

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 Moran Gilat²

¹Discipline of Physiotherapy, Faculty of Medicine and Health, University of Sydney

²Research Group for Neurorehabilitation (eNRGy), Department of Rehabilitation Sciences, KU Leuven

*email : colleen.canning@sydney.edu.au

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 unrealised potential exists for the use of VR to provide personalized assessment and rehabilitation that optimises motor learning both in the clinic and home environments, and adapts to change in individuals over time. Design of such systems will require collaboration between all stakeholders to maximise useability, engagement, safety and effectiveness.

[H1] INTRODUCTION

Parkinson disease (PD) is a complex, progressive multi-system neurodegenerative disorder associated with motor and non-motor impairments¹. The hallmark motor symptoms include bradykinesia, rigidity, tremor and postural instability,

though with time other complex motor symptoms such as freezing of gait also frequently emerge. PD affects the automaticity of movement and therefore motor deficits are more prominent with distraction, environmental complexity and dual-task load². Gait and balance are affected, influencing everyday mobility even in early disease³. Motor learning is impaired in PD, characterized by reduced consolidation and transfer of learning owing to worsening striatal function⁴. To compensate, people with PD use alternative neural circuits, usually involving attention, sensory stimuli and vision⁵. Falling is extremely frequent in PD⁶ and occurs two or three times more than in the healthy elderly population⁷; this factor, along with cognitive decline and other common non-motor impairments, such as fatigue, apathy, anxiety and depression, produce 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, optimised 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 PD¹⁰⁻¹². A variety of 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, multi-task training, and/or 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 in stance) 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; 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 outcomes¹³⁻¹⁵.

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 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 world¹⁶. A key feature of VR is immersivity, that is, the extent to which the user is fully integrated into the virtual environment¹⁷ (Box 1). Acknowledging that the definition of VR is a source of debate¹⁷⁻²⁰, 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 understanding²¹ and rehabilitation²²⁻²⁶ of gait and balance impairments, and this Review focuses on these VR applications compared to 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.

[H1] VR FOR EXPLORING UNDERLYING MECHANISMS

[H2] Rationale

Our understanding of the precise aetiology underlying gait and balance problems in PD, and in particular freezing of gait (FOG; an episodic symptom defined by a marked reduction or complete absence of forward progression of the feet despite the intention to walk²⁷) 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 neuropathology³². 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 dysfunction³³⁻³⁶. So far, assessing to what degree complex symptoms, such as FOG, can be attributed to underlying disease, 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 involved³⁷. FOG and falling frequently co-occur³⁸, but are extremely difficult to assess owing to their transient and complex nature. Additionally, people with PD often present with performance bias during testing³⁹, limiting 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 miniBESTest⁴⁰, which assesses anticipatory and reactive standing balance, dynamic gait, and response to different visual (for example, eyes open versus eyes closed) and somatosensory inputs (such as standing on floor versus standing on foam); 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 (re-)learn relations between their actions and associated sensory input⁴¹ 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 trials⁴². 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 ground⁴⁴. Third, people with PD have known proprioceptive⁴⁵, vestibular⁴⁶, gaze⁴⁷, cognitive⁴⁸ and perceptual⁴⁹ 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 balance⁵³. 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.

[H2] Behavioural results

[H3] 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 PD⁴⁴ after prior work based on questionnaire data indicated that these factors could be related⁵⁴. 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, while in the high-threat condition the virtual walkway was presented as if it was raised high above the ground⁴⁴ (Table 1). The VR paradigm successfully induced greater levels of anxiety and caused more FOG during the high-threat compared to low-threat condition. Although prior work had shown that subjective anxiety is increased in people with PD and FOG⁵⁴, this VR fear-of-height paradigm was the first to provide direct evidence that inducing anxiety during gait worsens FOG in PD⁴⁴.

[H3] 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 while the speed of the treadmill could be adjusted in a feedforward manner based on the acceleration of the legs⁵⁵. 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 episode⁵⁶) 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 harness⁵⁵. 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.

[H3] VR foot-pedal paradigm

A functional magnetic resonance imaging (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 laying supine⁵⁷. Users navigated a 2D virtual corridor through a first-person perspective by 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 conditions⁵⁷. 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 FOG⁵⁷. 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 stepping³⁰.

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 (such as the word red written in the colour red) that were implicitly associated with stopping⁶⁰. People with PD and FOG also experienced significant delays when needing to execute stopping in response to incongruent cues, indicating an impaired ability to inhibit ongoing stepping movements⁶². Furthermore, delays were observed in people with PD and FOG when initiating the ‘first step’ forward during VR task performance⁶², 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 FOG⁶³⁻⁶⁵, 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}.

[H3] 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 FOG⁶⁹. 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 assessments⁶⁶. 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 risk of tripping and falling during testing. Third, dual-task conditions were presented virtually and made to appear suddenly (for example, changes in gait speed) in order to assess gait adaptability⁶⁶. 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 consequent rehabilitation programs could be tailored to these results^{47, 66}. This idea also holds promise for fully immersive VR in combination with treadmill walking⁷⁰. As treadmills become increasingly versatile and offer split belt facilities (that is, one belt per leg)⁷¹ and belt perturbations in multiple directions⁷⁰, it will also be possible to test proprioceptive and vestibular manipulations while walking in virtual environments.

[H3] VR for assessing balance

In addition to assessing gait, VR also offers opportunities to induce varying levels of visual perturbation during balance tests. Compared to 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 training⁷². These systems also allow balance to be assessed in all planes, thereby enabling therapists to better personalize their interventions to the individual's balance deficit⁷⁴. 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 FOG⁷⁵.

[H2] 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 have been used²⁸. These techniques activate neurons across similar circuits as during real motor tasks⁷⁸. However, no ongoing behavioural output is generated to ensure that participants are engaged in the task. Furthermore, such techniques preclude assessment of multi-sensory processing⁵⁰ and motor automaticity deficits³¹ that underlie gait difficulty in PD.

fMRI results⁵⁷ 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, 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 (preSMA) and inversely correlated with the degree of functional connectivity between the preSMA and subthalamic nucleus, two main regions of the hyper-direct cortico-basal ganglia inhibitory pathway⁸¹. Together, these findings corroborate the idea that FOG is associated with basal ganglia hypoactivation and a resulting overdrive of inhibitory projections to brainstem locomotor centers, 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 the motor operating circuits fail. Abnormally increased connectivity between limbic regions, in particular the amygdala, and the motor striatum also feed into this mechanism⁷⁹, 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 foot 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 hemispheres³⁰. 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 tasks³⁰.

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 gait⁵⁸, 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-ratio⁸² resembling the severe trembling of the legs observed during FOG in the clinic⁸³. 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 control²¹.

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 interventions²⁹.

[H1] VR FOR REHABILITATION

[H2] 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, multi-task training, cueing and compensatory movement strategies. Evidence from high quality systematic reviews and randomised 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 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 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 adherence⁹¹. 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 activity⁹⁴ 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 to 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 complexity⁹⁵. In a motor learning disease such as PD, targeting motor–cognitive interactions could be particularly beneficial in early disease stages, enhancing motor performance and generalisation to real life. However, with disease progression motor–cognitive impairments might pose constraints on learning ability⁹⁷. In PD, the learning process relies on altered subcortical and cortical plasticity mechanisms, making learners particularly dependent on external sources of feedback (reviewed elsewhere⁴). 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.

[H2] 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 quality¹¹⁶ 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 to active but non-VR rehabilitation²⁶. 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 important¹¹⁸. 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 9.7cm, 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 1 summarises 17 such trials¹¹⁹⁻¹⁴⁰ of moderate to high quality¹⁴¹ (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). All but one trial delivered non-immersive VR with visual feedback, with or without additional auditory or haptic feedback, while the remaining trial¹²⁰ 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 commercialised rehabilitation-specific systems^{133, 138}, and four used customised 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 which trained dance moves¹²³, and another which trained treadmill walking¹²⁶. 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 exercise-based, interactive, videogames with additional motor and/or cognitive task requirements including response inhibition)^{120,129}.

[H3] 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 customised VR treadmill training (Table 2) which provided motor–cognitive challenges in a simulated, real-life but safe environment, compared to the same dose of treadmill training alone. In the subgroup of people with PD (n=130), those people in the VR group had a reduction in fall rates above and beyond the reduction seen in the treadmill group¹²⁶. 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 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}.

[H3] 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, customised VR stepping exercise was compared to an inactive control group¹³⁶. Although the VR group perceived improved mobility compared to the inactive group, this difference was not reflected in measured physical outcomes. Further sub-group 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 under dosing and/or inadequate supervision in the home environment.

[H3] Influence of key trial design features on outcomes of VR rehabilitation

Some reports suggest that practicing 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 generalisability of tasks practised in the VR environment to performance of everyday activities in real life^{124, 126, 137}. Notably, the aforementioned V-time trial¹²⁶ 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 above¹³⁶ was the only study to show a decrement in everyday task performance, that is, the time taken to complete the Timed Up and Go (TUG) test. In this case, the emphasis on accurate, safe stepping in the VR program might have carried over to a slower, but potentially safer, TUG performance and time. In addition, it should be noted that the V-time intervention¹²⁶ was fully-supervised and utilised 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 to 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 was generally poorly reported (Supplementary Table 2), with four trials providing no feasibility, safety or acceptability data¹¹⁹⁻¹⁴⁰. 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 one¹³⁶ 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, adherence to non-VR rehabilitation reported in five trials was also high (range 90 to 100%, median 100%)^{131, 133, 135, 137, 138}. Given that most trials were fully-supervised, this information might not reflect safety of and adherence to home-based VR interventions. The aforementioned V-time trial was the only trial to explicitly report acceptability¹²⁹. All participants, including those with PD, completed questionnaires

which showed 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 costs¹²² found that the cost of VR delivered via telerehabilitation (€384 per participant) was less than 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.

[H3] Summary

In summary, little evidence exists of 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 customised 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 generalised 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 environment¹⁴³. Both VR-aerobic cycling and non-VR stretching exercise were conducted at home, supported by a motivational app and remote supervision. Both groups showed high adherence (>2.5/3 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.

[H1] FUTURE RESEARCH DIRECTIONS

[H2] 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 the person’s clinical presentation, genes, lifestyle and environment¹⁴⁴. For this purpose, large scale projects are required to identify biomarkers that predict prognosis and response to treatment, such as the Personalized Parkinson Project¹⁴⁵ and Mobilise-D¹⁴⁶. Although precision medicine with respect to medical management of PD is in its infancy¹⁴⁴, 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 rehabilitation⁹⁸ 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 stroke¹⁴⁷ provides a useful basis for applying such an approach to PD rehabilitation. We propose such a model (Figure 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 to an appropriate VR type and location, or sequence of types and locations in time. Our model also illustrates that over the course of the disease compensatory network capabilities will change^{32,36,148}, 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 determine how such phenotypes change over time.

[H2] Future VR design

VR is an evolving concept. To date, VR assessment and rehabilitation applications have been developed in parallel with little cross-talk 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 multi-sensory 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, 149}. 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 first³¹, followed by increasing levels of distraction that might enhance automaticity of walking¹⁵⁰. Similarly, feedback on performance might be enhanced by external stimuli during initial acquisition of an optimal gait pattern¹⁵¹. Subsequently, such input might be faded and then withdrawn to enhance retention¹⁵². Cognitive dual-tasks could also be added to immersive VR systems to train motor-cognitive processing in people with PD¹⁵³. Such VR systems are ideally suited to in-clinic rehabilitation, when 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 for⁹⁹. For example, the walkway in a VR fear-of-height paradigm might only need to be raised slightly above ground floor 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, gradually raising the walkway on the basis of physiological measures of anxiety). Similarly, during home-based VR-rehabilitation, progression rules or algorithms^{154, 155} 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), VR system used, immersivity of the system, level of motor–cognitive challenge and progression rules. To guide implementation, information about the feasibility, safety and acceptability of VR interventions are required. With respect to acceptability to participants, the use of questionnaires to assess the sense of presence experienced in VR-rehabilitation¹⁵⁶ 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 forward is to keep pace with technological innovations. To prevent redundancy, developers should ensure that VR systems are flexible and adaptable to ongoing technological advances¹⁵⁷. 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.

[H1] CLINICAL IMPLICATIONS

Current evidence indicates that training outcomes are similar for VR versus non-VR based rehabilitation in 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 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, fall risk, 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 to traditional cueing strategies⁶⁷. This limited effect was attributed to the HMD being too heavy and uncomfortable to wear, a limited field of view, and insufficient familiarization causing distraction⁶⁷. In addition, some individuals experience motion sickness when using VR, particularly with immersive systems¹¹⁴. By contrast, a non-immersive paradigm in which participants navigated a VR maze under time pressure by stepping on a balance board showed improvement in dual-task performance and reduction in FOG⁶⁸. Furthermore, recreational commercial systems can be too difficult and/or unsafe for some people with PD²², and vary in their effect on cognitive demands, such as decision-making, response inhibition, divided attention and working memory¹⁰². Although some attempts have been made to assist clinicians to identify appropriate commercial systems and games matched to the individual's impairments^{102, 158}, criteria are lacking to help guide clinical decision making in 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 VR 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 has been reported to occur when recreational VR systems are used in rehabilitation of gait and balance after stroke¹⁵⁹. Adherence to VR might also wane quickly as users get tired of playing the same game. A variety of games with motor–cognitive demands tailored to individual impairments and preferences is 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 commercialised 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 effect 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 abilities¹⁶⁰. 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 perception¹⁶¹. Though speculative at present, this imbalance could lead to unwanted embodied simulations during VR¹⁶² 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 hallucinations¹⁶¹. 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.

[H1] CONCLUSIONS

VR has 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 been achieved yet. To date, little evidence exists of superiority of VR rehabilitation compared to non-VR rehabilitation on gait and balance outcomes, though 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 optimise 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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Author contributions

C.G.C., N.E.A., S.S.P. and M.G researched data for the article, made a substantial contribution to discussion of content, wrote and reviewed/edited the manuscript before submission. E.N. and A.N. made a substantial contribution to discussion of content, wrote and reviewed/edited the manuscript before submission. All authors approved the final version of this manuscript.

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 PD. 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.

KEY POINTS

1. Virtual reality (VR) might provide unique opportunities to improve understanding of the behavioural and neural underpinnings of gait and balance in people with Parkinson disease.
2. 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.
3. Non-immersive VR rehabilitation improves gait and balance when compared to no intervention, but is not superior to non-VR rehabilitation of similar exercise type and dose.
4. Future applications of VR should be tailored to deliver personalized interventions according to each person's profile of deficits and rehabilitation needs.
5. 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.
6. Therapists should consider the conceptual framework, along with the pros and cons, when selecting VR paradigms to optimise training effects with carry-over into everyday activities.

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 heights paradigm to safely assess 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 (fMRI) 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/fNIRS) 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; fMRI, functional magnetic resonance imaging; fNIRS,

functional near infrared spectroscopy; FOG, freezing of gait; HMD, head mounted display; PD, Parkinson disease; VR, virtual reality.

Table 2. Examples of VR systems available for PD rehabilitation^a

Immersivity	VR Example	Features	Purpose
<i>Category 1. Recreational, commercially available</i> <i>(Target population: able-bodied people, including children)</i>			
Non-immersive	Nintendo Wii (<i>Nintendo</i>)	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 2D screen.	Not designed specifically for rehabilitation purposes, but these systems have been researched and are currently the most commonly used in rehabilitation.
Non-immersive	Xbox Kinect (<i>Microsoft</i>)	A camera and depth sensors are used to capture 3D motion. Displayed on 2D screen	
<i>Category 2. Rehabilitation-specific, commercially available</i> <i>(Target population: people with disability from neurological and/or other disorders)</i>			
Non-immersive to immersive	Caren (Motek)	VR environment is integrated with an instrumented dual-belt treadmill, 6-degrees of freedom standing platform and 3D motion capture system. Display varies from 2D flat screen to 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.
Non-Immersive	Humac balance system (CSMi for Dynatronics)	Utilises 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.	IMAGE Aim is to assess and train balance, where balance training tasks are tailored to level of performance.

<i>Category 3. Rehabilitation-specific, customized, not commercially available yet (Target population: people with disability from neurological and/or other disorders)</i>			
Immersive ⁴²	HMD (HTC VIVE®) with controllers attached to legs and pressure sensitive gait mat	Utilises 3-D head mounted display with controllers attached to legs to produce visual-proprioceptive conflict in VR environment while walking on a pressure sensitive mat. Safety harness can be applied.	<p>IMAGE</p> <p>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.</p>
Non-immersive ¹²⁶	Camera-based motion capture (modified Microsoft Kinect) plus virtual environment	Utilises camera-based motion capture of feet while walking. Feet are projected into the VR environment in real time on a 2-D screen. Safety harness is used.	<p>IMAGE</p> <p>Aim is to reduce falls in people with PD. VR environment systematically increases the size of virtual objects to step over and number of distractions to progress motor-cognitive challenge while walking.</p>

^aThese are a selection of the available VR systems across the three categories.

HMD, head mounted display; PD, Parkinson disease; VR, virtual reality.

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	Ref^{a,b}
8 RCTs (370 participants); 10 non-RCTs (143 participants)	Low (overall; Newcastle Ottawa Scale ¹⁶³ and CONTENT scale ¹⁶⁴). Moderate (RCTs; Cochrane risk of bias tool ¹⁶⁵ and CONTENT scale ¹⁶⁴)	Recreational systems: 11 studies (10 balance board, 1 hand-held remote) Customised systems: 7 studies (4 balance board, 1 3D motion capture, 2 VR treadmill training)	Effectiveness compared to 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
8 RCTs (263 participants)	Low (Cochrane risk of bias tool ¹⁶²)	Recreational systems: 6 (4 balance board, 2 hand-held remote) Customised systems: 2 trials (both balance board)	Effectiveness compared to active control: ↑ Step and stride length ^e (Grade: low certainty) Effectiveness compared to non-active control: ↑ Step and stride length (Grade: very low certainty); ↑ Balance ^e (composite measures) (Grade: very low certainty); ↓ PDQ-39 ^d (Grade: very low certainty); ↓ UPDRS-2 (ADL) ^d (1 study) Safety: No adverse events reported Feasibility: No difference in drop-out rates	23
4 RCTs (60 participants); 2 non-RCTs (24 participants)	Moderate to good (PEDro score)	Recreational systems: 3 studies (2 balance board, 1 3D motion capture) Customised systems: 3 studies (all with balance boards)	Effectiveness compared to active control: no difference (mixed results) Safety: NR Feasibility: NR	117 ^c
12 RCTs (419 participants)	Moderate to good (PEDro score)	Recreational systems: 8 (5 balance board, 2 3D motion capture, 1 hand-held remote) Customised systems: 1 dance mat and force plate, 1 force plate and inertial sensors Not reported ^f : 2	Effectiveness compared to active control: ↑Berg Balance Scale ^e (Grade: moderate certainty); ↓Timed Up and Go ^{de} (Grade: low certainty); ↑Stride length ^e (Grade: very low certainty) Safety: NR Feasibility: NR	26

^aStudies listed alphabetically by first author; ^bRefs 99, 117 and 26 were moderate quality, and ref 23 was high quality according to AMSTAR 2 (a critical appraisal tool for systematic reviews¹¹⁶). ^cPD subgroup of VR rehabilitation review of neurological conditions; ^dLower score is better score. ^eMeta-analysis showing statistically significant difference improvement in the VR rehabilitation group compared with the control/other intervention group. ^fFull text available in Chinese only.

PEDro, Physiotherapy Evidence Database¹⁴¹; NR, not reported, RCT, randomized controlled trial; PDQ-39, Parkinson's Disease Questionnaire – 39 (measures Parkinson's disease health-related quality of life); UPDRS-2 (ADL): Unified Parkinson's Disease Rating Scale- 2 (Activities of Daily Living section)

Table 4: RCTs of effectiveness of VR rehabilitation interventions in people with PD showing statistically significant differences between groups

Comparisons (number of participants)	Exercise dose	VR versus non-VR	VR versus inactive control	Ref^a 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, 4 times per week for 12 weeks	↑ Berg Balance Scale ↓ Timed up and go ^b ↑ Functional Gait Assessment	NA	120 PEDro 7
VR: Exergames: balance and strength (n=22) Non-VR: Functional training (balance and strength exercises) (n=25)	50 min, 3 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, 3 times per week for 7 weeks	↑ Berg Balance Scale	NA	122 PEDro 6
VR: Exergames: yoga, strengthening and balance games + 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 ^b ↑ Gait velocity + stride length ↑ Functional Gait Assessment	124,125

			↑ Lower limb muscle strength ↓ PDQ-39 ^b ↓ Fear of falling (FES-D) ^b	PEDro 7
VR: Treadmill walking through VR environment, negotiating obstacles, distractors and multiple routes (n=66) Non-VR: Treadmill training (n=64)	45 min, 3 times per week for 6 weeks	↓ Rate of falls ^b ↓ Gait speed variability ^b ↑ Foot clearance ↑ 2 minute 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, 3 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, 3 times per week for 12 weeks	NA	↑ Timed Up and Go ^b , ↑ self-reported mobility	136 PEDro 8
VR: Exergames: balance and gait (n=25) Control: Usual care (n=24)	60 min, 5 times per week for 5 weeks	NA	↑ Berg Balance Scale ↑ Dynamic Gait Index ↑ 6 minute walk distance ↓ Standing posturography ^b ↓ Beck Depression Index ^b ↑ EuroQOL-5D ↓ UPDRS-2 (ADL) ^b ↑ Schwab & England ADL ↓ PDQ-39 ^b total + mobility	137

				PEDro 6
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 mins, twice a week for 6 weeks	Nil	↑ SOT-6: with and without dual task	140 PEDro 7

^aStudies listed alphabetically by first author; ^bLower score is better score

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; PDQ-39: Parkinson's disease Questionnaire-39; PEDro, Physiotherapy Evidence Database randomised controlled trial quality score¹⁴¹; SOT, Sensory Organisation Test; SPPB, Short Physical Performance Battery; UPDRS-2 (ADL), Unified Parkinson's Disease Rating Scale- 2 (Activities of Daily Living section).

Figure 1. Model of precision rehabilitation using VR to stratify and treat different deficit profiles in PD

A - Top panel presents core motor, proprioceptive, visual and cognitive neural systems that couple with the striatum to facilitate gait and postural control in healthy adults. The bottom panel highlights between-person heterogeneity in the level of deficit in people with PD against the background of increasingly affected striatum and extra-striatal cortical circuits with disease progression (indicated by black colour). Three different profiles of impaired neural activity are shown. Person 1 has early deterioration of cognitive function (indicated by dotted area and becoming black with time). Person 2 starts with deterioration in proprioceptive/sensory integration. Person 3 is characterised 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 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 exposed to Stroop dual tasking to train executive function. Person 2 exposed to walking in the dark towards a narrow doorway to reweight proprioceptive/sensory systems. Person 3 exposed to stepping over obstacles of different heights to train visuo-motor control.

PD, Parkinson disease; VR, virtual reality.

Box 1 - Immersivity in VR

VR technology has the capacity to integrate or ‘immerse’ users into the virtual environment¹⁹. 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 hypothesis¹⁶². 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^{162, 166}. 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 world¹⁶².

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 world¹⁶, such as those that impose a high risk of falls in people with PD. Fully-immersive VR systems use 3D environments, blocking out the perception of the real world, while semi-immersive and non-immersive systems involve varying degrees of perception of both the real world and 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 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.

Box 2. Advantages and disadvantages of VR rehabilitation in PD^a

[b1] Advantages

[b2] Clinical

Promote 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 performance¹⁰² 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}

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 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 program^{98, 99, 102, 109,b}

Provision of real-time multisensory feedback^{98, 102, 109,b}

[b2] 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 lower 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}

[b1] Disadvantages

[b2] Clinical

Physical and cognitive challenges leading 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, 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, reinforcing inappropriate movement strategies^{105,c}

Excessive feedback causing 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}

[b2] Feasibility

Lack of ability to customise recreational systems to ability level, with some games in recreational systems too hard cognitively, motorically or both^{102, 113, 115,b,c}

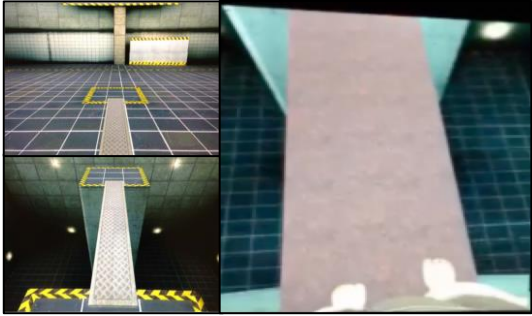
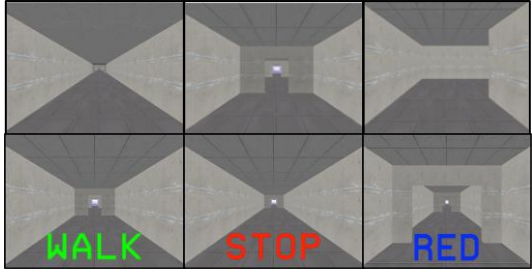
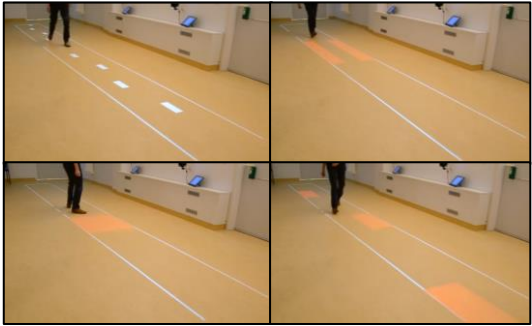
Technical difficulties and difficulty manipulating devices^{105,c}

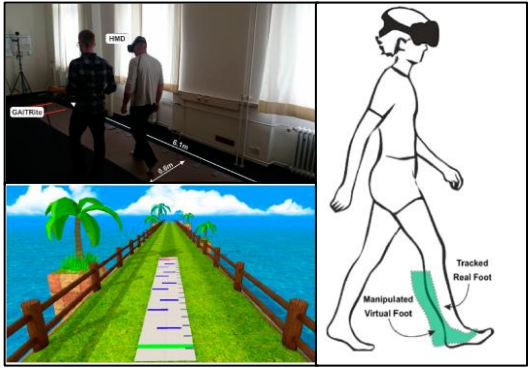

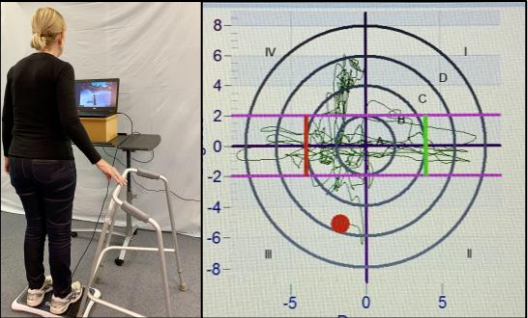
More sophisticated rehabilitation systems are costly and not readily accessible^{105, c}

Difficulty finding physical space for VR system in the home^{113,c}

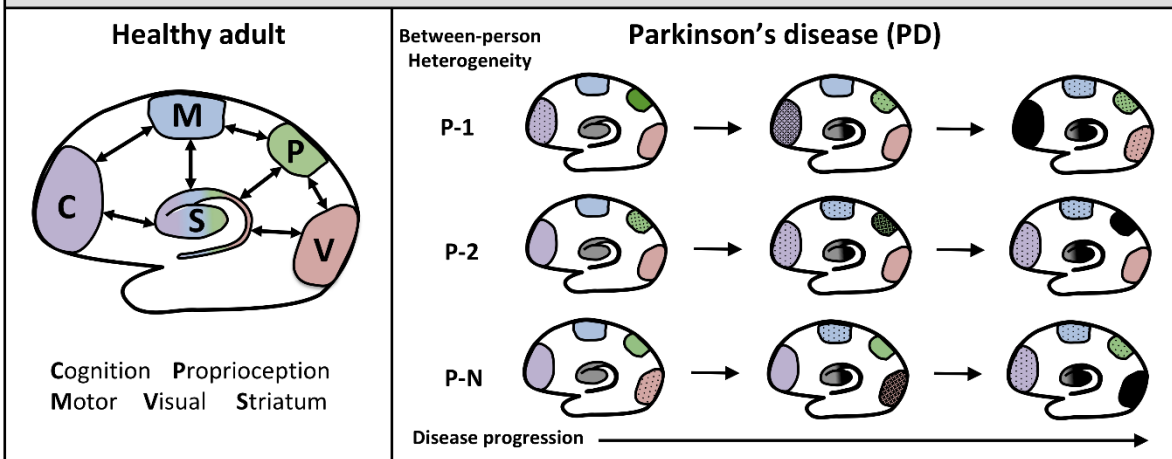
Recreational system visuals can be child-like and therefore less appealing^{115,c}

^aOwing 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. ^bPD rehabilitation literature. ^cNeurological rehabilitation literature. ^dNon-neurologically impaired population literature. PD, Parkinson disease; VR, virtual reality.

A. Understanding impairments			
Type of VR	Modality	Illustrations	Utility
Immersive ⁴⁴	HMD combined with motion tracking and/or other objective measures of gait and physiological status of the user		<ul style="list-style-type: none"> -Perform experiments that are unsafe or too cumbersome in real life, such as a fear of heights paradigm to safely assess 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		<ul style="list-style-type: none"> -Combine with neuroimaging techniques (fMRI) 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		<ul style="list-style-type: none"> -Combine with mobile neuroimaging (EEG/fNIRS) to study the pathophysiology underlying gait and FOG in PD; -Obstacle avoidance with reduced risk for falls due to tripping over obstacles; -Ability to manipulate gait conditions without requiring verbal instructions. -Safety harness can be applied

B. Rehabilitation			
<p>Immersive (customised) (with virtual manipulation creating visual-proprioceptive conflict)^{104*}</p>	<p>HMD (HTC VIVE®) with controllers attached to legs to present visual virtual feet plus pressure sensitive gait mat projected on virtual environment</p>		<ul style="list-style-type: none"> - Aim 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 on that side - Safety harness can be applied
<p>Non-immersive (customised)¹²⁴</p>	<p>Camera-based motion capture (modified Microsoft Kinect) plus virtual environment displayed on screen</p>		<ul style="list-style-type: none"> - Aim to reduce falls in people with PD - Camera records movement of feet while walking and feet are projected in real time into the VR environment on the screen. - VR environment systematically increase size of virtual objects and distractors provide motor-cognitive challenge - Safety harness is used
<p>Non-immersive (commercially available)*</p>	<p>Humac balance system, incorporates software plus balance board, projected onto screen</p>		<ul style="list-style-type: none"> - Aim to assess and train balance, where balance training tasks are tailored to assessment results - Safety harness or stable support (walking frame) can be applied

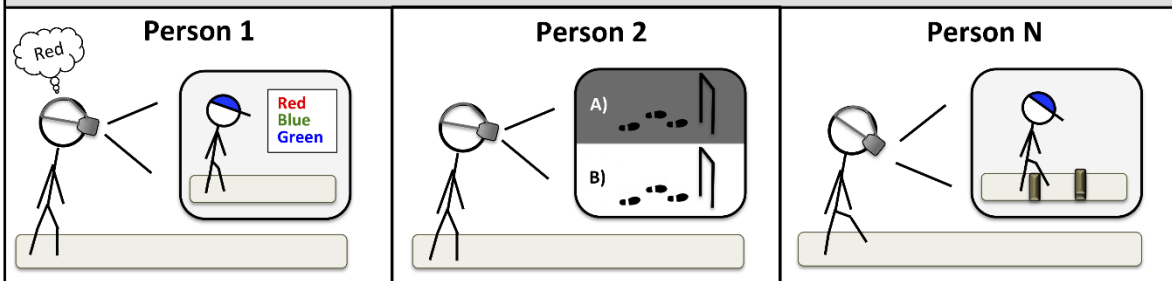
A) Sensory-cognitive-motor integration during gait and balance in healthy and PD



B) Using VR to disentangle sensory-cognitive-motor deficits and compensation in PD



C) Personalised VR rehabilitation designed to the evolving needs of each person



Supplementary Table 1: Pros and cons of neuroimaging techniques for studying PD gait and balance

Type	Subtype	Pros	Cons
<i>Cortex only</i>			
fNIRS	NA	Mobile (measurement during actual gait and balance tasks)	Does not cover subcortical structures involved in gait and balance Limited spatial resolution
EEG	NA	Good temporal resolution	Sensitive to motion artefact
<i>Whole brain</i>			
Nuclear imaging	PET & SPECT	Whole-brain coverage Sufficient spatial resolution	Invasive and requires radioactive tracers (nuclear imaging) Movement restrictions (supine with head fixed and motionless) Only indirect correlations to gait and balance performance assessed outside the scanner Poor temporal resolution
MRI	Structural & Resting state	Whole-brain coverage Sufficient (resting MRI) to excellent (structural MRI) spatial resolution	Movement restrictions (supine with head fixed and motionless) Only indirect correlations to gait and balance performance assessed outside the scanner Poor temporal resolution
fMRI	Task-based	Whole-brain coverage Records BOLD-responses during actual task performance Good spatial resolution	Movement restrictions (supine with head fixed and motionless) Limited temporal resolution Poor signal to noise ratio

Abbreviations: BOLD, blood oxygen level-dependent; EEG, electroencephalography; fNIRS functional near infrared spectroscopy; fMRI, functional magnetic resonance imaging; NA, not applicable; PD, Parkinson disease; PET, Positron Emission Tomography; SPECT, Single-Photon Emission Computed Tomography.

Supplementary Table 2: Seventeen randomized controlled trials of VR rehabilitation interventions for gait and balance in people with PD

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
De Melo 2018 ¹¹⁹ # Pedro 6 Brazil	H&Y 1-3	13 1 15 2 14 2	Kinect Xbox 360 (Microsoft, Redmond, WA, USA), on treadmill Non-immersive	Virtual reality exergame: Your Shape – Fitness Evolved 2012 – Run the World projected onto a screen in front of the participant. Participant marched on the spot to simulate walking/running in the game (VR) Treadmill (walk or run) (TM) Conventional gait training (including obstacle course, steps, walking with cues) (GT)	Visual – simulated walking/running on the screen Progression NR	20 minutes 3/week 4 weeks	Facility Method NR 100% Physiotherapist supervised	Post-intervention and 1-month follow-up Motor 6 minute walk distance* (VR vs GT, TM vs GT) Gait speed* (VR vs GT, TM vs GT) Gait symmetry Other Heart rate before 6 minute walk test* (VR vs GT^b, TM vs GT^a) Heart rate after 6 minute walk test Blood pressure Oxygen saturation* (TM vs GT^b) BORG Rating of Perceived Exertion* (VR vs GT^b, TM vs GT^b)	Safety NR Feasibility NR Acceptability NR
Feng et al 2019 ¹²⁰ PEDro 7 China	H&Y 2.5-4	14 0 14 0	VR system NR Level of immersion NR	Virtual reality training of balance and walking (VR) Traditional rehabilitation training according to 2014 Chinese guide to treatment of PD (balance exercises in standing and walking; strength, walking and rhythm training; visual, auditory and mirror feedback to train body posture control; in-bed translation training) (TE)	Visual feedback Progression NR	45 minutes 5/week 12 weeks	Facility Method NR 100% Physiotherapist supervised	Post intervention Motor: Berg Balance Scale Timed Up and Go UPDRS-III (motor) Functional Gait Assessment	Safety NR Feasibility NR Acceptability NR

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Ferraz et al 2018 ¹²¹ PEDro 7 Brazil	H&Y 2-3	22 2 25 2 25 5	Kinect Xbox 360 (Microsoft, Redmond, WA, USA) Non-immersive	Virtual reality exergames from Kinect Adventures. (VR) Functional training (balance and strength exercises) (F) Stationary bike (B)	Visual - Full- body motion via avatar on screen Progression NR	50 minutes 3/week 8 weeks	Facility Method NR 100% Physiotherapist supervised	Post intervention Motor: 6 minute walk test 10 m walk Sit to stand time Other: Body Mass Index Abdominal circumference PDQ-39 EuroQol-5D World Health Organisation Disability Assessment schedule 2.0 Geriatric Depression Scale	No adverse events associated with the intervention Feasibility NR Acceptability NR
Gandolfi 2017 ¹²² # PEDro 6 Italy	H&Y 2.5-3	38 2 38 4	Nintendo Wii Fit (Nintendo Inc., Japan) with balance board Non-immersive	Virtual reality balance exergames delivered via telerehabilitation, and a balance board and screen utilising a menu of 10 games focusing on motor and cognitive training (VR). Sensory integration balance training: balance exercises under different sensory conditions (eyes open, blindfolded, visual conflict dome, firm/compliant surfaces, and neck extensions), internal and external perturbations, and dual-tasks progressed over time (SI).	Visual and auditory feedback Progression based on motor-cognitive challenge of games, clinical condition and progress of participant	50 minutes 3/week 7 weeks	VR: One session Facility, then Home via videoconference Individual, (2 participants supervised simultaneously, + caregiver) 100% Physiotherapist SI: Facility Individual 100% Physiotherapist supervised	Post intervention and 1-month follow-up Motor Berg Balance Scale ^{*b} Gait velocity (fast) Dynamic Gait Index Rate of falls (previous month) Other Activities-Specific Balance Confidence Scale PDQ-8	No adverse events Satisfaction same in both groups (satisfaction questionnaire) VR telerehabilitation cost less(€384/participant) than SI (€602/participant)
Lee 2015 ¹²³ ^#~ PEDro 4 Korea	NR Independent ambulation	10 NR 10 NR	Nintendo Wii (Nintendo Inc., Japan) Non-immersive	Virtual reality dance exergame (K-Pop Dance Festival), mimicking avatar on screen (30 mins), plus neurodevelopmental treatment and functional electrical stimulation (45 min) (VR) Neurodevelopmental treatment and functional electrical stimulation (C)	Auditory (heard word 'perfect') and haptic (vibration of controller) for successful performance Progression NR	VR: 75 minutes 5/week 6 weeks C: 45 minutes 5/week 6 weeks	NR	Post intervention Motor Berg Balance Scale [*] Other Modified Barthel Index [*] Beck Depression Inventory [*]	Safety NR Feasibility NR Acceptability NR

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Liao 2015 ¹²⁴ Liao 2015 ¹²⁵ ^#~Y PEDro 7 Taiwan	H&Y 1-3	12 0 12 0 12 1	Nintendo Wii Fit Plus (Nintendo Phuten Co, Ltd, Taiwan) with balance board Non-immersive	Virtual reality exercises and exergames: yoga, strengthening (ankle weights) and balance games (45 min) + treadmill training (15 min) (VR) Traditional exercise: stretching, strengthening (ankle weights) and balance (45 min) + treadmill training (15 min) (TE) Control: fall prevention advice + continued usual physical activity (C)	Visual and auditory feedback. Total score displayed at end of game Progression NR	60 minutes 2/week 6 weeks	Facility Individual 100% Physiotherapist supervised	Post-intervention and 1-month follow up Motor Obstacle crossing stride velocity and length* (VR vs C ^a) (TE vs C ^a) Toe-obstacle clearance Forward maximal excursion* (VR vs C ^a) Sideways maximal excursion* (VR vs C ^c) Forward movement velocity* (VR vs C and TE ^a) (TE vs C ^a) Sideways movement velocity* (VR vs C and TE ^a) (TE vs C ^b) Forward and sideways directional control* (VR vs C ^a) Sensory organisation test* Overall (VR vs C ^a) (TE vs C ^a) Vestibular (VR vs C ^a) (TE vs C ^a) Vision (VR vs C ^a) Somatosensory Timed up and go* (VR vs C ^a) (TE vs C ^a) Level walking velocity and stride length* (VR vs C ^a) (TE vs C ^a) Functional Gait Assessment* (VR vs C ^a) (TE vs C ^a) Lower limb muscle strength* (VR vs C ^a) (TE vs C ^a) Other PDQ-39* (VR vs C ^a) (TE vs C ^c) FES-I* (VR vs C ^a) (TE vs C ^a)	Safety harness used for treadmill training in both exercise groups No adverse events Feasibility NR Acceptability NR

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Mirelman 2016 ^{126~} PEDro 8 Belgium, Israel, Italy, Netherlands, UK	H&Y 2-3 PD subset of larger trial	66 (NR for PD only) 64 (NR for PD only)	VR system with motion capture camera recording footsteps, screen with a virtual environment plus the footsteps projected onto it, and a treadmill. Non-immersive	Virtual reality treadmill training: walking through a virtual environment while negotiating challenges such as obstacles, multiple pathways and distractors – inducing a cognitive load demanding attention, planning, dual- tasking, response selection and processing of auditory and visual stimuli. Treadmill training alone	Visual and auditory KP and KR during training and as a session summary VR Progression: increasing motor and cognitive challenges individualized to participants, via speed of treadmill, duration of walking bouts within a session, size and frequency of virtual obstacles and distractors.	45 minutes 3/week 6 weeks	Facility Individual 100% Trainer supervised	Post intervention and 6 month follow up Motor Gait speed variability and foot clearance^{*a} (during obstacle negotiation) Gait speed variability (during usual walking) Gait speed (during usual walking and obstacle negotiation) 2 minute walk test^{*a} SPPB total SPPB balance^{*a} SPPB gait speed^{*a} SPPB sit to stand time Cognitive Attention and executive function Other Rate of falls^{*c} Proportion of repeat fallers Short form-36 physical Short form-36 mental fMRI improvements[*] (during imagined walking with and without obstacles) fNIRS improvements[*] (during walking with and without obstacles and dual-tasks) Attitudes towards fall prevention exercise^{*a} User satisfaction questionnaire	Safety harness used for treadmill training in both groups No adverse events associated with the intervention Feasibility NR Acceptability NR
Maidan 2017 ¹²⁷ PEDro 4	PD subgroup (fMRI)	17 17	As above						
Maidan 2018 ¹²⁸ PEDro 4	PD subgroup (fNIRS)	30 34	As above						
Dockx 2017 ¹²⁹ PEDro 5	Full sample	144 137	As above						
Pedreira 2013 ^{130^} Brazil PEDro 4	H&Y 1-3	22 6 22 6	Nintendo Wii (Nintendo Inc., Japan) Non-immersive	Virtual reality exergames focusing on strength, balance and aerobics Physical therapy: trunk and limb mobilisation, balance, muscle strengthening, rhythmic movement, postural alignment, dual task practice, bimanual tasks, and cardiorespiratory and gait training.	Visual and auditory feedback Progression NR	50 minutes 3/week 4 weeks	NR	Post intervention Other PDQ-39 total PDQ-39 mobility PDQ-39 ADL PDQ-39 Emotional well being PDQ-39 Stigma PDQ-39 Social support PDQ-39 Cognition PDQ-39 Communication PDQ-39 Bodily discomfort	Safety NR Feasibility NR Acceptability NR

Author PEDro Score Country	Population		Intervention	Training	VR Feedback VR Progression	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion					Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Pompeu 2012 ^{131^#} Pedro 5 Brazil	H&Y 1-2	16 0 16 0	Nintendo Wii Fit (Nintendo Inc., Japan) with balance board Non-immersive	Global exercises (30 min) + virtual reality exergame balance exercises, 10 games focusing on motor and cognitive training (30 mins) Global exercises (30 min) + balance exercises (30 min): similar to Wii Fit exercises without the provision of external cues, feedback and cognitive stimulation	Visual and auditory feedback Progression NR	60 minutes 2/week 7 weeks	Facility Individual 100% Physiotherapist supervised	Post-intervention and 2 month follow up Motor Berg balance scale Single leg stand time Cognitive Montreal Cognitive Assessment Motor-cognitive Single leg stand time with dual- task Other UPDRS-2 (ADL)	No adverse events associated with the intervention 100% adherence ^{oo} in both groups Acceptability NR
Ribas 2017 ^{132#} PEDro 7 Brazil	H&Y 1-3	10 0 10 0	Nintendo Wii Fit (Nintendo Inc., Japan) with balance board Non-immersive	Virtual reality balance exergames from a menu of 7 games Conventional exercise including stretching, resistance and diagonal movements	Visual and auditory feedback Progression NR	30 minutes 2/week 12 weeks	Facility Unclear 100% Physiotherapist supervised	Post-intervention and 60 days follow up Motor Berg Balance Scale* ^b 6-minute walk test distance Other Fatigue Severity Scale* ^b PDQ-39 domains (mobility, ADL, social well being, stigma, social support, cognition, communication, bodily discomfort)	No adverse events associated with the intervention Feasibility NR Acceptability NR
Shen 2014 ^{133^#} Shen 2015 ^{134^A} PEDro 7/8 Hong Kong	H&Y 2-3	26 8 25 8	Computerised dancing system (KSD Technology Co Ltd. Shenzhen, China) with dance mat, light- sensitive rods and screen; plus Smart- EquiTest Balance Master with force plate and screen (NeuroCom International Inc, Clackmas OR) Non-immersive	Technology-assisted balance exercises - Facility: reaching and stepping dance mat (15 minutes) and force plate step amplitude (15 minutes) exercises; responding to external perturbations in 4 directions via unexpected stopping and starting on a treadmill, or during overground walking with perturbations delivered by a therapist (30 minutes). Home: practice of balance-demanding activities, e.g. standing up from sitting, turning and walking quickly with large steps (20 minutes). Strength exercises – Facility: lower limb progressive resistance exercises, stepping and walking with leg weights (60 minutes). Home: stepping and walking with leg weights (20 minutes).	Forceplate: visual KP Forceplate and dance mat visual KR– score out of 100% Progression: when score ≥ 80%, speed and/or step amplitude are increased, stepping pattern is changed and/or stepping over an obstacle is added	60 minutes facility sessions 3/week (weeks 1-4 and 9-12); + 20 minutes home sessions 5/week (weeks 5- 8) 12 weeks	Facility and home Facility unclear Home individual Facility 100% Home 0% Overall 55% Physiotherapist supervised	Post intervention, 3 month and 12 month follow up Motor Limit of stability test (movement velocity and end- point excursion) Single leg stance time* ^c (3 & 12 month) Gait velocity (preferred speed) Stride length (preferred speed) * ^a (all time points) Motor control test (speed of response to backwards external perturbation)* ^a (all time points) Other Fall rate* ^a (post and 3 months) Number of fallers* ^a (all time points) Time to first fall Activities-Specific Balance Confidence Scale	Safety harness used during treadmill perturbations No adverse events associated with the intervention Adherence ^{oo} the same in both groups: 97% technology group vs 96% strength group

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Shih 2016 ^{135#~Y} PEDro 6 Taiwan	H&Y 1-3	11 10 11 10	Kinect sensor (Microsoft Corporation, Redmond, WA, USA) and screen Non-immersive	Virtual reality exergame balance training using 4 bespoke games (2 x standing reaching tasks, 1 x obstacle avoidance task and 1 x marching task). Conventional balance training using reaching, weight-shifting and marching.	Visual - full- body motion via avatar on screen and score Progression: increasing the amplitude, frequency, speed, complexity and number of hints	50 minutes 2/week 8 weeks	NR NR 100% Therapist supervised	Post intervention Motor Limit of stability test (directional control* , reaction time, movement velocity, endpoint excursion) Single leg stance time Berg Balance Scale Timed Up and Go	No adverse events associated with the intervention 100% adherence ^{oo} in participants who completed the intervention (10 of 11 in each group)
Song 2018 ¹³⁶ PEDro 8 Australia	MDS-UPDRS part III 32 (12)	31 3+6 29 4	Modified StepMania game from Dance Dance Revolution Non-immersive	Exergame dance stepping exercise using a step mat and screen, with cognitive load as 3 different targets required 3 different motor responses. Control: usual care	Visual – word (perfect, good, miss)presented on screen after each step. Numerical score after each trial. Progression: according to participant performance from novice, easy, medium to hard levels.	≥ 15 minutes 3/week 12 weeks	Home Individual 8% Physiotherapist supervised	Post intervention, 6 month follow up for fall rate only Motor Choice stepping (reaction time, movement time, total response time) Functional Gait Assessment Hip abductor muscle power Timed Up and Go^s Gait adaptability (velocity of stride preceding obstacle, target stepping accuracy) Hand reaction time New Freezing of gait Questionnaire Perception of overall change in mobility* and balance Cognitive Montreal Cognitive Assessment Trail Making Tests Part A and B Other Fall rate Falls Efficacy scale - International	One non-injurious fall during VR training Two ceased training due to pre-existing low back pain exacerbated by training 88% completing the intervention progressed in level of game-play 86% overall adherence ^{oo}

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Tollar 2019 ¹³⁷ PEDro 6 Country NR	H&Y 2-3	25 0 25 0 24 0	Kinect Xbox 360 (Microsoft, Redmond, WA, USA) Non-immersive	Virtual reality exergames from Kinect Adventures: 3 games focusing of responding quickly, reaching targets with limbs and whole body, generating and combining movement sequences (VR) Stationary cycling: Spin class, cycling at 110-140 bpm to music in 5-min bouts, interspersed with 1-min freewheeling. (SC) Control: continued usual physical activity (C)	Visual - full- body motion via avatar on screen Progression NR	60 minutes 5/week 5 weeks	Facility Group (4-8 participants) 100% Physiotherapist supervised	Post intervention Motor: Berg Balance Scale* (VR vs SC, VR vs C, SC vs C) Dynamic Gait Index* (VR vs C) 6 minute walk test* (VR vs C, SC vs C) Standing posturography* (wide stance, narrow stance, tandem stance) (VR vs C) BESTest Tinetti Assessment Tool Other: UPDRS-2 (ADL)* (VR vs C, SC vs C) Schwab & England ADL* (VR vs C) Beck Depression Index* (VR vs C, SC vs C) PDQ-39 total + mobility subscore* (VR vs C, SC vs C) EuroQOL-5D* (VR vs C, SC vs C)	No adverse events associated with the intervention 100% adherence ^{oo}
van den Heuvel 2014 ^{138^#} PEDro 8 Netherlands	H&Y 2-3	17 0 16 2	Motek Medical (Motek Medical, Amsterdam, The Netherlands), with force plate and inertial sensors Non-immersive	Virtual reality exergame balance training: 6 games (4 x leaning, 1 x stepping and 1 x sit-to-stand) Conventional balance training	Visual feedback via avatar on screen Points accrued for faster and more accurate performance Progression: via adjustment of sensitivity to movement along each axis and speed, and increase duration of games	60 minutes 2/week 5 weeks	Facility Group – worked in pairs 100% Physiotherapist supervised	Post intervention Motor: Functional Reach Berg Balance Scale Single leg stand time 10 m walk Other: UPDRS (total, motor subscore and posture and gait subscore) Falls Efficacy scale - International PDQ-39 Hospital Anxiety and Depression Scale Multidimensional Fatigue Inventory	No adverse events associated with the intervention Adherence similar in each group with both attending 9 (8 – 10) (median (IQR)) sessions Participants with more advanced disease required some assistance with VR equipment. VR training equipment considered suitable for use in a group setting. Therapists felt participants liked the games and feedback scores.

Author PEDro Score Country	Population		Intervention	Training	VR Feedback	Dose minutes frequency weeks	Delivery Location Method ^v Supervision (%)	Results	
	Disease severity	Initial group sizes Dropouts + discontinue	VR system Level of immersion		VR Progression			Between groups comparisons (significant differences shown in bold)	Safety Feasibility Acceptability of the VR intervention
Yang 2016 ¹³⁹ ^#~Y PEDro 7 Taiwan	H&Y 2-3	11 1 12 1	Custom-made wireless balance board (Cycling and Health Centre of Taichung, Taiwan) + 22-inch touchscreen. Centre of pressure signal used for controlling virtual objects or human avatar Non-immersive	Virtual reality exergame balance training with bespoke games focusing on static posture and dynamic weight shift (3 x basic, 3 x indoor daily tasks, 3 x outdoor daily tasks) Conventional balance training	Instantaneous visual and auditory feedback. Game scores. Progression: sensitivity of balance board adjusted, plus manipulative task and/or standing on foam	50 mins 2/week 6 weeks	Home Individual 100% Physiotherapist supervision	Post intervention and 2 week follow up Motor: Berg Balance Scale Dynamic Gait Index Timed Up and Go UPDRS-III (motor) Other: PDQ-39	Safety NR Feasibility NR 1 participant in the VR group ceased training as they preferred conventional physiotherapy.
Yen 2011 ¹⁴⁰ ^~Y PEDro 7 Taiwan	H&Y 2-3	14 2 14 2 14 6	Custom-made wireless balance board with dual-hinge tiltable foot plate (multiplanar movements) (Cycling and Health Centre of Taichung, Taiwan) + 22-inch touchscreen. Signal from sensor detecting body weight shift used to control the virtual board in the VR environment. Non-immersive	Virtual reality exergame balance training with bespoke exercises (2 x games focusing on weight shifting) (VR) Conventional balance training (B) Control: No physiotherapy (C)	Visual feedback Progression: decreasing weight shifting sensitivity and using reverse mode (direction of weight shift had opposite effect on virtual board in VR environment)	30 mins (10 min warm up, 20 min training) 2/week 6 weeks	Facility NR 100% Physiotherapist supervision	Post intervention and 4 week follow up Motor: Sensory Organisation Test Equilibrium Score SOT-6* (VR vs C ^b) SOT-5* (B vs C ^b) SOT-1 to 4 Sensory Organisation Test Sensory Ratio Vestibular* (B vs C ^b) Somatosensory Vision preference Cognitive: Verbal reaction time (simple subtraction after auditory cue) in sitting Motor-cognitive: Sensory Organisation Test Equilibrium Score with dual task SOT-6* (VR vs C ^b) SOT-5* (B vs C ^b) SOT-1 to 4 Sensory Organisation Test Sensory Ratio with dual task Vestibular* (B vs C ^b) Somatosensory Vision preference Verbal reaction time with a dual task	No adverse events associated with the intervention Therapists needed to assist participants to prevent falls Feasibility NR Acceptability NR

Bold*: statistically significant improvement in the VR-intervention group compared with the comparison group;

Bold[§]: statistically significant improvement in the comparison group compared with the VR- intervention group;

[^] trial included in Dockx (2016) systematic review;

[#] trial included in Wang (2019) systematic review;

[~] trial included in Cano Porras (2019) systematic review;

[‡] trial included in Juras (2019) systematic review

[‡] Method: individual, group or both;

[‡]Improved at both post-test and follow-up;

[‡]Improved at post-test only;

[‡]Improved at follow-up only;

[‡]Supervision (%) = % of sessions supervised/sessions prescribed;

[‡]Adherence = % of sessions completed/sessions prescribed;

Grey shading = primary outcome/s, as identified by authors;

EuroQOL-5D: Euro Quality of Life-5D; FES-I: Falls Efficacy Scale-International; fNIRS: functional near infrared spectroscopy; fMRI: functional magnetic resonance imaging; LOS: Limits of stability test; NA: not applicable; NR: not reported; PEDro – Physiotherapy Evidence Database¹⁴¹; UPDRS-2 (ADL): Unified Parkinson’s Disease Rating Scale- 2 (Activities of Daily Living section); PDQ-39: Parkinson’s disease Questionnaire-39; SPPB: Short Physical Performance Battery

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