activities, real-world environments at different stages of the disease, their association to clinical measures, and their predictive value; exploring whether regular quantitative assessment leads to early identification of risk of falling, reduced falls, or use of health-care services
The ability to reliably identify and quantify freezing of gait outside of the laboratory and clinic settings is needed; other than self-report, no information on how frequently freezing of gait occurs per day, why, or when is available	Studies developing and validating ways to identify freezing of gait in the home and during everyday activities to objectively quantify the frequency and severity of freezing of gait
The optimal number and placement of wearable sensors for continuous monitoring needs to be determined	Investigations directly comparing different configurations of sensors (eg, wrist, lower back, sternum, wrist and lower back) to quantify trade-offs related to accuracy, sensitivity, specificity, and compliance for different aspects of gait and motor symptoms in patients with Parkinson's disease
Mechanisms of gait impairment	
Reference ranges and expected stability and progression of phenotypic subtypes of Parkinson's disease are not well established	Studies designed to investigate phenotypic subtypes as a multidimensional continuum, influenced by various modifiers, including non-motor symptoms
Methods for predicting and preventing freezing of gait are insufficient	The evaluation of interictal gait segments and the use of computational methods to better understand imminent episodes of freezing of gait in the home setting; imperative for developing preventive interventions
There is incomplete evidence on longitudinal changes in brain structure and function of brain areas related to gait with disease progression; the impact of interventions on structure and function of these brain areas is poorly understood	Incorporating dynamic imaging technology during walking (eg, functional near-infrared spectroscopy, EEG) to enhance the understanding of the mechanisms of gait impairments in patients with Parkinson's disease; could potentially reveal new targets for treatment
Interventions	
There is an inadequate identification of the optimal components of non-pharmacological interventions	Development and assessment of optimal (and minimal) components needed to improve gait
There is an absence of studies examining the effects of preventive rehabilitation	Studies on exercise in the early stages of the disease to establish the impact on disease modification and progression
Previous studies focused on patients actively taking medication, limiting understanding of the impact of pathology on gait; motor performance might depend on pharmacokinetics and the interactions between medications (dopaminergic and non-dopaminergic)	Evaluation of performance while patients are both on and off medication in large-scale studies is needed; studies should incorporate a detailed evaluation of types, doses, and times since medication in different stages of the disease to determine the influence of medication on gait and risk of falling
There is an absence of studies examining the potential of interventions to improve gait in the advanced disease stages	Most intervention studies exclude patients with a score larger than 3 on the Hoehn and Yahr scale; studies of advanced disease stages could open new ways for treatment
There is incomplete knowledge about the long-term effects of stimulation (deep-brain stimulation, spinal cord stimulation, non-invasive stimulation) on gait measures and risk of falling	Longitudinal studies exploring the effects of deep-brain stimulation, spinal cord stimulation, and non-invasive brain stimulation (eg, transcranial direct-current stimulation) and the properties of treatment on gait over time
The optimal dosage and long-term delivery for exercise and other non-pharmacological interventions need to be determined	Studies have shown the efficacy of a variety of non-pharmacological interventions, but the optimal dosage (eg, frequency, intensity) and the benefits of maintenance or booster paradigms needs clarification
The value of multimodal interventions has not been fully investigated	Multimodal interventions might be able to maximise the effect of more than one type of intervention or specific intervention target (eg, motor, cognitive), potentially enhancing and augmenting the effect; although there are promising initial studies, additional work is needed
Overarching issues	
There is an absence of a clear understanding linking specific gait impairments, their underlying mechanisms, and treatment options	The field needs to move beyond a one-size-fits-all approach to assessment and treatment of gait impairments and toward actionable outcomes and tailored interventions, where the therapy matches the underlying aetiology and specific gait impairments
Currently, assessment of gait in different populations (eg, Parkinson's disease, post-stroke, multiple sclerosis, ageing) use different approaches and have different foci of gait and motor function; although there is rationale for this separation, it might hamper the wider understanding of the mechanisms of gait impairments and the clinical utility of interventions	Adaptations of the lessons learned from studies of one cohort and patient population to other cohorts could foster the creation of common nomenclature and maximise the potential to accelerate the development of the field

Items are listed in order of the authors' priority for each category.

Table 2: **Gaps in knowledge on gait impairments in patients with Parkinson's disease and potential future directions for research**

Parkinson's disease. Findings from a pilot study in five patients with advanced Parkinson's disease suggests that this procedure might improve gait and even freezing of gait.[98] However, the mechanism of spinal cord stimulation is unclear and further research is needed to assess the long-term benefits of both this technique and deep brain stimulation throughout the course of disease.

Conclusions and future directions

Walking is fundamental to everyday functioning and independence, and Parkinson's disease markedly affects this ability. A better understanding of the reasons and ways in which the motor and non-motor features of Parkinson's disease impact on gait can inform and enhance clinical care and provide a roadmap for future research. Therefore, in this Review, we summarised recent advances on assessment, mechanisms, and treatments of gait impairments in Parkinson's disease. Evidence suggests that multiple aspects of gait, such as pace, rhythmicity, and asymmetry, should be considered to improve the specificity of diagnosis in patients with Parkinson's disease and to better track disease progression.[6,11,39] Insights into everyday function and motor-cognitive interactions can be gained by studying gait in complex situations (ie, turning, dual-tasking, and daily living),[10,31,62,99] and these paradigms can uncover difficulties in gait and compensation strategies that probably contribute to disease burden. Non-motor symptoms,[50,51] frontal-striatal connections, and non-dopaminergic networks[51,67] play a prominent part in these situations and their contributions to gait impairment have become increasingly recognised. These insights also have implications toward the identification of subtypes of gait impairments, such as freezing of gait or the PIGD phenotype,[68] and can inform both pharmacological and non-pharmacological disease management. In this context, multimodal interventions combining several forms of exercise that simultaneously target multiple sources of impairment show great promise in improving gait speed, step length, and endurance and in reducing falls.[24,26]

Despite the advances in quantitative assessments of gait, imaging, and treatment interventions, there are still several knowledge gaps (table 2). Over the past 5 years, only seven prospective, observational studies have been done.[2,18,34,50,54,64,71] The paucity of such studies limits the understanding of how different measures of gait evolve with disease progression, change across phenotypes, and how they interact with other symptoms and treatments. For example, much of the research on mechanisms used structural and functional MRI, mainly comparing patients with different subtypes of symptoms. This approach led to the description of status, without knowledge of the development, progression, or timing of impairments. Prospective imaging studies could enhance the understanding of underlying mechanisms and identify new targets for treatment and care. Additionally, low-cost technologies (eg, accelerometers and gyroscopes) that enable the quantitative measurement of gait parameters in the clinic have become available. Real-world monitoring of gait through wearable devices is a promising research area.[29,100] Still, work is needed to better understand the data collected by these devices, and optimisation of the number, type, and location of sensors needs to be done. However, regulatory issues would need to be addressed and clinicians, researchers, pharmaceutical companies, and policy makers need to strive toward better interpretation and consensus regarding the new measures, their properties, and their associated guidelines. It is also thus important to refrain from selective inferences by reporting only positive statistical results so that both effective and ineffective approaches can be identified to improve decisions on treatment.

If the current gaps in knowledge can be addressed (table 2), technology-assisted assessment will probably become implemented in routine practice. Quantification of gait speed[36] and, when possible, other features of gait should be part of every clinical and research assessment of a patient with Parkinson's disease. Including such measurements in the patient's medical record can provide objective and precise information about changes in their symptoms over time. Clear links need to be developed between specific gait impairments, their underlying mechanisms, and treatments, and to move on from a one-size-fits-all approach[101] toward a personalised approach. Additionally, many neurological conditions (eg, post-stroke, multiple sclerosis, Alzheimer's disease) share similar deficits in mobility and complexities, such as the interactions between motor and cognitive function, to Parkinson's disease. The lessons learned from research on gait in patients with Parkinson's disease (eg, moving beyond simple quantifications of gait speed, the value of quantifiable measures, the importance of assessment in challenging conditions, and the potential of home-based and continuous monitoring) could also be applied to other neurological conditions to improve treatment and care.

Search strategy and selection criteria

We searched PubMed for articles published in English between Jan 1, 2013, and Dec 31, 2018, using the search terms "gait" (OR "ambulation" OR "locomotion" OR "walking") and "Parkinson's disease". We selected research articles whose primary focus was related to gait and that had results relevant to assessment, mechanisms, or interventions that address impairments of gait in patients with Parkinson's disease.

Contributors

AM, PB, RC, TDE, JMH, CJH, EP, and QJA developed the concept for this Review. AM, PB, RC, TDE, NG, JLH, JMH, CJH, EP, and QJA wrote and critically revised the manuscript. All authors approved the final version.

Declaration of interests

AM, JMH, and NG have submitted a patent application for the use of virtual reality for diagnosis and treatment of movement disorders. The intellectual property rights for this patent application are held by the

Tel Aviv Medical Center, Tel Aviv, Israel. NG has also received consultancy fees for Lysosomal Therapeutics, Neuroderm, Intec Pharma, Sanofi Genzyme, Biogen, and Denali. PB, RC, TDE, CJH, EP, QJA, and JLH declare no competing interests.

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