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Virtual reality in research and rehabilitation of gait and balance in Parkinson disease

Colleen G. Canning[1]✉, *Natalie E. Allen*[1], *Evelien Nackaerts*[2], *Serene S. Paul*[1], *Alice Nieuwboer*[2] and *Moran Gilat*[2]

Abstract | Virtual reality (VR) technology has emerged as a promising tool for studying and rehabilitating gait and balance impairments in people with Parkinson disease (PD) as it allows users to be engaged in an enriched and highly individualized complex environment. This Review examines the rationale and evidence for using VR in the assessment and rehabilitation of people with PD, makes recommendations for future research and discusses the use of VR in the clinic. In the assessment of people with PD, VR has been used to manipulate environments to enhance study of the behavioural and neural underpinnings of gait and balance, improving understanding of the motor–cognitive neural circuitry involved. Despite suggestions that VR can provide rehabilitation that is more effective and less labour intensive than non-VR rehabilitation, little evidence exists to date to support these claims. Nevertheless, much unrealized potential exists for the use of VR to provide personalized assessment and rehabilitation that optimizes motor learning in both the clinic and home environments and adapts to changes in individuals over time. Design of such systems will require collaboration between all stakeholders to maximize useability, engagement, safety and effectiveness.

Parkinson disease (PD) is a complex, progressive multisystem neurodegenerative disorder associated with motor and non-motor impairments[1]. The hallmark motor symptoms include bradykinesia, rigidity, tremor and postural instability; over time, other complex motor symptoms (such as freezing of gait (FOG)) also frequently emerge. PD affects the automaticity of movement and therefore motor deficits are more prominent with distraction, environmental complexity and dual-task load[2]. Gait and balance are affected, influencing everyday mobility even in early disease[3]. Motor learning is impaired in PD, characterized by reduced consolidation and transfer of learning owing to worsening striatal function[4]. To compensate, people with PD use alternative neural circuits, usually involving attention, sensory stimuli and vision[5]. Falling is extremely frequent in PD[6] and occurs two or three times more than in the healthy elderly population[7]; this factor, along with cognitive decline and other common non-motor impairments, such as fatigue, apathy, anxiety and depression, produces challenges for engagement in rehabilitation[8,9]. Taken together, optimal training environments for people with PD require consideration of sensory–motor and cognitive input, finely graded progression levels, optimized adaptation of learning and, critically, safety.

Mounting evidence supports the benefits of rehabilitation, in addition to optimal medical and/or surgical management, for improving gait and balance in people with PD[10–12]. Various evidence-based approaches are used, singly or in combination, including individual or group exercise (balance and/or strength and/or aerobic), overground and/or treadmill walking, multitask training and compensatory movement strategies (that is, directing attention towards key aspects of movement, such as deliberately adopting a wide base of support during a functional task), including cueing (directing attention towards internal cues, such as counting, or external cues, such as floor markers, to regulate stepping behaviour)[13]. However, research to date has focused on overall group-level effects; the optimal exercise type, dose and delivery mode for different subgroups of people with PD have not been determined. Therefore, rehabilitation approaches have been limited in their ability to deliver optimal training in a personalized and precise manner across the disease spectrum and the current 'one size fits all' approach is unlikely to provide optimal outcomes[13–15].

Virtual reality (VR) technology has emerged as a promising tool for researching complex impairments in people with PD and for providing personalized rehabilitation. The goal of using VR in neurorehabilitation is to

[1]Discipline of Physiotherapy, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia.

[2]Research Group for Neurorehabilitation (eNRGy), Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium.

✉e-mail: colleen.canning@sydney.edu.au

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Key points

- Virtual reality (VR) might provide unique opportunities to improve understanding o f the behavioural and neural underpinnings of gait and balance in people with Parkinson disease.
- VR environments can be manipulated in ways that are not possible and/or safe in the real world, with the potential to improve assessment and training of multisensory motor–cognitive integration.
- Non-immersive VR rehabilitation improves gait and balance when compared with no intervention, but is not superior to non-VR rehabilitation of similar exercise type and dose.
- Future applications of VR should be tailored to deliver personalized interventions according to each person's profile of deficits and rehabilitation needs.
- Future developments of VR rehabilitation interventions require collaboration between therapists, technology experts and people with Parkinson disease to ensure optimal, engaging exercise that is acceptable for long-term use.
- Therapists should consider the conceptual framework, along with the pros and cons, when selecting VR paradigms to optimize training effects with carry-over into everyday activities.

evoke and/or train brain and behavioural responses, in a controlled laboratory or clinical setting, that are analogous to those that occur in the real world[16]. A key feature of VR is immersivity, that is, the extent to which the user is fully integrated into the virtual environment[17] (BOX 1). Acknowledging that the definition of VR is a source of debate[17–20], for the purposes of this Review we define VR broadly as "the application of visual simulations created with computer software that mimic real world or conceivable environments, objects and events in real time, and demand interactivity via ongoing behavioural responses of the user".

The use of VR in people with PD has been largely limited to applications relating to the understanding[21] and rehabilitation[22–26] of gait and balance impairments, and this Review focuses on these VR applications compared with the real-world environment. Specifically, we examine the rationale for the use of VR in research and rehabilitation of people with PD, provide a critical appraisal of the current state of the art, make recommendations for future research and outline clinical implications.

VR for exploring underlying mechanisms

Rationale

Our understanding of the precise aetiology underlying gait and balance problems in PD, and in particular FOG (an episodic symptom defined by a marked reduction or complete absence of forward progression of the feet despite the intention to walk[27]), is limited[28,29]. Impaired automaticity forces people with PD to increasingly rely on compensatory neural circuits to control their movements[2,30,31]. Complex gait and balance problems probably arise as the compensatory circuits eventually become affected by progressing nigral and extra-nigral neuropathology[32]. Compensatory motor control then becomes vulnerable to interference from simultaneous task demands[28,29,31]. These compensatory circuits typically involve fronto-parietal cortices and the cerebellum, although any node that can modulate the motor control networks could be implicated in PD gait and balance dysfunction[33–36]. So far, assessing to what degree complex symptoms, such as FOG, can be attributed to underlying disease or a failure of compensatory circuits, or both, has been difficult. Furthermore, conclusive evidence is lacking as to which nodes in the motor–compensatory circuitry are most involved[37]. FOG and falling frequently co-occur[38], but are extremely difficult to assess owing to their transient and complex nature. Additionally, people with PD often present with performance bias during testing[39], limiting the translation of research findings to everyday situations. Furthermore, current neuroimaging techniques do not allow for the study of whole-brain activity during ambulation.

These challenges also apply to clinical assessment of gait and balance. Typically, a range of assessment measures are used, including the following: performance-based measures (such as gait speed and variability with or without additional cognitive and/or manual tasks); balance assessment tools (such as the miniBESTest[40], which assesses anticipatory and reactive standing balance, dynamic gait and response to different visual (for example, eyes open versus eyes closed) and somatosensory (such as standing on the floor versus standing on foam) inputs); and self-assessment questionnaires reporting the person's experience of FOG and fear of falling. These assessments are limited in their ability to simulate 'real-life' conditions and to tease out the contributions of various motor and non-motor impairments to gait and balance performance in each individual presenting with PD.

VR has the potential to address many of the limitations outlined above. First, VR offers an opportunity to study people during the manipulation of sensorimotor contingencies (whereby individuals learn or relearn relations between their actions and associated sensory input[41] that are relevant for gait and balance). For example, in order to improve stepping amplitude symmetry, sensorimotor contingencies can be manipulated in VR so that people with PD step to a target that is visually perceived to be of a smaller range of motion than is actually achieved, thereby training their motor systems to produce larger movements during subsequent trials[42]. Moreover, objective behavioural outcomes, physiological measures as well as mobile neuroimaging can all be collected in a highly controlled and safe laboratory setting while participants feel as if they are ambulating in real-life scenarios[16,43]. Second, VR can simulate situations that would be too dangerous or cumbersome to perform in a clinical setting. For example, having fall-prone people with PD perform gait and balance tasks on raised platforms to elicit anxiety is too dangerous, but immersive VR technology provides the opportunity to induce similar fear responses while participants remain safely on the ground[44]. Last, people with PD have known proprioceptive[45], vestibular[46], gaze[47], cognitive[48] and perceptual[49] deficits that influence their gait and balance performance[50,51]. The effect of multisensory–cognitive–motor integration deficits[50,52] is unclear as disentangling these modalities in real-world experiments is difficult. VR offers the unique capability to manipulate sensory feedback in order to study the effect of multisensory–motor mismatch in PD gait and balance[53]. Taken together, VR provides multiple avenues for gaining insight into pathophysiological processes underlying gait and balance impairments in PD for research purposes as well for clinical assessment, although the use of VR for clinical assessment is still in its infancy.

Behavioural results

VR fear-of-height paradigm. VR paradigms that purposefully manipulate sensory information to provoke FOG are revealing valuable insights into FOG triggers, potential pathophysiological processes and possible rehabilitation strategies. A VR-based fear-of-height paradigm was designed to investigate the immediate effect of anxiety on FOG in PD[44] after prior work based on questionnaire data indicated that these factors could be related[54]. People with PD walked overground while a head-mounted display (HMD) visually immersed them in one of two VR environments. In the low-threat condition, the virtual walkway was presented on ground level, whereas in the high-threat condition the virtual walkway was presented as if it was raised high above the ground[44] (TABLE 1). The VR paradigm successfully induced greater levels of anxiety and caused more FOG during the high-threat compared with low-threat condition. Although prior work had shown that subjective anxiety is increased in people with PD and FOG[54], this VR fear-of-height paradigm was the first to provide direct evidence that inducing anxiety during gait worsens FOG in PD[44].

VR-based treadmill controller. Similarly, a VR-based treadmill controller interface was developed whereby FOG-provoking scenarios, such as narrow passages, were presented on a large screen and the speed of the treadmill could be adjusted in a feedforward manner based on the acceleration of the legs[55]. This controller interface required people with PD to initiate the first step and allowed for natural stopping of the gait cycle as well as testing for the 'sequence effect' (that is, the rapid sequential reduction in step length that often occurs just before a FOG episode[56]) by imposing incremental reductions in step length. All of these potential FOG triggers are missed when using conventional treadmills. This VR-based treadmill controller elicited FOG in two out of three people with PD while their safety was assured with a harness[55]. Such adaptive treadmill–VR interfaces might thus help to overcome the difficulty in eliciting FOG in clinical and research settings and identify person-specific FOG triggers as a basis for personalizing rehabilitation interventions.

VR foot pedal paradigm. A functional MRI (fMRI)-compatible, semi-immersive VR foot pedal paradigm was designed to study the behavioural and neural correlates underlying gait impairment in PD, and FOG in particular, while participants were lying supine[57]. Users navigated a 2D virtual corridor through a first-person perspective using their feet to alternatively depress a set of foot pedals. Although a true sense of presence could not be achieved, this user–VR interaction did generate a sense of forward progression (TABLE 1) and required visuomotor and proprioceptive-motor processing that mimicked actual gait. Importantly, the timing interval between alternate foot pedal presses during the VR task was linked to the neural responses obtained with fMRI and real-life gait parameters[57,58]. Finally, the VR environment was designed to present several FOG-provoking features, such as environmental triggers (for example, doorways and turns)[59,60] and cognitive dual-task conditions[57]. In this study, the behavioural measure of FOG was defined as any between-foot press latency greater than two times the modal foot press latency, the frequency of which correlated with the severity of clinically observed FOG[57]. Between-foot press latencies during VR performance were also characterized by an increase in step-time variability as seen during actual gait[30,61]. High step-time variability is reflective of reduced gait automaticity and indicates that people with PD who experience FOG are reliant on compensatory attentional circuits to control their stepping[30].

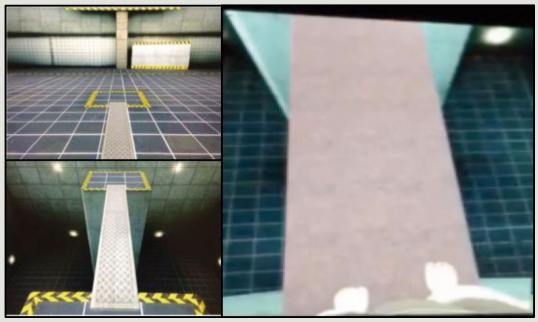
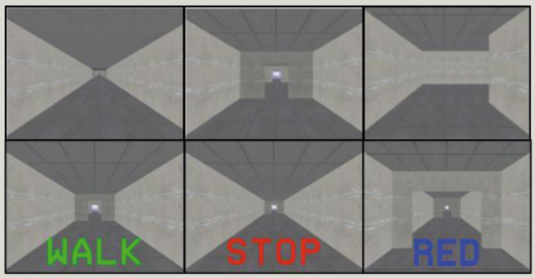
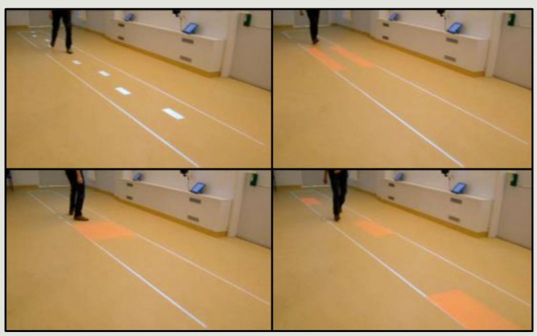
Two different studies combined the same VR foot pedal paradigm with a Stroop-like response-inhibition task, whereby participants were instructed to continue stepping during presentation of congruent colour–word combinations (for example, the word green written in the colour green) and to stop upon presentation of incongruent colour–word combinations (for example, the word green written in the colour blue)[60,62]. These studies revealed that people with PD and FOG responded well to 'simple' congruent cues (such as the word green written in the colour green), but showed considerable delays in their foot press latencies when needing to respond to 'complex' congruent cues that were implicitly associated with stopping (such as the word red written in the colour red)[60]. People with PD and FOG also experienced

Box 1 | Immersivity in VR

Virtual reality (VR) technology has the capacity to integrate or 'immerse' users into the virtual environment[19]. Bohil et al. suggested that "the level of immersion is determined by the number and range of sensory and motor channels connected to the VR environment and the extent and fidelity of sensory stimulation and responsiveness to motor inputs from the user"[16]. The level of immersion is thought to be important as it imitates the mechanism by which the brain operates, as described by the predictive coding hypothesis[164]. This hypothesis postulates that the brain actively maintains an internal model (simulation) of the body and surrounding space based on sensory and motor experiences. The brain does this in order to make predictions about upcoming sensory input and to select the best actions that minimize the amount of prediction error[164,168]. VR is thought to operate in a similar way by using computer technology to predict the sensory consequences of the user's movements. The unique opportunity to synchronize multiple sensory channels at once thereby allows immersive VR to induce simulations that recreate brain and behavioural responses that a person would also experience in the real world[164].

Immersivity is thus an essential feature of VR for aiding neurorehabilitation as it allows users to safely engage in simulations of challenging situations from the physical world[16], such as those that impose a high risk of falls in people with Parkinson disease. Fully immersive VR systems use 3D environments, blocking out the perception of the real world, whereas semi-immersive and non-immersive systems involve varying degrees of perception of both the real world and the VR environment. Greater immersivity is considered a key element in achieving embodied simulations and inducing a sense of presence, that is, the psychological product or feeling of the user being physically present in the VR environment. Greater immersivity can be achieved by increasing multimodal stimulus control (for example, changing the field of view on the basis of head position is more immersive than watching a static screen), thereby promoting realistic user–environment interactions[16,17,20]. In addition, VR environments can be manipulated in a manner that is not possible in the real world (for example, using transient visual perturbations of the VR scene to simulate slipping while walking)[111], facilitating safety during assessment and training of user responses.

Table 1 | **Examples of VR for understanding impairments in PD**

Type of VR	Modality	Illustration	Utility
Immersive[44]	HMD combined with motion tracking and/or other objective measures of gait and physiological status of the user		Perform experiments that are unsafe or too cumbersome in real life, such as a fear-of-height paradigm, to safely assess the impact of anxiety on gait and balance in PD; combine with objective measures of gait and balance and other physiological measures, such as galvanic skin conductivity and heart rate variability; manipulate multisensory feedback
Semi-immersive[59,62]	Operate foot pedals to navigate a virtual corridor		Combine with neuroimaging techniques (functional MRI) or DBS surgery to investigate the pathophysiology underlying gait deficits and FOG in PD; ability to present environmental and/or cognitive triggers known to exacerbate gait impairment in real life
Non-immersive[66]	Virtually projected walkway		Combine with mobile neuroimaging (EEG/functional NIRS) to study the pathophysiology underlying gait and FOG in PD; obstacle avoidance with reduced risk of falls owing to tripping over obstacles; ability to manipulate gait conditions without requiring verbal instructions; safety harness can be applied

DBS, deep brain stimulation; EEG, electroencephalography; FOG, freezing of gait; HMD, head-mounted display; NIRS, near-infrared spectroscopy; PD, Parkinson disease; VR, virtual reality. Top left panels, reprinted from REF.[44], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Top right panel figure, image courtesy of K. A. Ehgoetz-Martens. Bottom panel figures, reprinted from REF.[66], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

significant delays when needing to execute stopping in response to incongruent cues, indicating an impaired ability to inhibit ongoing stepping movements[62]. Furthermore, delays were observed in people with PD and FOG when initiating the 'first step' forwards during VR task performance[62], indicating an inability to overcome motor inhibition and generate the first stepping response. In agreement with prior findings from neuropsychological testing of executive functioning in PD and FOG[63–65], these findings corroborate the notion that reduced control over the response inhibition-related brain circuits, such as the meso-corticolimbic and cortico-basal ganglia hyper-direct pathways, is implicated in the pathophysiology underlying FOG[60,62].

Non-immersive VR via visual augmentation. Non-immersive VR via visual augmentation has been applied to study gait and balance while people with PD stand on a platform, walk on a treadmill or walk overground. Systems with embedded motion capture are usually confined to research settings[43,55,66,67]; however, other systems can be more easily translated to the clinic. For example, participants with and without FOG were studied while stepping in place on a balance platform in order to navigate through narrow and wide virtual corridors (which often trigger FOG in real life)[68]. Cognitive dual tasks were superimposed, and statistically significant differences were found between participants with and without FOG in both single-task and dual-task outcomes of stepping time, rhythmicity and symmetry, which is in agreement with previously described gait disturbances in people with PD and FOG[69]. This finding indicates that people with PD and FOG have difficulty dividing attention between motor and cognitive processes or segregating the task components. Another study reported results from an interactive walkway paradigm (TABLE 1), whereby a standard walkway was augmented with virtual visual patterns to complete complex walking assessments[66]. First, the location and timing of the visual pattern was controlled in real time on the basis of full-body kinematics of the individual. Second, virtually presented obstacles reduced the risk of tripping and falling during testing. Last, dual-task conditions were presented virtually and made to appear suddenly (for example, changes in gait speed) in order to assess gait adaptability[66]. Assessment using this interactive system was superior to standard clinical tests for distinguishing individuals with and without FOG. This methodology might not only be a useful assessment tool to understand the visual and cognitive compensatory strategies that people with PD and FOG rely on to overcome impairments in motor automaticity while walking in settings approximating real life but also consequent rehabilitation programmes could be tailored to these results[47,66]. This idea also holds promise for fully immersive VR in combination with treadmill walking[70]. As treadmills become increasingly versatile and offer split belt facilities (that is, one belt per leg)[71] and belt perturbations in multiple directions[70], it will also be possible to test proprioceptive and vestibular manipulations while walking in virtual environments.

VR for assessing balance. In addition to assessing gait, VR also offers opportunities to induce varying levels of visual perturbation during balance tests. Compared with the commonly used eyes-open or eyes-closed conditions, immersive VR applications can decouple the visual and vestibular systems in a more fine-grained manner by providing a wide range of visual perturbations. This feature allows for sensitive measures of balance to be calculated, such as determining the exact thresholds of visual perturbation required to induce falls[16,72,73]. Such systems can be low cost, for example by combining the commercially available Wii balance board (Nintendo) with an immersive VR HMD system, which has been validated against the (more expensive) gold-standard Equitest dynamic posturography machine (Neurocom Inc.)[74]. Cheap and widely available VR-based balance assessments might prove useful for identifying those people with PD at high risk of falls owing to balance impairment and those who would benefit most from balance training[72]. These systems also allow balance to be assessed in all planes, thereby enabling therapists to better personalize their interventions to the individual's balance deficit[74]. This idea is of particular interest to people with PD who experience FOG, as postural instability, and in particular deficits in medio-lateral weight shifting, have been linked to worse FOG[75].

Brain imaging results

Task-based fMRI still holds the greatest potential to study the neural control of gait and balance, although mobile systems are being validated for assessing cortical activity during actual gait and balance in PD (Supplementary Table 1). To overcome the movement restrictions of fMRI, visual and motor imagery (imagining the movement without actually moving)[76] or action observation (watching someone else perform the movement)[77] of gait and balance-related tasks has been used[28]. These techniques activate neurons across similar circuits to those during real motor tasks[78]. However, no ongoing behavioural output is generated to ensure that participants are engaged in the task. Furthermore, such techniques preclude assessment of multisensory processing[50] and motor automaticity deficits[31] that underlie gait difficulty in PD.

fMRI results[57] from the VR foot pedal paradigm (described earlier) have contributed to our understanding of the neural correlates underlying gait de-automatization and FOG[30,57,79,80]. In brief, freezing episodes were characterized by motor (that is, primary, supplementary motor areas)–cognitive (that is, prefrontal, posterior parietal) circuitry decoupling and decreased activity in the caudate, thalamus, globus pallidus and subthalamic nucleus at the subcortical level[57,80]. In addition, the presentation of narrow passages in VR induced footstep delays in people with PD and FOG, which were associated with hypo-activation across the pre-supplementary motor area and were inversely correlated with the degree of functional connectivity between the pre-supplementary motor area and the subthalamic nucleus, two main regions of the hyper-direct cortico-basal ganglia inhibitory pathway[81]. Together, these findings corroborate the idea that FOG is associated with basal ganglia hypo-activation and a resulting overdrive of inhibitory projections to brainstem locomotor centres, and that, to compensate, people with PD engage alternative circuits associated with goal-directed and task-related commands to control their gait[34,80,81]. According to these findings, FOG occurs when the communication between these compensatory cognitive and motor operating circuits fails. Abnormally increased connectivity between limbic regions, in particular the amygdala, and the motor striatum also feed into this mechanism[79], which might underpin the influence of anxiety in exacerbating FOG[44,79].

As mentioned earlier, increased variability in foot press latencies was also found during VR pedal pedal task performance, reflecting reduced motor automaticity, which is considered a hallmark feature of PD and FOG[30,61]. Combined fMRI and behavioural results showed for the first time that periods of reduced motor automaticity of stepping movements were associated with increased activity and connectivity across the cognitive control network and orbitofrontal–ventral–striatal limbic circuits in people with PD 'off' their dopaminergic medications; by contrast, during the 'on' dopamine state, people with PD had lower step-time variability and recruited the bilateral cerebellar hemispheres[30]. This VR study thereby provided further evidence of the compensatory cognitive control and cerebellar circuits recruited by people with PD to perform otherwise automatic lower-limb motor tasks[30].

Despite advances, the VR foot pedal paradigm also has several limitations. The behavioural responses have so far only been derived from foot press latencies. The definition of FOG in this VR paradigm therefore remains arbitrary[21,27]. Still, the degree of FOG tested during the VR task correlated with FOG during actual gait[58], and a study using electromyography of the legs showed that VR-defined FOG events in eight people with PD were characterized by an increased freezing ratio[82] resembling the severe trembling of the legs observed during FOG in the clinic[83]. Future studies adopting electromyography or position data of the feet in large samples are needed to fully validate this paradigm. Furthermore, although alternate foot presses resulted in forward progression, participants were not able to control their virtual step length or gaze directions as in actual gait. Although inherently difficult during fMRI with the head fixed, restricted visual exploration of space limits the sense of presence and translation to real-life situations. Finally, any task performed in a supine position lacks vestibular and postural influences as well as the whole-body coordination required for gait and balance control[21].

In summary, VR offers unique opportunities to improve our understanding of the behavioural and neural underpinnings of gait and balance impairment in PD. These insights, in turn, will inform development of innovative rehabilitation interventions[29].

VR for rehabilitation

Rationale

Current gait and balance rehabilitation interventions for people with PD include overground and/or treadmill walking, balance exercises (including tai chi and dance), strength exercises, multitask training, cueing and compensatory movement strategies. Evidence from high-quality systematic reviews and randomized controlled trials (RCTs) shows that these interventions improve gait and balance[10–12,84–87]. However, substantial variability exists in the response of individual people with PD to rehabilitation[9,88], with, for example, some interventions reducing falls in people with mild disease but increasing falls in people with more severe disease[89,90]. This variability suggests that the increasing load of motor and non-motor impairments associated with severe disease affects the potential for learning, and compensation becomes increasingly compromised. Evidence-based rehabilitation approaches are clearly limited by the extent to which they can be safely tailored to the individual profile of the person with PD, in terms of the type, dose and delivery mode, as well as adaptability to immediate and long-term changes in performance. Additionally, rehabilitation interventions tested in RCTs are mostly delivered over a short time period (<6 months), with feedback provided by the therapist in fully supervised settings, thus facilitating high levels of adherence[91]. However, for optimal outcomes to be achieved in the real world, rehabilitation would ideally be available throughout the course of the disease, starting at diagnosis when deficits in gait and balance[92,93] and reduced physical activity[94] are already evident. However, fully supervised, long-term gait and balance exercise for people with PD is neither fundable nor sustainable globally. Novel methods of tailoring rehabilitation and providing feedback in a manner that is challenging and fun, therefore promoting ongoing adherence, are required.

VR rehabilitation has the potential to address these issues to facilitate practice of gait and balance activities. Examples of VR systems used in gait and balance rehabilitation are presented in TABLE 2. VR rehabilitation applications typically combine real-time motion detection within a virtual environment in the context of a (video)game. The user physically interacts with the virtual environment, viewing an avatar (a character or graphical representation of the user) that mimics the user's movements. Feedback about performance and success is provided both concurrently (during game play) and terminally (at the end of the game). The VR systems most commonly researched in PD rehabilitation to date are non-immersive.

On the basis of evidence in healthy older adults (aged 60–80 years), complex motor–cognitive interaction is known to enhance neuroplasticity and motor learning to a greater degree than simple repetitive motor task learning with no variation[95,96]. The benefits of motor–cognitive interactions are particularly pronounced for the retention and transfer of learning, although initial learning gains might be compromised by increased complexity[95]. In a motor learning disease such as PD, targeting motor–cognitive interactions could be particularly beneficial in early disease stages, enhancing motor performance and generalization to real life. With disease progression, however, motor–cognitive impairments might pose constraints on learning ability[97]. In PD, the learning process relies on altered subcortical and cortical plasticity mechanisms, making learners particularly dependent on external sources of feedback (reviewed elsewhere[4]). The many features of PD influence the learning profiles of individuals, and therefore VR-based applications are theoretically better able to address variations in learning profiles than traditional rehabilitation approaches.

A summary of the proposed advantages[20,22,24,42,98–114] and disadvantages[17,22,42,100,102,105,111–115] of VR rehabilitation is provided in BOX 2, with reference to PD-specific literature where available. Importantly, owing to variations in VR rehabilitation systems, user characteristics, supervision schedules and delivery settings, some features might be an advantage in one context and a disadvantage in another.

Evidence

The many potential advantages of VR rehabilitation outlined above suggest that it is likely to be more effective than other forms of rehabilitation, while providing challenging yet safe and engaging activities. However, little evidence exists to support these claims. Four systematic reviews (TABLE 3) of high to moderate quality[116] have investigated VR rehabilitation targeting balance and gait in PD[23,26,99,117]. Meta-analyses of RCTs in these reviews provided moderate certainty of improvement in balance following VR rehabilitation compared with active but non-VR rehabilitation[26]. However, the effect size was small, with the mean difference of 2.7 (95% CI 1.4–4.0) in the Berg Balance Scale unlikely to be clinically important[118]. Additionally, there was low to very low certainty of an improvement in stride length[23,26], with an effect size that is more likely to be clinically important (mean difference 9.7 cm, 95% CI 4.3–15.0)[26].

Further detail regarding the effectiveness, safety, feasibility and acceptability of VR rehabilitation can be gained by examining individual RCTs targeting gait and balance in people with PD. Supplementary Table 2 summarizes 17 such trials[119–140] of moderate to high quality[141] (13 of which were included in one or more of the systematic reviews mentioned above, plus an additional 4 RCTs published more recently[120,121,136,137]). Nearly all trials delivered gait and balance interventions to people with mild to moderate PD (that is, people who have some postural instability but are physically independent).

Table 2 | **Examples of VR systems available for PD rehabilitation**[a]

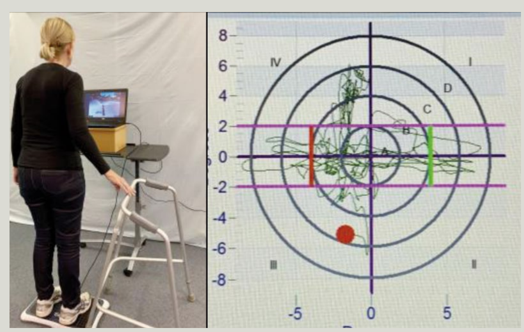
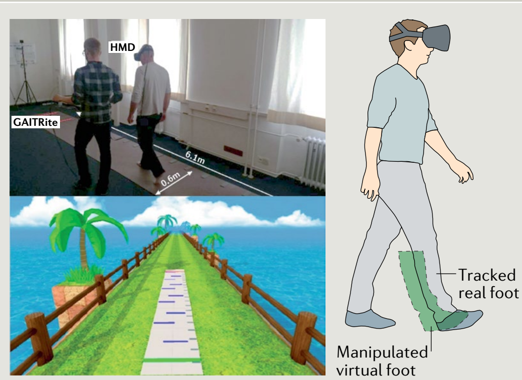
Type of VR	VR example	Features	Purpose	Illustration
Recreational, commercially available (target population: able-bodied people, including children)				
Non-immersive	Nintendo Wii (Nintendo)	Hand-held controllers that are sensitive to changes in direction and acceleration; might include a balance board, that is, a force plate, enabling the user to control the displacement of their centre of pressure in real time; displayed on a 2D screen	Not designed specifically for rehabilitation purposes, but these systems have been researched and are currently the most commonly used in rehabilitation	NA
Non-immersive	Xbox Kinect (Microsoft)	A camera and depth sensors are used to capture 3D motion; displayed on a 2D screen		
Rehabilitation-specific, commercially available (target population: people with disability from neurological and/or other disorders)				
Non-immersive to immersive	Caren (Motek)	VR environment is integrated with an instrumented dual-belt treadmill, a six-degrees-of-freedom standing platform and a 3D motion capture system; display varies from a 2D flat screen to an immersive dome; allows manipulation of visual, somatosensory, auditory and vestibular input, for assessment and training; safety harness can be applied	Primarily utilized by researchers and well-resourced specialized rehabilitation clinics	NA
Non-Immersive	Humac balance system (CSMi for Dynatronics)	Utilizes a balance board and software with games and activities designed for people undergoing rehabilitation; displayed on a 2D screen; safety harness or stable support (for example, walking frame) can be applied	Aim is to assess and train balance, where balance training tasks are tailored to level of performance	
Rehabilitation-specific, customized, not yet commercially available (target population: people with disability from neurological and/or other disorders)				
Immersive[42]	HMD (HTC VIVE®) with controllers attached to legs and pressure-sensitive gait mat	Utilizes a 3D HMD with controllers attached to legs to produce visual–proprioceptive conflict in a VR environment while walking on a pressure-sensitive mat; safety harness can be applied	Aim is to improve gait symmetry in people with PD and FOG; visual–proprioceptive conflict condition whereby virtual foot placement is shifted backwards on the shorter side to promote taking a longer step	

Table 2 (cont.) | **Examples of VR systems available for PD rehabilitation[a]**

Type of VR	VR example	Features	Purpose	Illustration
Rehabilitation-specific, customized, not yet commercially available (target population: people with disability from neurological and/or other disorders) (cont.)				
Non-immersive[126]	Camera-based motion capture (modified Microsoft Kinect) plus a virtual environment	Utilizes camera-based motion capture of feet while walking; feet are projected into the VR environment in real time on a 2D screen; safety harness is used	Aim is to reduce falls in people with PD; the VR environment systematically increases the size of virtual objects to step over and the number of distractions to progress motor–cognitive challenge while walking	

FOG, freezing of gait; HMD, head-mounted display; NA, not available; PD, Parkinson disease; VR, virtual reality. [a]A selection of VR systems are available across the three categories. Middle figure, adapted from REF.[42], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Bottom figure, reprinted from *The Lancet*, **388**, Mirelman, A. et al., Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. 1170–1182 (2016)[126], with permission from Elsevier.

All but one trial delivered non-immersive VR with visual feedback, with or without additional auditory or haptic feedback, whereas the remaining trial[120] did not provide information about the VR system used. The majority of trials used recreational systems[119,121–124,126,130–132,135,137], two used commercialized rehabilitation-specific systems[133,138] and four used customized systems[126,136,139,140]. The majority of trials trained standing balance tasks without a change in base of support and/or stepping tasks, except for one trial that trained dance moves[123] and another that trained treadmill walking[126]. Despite the potential of VR systems to target motor–cognitive tasks, only four trials[122,126,131,136] explicitly described how this approach was achieved, including planning, decision-making and response-inhibition tasks (for example, specific exergames (that is, exercise-based, interactive, video games) with additional motor and/or cognitive task requirements, including response inhibition)[120,129].

VR versus non-VR rehabilitation of similar type and dose. A key shortcoming of systematic reviews to date is the confounding influence of exercise type and dose when comparing VR and non-VR rehabilitation. When considering the 11 trials that compared VR and non-VR rehabilitation of a similar type and dose (TABLE 4; Supplementary Table 2), no consistent evidence exists of VR rehabilitation being more effective in improving gait or balance[120–122,124,125,130,131,135,138–140]. However, the largest and most comprehensive trial to date (the V-TIME trial)[126–129,142] did report some important extra benefits of VR. This trial aimed to reduce fall rates in people at high risk of falls (including a subgroup with PD) using customized VR treadmill training (TABLE 2), which provided motor–cognitive challenges in a simulated, real-life but safe environment, compared with the same dose of treadmill training alone. In the subgroup of people with PD ($n = 130$), those in the VR group had a reduction in fall rates above and beyond the reduction seen in the treadmill group[126]. In two PD subsets, changes in brain activation patterns were observed during actual and imagined complex walking tasks in the VR group, which involved different networks than those in the treadmill group[127,128]. This finding supports the authors' claim that VR rehabilitation promotes neuroplasticity and motor learning, involving a different recruitment of brain regions than motor training alone[127,128].

VR rehabilitation versus inactive control interventions. Further insights can be gained by exploring the four RCTs[124,125,136,137,140] that included an inactive control group (TABLE 4; Supplementary Table 2). VR rehabilitation was superior to no intervention[124,125,137,140] in the three facility-based trials. The remaining trial was the only home-based trial, in which minimally supervised, customized VR stepping exercise was compared with an inactive control group[136]. Although the VR group perceived improved mobility compared with the inactive group, this difference was not reflected in measured physical outcomes. Further subgroup analysis found a differential effect of intervention according to disease severity, with positive effects for the low-severity group and potentially negative effects for the higher severity group, suggesting that more severely affected people might require greater supervision and tailoring of exercise to be effective. In addition to the effect of disease severity, the findings of this study might reflect underdosing and/or inadequate supervision in the home environment.

Influence of key trial design features on outcomes of VR rehabilitation. Some reports suggest that practising tasks in immersive VR environments might impair balance and gait performance in the short term[42,111,112]. However, when considering all 17 trials of non-immersive VR rehabilitation interventions reported in Supplementary Table 2, evidence supports the generalizability of tasks practised in the VR environment to performance of everyday activities in real life[124,126,137]. Notably, the aforementioned V-TIME trial[126] is an example of a VR intervention that closely replicated the target activity, that is, walking under specifically tailored and progressively challenging motor–cognitive conditions. By contrast, the home-based trial mentioned above[136] was the only study to show a decrement in everyday task performance, that is, the time taken to complete the Timed Up and Go test. In this case, the emphasis on accurate, safe stepping in the VR programme might have carried over to a slower, but potentially safer, Timed Up and Go performance and time. In addition, it should be noted that the V-TIME intervention[126] was fully supervised and utilized a safety harness. Indeed, of those trials that reported location and supervision, the majority were performed in a facility with full supervision by a physiotherapist or trainer[119,121,125,126,131–133,137,138,140].

VR rehabilitation is thought to effect complex motor–cognitive processes underlying motor learning. Therefore, VR rehabilitation might also improve cognition. However, the focus of reporting to date has been largely on motor outcomes (Supplementary Table 2). Four trials reported cognitive outcomes[126,131,136,140] showing no effect of VR rehabilitation compared with inactive controls[136,140] or non-VR rehabilitation[126,131,140]. Similarly, only two trials reported motor–cognitive outcomes (that is, dual-tasking)[131,140] and found no superiority to comparable non-VR rehabilitation.

Feasibility, safety and acceptability of VR rehabilitation were generally poorly reported (Supplementary Table 2), with four trials providing no feasibility, safety or acceptability data[119–140]. Of the 12 trials that reported adverse events associated with the VR intervention[119,121–123,125,126,130–133,135–138,140], 11 reported no adverse events and 1 trial[136] reported a non-injurious fall during unsupervised VR stepping training. Six trials reported adherence to VR rehabilitation, which ranged from 86 to 100% (median 98%)[131,133,135–138]. Although high, the adherence to non-VR rehabilitation reported in five trials was also high (range 90–100%, median 100%)[131,133,135,137,138]. Given that most trials were fully supervised, this information might not reflect the safety of and adherence to home-based VR interventions. The aforementioned V-TIME trial was the only trial to explicitly report acceptability[129]. All participants, including those with PD, completed questionnaires that showed that the VR group were more likely to recommend the intervention to others, reporting greater engagement, challenge and perceived benefits on concentration and obstacle negotiation than the treadmill group. No difference existed between the groups in overall satisfaction.

Despite the proposed lower costs of VR rehabilitation, the only trial that reported on costs[122] found that the cost of VR delivered via telerehabilitation (€384 per participant) was less than that of facility-based rehabilitation (€602 per participant). However, this difference was probably due to the VR intervention being delivered in pairs, whereas the facility-based intervention was delivered individually.

Summary. Little evidence exists for superiority of VR rehabilitation over non-VR rehabilitation on gait and balance outcomes, although both are superior to no intervention when delivered in a fully supervised mode. However, most research has used non-immersive, recreational VR systems that might not be optimal as they are not customized to the varied learning difficulties that people with PD experience[22,102]. Additionally, VR rehabilitation has primarily been delivered in fully supervised, facility-based environments. Therefore, a major limitation of the research to date is that the modest evidence currently supporting VR rehabilitation cannot be generalized to minimally supervised or unsupervised training conditions in which safety, efficacy and adherence might be compromised. However, a high-quality RCT targeting aerobic capacity (rather than balance and gait) in people with PD using non-immersive VR shows promise for incorporation of VR rehabilitation in the home environment[143]. Both VR aerobic cycling and non-VR stretching exercise were conducted at home,

Box 2 | **Advantages and disadvantages of VR rehabilitation in Parkinson disease[a]**

Advantages

Clinical

- Promotes neuroplasticity and motor learning[99,109,b]
- Tailored motor–cognitive or limbic challenges directed by visual, auditory or haptic stimuli could lead to improved game performance[102] and more effective outcomes[99,109], such as transfer to performance of daily activities[24,102,110,b]
- Facilitates standardization and personalized interventions[107,c]
- Facilitates practice of challenging tasks in a safe environment[102,104,109,b,c]
- Potential to safely manipulate sensorimotor conflict as a training strategy with immersive virtual reality (VR)[42,111,112,b,d]
- High-dose practice[20,102] and adherence[113], and quantification of both without relying on self-report[20,22,104,b,c]
- Inbuilt task variation and progression in the programme[98,99,102,109,b]
- Provision of real-time multisensory feedback[98,102,109,b]

Feasibility

- Some VR systems are portable[20,102,113], broadly accessible[105,113] and easy to use[102,105,113,b,c]
- Some VR systems might reduce costs by reducing need for supervision[102], thus facilitating home-based rehabilitation[103,106,b,c]
- Increased motivation, enjoyment and acceptability[22,100–102,104,108,b,c]

Disadvantages

Clinical

- Physical and cognitive challenges might lead to excessive fatigue[100,c]
- Increased risk of falls or injury when unsupervised in the home environment[22,115,b,c]
- Short-term deterioration in gait with immersive VR[42,111,112,b,d]
- Eyestrain, dizziness, loss of coordination and motion sickness[17,114,c,d]
- Inaccurate knowledge of performance feedback — correct movement displayed on screen despite use of compensatory movements in the real world might reinforce inappropriate movement strategies[105,c]
- Excessive feedback causes uncertainty about where to direct attention[105,c]
- Inability to fade feedback, leading to reliance on feedback[105,c]
- Discouraging feedback (for example, 'unbalanced' in Nintendo Wii Fit) with large improvements required to progress[105,113,c]
- Feedback does not provide specific information about how to improve[105,c]
- Difficulty learning to use the VR system[113,c]

Feasibility

- Lack of ability to customize recreational systems to ability level, with some games in recreational systems too hard cognitively, motorically or both[102,113,115,b,c]
- Technical difficulties and difficulty manipulating devices[105,c]
- More sophisticated rehabilitation systems are costly and not readily accessible[105,c]
- Difficulty finding physical space for VR system in the home[113,c]
- Recreational system visuals can be childlike and therefore less appealing[115,c]

[a]Owing to variations in VR rehabilitation systems, user characteristics, supervision schedules and delivery settings, some features can be an advantage in one context and a disadvantage in another. [b]Parkinson disease rehabilitation literature. [c]Neurological rehabilitation literature. [d]Non-neurologically impaired population literature.

Table 3 | **Systematic reviews of effects of VR rehabilitation interventions in people with PD**

Studies and participants with PD	Primary study quality	Primary study interventions	Key findings on effectiveness, safety and feasibility	Refs[a,b]
Eight RCTs (370 participants); ten non-RCTs (143 participants)	Low (overall; Newcastle–Ottawa Scale[165] and CONTENT scale[166]) Moderate (RCTs; Cochrane risk of bias tool[167] and CONTENT scale[166])	Recreational systems: 11 studies (10 balance board, 1 hand-held remote) Customized systems: 7 studies (4 balance board, 1 3D motion capture, 2 VR treadmill training)	Effectiveness compared with active control: no difference Safety: 5 studies report safety but details not provided Feasibility: 12 studies reported progression, 6 studies reported enjoyment/adherence but details not provided	99[c]
Eight RCTs (263 participants)	Low (Cochrane risk of bias tool[167])	Recreational systems: six (four balance board, two hand-held remote) Customized systems: two trials (both balance board)	Effectiveness compared with active control: ↑ step and stride length[d] (grade: low certainty) Effectiveness compared with non-active control: ↑ step and stride length (grade: very low certainty); ↑ balance[d] (composite measures) (grade: very low certainty); ↓ PDQ-39[e] (grade: very low certainty); ↓ UPDRS-2 (ADL)[e] (one study) Safety: no adverse events reported Feasibility: no difference in drop-out rates	23
Four RCTs (60 participants); two non-RCTs (24 participants)	Moderate to good (PEDro score)	Recreational systems: three studies (two balance board, one 3D motion capture) Customized systems: three studies (all with balance boards)	Effectiveness compared with active control: no difference (mixed results) Safety: NR Feasibility: NR	117[c]
12 RCTs (419 participants)	Moderate to good (PEDro score)	Recreational systems: eight (five balance board, two 3D motion capture, one hand-held remote) Customized systems: one dance mat and force plate, one force plate and inertial sensors Not reported[f]: two trials	Effectiveness compared with active control: ↑ Berg Balance Scale[d] (grade: moderate certainty); ↓ Timed Up and Go[d,e] (grade: low certainty); ↑ stride length[d] (grade: very low certainty) Safety: NR Feasibility: NR	26

↑, increased; ↓, decreased; NR, not reported; PD, Parkinson disease; PDQ-39, Parkinson's Disease Questionnaire, 39 items (measures PD health-related quality of life); PEDro, Physiotherapy Evidence Database[141]; RCT, randomized controlled trial; UPDRS-2 (ADL), Unified Parkinson's Disease Rating Scale 2 (Activities of daily living section); VR, virtual reality. [a]Studies listed alphabetically by first author. [b]REFS[99,117,26] were of moderate quality and REF.[23] was of high quality according to AMSTAR 2 (a critical appraisal tool for systematic reviews[116]). [c]PD subgroup of VR rehabilitation review of neurological conditions. [d]Meta-analysis showing statistically significant improvement in the VR rehabilitation group compared with the control or other intervention group. [e]Lower score is a better score. [f]Full text available in Chinese only.

supported by a motivational app and remote supervision. Both groups showed high adherence (>2.5 or 3 prescribed sessions per week) and few adverse events. Importantly, the VR aerobic group showed less attenuation of off-state MDS-UPDRS (Movement Disorder Society — Unified Parkinson Disease Rating Scale) motor scores over the 6-month intervention period, suggesting a disease-modifying effect with adequately dosed aerobic exercise that is feasible in the home environment. Given the potential benefits of VR rehabilitation and the limitations of current research, there is broad scope for further research and development in this area.

Future research directions

VR in precision medicine

A new direction in PD research is required, moving from the current 'one size fits all' approach to a 'precision medicine' approach, taking into account[144–147] the person's clinical presentation, genes, lifestyle and environment[146]. For this purpose, large-scale projects are required to identify biomarkers that predict prognosis and response to treatment, such as the Personalized Parkinson Project[148] and Mobilise-D. Although precision medicine with respect to medical management of PD is in its infancy[146], rehabilitation is likely to benefit from this ongoing body of work in the future. In the short term, however, VR has the potential to personalize rehabilitation[98] in a manner that could complement current practice. Specifically, the ability to manipulate sensorimotor contingencies by simulating tasks that are not possible in the real world and the availability of real-time feedback on performance have the potential to achieve highly personalized assessment and training strategies tailored to both motor and non-motor deficits. For example, VR environments can be used to manipulate situations that provoke FOG and other impairments contributing to fall risk, such as distraction and anxiety. In addition, the potential for VR rehabilitation to provide a more personalized approach by specifically training remediable targets is likely to stimulate the effort, motivation and adherence of the individual beyond that achieved in current practice.

A longitudinal personalized rehabilitation–treatment design for people with long-term upper-limb disability after stroke[149] provides a useful basis for applying such an approach to PD rehabilitation. We propose such a model (FIG. 1), illustrating how VR technology could be used to tease out impairments across compensatory circuits that people with PD rely on to maintain gait and balance[30,32]. Subsequently, people with PD are stratified and matched

Table 4 | **RCTs of effectiveness of VR rehabilitation interventions in people with PD[a]**

Comparisons (number of participants)	Exercise dose	VR versus non-VR	VR versus inactive control	Ref.[b] (PEDro score /10)
VR: training of balance and walking, VR method not reported (*n* = 14) Non-VR: traditional rehabilitation training of balance and walking (*n* = 14)	45 min, four times per week for 12 weeks	↑ Berg Balance Scale ↓ Timed Up and Go[c] ↑ Functional Gait Assessment	NA	[120] (PEDro 7)
VR: exergames[d] — balance and strength (*n* = 22) Non-VR: functional training (balance and strength exercises) (*n* = 25)	50 min, three times per week for 8 weeks	Nil	NA	[121] (PEDro 7)
VR: balance exergames delivered via telerehabilitation (*n* = 38) Non-VR: sensory integration balance training, internal and external perturbations, dual tasks (*n* = 38)	50 min, three times per week for 7 weeks	↑ Berg Balance Scale	NA	[122] (PEDro 6)
VR: exergames — yoga, strengthening and balance games and treadmill training (*n* = 12) Non-VR: stretching, strengthening and balance, and treadmill training (*n* = 12) Control: fall prevention advice and continued usual physical activity (*n* = 12)	60 min, twice a week for 6 weeks	Limits of stability: ↑ velocity of COG	Obstacle crossing while walking: ↑ velocity and ↑ stride length Limits of stability: ↑ velocity, ↑ excursion and ↑ movement in intended direction of COG ↑ SOT ↓ Timed Up and Go[c] ↑ Gait velocity and stride length ↑ Functional Gait Assessment ↑ Lower limb muscle strength ↓ PDQ-39[c] ↓ Fear of falling (FES-I)[c]	[124,125] (PEDro 7)
VR: treadmill walking through VR environment, negotiating obstacles, distractors and multiple routes (*n* = 66) Non-VR: treadmill training (*n* = 64)	45 min, three times per week for 6 weeks	↓ Rate of falls[c] ↓ Gait speed variability[c] ↑ Foot clearance ↑ 2-min walk distance ↑ SPPB: balance, gait speed	NA	[126] (PEDro 8)
VR: exergames focusing on strength, balance and aerobics (*n* = 22) Non-VR: physical therapy focusing on strength, balance and aerobics (*n* = 22)	50 min, three times per week for 4 weeks	Nil	NA	[130] (PEDro 4)
VR: global exercises and exergame balance exercises (*n* = 16) Non-VR: global exercises and balance exercises (*n* = 16)	60 min, twice a week for 7 weeks	Nil	NA	[131] (PEDro 5)
VR: custom-written balance exergames (*n* = 11) Non-VR: conventional balance exercises (*n* = 10)	50 min, twice a week for 8 weeks	Limit of stability test: ↑ movement in intended direction	NA	[135] (PEDro 6)
VR: exergame — dance stepping exercise (*n* = 31) Control: usual care (*n* = 29)	≥15 min, three times per week for 12 weeks	NA	↑ Timed Up and Go[c] ↑ Self-reported mobility	[136] (PEDro 8)
VR: exergames — balance and gait (*n* = 25) Control: usual care (*n* = 24)	60 min, five times per week for 5 weeks	NA	↑ Berg Balance Scale ↑ Dynamic Gait Index ↑ 6-min walk distance ↓ Standing posturography[c] ↓ Beck Depression Index[c] ↑ EuroQOL-5D ↓ UPDRS-2 (ADL)[c] ↑ Schwab & England ADL ↓ PDQ-39[c] (total and mobility)	[137] (PEDro 6)

Table 4 (cont.) | **RCTs of effectiveness of VR rehabilitation interventions in people with PD**

Comparisons (number of participants)	Exercise dose	VR versus non-VR	VR versus inactive control	Ref.[b] (PEDro score /10)
VR: exergame balance training (*n* = 17) Non-VR: conventional balance training (*n* = 16)	60 min, twice a week for 5 weeks	Nil	NA	[138] (PEDro 8)
VR: exergame balance training with custom-written exercises (*n* = 11) Non-VR: conventional balance training (*n* = 12)	50 min, twice a week for 6 weeks	Nil	NA	[139] (PEDro 7)
VR: exergame balance training with custom-written exercises (*n* = 14) Non-VR: conventional balance training (*n* = 14) Control: usual care (*n* = 14)	30 min, twice a week for 6 weeks	Nil	↑ SOT-6: with and without dual task	[140] (PEDro 7)

↑, increased; ↓, decreased; ADL, Activities of daily living; COG, centre of gravity; EuroQOL-5D, Euro Quality of Life-5D; FES-I, Falls Efficacy Scale — International; NA, not applicable; PD, Parkinson disease; PDQ-39: Parkinson's Disease Questionnaire, 39 items (measures PD health-related quality of life); PEDro, Physiotherapy Evidence Database[141]; RCT, randomized controlled trial; SOT, Sensory Organization Test; SPPB, Short Physical Performance Battery; UPDRS-2 (ADL), Unified Parkinson's Disease Rating Scale 2 (Activities of daily living section); VR, virtual reality. [a]Showing statistically significant differences between groups. [b]Studies listed alphabetically by first author. [c]Lower score is a better score. [d]Exercise-based, interactive, videogames.

to an appropriate VR type and location, or a sequence of types and locations in time. Our model also illustrates that compensatory network capabilities will change over the course of the disease[32,36,150], requiring adjustments to the therapeutic approach taken. Future studies are needed to test the idea of using VR methodologies for distinguishing between rehabilitation profiles and to determine how such phenotypes change over time.

Future VR design

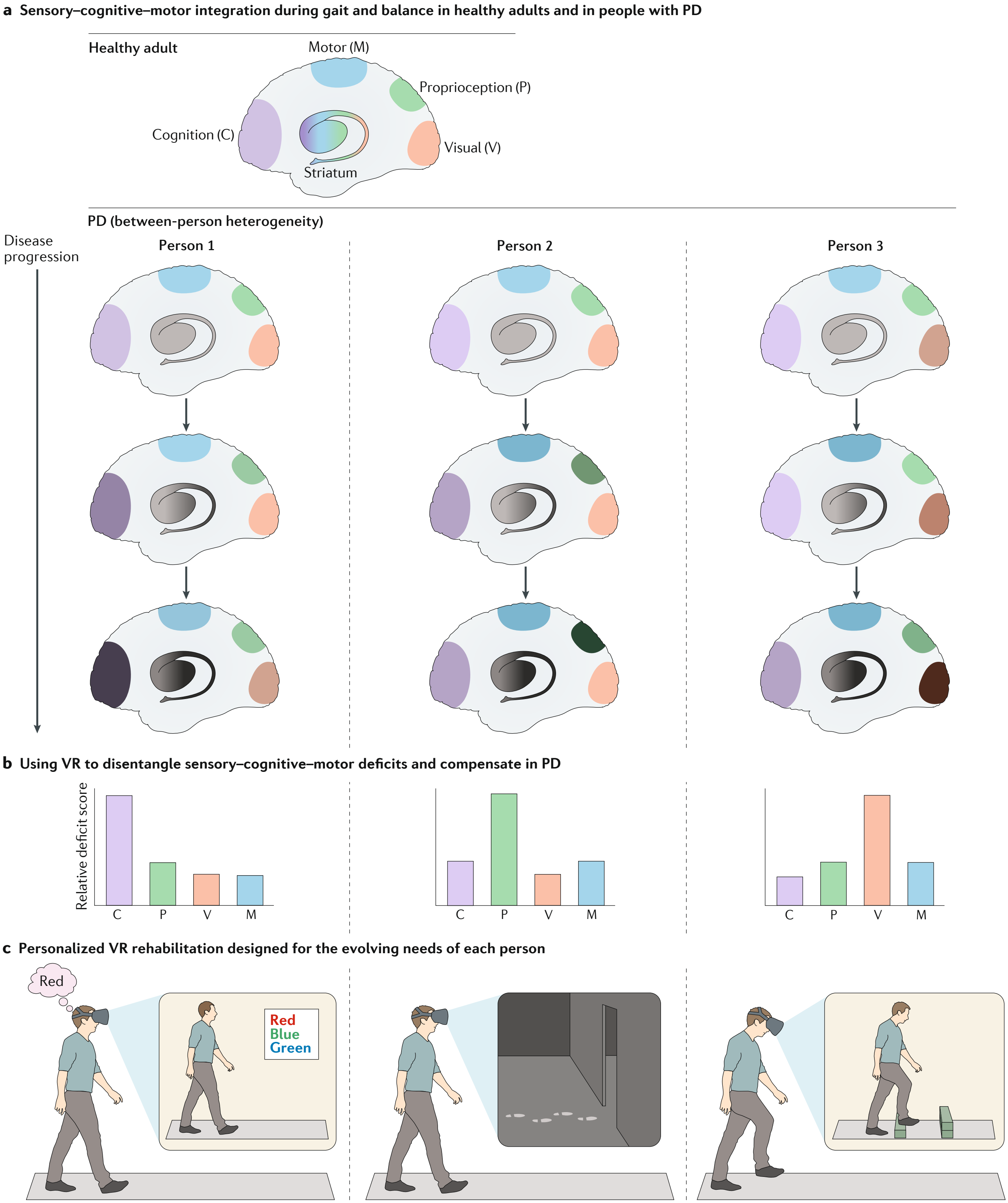
VR is an evolving concept. To date, VR assessment and rehabilitation applications have been developed in parallel, with little crosstalk between them. The scope to adapt the most promising immersive VR applications to produce customized dual-purpose applications is enormous. This development requires collaboration between technology experts, therapists and people with PD to ensure that systems provide optimal exercise and motor learning conditions, are reliable and easy to use in the clinic or home environment and are engaging and acceptable for long-term use.

With respect to facility-based VR rehabilitation systems, synchronized multisensory inputs and the inclusion of motor–cognitive outcomes need to be incorporated into future designs to facilitate a sense of presence and ecological validity. VR interventions also need to be developed in the context of a cogent theoretical framework with a clear rationale for the added benefit of VR[99,151]. For instance, VR training can be designed with the aim to gradually improve gait parameters over time in a personalized manner. Feedback might be offered without distraction first[31], followed by increasing levels of distraction that might enhance automaticity of walking[152]. Similarly, feedback on performance might be enhanced by external stimuli during initial acquisition of an optimal gait pattern[153]. Subsequently, such input might be faded and then withdrawn to enhance retention[154]. Cognitive dual tasks could also be added to immersive VR systems to train motor–cognitive processing in people with PD[155]. Such VR systems are ideally suited to in-clinic rehabilitation, where physiotherapists are available to fine tune these parameters on the basis of VR-system outcome measures and observational analysis of the individual's performance.

Ongoing technological advancements might soon allow VR environments to adapt in real time on the basis of biofeedback obtained from the user's performance. Intra-individual levels of attenuation and inter-individual variability in the effects of VR on physiological measures could be accounted for[99]. For example, the walkway in a VR fear-of-height paradigm might only need to be raised slightly above ground level to induce a fear response in individuals with trait anxiety, whereas for non-anxious individuals the walkway might need to be raised higher to induce a similar fear response. If attenuation occurs, the VR environment can be modified to maintain challenge (for example,

Fig. 1 | **Model of precision rehabilitation using VR to stratify and treat different deficit profiles in PD.** **a** | Top panel: core motor, proprioceptive, visual and cognitive neural systems that couple with the striatum to facilitate gait and postural control in healthy adults. Bottom panels: between-person heterogeneity in the level of deficit in people with Parkinson disease (PD) against the background of increasingly affected striatal and extra-striatal cortical circuits with disease progression (indicated by increasingly dark shading). Three different profiles of impaired neural activity are shown. Person 1 has early deterioration of cognitive function. Person 2 starts with deterioration in proprioceptive/sensory integration. Person 3 is characterized by early loss of compensatory visual (attention) function. Notably, with time, the spread of degeneration might affect alternative systems in a variable manner, that is, within-person heterogeneity. **b** | Potential output of virtual reality (VR) tests in which the various affected systems are loaded and receive a relative deficit score with different projected outcomes for the three different profiles. **c** | Precise targeting of deficient compensatory functions during locomotion using VR. Person 1 is exposed to Stroop dual tasking to train executive function. Person 2 is exposed to walking in the dark towards a narrow doorway to reweight proprioceptive/sensory systems. Person 3 is exposed to stepping over obstacles of different heights to train visuo-motor control.

gradually raising the walkway on the basis of physiological measures of anxiety). Similarly, during home-based VR rehabilitation, progression rules or algorithms[156,157] could be built into VR applications in which user performance triggers automatic adjustment of VR training parameters to the user's changing performance levels. For example, gait speed and more advanced gait activities are only accessible after users reach a certain level of stability in order to minimize fall risk. These projected innovations will need to be tested in robust RCTs that



include comprehensive reporting of the VR intervention protocols (including conceptual framework), the VR system used, the immersivity of the system, the level of motor–cognitive challenge and the progression rules. To guide implementation, information about the feasibility, safety and acceptability of VR interventions is required. With respect to acceptability to participants, the use of questionnaires to assess the sense of presence experienced in VR rehabilitation[158] is recommended. In addition, taking advantage of technology-based methods will ensure accurate reporting of adherence. With respect to acceptability to health-care providers, cost-effectiveness analyses are crucial to inform implementation decisions.

A major challenge going forwards is to keep pace with technological innovations. To prevent redundancy, developers should ensure that VR systems are flexible and adaptable to ongoing technological advances[159]. An overall risk, however, is that VR paradigms over time might become so complex (such as immersive whole-body VR) and costly that they would not meet the need for enhancing practice in supervised and unsupervised environments.

Clinical implications

Current evidence indicates that training outcomes are similar for VR versus non-VR-based rehabilitation in people with PD. In addition, all rehabilitation interventions, including VR interventions, have advantages and disadvantages that vary according to the needs and preferences of the people with PD, the type of VR system and the specific training protocol used. The skill of the health professional is to analyse these factors and prescribe an intervention accordingly. At this stage, the evidence does not support a solely VR rehabilitation approach. However, identifying people with PD who would gain the greatest benefits from the motivational and engaging aspects of VR to sustain high-dose practice might be useful. Therapists should explore available options with the individual to inform this choice, taking into account motor and non-motor impairments, the fall risk, the FOG likelihood and previous experience using computer technology with or without VR. If unsupervised practice is being considered, then a risk analysis needs to be undertaken to ensure that a safety and monitoring plan for unsupervised practice is in place and adequate training to operate the VR system has been provided.

Therapists should carefully consider the pros and cons when selecting the VR paradigm to achieve optimal training effects. For example, an HMD that presented visual augmented cues during gait did not reduce the severity of FOG compared with traditional cueing strategies[67]. This limited effect was attributed to the HMD being too heavy and uncomfortable to wear, a limited field of view and insufficient familiarization causing distraction[67]. In addition, some individuals experience motion sickness when using VR, particularly with immersive systems[114]. By contrast, a non-immersive paradigm in which participants navigated a VR maze under time pressure by stepping on a balance board showed an improvement in dual-task performance and a reduction in FOG[68]. Furthermore, recreational commercial systems can be too difficult and/or unsafe for some people with PD[22], and vary in their effect on cognitive demands, such as decision-making, response inhibition, divided attention and working memory[102]. Although some attempts have been made to assist clinicians to identify appropriate commercial systems and games matched to the individual's impairments[102,160], criteria are lacking to help guide clinical decision-making for PD; and, where available, this information will rapidly become outdated. Therefore, the conceptual framework, promises and pitfalls of technological applications, including VR, need to be incorporated into educational curricula for health professionals involved in rehabilitation.

When selecting VR paradigms, task specificity for obtaining optimal carry-over to everyday activities is an important consideration. During VR implementation, therapists are encouraged to ensure individuals are not using inappropriate movement strategies to meet the goal of the game when exercising, as this issue has been reported to occur when recreational VR systems are used in rehabilitation of gait and balance after stroke[161]. Adherence to VR might also wane quickly as users get tired of playing the same game. Various games with motor–cognitive demands tailored to individual impairments and preferences are likely to enhance motivation and promote adherence.

Given the dopaminergic denervation in PD, any potentially demotivating aspects of VR must be considered, such as negative feedback or having to start over once a mistake is made. Most commercialized VR applications are designed to reach higher scores over time, which are displayed to the user and might negatively impact the user's sense of achievement. This factor might reduce adherence rates and affect motor learning outcomes in people with PD. In the long term, people with PD will need ongoing support to deal with the deterioration in their abilities[162]. Monitoring performance in the clinic or remotely will assist therapists to set realistic expectations and collaboratively adjust complexity as the disease progresses. Similarly, subgroups of people with PD, especially in the later stages of the disease, might be impaired in their ability to balance sensory input and cognitive 'top-down' influences over perception[163]. Although speculative at present, this imbalance could lead to unwanted embodied simulations during VR[164] and affect people's ability to benefit from VR interventions, and might in cases of extreme sensory manipulation lead to adverse outcomes, such as visual hallucinations[163]. Future studies are needed to determine whether people with PD who experience sensory misperceptions or hallucinations are equally able to benefit from immersive VR systems for rehabilitation purposes.

Conclusions

VR has the potential to improve our understanding and ability to treat complex impairments in PD by engaging people with PD in enriched and highly individualized complex environments, mimicking real-world situations while minimizing risk. However, the full utility of VR for PD rehabilitation has not yet been achieved. To date, little evidence exists for superiority of VR rehabilitation compared with non-VR rehabilitation on gait and balance outcomes, although both are superior to no intervention when delivered in a fully supervised mode. VR offers opportunities to safely identify an individual's specific FOG triggers and balance deficits, thus informing personalized training targets. To exploit the potential of VR rehabilitation and to optimize rehabilitation outcomes, researchers are encouraged to design immersive VR applications with integrated assessment and training modules that are tailored to the needs of people with PD and health-care providers.

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Competing interests
The authors declare no competing interests.

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Review criteria
To identify relevant virtual reality (VR) studies we searched for articles from 1 January 2010 to 1 November 2019. A PubMed search was performed using the terms: "parkinson*" AND "virtual reality" OR "augmented reality" AND "gait" OR "balance" OR "freezing". The resulting 33 hits and their reference lists were screened for possible insights into the use of VR for exploring the underlying mechanisms of gait and balance impairments in Parkinson disease. To identify relevant systematic reviews of VR interventions, a PubMed search was performed using the terms: "parkinson*" AND "virtual reality" OR "virtual rehabilitation" OR "augmented reality" OR "exergam*" OR "videogam*" OR "video gam*" AND "systematic review". From the 398 reviews we identified 11 relevant systematic reviews published in English. To identify relevant randomized controlled trials, the reference lists of all relevant systematic reviews were reviewed and relevant randomized controlled trials were extracted. In addition, a PubMed search was performed using the terms: "parkinson*" AND "virtual reality" OR "augmented reality" OR "exergam*" OR "videogam*" OR "video gam*" AND "random*". These two strategies yielded a total of 828 articles including 17 relevant randomized controlled trials published in English.

Supplementary information
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