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Meta Analysis

Rehabilitation Interventions Using Immersive Virtual Reality for People With Parkinson's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Research into motor rehabilitation using Immersive Virtual Reality [Immersive Virtual Reality] for people with Parkinson's Disease s rapidly growing in popularity. The aims of this review were to investigate the effect of VR interventions on lower limb and upper limb function in people with Parkinson's disease and determine whether the type of virtual reality intervention used influences intervention effect.

Method: Seven databases [PubMed, EMBASE, Scopus, CINAHL, SPORTDiscus, TRIP database, google scholar] were searched using keywords relating to Parkinson's disease, immersive virtual reality and lower limb.

Results: Sixteen articles were included: two randomised controlled trials and fourteen quasi-experimental designs. Augmented reality or immersive virtual reality technologies were used in interventions. Three studies looked at the upper limb, and thirteen the lower limb. For the upper limb, the box and block test was used in two studies but only one produced relevant data for meta-analysis. For the lower limb, six studies had relevant data [gait analysis] for meta-analysis: Using Augmented Reality, cadence, standardised mean difference = -0.08, 95% CI [0.54 to 0.28], I2 = 52%; Length standardised mean difference= -0.00, 95% CI [0.21 to 0.20], I2= 0%; Speed standardised mean difference= -0.08, 95% CI [0.32 to 0.16], I2= 0%. Using Immersive Virtual Reality, cadence standardised mean difference = -0.16, 95% CI [1.89 to 2.21], I2 = 71%; Length standardised mean difference= -0.28, 95% CI [1.73 to 1.13], I2=44%; Speed standardised mean difference= -0.06, 95% CI [1.44 to 1.34], I2=71%.

Conclusion: There is therefore no clear evidence that either Immersive Virtual Reality or Augmented Reality is effective in improving motor function in the lower limb or upper limb. There is no clear consensus on which virtual reality-based approach out of Augmented Reality or Immersive Virtual Reality is the most effective. Moreover, risk of bias is high as many of the studies used non-randomised methods.

KEYWORDS: Parkinson's disease, Rehabilitation, Virtual reality, Augmented reality, gait.

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INTRODUCTION

Parkinson's disease: Parkinson's disease is one of the most common neurodegenerative disorders worldwide [1]. It is mainly associated with a loss of dopaminergic neurons in the substantia nigra pars compacta [2].

Bradykinesia, rigidity, resting tremor, and postural instability are the hallmarks of the disease and have a negative impact upon movement quality, gait and balance, and fall risk [3]. Multidisciplinary input is increasingly recognised as important in Parkinson's disease management [4]. Physiotherapy is encouraged in addition to the well established pharmacological and surgical interventions from the early disease stages onwards [5]. The review by Tomlinson [5], analysed 39 trials involving a total of 1827 participants with Parkinson's disease to determine the effectiveness of physiotherapy. Significant short term benefits were demonstrated for gait, endurance, balance, and global motor function[6].

Considering the progressive nature of the disease, sustained exercise is considered essential to obtain optimal performance and maintain independence in daily life activities [7].

VR/Augmented Reality: Immersive Virtual Reality refers to immersion within a completely virtual environment. It is most easily achieved by taking over a participant's entire peripheral field-of-view via a head-mounted display. Cave Automatic Virtual Environments are also used. The virtual environment is created by a series of room projectors displaying images on the room walls. The images are synchronised to shutter glasses worn by the user to demultiplex the projected stereoscopic views [8]. Virtual reality [VR] is arousing keen interest in the health sector, as it offers many opportunities to improve the assessment and treatment of many health problems [9]. It is playing a growing role in rehabilitation. It is considered to be a potential strategy to improve motor performance, as it uses visual, sensory and auditory information in virtual environments and allows users to increase the duration, intensity and number of repetitions needed to improve the efficiency of exercise [10] rehabilitation programmes. However, the range of relatively diverse descriptions in the literature highlights the lack of standardisation and inconsistency of terminology [11].

We propose that a standardised classification of VR levels should be adopted: VR: low, VR: medium or VR: high. These levels would bring greater clarity to authors, readers and developers. This terminology will be used in this review and is defined as follows:

Low VR: A computer screen with a limited field of vision is presented, involves only one sensory modality.

Medium VR: Projection on a large screen with a wide field of vision, involves one or two sensory modalities.

High VR: Head mounted device or 360 ° projection, involves at least two sensory modalities.

Advances in technology have made it possible to start using immersive virtual reality [High VR] as a therapeutic approach to improving motor function in Parkinson's or other neurological diseases, as well as in physical therapy, acute and chronic pain management, clinical education, cognitive and motor rehabilitation, anxiety management, and communication skills training [12-14].

Augmented reality is a technology that superimposes digital information over objects or places in the real world for the purpose of enhancing the user experience. Augmented reality has the ability to combine reality and digital information [15].

In Augmented Reality, smart glasses have the potential to provide cues in an Augmented Reality overlay on top of a user's visual field. These cues are portable and personalised. Augmented Reality systems range from simple handheld displays showing models superimposed on real-world video images to head-mounted devices that allow wearers to visualise virtual elements superimposed on the surrounding real-world environment [8].

Immersive Virtual Reality and Augmented Reality aim to deceive the brains of patients by making them believe that they are in other places than the real one [16]. These technologies can reduce patient hospitalisation times and costs and increase the number of patients who can be treated at the same time.

Objectives: The objective of this review is to summarise the current best evidence for the effectiveness of Immersive Virtual Reality and Augmented Reality interventions for lower limb or upper limb rehabilitation in people with Parkinson's disease in comparison with 1] conventional interventions, and 2] non-immersive VR interventions. The primary goal is to determine the effect of immersive VR training on gait and balance for the lower limb, gripping for the upper limb. Secondary goals are to examine the effects of VR on global motor function, activities of daily living and quality of life.

METHODS

Criteria for considering studies for this review:

Types of studies: All randomised controlled trials in which at least one of the interventions was an ongoing programme of immersive VR exercise or training were considered for inclusion in the review. We allowed both random and quasi random methods.

Types of participants: We included studies involving participants with a clinically definite diagnosis of idiopathic Parkinson's disease, as defined by Michael T Hayes [17]. We made no restrictions with regard to gender, age, disease duration, or disease severity. We included trials reporting an intervention carried out in a mixed sample of participants if data for participants with Parkinson's disease were provided separately.

Participants with a diagnosis of Parkinson's disease [as defined by the authors of the studies] included those who:

• Had any duration of Parkinson's disease.

• Were any age.

• Had undergone any drug therapy.

• Had undergone any duration of physiotherapy treatment.

Types of interventions: The intervention group had to be treated with Immersive Virtual Reality therapy including 3D glasses [Augmented Reality], helmet or immersive virtual reality, Cave Automatic Virtual Environments system or other device involving at least two sensory modalities.

Types of outcome measures

Primary outcomes: Primary outcomes were assessed using The International Classification of Functioning, Disability and Health as Applied to Parkinson's Disease [18].

The list of outcomes was compared to the Core Set of Outcome Measures from the Academy of Neurologic Physical Therapy [19].

Lower limb:

• **Walking speed**

• **10 or 20 metre walk test[s]-**measures the time in seconds that a person takes to walk 10 or 20 metres, thereby providing a measurement of gait speed [20].

• **Speed [m/s]-** measures the rate of change of position, recorded in metres per second [21].

• **Cadence [steps/min]-** measures the number of steps taken in a given period, which is then converted into the number of steps taken per minute [22].

• **Stride length [m] -** measures the average distance [in metres] between two successive placements of the same foot [22].

• **Step length [m]-** measures the average distance [in metres] between successive foot to floor contacts with opposite feet [23].

• **Freezing of Gait Questionnaire -** validated questionnaire for the assessment of freezing of gait. The questionnaire consists of six items, and scores range from 0 to 24, with higher scores corresponding to more severe freezing of gait [24].

Upper limb [25]:

• **ugl-Meyer Motor Assessment Scale:** The Fugl-Meyer Assessment [FMA] scale is an index to assess sensorimotor impairment

• **Action Research Arm Test:** a 19-item observational measure used by physical therapists and other health care professionals to assess upper extremity performance [coordination, dexterity and functioning]

• **Nine-Hole Peg Test [9HPT]:** used to measure finger dexterity in patients with various neurological diagnoses.

• **Wolf Motor Function Test [WMFT]:** a quantitative measure of upper extremity motor ability using timed and functional tasks.

• **The Purdue Pegboard Test [PPT]:** is considered to be a gold standard measure of manual dexterity and is the one most frequently used in clinical practice

• The Box and Block Test measures unilateral gross manual dexterity. It is a quick, simple and inexpensive test. It can be used with a wide range of populations [26].

Secondary outcomes

The two or six minute walk test [m] measures the number of metres a person can walk in two or six minutes, thereby providing a measurement of walking endurance [20].

For Global motor function: the Unified Parkinson's Disease Rating Scale is designed to assess motor impairment and disability in Parkinson's disease. Higher scores correspond to greater disability [27]

- **Total -** scores range from 0 to 176.
- **Mental -** scores range from 0 to 16.
- **ADL -** scores range from 0 to 52.
- **Motor -** scores range from 0 to 108.

Activities of daily living [ADL]: Physical Activity Scale for the Elderly, Unified Parkinson's Disease Rating Scale part II, Barthel Index of Activities of Daily Living and other measures of ADL function.

Quality of life: history of falls questionnaire, SF-12, SF-36, World Health Organization Quality of Life - BREF [WHOQOL-BREF]

Timing of outcome measures: The time points for outcome assessments were: short-term [immediately after intervention or within three months] and long-term [more than three months from the start of the intervention].

Search methods for identification of studies

Electronic searches: We searched the following electronic bibliographic databases: PubMed, EMBASE, Scopus, CINAHL, SPORT Discus, TRIP database and google scholar, from their inception up to November 2020, without language restrictions. We combined search terms related to Parkinson's disease, virtual reality, immersive, gaming and rehabilitation. The searches were re-run just before the final analyses and further studies retrieved for inclusion.

Searching other resources: In addition to the electronic database search, other potentially eligible studies were identified by reviewing the references of each of the eligible articles.

We searched trials registers such as Clinical Trials. gov [clinicaltrials.gov/] World Health Organization International Clinical Trials Registry Platform [WHO ICTRP] [apps.who.int/trialsearch/]; and manually searched relevant conference proceedings.

Data collection and analysis:

Selection of studies: Two review authors independently screened all search results [title, abstract, and descriptors] to identify studies for possible inclusion in the review. After the initial screening, te twice authors assessed all included trials for eligibility based on the full text. Any disagreements were resolved through discussion or, if necessary, through independent arbitration. Where required, we contacted study authors for additional information.

Data extraction and management: Relevant articles were retrieved and reviewed by three independent review authors to ensure that all included studies met the inclusion criteria.

The following data were extracted:

- Author[s], year of publication and research design
- Study population and sample size
- Virtual reality type
- Comparator types
- Virtual reality dose
- Intervention setting
- Outcomes setting

Assessment of risk of bias in included studies: The PEDro and Cochrane approaches to identifying RCTs of adequate quality led to different sets of trials and different combined treatment estimates from meta-analyses of these trials. A consistent approach to assessing RoB in trials of physical therapy based on the Cochrane RoB tool rather than a summary score from the PEDro scale was adopted [28]. The Risk of Bias 2 [RoB 2] tool is an update to the original risk of bias tool that was launched in 2008 by Cochrane. RoB2 include: Bias arising from randomisation process, bias due to deviations from intended intervention, bias due to missing outcomes data, bias in measurement of the outcome, bias in the selection of reported results, signalling questions answered. "ROB2_IRPG_beta_v7" was used for assessment [29].

Measures of treatment effect: Extracted data were analysed using R Statistic version 3.5.2. [2018-2020], packages "tidyverse" 1.3.0, "meta" 4.15-1, "metafor" 2.4-0. Forest plots were made based on the outcomes to demonstrate the cumulative effect of VR therapy. Continuous data using the same scale and units were presented as mean differences [MD] and 95% confidence intervals [95% CI]. A standardised mean difference or effect size with 95% CI was calculated for other outcome measures.

Assessment of heterogeneity: The heterogeneity of data is assessed with the I^2 statistic. Where I^2 greater than 50% was identified as heterogeneity, studies used the random effects model.

RESULTS

Description of the studies

Results of the electronic search: The systematic search information flow is depicted in Fig. 1. The primary search returned 608 records, and an additional 23 were added through secondary manual searches [search by ascending bibliographies of systematic reviews]. After the elimination of duplicate studies, 414 publications were screened based on a review of the titles and abstracts. A total of 393 articles were excluded [39 no rehabilitation, 292 no Parkinson's, 44 non-immersive, 14 systematic reviews, 1 poster, 3 with study designs not meeting the inclusion criteria]. After eligibility assessment 55 studies consisting of seven observational prospective studies and 48 RCTs [including six studies focused on vaccination] met the inclusion criteria. The full texts of 21 studies were screened and 7 more were excluded as the methods were non-immersive. Subsequently, 14 studies were included in the qualitative synthesis, and 7 studies were included in the quantitative synthesis [meta-analysis].

The characteristics of these studies are given in Table 1.

Included studies: Most of studies included were not randomised clinical trials but had a quasi-experimental design.

Worrall [30] criticises this 'gold standard' conception of randomisation and says it creates the impression that randomisation 'plays a uniquely privileged role' in scientific inquiry and that 'RCTs carry special weight. However, the results of meta analyses based on quasi experimental studies are suspect and require an initial study by study examination that considers and rules out plausible alternative explanations [31].

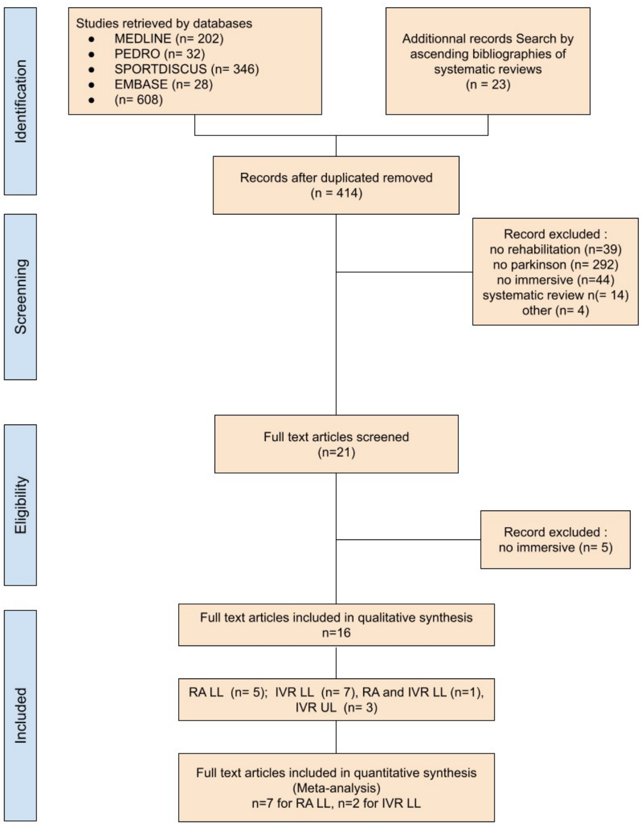

Fig. 1: Flowchart showing the search results of the meta-analysis. RALL = augmented reality lower limb, IVRLL = immersive virtual reality lower limb, IVRUL = immersive virtual reality upper limb.

Table 1: Characteristics of included studies.

Studies	VR system	Limb	Design (Portney Watkins 2015) (Portney & Watkins, 2015)	Intervention	Control	Sample Exp/Con	Outcome
Calabro 2020 (Calabrò et al., 2020)	IVR: CAREN System	lower	Quasi-experimental one group pre-test post-test design	Four virtual scenarios, MMboat, a walk across the board, active balance, road encounters	no CG, compare baseline, paired test	22	10MWT, BBS, FES-I, TUG, UPDRS II and III
Cikajlo 2019 (Cikajlo & Peterlin Potisk, 2019)	Oculus rift	upper	Randomised clinical trial	Training with a pick and place task in the virtual world requiring precise hand movement to manipulate the virtual cubes.	laptop	10-Oct	Box & Blocks Test (BBT), UPDRS
Badarny 2014(Badarny et al., 2014)	AR: glasses, augmented reality	lower	Quasi-experimental one group pre-test post-test design	Walking a straight track of 10 m (baseline and display on), visual cues for steps)	No CG, compare display off/on paired test	20	speed, stride length
Espay 2010 (Espay et al., 2010)	AR: Virtual (augmented) reality goggles	lower	Quasi-experimental one group pre-test post-test design	Visual and auditory feedback, training at home	No CG, compare visual Feedback off/on	6	walk on GAITRite, velocity, stride length, cadence
Gomez 2018 (Gómez-Jordana et al., 2018)	IVR: Oculus rift	lower	Quasi-experimental non-equivalent group design	Walk in virtual environment representing a hallway, six different cue conditions (two spatial only and four spatio-temporal)	CG: healthy people	12/10	Step length, Step cadence, Step velocity
Griffin 2011 (Griffin et al., 2011)	AR: Virtual reality glasses (VRG)	lower	Quasi-experimental one group time series design	Cueing interventions were presented via virtual reality glasses (VRG rhythmic, visual flow and static placebo cues), and as transverse lines (TL) on the walkway	no CG, compared with on/off, paired test	19	task completion time; velocity, cadence, stride length; FoG frequency
Janeh 2019 (Janeh et al., 2019)	IVR: HMD HTC Vive 3D	lower	Quasi-experimental one group pre-test post-test design	Walk 10 m in a virtual environment on the HMD. simple visual targets, multiple visual signals	no CG, compared with baseline, paired test	15	GAITRite: ratio of longer step length/short step length, stride velocity, step time, step width; SSQ
Janssen 2017 (Janssen et al., 2017)	RA: smart glasses system	lower	Quasi-experimental one group pre-test post-test design	15 m walking with cue: 3D augmented transverse bars (AB), 3D augmented staircase (AS)	no CG, compared with baseline, paired test	25	Stride length (m), Cycle time (s), Cadence, Speed (m/s)
Janssen 2020 (Janssen et al., 2020)	RA: holographic augmented reality headset	lower	Quasi-experimental one group time series design	Visual cues for walking and half turn	no CG, compared with switched off system, paired test	16	percent time frozen, number and duration of FOG episodes, maximum head–pelvis separation
Kim 2017 (Kim et al., 2017)	IVR: Occulus rift	lower	Quasi-experimental one group pre-test post-test design	Walk (cityscape with buildings, animated avatars, and an 800 m straight sidewalk)	no CG, compared with baseline, paired test	11	10m walk, speed walk, mini best, cop, SSQ, presence questionnaire
Lheureux 2020 (Lheureux et al., 2020)	VR: HMD (HTC, Vive)	lower	Quasi-experimental one group time series design	Walk in a randomised order under three conditions: Overground Walking (OW), Treadmill Walking (TW), and immersive Virtual Reality on Treadmill Walking (iVRTW)	No CG, compared three conditions, paired test	10	Gait speed, Cadence (steps. min−1), Step length (m), Mean stride duration, SSQ
Messier 2007 (Messier et al., 2007)	IVR: HMD (Virtual Inc. V–8 headset)	upper	Quasi- experimental non-equivalent group design	Asked to point in front of themselves at eye level in the VR environment and feedback on the trajectory in the previous trial.	2 CG: older healthy, young healthy	08-Oct	constant horizontal pointing errors, horizontal constant errors
Penko 2018 (Penko et al., 2018)	IVR: CAREN System	lower	Quasi-experimental one group pre-test post-test design		No CG compared single-task and dual-task conditions, test paired	23	Step cadence (steps/min), velocity (m/s), step length (m), step width (m)
Robles Garcia 2016 (Robles-García et al., 2016)	IVR: head mounted display (HMD)	upper	Randomised clinical trial	4-weeks imitation-therapy imitating full-amplitude movement shown by the avatar	CG: active	08-Aug	Cycle duration (ms), movement amplitude (grades), coefficients of variation (CVcycle-duration)
Sanchez (Sánchez-Herrera-Baeza et al., 2020)	LMC systems mounted	upper	Quasi-experimental one group pre-test post-test design	Four video games with functionalities, such as reaching, grasping, pronation, or different combinations of these	No CG	6	Box and block test BBT, action research arm test (ARAT), client satisfaction questionnaire (CSQ-8)
Tunur 2020 (Tunur et al., 2020)	AR: Google Glasses	lower	Quasi-experimental one group pre-test post-test design	Moving Through Dance modules for three weeks at home	no CG, compared with baseline, test paired	7	Mini-BESTest, Timed Up and Go, Dual-Task, One-Leg Stance, Beck's Depression Inventory

Table 2: Clinical characteristics of Parkinson's disease patients at baseline.

Studies	Age mean (SD)	Hoehn and Yahr Scale	MDS-UPDRS part III, mean (SD)	Duration (SD)	Diagnostic procedure	Visual impairment in inclusion or exclusion criteria
Badarny 2014 (Badarny et al., 2014)	71.25 (NA)	2.5-4	NA	5.7 (NA)	NA	No
Calabro 2020(Calabrò et al., 2020)	66 (±4)	01-Mar	NA	7 (±1.9)	Movement Disorder Society Clinical Diagnostic	absence of disabling sensory alterations
Cikajlo 2020 (Cikajlo & Peterlin Potisk, 2019)	71.3 (±8.4)	02-Mar	NA	6.5 (±2.8)	NA	No
Espay 2010 (Espay et al., 2010)	73.3 (±11.7)	NA	29	12.1 (±4.2)	NA	No
Gomez 2018 (Gómez-Jordana et al., 2018)	63 (±8.6)	NA	30.33 (NA)	5.3 (±2.1)	NA	No
Griffin 2011 (Griffin et al., 2011)	64.1 (±6.73)	mean: 2.34	25.6 (7.9)	NA	PDS Brain Bank criteria	No
Janeh 2019 (Janeh et al., 2019)	67.6 (±7)	NA	15.5 (7.2)	9.5 (±4.9)	UK PD Society Brain Bank criteria	No
Janssen 2017 (Janssen et al., 2017)	72 (NA)	NA	34 (NA)	median 10	UK Brain Bank criteria	severe bilateral visual or auditory impairment
Janssen 2020 (Janssen et al., 2020)	69 range 65-79	NA	38 (NA)	median 11 (3-20)	UK Brain bank criteria	severe bilateral visual or auditory impairment
Kim 2017 (Kim et al., 2017)	65 (±7)	01-Mar	17 (8)	7.0 (±8.7)	NA	No
Lheureux 2020 (Lheureux et al., 2020)	63.7 (±10.6)	NA	24.9 (15)	NA	UK Brain Bank Criteria	no uncorrected visual deficiency
Messier 2007 (Messier et al., 2007)	71 range 61-79	02-Mar	range 25.5 - 48	10.7 (±2.9)	NA	No
Penko 2018 (Penko et al., 2018)	63.7 (±7)	02-Apr	33 (13.1)	6.2 (±4.0)	NA	No
Robles Garcia 2016 (Robles-García et al., 2016)	66 ()	NA	23.2	5.4 (±4.7)	NA	visual dysfunctions
Sanchez 2020 (Sánchez-Herrera-Baeza et al., 2020)	74.50 (±4.72)	02-Apr	NA	NA	Brain Bank of the United Kingdom	No
Tunur 2020 (Tunur et al., 2020)	69 (±5)	02-Mar	42. (9.2)	6.9 (±6.9)	self-reported diagnosis	No

Participants: The patients recruited were people with Parkinson's disease. The average age ranged from 63.0 [37] to 73.3 [36]. Motor impairments were identified either by the Hoehn and Yahr scale or by the -Unified Parkinson's Disease Rating Scale III. The patients were mainly stage 2-3 on the HY scale, although stage 1 [41]and [33], and stage 4 [45] were seen in some studies. The Unified Parkinson's Disease Rating Scale III averages ranged from 23.2 [46] to 42 [48].

Interventions: Two types of hardware environments were used to create virtual environments:

Augmented Reality: The basic concept entails implanting virtual objects in the real visual environment. Specific glasses are required to use as the screen on which virtual objects are implanted, which are known as augmented reality glasses [35,36,38,40,41,48]. Several types of objects can be set up: landmarks on the ground, objects to bypass or step over, directional information.

Immersive Virtual Reality: The basic concept entails modifying the entire visual and auditory environment, and there are two technologies used. The first is 3D projection around the person, such as the Computer Assisted Rehabilitation Environment System [33] [45] . It offers a dual-belt instrumented treadmill mounted on a 6 degrees-of-freedom movable platform, a motion capture system, and immersive and interactive environments. Movements in the various available environments are studied.

The second technology is a virtual reality headset: head Mounted Display [37, 39,42,43,46].

Augmented Reality glasses create a more limited virtual environment but offer the advantage of keeping the real environment as a support and therefore facilitating the transfer of skills. The environment in Immersive Virtual Reality is more varied and richer, resulting in much improved reactions and adaptations but these are less connected to reality.

Excluded studies

Seven studies were excluded:

- Three used a large screen: Mirelman 2010 [49] Park 2011 [50] and Gallagher 2016 [51]

- Ma 2011 [52] assessed the impact of VR on posture compared with reality.

- Melo 2018 [53] used a multimedia projector on a large screen and Kinect Xbox 360.

Risk of bias in included studies

The risk of bias was independently assessed by two authors and discrepancies discussed with a third reviewer, allowing problems to be resolved with a unanimous decision.

An overall overview of the outcomes of the RoB 2 assessment is presented in Figure 2-3. When the analyses were addressed, no study required a third opinion.

Trial Design

Design according to Portney [32] are distributed as follows:

• 2 studies are randomised clinical studies with an experimental group and a control group

• 9 are of the quasi-experimental "one group pre-test post-test design" type

• 2 are "quasi-experimental no equivalent group design"

• 3 are "quasi-experimental one group time series design" studies

As previously stated, the results of meta analyses based on quasi experimental studies are suspect and require an initial study by study examination that considers and rules out plausible alternative explanations [31].

Fig. 2: Risk of bias ROB2, traffic-light plots, green=low risk, yellow=some concern, red=high risk.

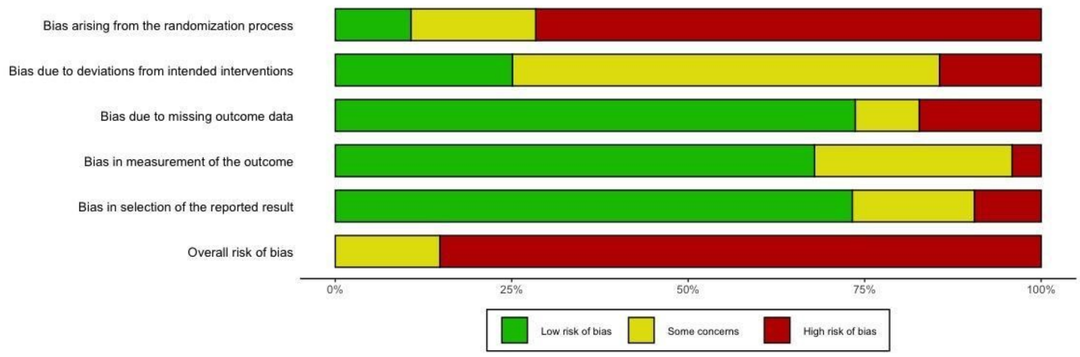

Fig. 3: Risk of bias ROB2, weighted barplots, green=low risk, yellow=some concern, red=high risk.

Sample Size: No studies reported a sample size calculation in the trial report.

Eligibility Criteria: The level of detail provided in the eligibility criteria was variable, with some studies providing a detailed description of the entry criteria, and others just stating "patients with Parkinson's disease." Eight trials stated that a diagnosis of Parkinson's disease was required and specified the origin of the diagnosis. Only five trials stated whether visual impairment was in the inclusion or exclusion criteria.

Randomisation Method and Concealment of Allocation

No randomisation process is described exactly in the studies. Two trials were considered to be "low risk" of bias, two had "some concerns" and the other twelve were considered "high risk".

Blinding of Assessors: It would be impossible to blind participants and therapists to randomised treatment allocation in trials of physiotherapy. Therefore, such trials are open label by nature, and are consequently liable to the possibility of both performance and attrition bias. However, assessors could be blinded to try to reduce the possibility of bias. In five studies the reviewers were blinded, while 10 did not specify whether reviewers were blinded. However, nine studies showed results from computer records [length, pace, walking speed], thus reducing assessor bias.

Data Available for Analysis: No trials were reported as abstracts only. Sufficient data were available for meta analysis for six of the 14 studies.

Seven studies used Immersive Virtual Reality for rehabilitation of the lower extremities [33,37,39,42,-46]. Of these, two studies presented results for walking speed, cadence and stride length that could be used in the meta-analysis. One further trial had relevant data but this could not be extracted as it was available only in graph form.

Six studies used augmented reality [35,36,38,40,41,48]. Of these, five presented results that could be used in the meta-analysis. Two trials had relevant data that could not be extracted as it was available only in graph form [33,36].

Three studies presented results for Immersive Virtual Reality applied to the upper limb, but only one of these produced data that could be used for a meta-analysis.

Effects of interventions

Primary outcomes

VR system used for upper limb: Sanchez 2020 [47] enrolled six patients with Parkinson's disease and calculated Cohen's d to show a medium effect size for jamar, the box and block test [only for the more affected limb] and the Purdue pegboard test. A sense of competition against the machine was perceived as a facilitator by all patients. They concluded that the new treatment in Immersive Virtual Reality did not replace conventional treatment, but rather complemented it.

Cikaljo 2020 [34] compared two randomised groups, Immersive Virtual Reality with head Mounted Display and laptop. The two groups substantially improved their Box and Block Test scores with training. However, there were no statistically significant differences in clinical tests between the groups.

Robles Garcia 2016 [46] suggests that movement imitation therapy enhances the effect of motor practice in patients with Parkinson's disease.

Note that Sanchez and Cikaljo used Box and Block Test but the conditions they compared differ: laptop vs head Mounted Display and physiotherapy vs head Mounted Display.

Only one study of these had suitable data for meta-analysis [Cikajlo [34]]

Immersive Virtual Reality system used for lower limb

Calabro [33] All Parkinson's disease patients underwent 20 conventional physiotherapy sessions followed by 3 months of rest. Then, the patients were provided with 20 sessions of Computer Assisted Rehabilitation Environment System. All patients completed both of the rehabilitation programmes without any adverse events. All considered scales improved significantly at the end of both rehabilitation programmes. Patients presented with a greater clinical improvement after the Computer Assisted Rehabilitation Environment System training than after conventional physiotherapy training.

Gomez [37] compared two groups of participants: one group of healthy controls and one group of idiopathic Parkinson's disease patients. Two different types of visual cues were created: one representing step length and the other representing step length and cadence. The results showed that spatial information had a significant effect, indicating a greater improvement in performance in the long step length condition than in normal conditions, and temporal information also had a significant effect.

Janeh [39] compared normal gait with glasses and using a head Mounted Display. Using diving glasses, no statistically difference from baseline was found. Using head Mounted Display, there was a statistically significant difference in cadence, and step time, although not for length and velocity.

Kim [42] compared healthy, older healthy and Parkinson's disease groups performing a twenty minute walk in a virtual city. No adverse effect was noted and the Parkinson's disease group had an increased level of arousal after exposure.

Lheureux [43] compared three conditions: Overground Walking , Treadmill Walking , and immersive Virtual Reality on Treadmill Walking. The study showed a statistically significant difference in cadence and step length [usable data].

Messier [44] compared healthy elderly subjects, healthy young adults and Parkinson's disease patients. No data about gait were provided. The study showed sensorimotor learning impairments in Immersive Virtual Reality.

Penko [45] studied performance on a motor-cognitive task. No data about gait parameters comparing baseline and Immersive Virtual Reality were provided. During dual-task gait, cognitive performance remained unchanged, with no difference found between single and dual-task cognitive scores.

Three studies presented outcomes for lower limb function and activity in a form suitable for inclusion in the meta analysis [38 participants] [39,42,43], and one further study with 49 participants was added for the variable velocity [42].

Comparison 1.1: baseline without Immersive Virtual Reality vs with Immersive Virtual Reality, cadence.

Three studies looked at step cadence in Immersive Virtual Reality in patients with Parkinson's disease [37,39,43]. These three studies involved a total of 38 patients. We did not find a significant difference in step rate with or without the immersive virtual reality system [SDM 0.16, 95% CI [-1.89; 2.21]]. A strong statistically significant heterogeneity was highlighted [I2 = 0.71, p = 0.03]. The results of Lheureux 2020 were very different from those of the other two studies. The parameters were measured in an intervention performed on a treadmill, unlike the other two studies which involved walking on the ground.

Comparison 1.2: baseline without Immersive Virtual Reality vs with Immersive Virtual Reality, step length. Three trials studied the step length with or without Immersive Virtual Reality in patients with Parkinson's disease [37,39,43]. A total of 38 patients were enrolled. We found no significant difference between with Immersive Virtual Reality and without Immersive Virtual Reality in Parkinson's disease patients [standardised mean difference -0.28 , 95% IC [-1.73; 1.16]]. No statistical heterogeneity was highlighted [I2 = 0.40, p=0.17].

Comparison 1.3: baseline without Immersive Virtual Reality vs with Immersive Virtual Reality, velocity Four trials studied velocity with or without Immersive Virtual Reality in patients with Parkinson's disease [37,39,42,43]. A total of 49 patients were enrolled. We found no significant difference between with Immersive Virtual Reality and without Immersive Virtual Reality in Parkinson's disease patients [standardised mean difference -0.06 , 95% IC [-1.46; 1.34]]. A statistical heterogeneity was highlighted [I2 = 0.71, p=0.02].

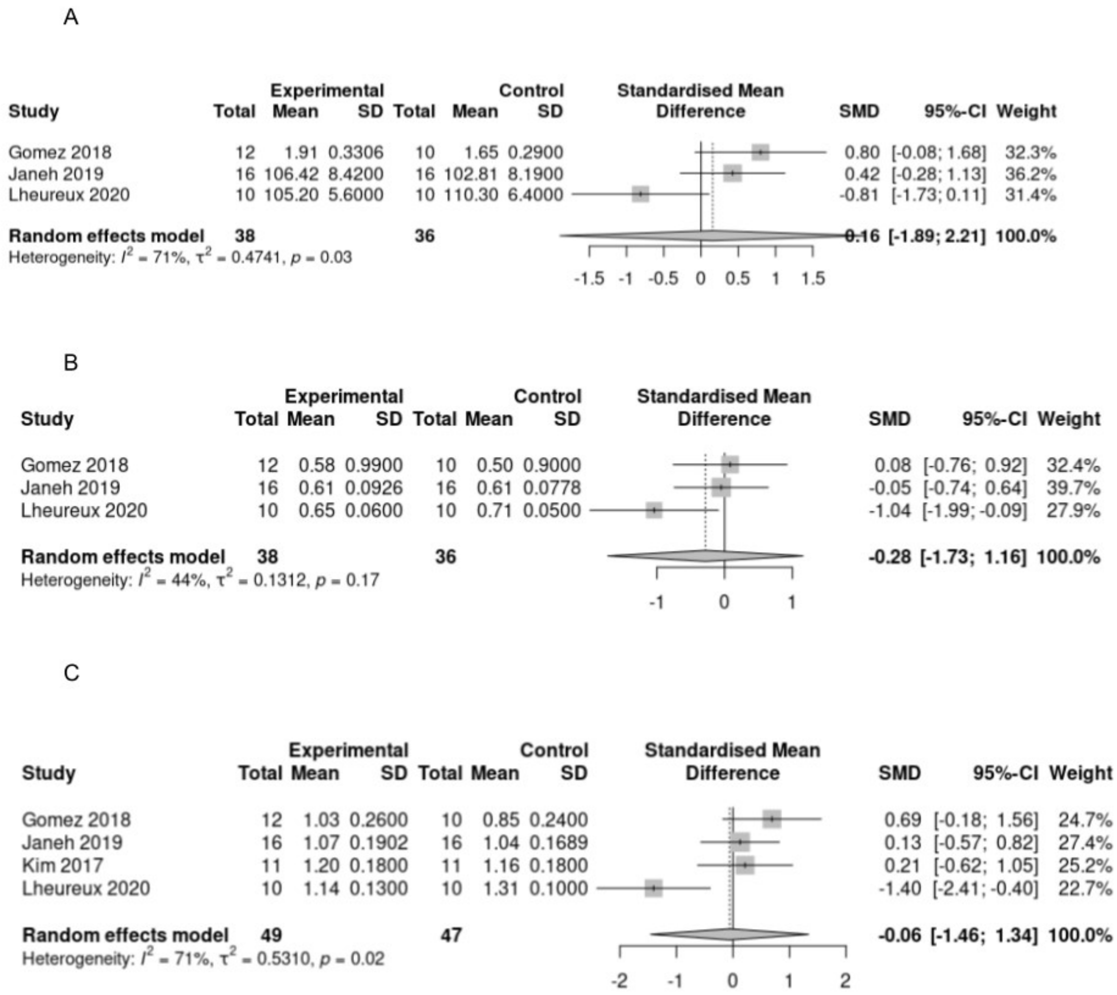

Fig. 4: Meta-analysis, effect of IVR on gait: A=cadence, B=length step, C=velocity

Augmented Reality system used for lower limb

The results are shown in Figure 5.

Badarny compared conditions with and without visual cues [switched on/off], and the data are presented in a table with means but without standard deviation. The author concludes that there was an improvement of 10% for 64% of the participants compared to the baseline, but there was also an improvement with the switched off system compared to the baseline, which puts the switched on effects into perspective. Standard deviations are not presented, and the data were not used for the meta-analysis.

Four studies presented outcomes for lower limb function and activity in a form suitable for inclusion in the meta analysis [123 participants, Espay 2010 [36], two comparisons, Griffin 2011 two comparisons [38], Janssen 2017 [40], Janeh 2019 [39]]. Espay and Griffin compared performances at baseline [without a device] and with placebo [device present but "switched off"]. The data included in the meta-analysis are those from the comparison with "switched off"]. Janeh only presents a comparison with baseline and switched on hardware.

Comparison 3.1 [Figure 5 A]: baseline [without Augmented Reality] vs experimental [with Augmented Reality], cadence.

The impact of Augmented Reality on lower limb function was not significant: standardised mean difference -0.06, 95% confidence interval [CI] [0.35 to 0.28]. No evidence of heterogeneity between the individual trials was obtained [I2 = 0%, P = 0.58]

Comparison 3.2 [Figure 5 B]: baseline [without Augmented Reality] vs experimental [with Augmented Reality], step length.

The impact of Augmented Reality on lower limb function was not significant: standardised mean difference 0.15, 95% confidence interval [CI] [0.25 to 0.55]. No evidence of heterogeneity between the individual trials was obtained [I2 = 32%, P = 0.20].

Comparison 3.3 [Figure 5 C]: baseline [without Augmented Reality] vs experimental [with Augmented Reality], speed.

The impact of Augmented Reality on lower limb function was not significant: standardised mean difference -0.01, 95% confidence interval [CI] [0.12 to 0.13]. No evidence of heterogeneity between the individual trials was obtained [I2 = 0%, P = 0.98].

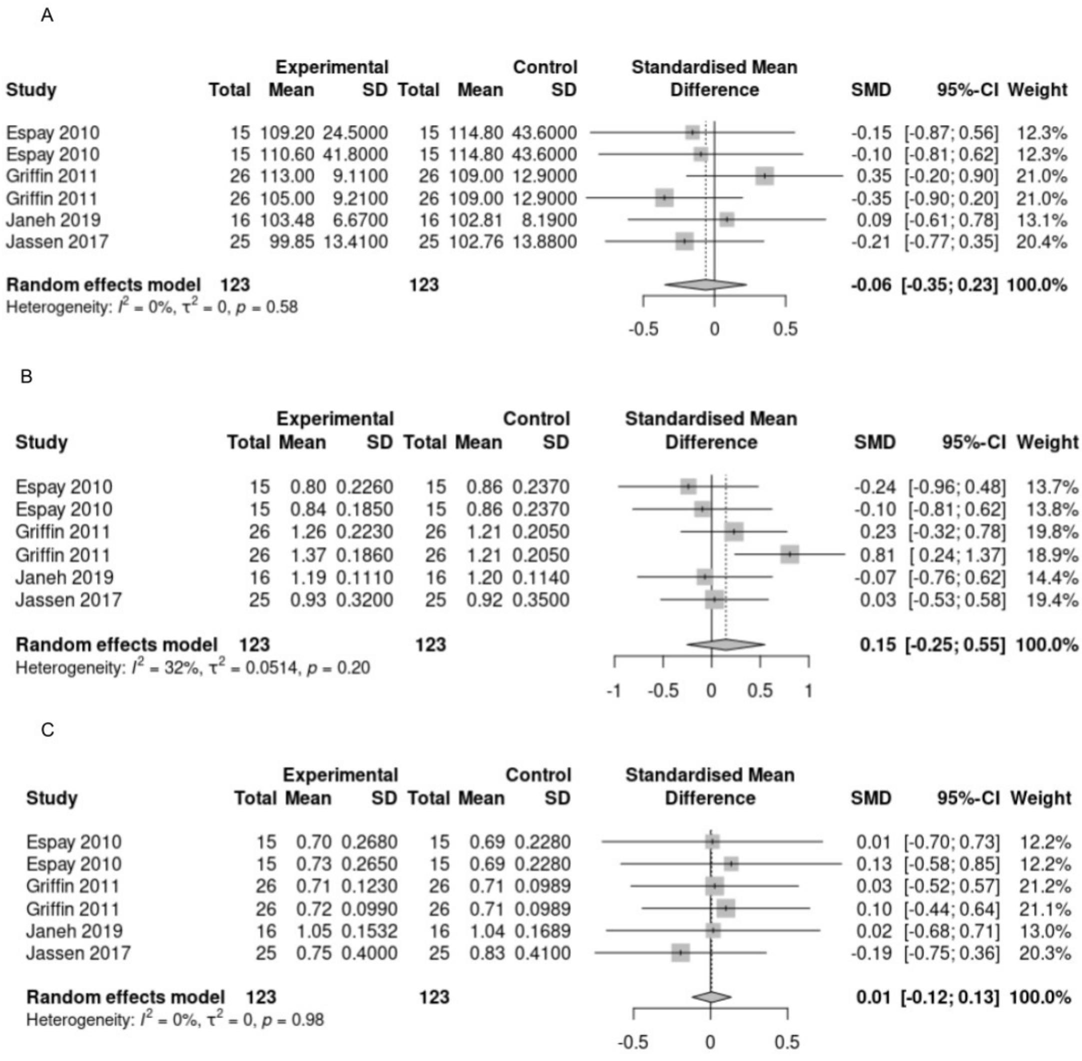

Fig. 5: Meta-analysis, effect of augmented reality on gait: A=cadence, B=length step, C=velocity [speed]

Secondary outcomes

Upper limb: In Sanchez 2020 [47], we find the Action Research Arm Test and PPT [Purdue pegboard test] in pre- and post-test evaluation. Cikajlo 2019 [34] calculated the pre- and post-test effect size using the Unified Parkinson's Disease Rating Scale.

Robles-Garcia 2016 [46] looked at cortico-spinal excitability in addition to the finger tapping test

Lower limb: We noted a great deal of heterogeneity in secondary outcome measures. The Unified Parkinson's Disease Rating Scale III was used in most instances to describe the features of the populations. Only Calabro [33] studied pre-, post-test and intergroup differences using this scale.

Tunur presented pre- and post-test results for the following criteria: mini BESTest, one leg stance, timed up and go test and Beck depression inventory.

The Berg Balance Test and 10MWT were also only used to describe the population [33] Griffin 2011 [38] identified episodes of FOG [freezing of gait] by video.

No data for the secondary outcome measures could be used in the meta-analysis.

DISCUSSION

The Cochrane review of 2016 [54] concluded that "Although the results were inconclusive, low quality evidence indicated that virtual reality [VR] training was at least as effective as conventional physiotherapy." This review looked at virtual reality solutions without distinguishing between immersive and non-immersive devices. The Wii device was the most widely used in the selection of studies looking at stride length, and the authors report that "the effect was medium to large, with a range from 0.51 to 0.86, for speed, the range was: 0.04 to 0.52." The authors also recommend: "Future research should standardise the outcome measures and realise adequate follow up of at least 12 weeks [preferably 12 months] to examine the long term effects of VR".

Santos 2019 [55] specifically examined the use of Wii [non-immersive] looking at balance and quality of life. The authors conclude that traditional physiotherapy combined with Wii use produced better effects but also underline that the studies were methodologically poor.

Chau 2021 [56] selected 28 studies for a literature review including seven using immersive technologies. There was no distinction in the latter group between Augmented Reality and Immersive Virtual Reality solutions and meta-analysis was not possible. The authors conclude that "VR therapy is a promising rehabilitation modality for Parkinson's disease but more studies are needed. Additional investigations of VR therapy and Parkinson's disease should include direct comparisons between immersive and non-immersive VR therapies." The authors think that results in immersive virtual reality were better. Fully immersive Immersive Virtual Reality seemed to achieve a more remarkable clinical improvement than that seen with conventional physiotherapy for gait velocity and stability and step width and length but the meta-analysis did not confirm this point. The Wang 2019 systematic review supported the use of VR to treat balance in people with Parkinson's disease, but found no defined effect on walking with use of virtual reality [57]. It included mainly non-immersive technologies.

No data confirmed the safety of Immersive Virtual Reality in our review.

Making a diagnosis: Seven studies specified the baseline for the diagnosis of Parkinson's in the inclusion criteria. The absence of this information can be confusing. For this reason, the diagnosis of Parkinson's disease must be recorded precisely in the inclusion criteria. There are a certain number of related pathologies which do not present the same reactivity to treatments and the same evolution. Lewy body disease is clinically and pathologically related to classical Parkinson's disease. Pathologically, in addition to the presence of Lewy bodies in the striatum, there is a generalised involvement of Lewy bodies in cortical neurons, while the neurofibrillary tangles and amyloid plaques associated with Alzheimer's disease are relatively rare. [17]. Furthermore, parkinsonism as a side effect of certain drugs is underdiagnosed [57]. It mainly occurs with first generation antipsychotics, many second generation antipsychotics, and can be seen with gastrointestinal prokinetics such as metoclopramide and domperidone [58].

Progressive supranuclear palsy can be initially diagnosed as Parkinson's disease, as early symptoms include difficulty getting up from a chair, sluggish gait and speech changes similar to those in Parkinson's disease. [59]. Over time, it diverges clinically from Parkinson's disease. Multisystem atrophy is a degenerative neurological disease in which several systems are involved [60]. These include the extrapyramidal system, cerebellum and autonomic nervous system. Multisystem atrophy subtypes are clinically determined by their predominant symptoms [61]. Corticobasal degeneration is similar to Parkinson's disease in that it has an asymmetric onset and asymmetric tremors and stiffness [62]. It appears mid to late in life, as does Parkinson's disease. It sometimes takes several years for the diagnosis to be revised when the symptoms change from those of Parkinson's disease. Researchers should be more rigorous about the process and certainty of the diagnosis. It is possible that several pathologies were included in the different studies without the authors' knowledge, constituting a significant bias in the results.

Visual problems and balance disorders: Four out of 16 studies list visual disturbances under inclusion or exclusion criteria without specifying the types of impairment. However, visual problems in Parkinson's patients are numerous. In our review, Messier [44] suggested that the ability to adapt to a sudden biaxial visuomotor discordance applied in three-dimensional space declines in normal ageing and in Parkinson's disease.

In addition, there are strong visual impairments in people with Parkinson's [63]. The following were found in the studies: a decrease in dopaminergic receptors and a thinning of the retina [64] and ocular nerve fibres [65] [66], impairment of eye tracking [67], the appearance of jerky movements [68], impairment of colour perception [69], and finally a decrease in high and low contrast visual acuity [70]. It is possible that these deficiencies were present in the recruited populations, which would explain the lack of evidence for the performance of Augmented Reality or Immersive Virtual Reality systems. The fitting of glasses or head Mounted Display, the restriction of the visual field and the modification of colours and contrasts could be elements that disrupt the motor skills, thus affecting the expected interventions. It would be desirable to study the impacts of virtual environments on sight, possibly adapting them or giving participants more time to get used to them. The Augmented Reality and Immersive Virtual Reality systems may also not be suitable for all Parkinson's disease patients due to these visual disturbances. None of the studies included in the meta-analysis mentioned visual problems as an inclusion or exclusion criteria. Espay and Griffin [36] [38] showed that while there was a progression in training, the recorded performance was better under placebo conditions [device without visual cue] than during the intervention [visual cue on].

Immersive Virtual Reality has also been shown to degrade the performance of postural reactions compared to a virtual environment [71]. This disturbance could be caused by the restriction of the visual field [72], loss of accommodation [73] and lack of self-vision affecting subjective verticality. One of the ways to improve this could be to use an avatar to represent the user's body [74].

Side effects: Motion sickness was often reported in Immersive Virtual Reality but not in Augmented Reality. Lheureux [43] reported that the SSQ total score as well as sub-score was low, varying very little between Treadmill Walk and Treadmill Walk with Immersive Virtual Reality. No patient complained verbally of motion sickness symptoms or discomfort linked to the headset. Kim in a post hoc analysis revealed that the Parkinson's disease group presented higher SSQ scores than healthy young and older groups but no participants verbally reported any symptoms. Janeh found no significant increase of symptoms over the time of the experiment [SSQ]. Gomez, Messier, Penko, Sanchez and Calabro [37] [44] [45] [47] [33] did not report an assessment of motion sickness. This suggests that there may be a small fraction of these populations who may not be good candidates for locomotor training in VR.

Interventions: The heterogeneity of results for virtual reality may be linked to differences in the intervention used by Lheureux [43] and in the other two studies, with people spontaneously performing better on the treadmill than on the floor. Indeed, Parkinson's disease subjects were shown to improve the internal regulation of stride length when walking on a treadmill [75]. Compared with higher-intensity treadmill exercise or resistance exercise, lower-intensity treadmill exercise resulted in the greatest improvement in gait speed [76]. Bello showed that treadmill walking is associated with several EMG differences compared with overground walking. The key finding of this study was that coactivation of the thigh muscles was significantly decreased [37%; p = 0.008] in Parkinson's disease subjects when walking on the treadmill in comparison with overground walking [77].

It is possible that Immersive Virtual Reality is more useful when combined with a treadmill.

Quality of the evidence: This quality of evidence is impacted by several factors.

Only two studies were randomised experimental studies and they did not fully describe their randomisation process.

Assessor blinding is mentioned in five studies, however, many of the measures are dependent on computer systems and do not include the clinical judgement of the assessor.

Regarding sample size, no study offered a calculation based on the detectable minimums of the different tests used and the variance of these variables.

It is therefore impossible to know whether the samples were sufficient to demonstrate the expected effects. The average number of participants in both Augmented Reality and Immersive Virtual Reality studies was small.

The studies are currently of the exploratory type, which explains their quasi-experimental design, so there are no intention-to-treat studies or long-term follow-up studies to assess whether the effects persist.

A variety of rating scales were used in the Augmented Reality and VR studies. This lack of uniformity in protocols and outcomes limited our ability to draw conclusions from these differing studies.

None of the studies included longer-term follow-up.

In view of all these parameters, the quality of the evidence is very low. The statistical significance of findings should be interpreted with caution. Finally, adequately powered future studies with standardised protocols would further improve the available evidence and support for immersive VR as a recommended intervention.

Limitation and Potential biases in the review process: Two review authors further selected relevant articles from this extensive list independently and agreed on a final list of studies to include by consensus between all four review authors. We applied a language restriction, although all the included trials were published in English.

Most studies had a quasi-experimental design. Results based on biased and confounded data, such as quasi experimental studies, are open to alternative explanations that reflect the biases and confounding factors [31].

Authors' conclusion

This systematic review does not allow a conclusion to be drawn on the effects of immersive virtual reality on motor performance in parkinsonian syndromes. The quality of the evidence is very low. Augmented Reality fails to show a clinically relevant effect. Immersive Virtual Reality may lead to improvements in walking parameters, particularly cadence, stride length and velocity, but these results may be affected by unfavourable visual conditions specific to Parkinson's disease.

No adverse effects were reported but none of the studies can show that Immersive Virtual Reality is a safe solution to address the balance of patients with Parkinson's disease.

Further studies are needed. Researchers should incorporate modifications to their approach:

1] A true experimental methodology with a process of randomisation and the comparison of comparable and intention-to-treat groups

2] Numbers calculated on an effect size and the variance of the selected judgment criteria.

3] The use of more homogeneous inclusion and exclusion criteria taking into account the origin of the diagnosis and visual problems.

4] The use of more homogeneous outcome measures.

Declaration of Interest:

The authors declare there are no competing interests.

Contributions:

PP PG conception and design of the study; **PP BF** acquisition of data, **CV PP** analysis of data, **PP PG EL BF** interpretation of data, PP drafting the article; **EL BF BF** revising; **PG PP** final approval of the version to be submitted.

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Conflicts of interest: None

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