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Benefits of virtual reality rehabilitation on neurodegenerative diseases: a systematic review

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Parkinson's disease, cognitive impairment, and multiple sclerosis are neurodegenerative conditions contributing to a huge health burden globally. Virtual reality rehabilitation has emerged as a promising intervention, but its comparative effectiveness across different types of neurodegenerative conditions must be further elucidated. Relevant studies were retrieved from the PubMed database, Cochrane Library, and Web of Science Core Collection database. Randomized controlled trials, meta-analyses, and systematic reviews investigating virtual reality interventions for neurodegenerative diseases were incorporated and evaluated. Following a thorough, methodical, and systematic screening process, 99 high-quality studies were ultimately incorporated. The findings corroborate the efficacy of immersive, semi-immersive, and non-immersive virtual reality interventions in cognitive and motor rehabilitation for patients with neurodegenerative diseases. Virtual reality rehabilitation shows great potential in improving motor function, cognitive function, and quality of life in patients with neurodegenerative diseases. Future research should focus on standardizing protocols and exploring the underlying neurobiological mechanisms to optimize its clinical use.

Neurodegenerative diseases are a class of chronic conditions characterized by a progressive loss of brain cells and their connections, involving the sustained and gradual degeneration of specific vulnerable neuronal populations in the brain or spinal cord. These conditions are classified according to their major clinical presentations as follows: Alzheimer's disease (AD) and related dementias, Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis, spinocerebellar ataxias, and motor neuron disorders[1]. Neurodegenerative diseases persistently damage the brain, spinal cord, or peripheral nerves, adversely affecting cognition, sensation, socio-emotional processing, motor function, and behaviour[2]. The complexity of these diseases and their extensive impact on neurological functions contribute to their growing societal burden.

The 2021 Global Burden of Disease study revealed that the increasing rate of neurological disorders is worsened by population aging. It also highlighted that over the past decade, the proportion of people aged 55 years and older living with disabilities due to PD and AD has continued to rise globally, with over 55 million people living with AD[3,4]. The World Health Organization projected that neurodegenerative diseases will become the second leading cause of death in developed nations by 2040, surpassed only by cardiovascular diseases[5]. The total global cost of dementia exceeded 1.3 trillion USD in 2019, far exceeding the capacity of healthcare systems[6]. By 2030, the global financial burden of dementia is estimated to rise to over 2.8 trillion USD, as reported by the official website of the World Health Organization. In the European Union, neurological disorders ranked third after cardiovascular diseases and cancers representing 13.3% (10.3–17.1) of total disability-adjusted life-years and 19.5% (18.0–21.3) of total deaths[7]. Moreover, patients with neurodegenerative diseases frequently exhibit a marked decline in quality of life, and caregivers confront a range of emotional, economic, and social challenges[8]. These increasing problems underscore the pressing need for novel, effective treatment modalities to support these conditions[9].

Traditional pharmacotherapies and conventional rehabilitation for neurodegenerative diseases have shown modest benefits[10], but they also have some limitations, such as high costs, low engagement, and poor compliance.

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These shortcomings collectively drive the need for more innovative, engaging, and accessible treatment approaches. To address these challenges, virtual reality (VR) rehabilitation has gradually been introduced into clinical practice, and its efficacy has been supported by clinical research[11,12]. By simulating real-life scenarios, VR technology carries therapeutic skills into daily life to enhance patient engagement and provide meaningful feedback. Within the virtual environment, the combined physical and cognitive demands closely mirror the real-world complexity that challenges patients with neurodegenerative diseases. VR systems are highly customizable, enabling therapists to tailor task difficulty to the individual's evolving capabilities, thereby optimizing the challenge level and promoting neuroplasticity. Moreover, the gamified nature of VR rehabilitation enhances patient motivation, adherence, and enjoyment, overcoming the drawbacks of traditional repetitive exercises.

According to the immersion and presence levels[13], VR systems are classified into: a. immersive VR uses head-mounted displays to create interactive synthetic environments with sensory feedback, offering moderate-to-high immersion and high presence at variable costs; b. non-immersive VR employs standard screens for cost-effective solutions such as home rehabilitation; c. semi-immersive VR, which offers greater accessibility and adherence potential, typically combines high-resolution three-dimensional projections on large screens with stereoscopic sound, enabling patients to remain aware of their physical surroundings with moderate sense of presence. Presence is created by task design, communication, and mental involvement. Each VR type serves distinct clinical purposes based on treatment objectives and patient requirements[14,15]. Higher levels of immersion and presence not only enhance motivation but also improve emotional regulation and foster neuroplasticity[16].

VR has emerged in neurorehabilitation as an engaging, interactive, patient-centred, and relatively cost-effective tool that enhances functional recovery[17]. Studies have confirmed that VR rehabilitation has benefits in strength, balance, and walking ability for patients with PD and MS[18–23]. Besides, VR interventions were effective for regaining upper limb capabilities in patients with MS[19,24]. VR-based physical and cognitive training substantially improved cognitive function, daily function, and neural efficiency in patients with cognitive impairment (CI)[25]. Even a short and structured VR intervention can effectively provide emotional well-being in patients with mild CI[12]. However, the extant literature is constrained by patient heterogeneity, technology disparity, and a narrow range of outcomes, and therefore cannot systematically summarize the comprehensive impact of VR rehabilitation on neurodegenerative diseases. Moreover, existing reviews predominantly study the effects of VR on the motor function in a certain type of neurodegenerative disease, lacking comparisons of therapeutic effects among different types of neurodegenerative conditions and exploration of the therapeutic mechanisms. The present study aimed to systematically evaluate the efficacy of VR rehabilitation for neurodegenerative diseases and to provide the mechanistic insights of VR rehabilitation. This systematic review particularly focused on the various benefits of VR rehabilitation at different levels of immersion and presence for patients with neurodegenerative diseases, such as motor function, cognitive function, mood, and quality of life.

Results

A preliminary search identified 560 articles on PD, 1483 articles on CI, and 419 articles on MS as relevant. Following the removal of duplicates, 1198 titles and abstracts were screened. Further review of 1264 full-text articles was conducted, and the final analysis yielded 20 studies on PD, 43 studies on CI, and 36 studies on MS (Fig. 1). Finally, our research team comprehensively evaluated and synthesized 28 systematic reviews and meta-analyses together with 31 RCTs. The designs and results of the studies included in the final review are listed in Tables 1 and 2.

Among the 31 RCTs included in this study, the VR interventions were classified according to their type as immersive, semi-immersive, and non-immersive VR interventions. Immersive VR interventions had only been implemented in RCTs involving individuals with CI, but not in those with PD or MS. None of the included meta-analyses conducted differentiated analyses among immersive, semi-immersive, and non-immersive VR interventions. Hence, meta-analytic findings regarding CI are presented in the immersive VR intervention section, and those for PD and MS are presented in the semi-immersive VR intervention section.

Immersive VR intervention for neurodegenerative diseases

Immersive VR intervention was principally employed in research involving patients with CI. The principal indicators for evaluating the efficacy of immersive VR rehabilitation were the temporal motor test, Korean cognitive assessment, and Montreal cognitive assessment (MoCA). The primary function of these tests is to assess cognitive function in patients with CI. Four RCTs and 12 meta-analyses were included.

Three RCTs compared immersive VR cognitive training with conventional methods[25–27], showing a significant higher score on the Korean cognitive assessment in the VR groups ($MD = 2.23$, $P = 0.01$)[26]. VR training also effectively reduced depression scores ($MD = -1.70$, $P < 0.001$) and improved daily living skills, such as shopping and financial management ($MD = 1.77$, $P = 0.006$)[25]. The VR groups significantly improved executive function ($MD = 26.88$, $P = 0.032$) and increased step frequency during multitasking ($MD = -0.08$, $P = 0.018$), indicating enhanced information processing capacity[27]. Baldimtsi et al.[28] found that VR intervention was superior to bicycle exercise for overall cognition with medium effect ($0.06 < \eta^2_p < 0.14$, $P = 0.006$), particularly in verbal learning, memory strategies, and short-term recall. VR therapy significantly boosted executive function and task-switching with medium effect ($0.06 < \eta^2_p < 0.14$, $P = 0.016$) compared with baseline[28]. These findings suggest that immersive VR rehabilitation training substantially enhances cognitive function of patients with CI.

Three meta-analyses reported that immersive VR rehabilitation had a beneficial effect on patients' memory function[29,30,31]. Yu et al. found that the VR group had better short-term memory than the control group ($MD = 0.64$, 95% CI [0.25, 1.03], $P = 0.001$)[29]. A 2020 meta-analysis also established that immersive VR rehabilitation significantly enhanced patients' overall cognitive function ($SMD = 0.87$, 95% CI [0.33, 1.40], $P = 0.002$) and executive function ($SMD = 1.08$, 95% CI [0.13, 2.03], $P = 0.025$)[30]. Immersive VR rehabilitation significantly enhanced patients' grip strength ($SMD = 0.35$, 95% CI [0.01, 0.69], $P = 0.05$) and balance function ($SMD = 0.79$, 95% CI [0.13, 1.45], $P = 0.02$)[31].

Semi-immersive VR intervention for neurodegenerative diseases

In patients with PD, the clinical effectiveness of semi-immersive VR therapy was primarily measured through three key assessment tools: the Unified Parkinson's Disease Rating Scale (UPDRS) for comprehensive motor symptom evaluation, the Boston Balance Scale (BBS) for balance control, and the Timed Up and Go Test (TUG) for dynamic balance and functional gait ability. Evidence from five RCTs and eight meta-analyses focusing on semi-immersive VR interventions was incorporated in the analysis. Feng et al. showed that the semi-immersive VR group achieved better balance than the traditional rehabilitation group, especially in dynamic balance ($MD = 4.14$, $P < 0.05$)[32]. The VR group also showed greater walking ability improvement ($MD = 0.58$, $P < 0.05$) and higher UPDRS-III scores ($MD = 0.28$, $P < 0.05$)[32]. Another study found that combining VR with neurodevelopmental therapy and electrical stimulation further improved static and dynamic balance ($MD = 1.70$, $P < 0.05$), daily living skills ($MD = 2.40$, $P < 0.05$), and reduced depression ($MD = -1.60$, $P < 0.05$)[33]. These results confirm VR therapy's clinical value in neurological rehabilitation. Seven meta-analyses demonstrated that the VR intervention group exhibited a significantly enhanced balance ability compared with the control group[34–40]. Moreover, the walking function of the VR intervention group was significantly enhanced compared with that of the control group ($MD = -1.66$, 95% CI [−2.74, −0.58], $P = 0.003$)[40].

In patients with CI, the principal indicators for evaluating the efficacy of semi-immersive VR rehabilitation include executive function and MoCA, which were used to assess cognitive function. Three RCTs were included in the analysis. Compared with the treadmill training group, the VR

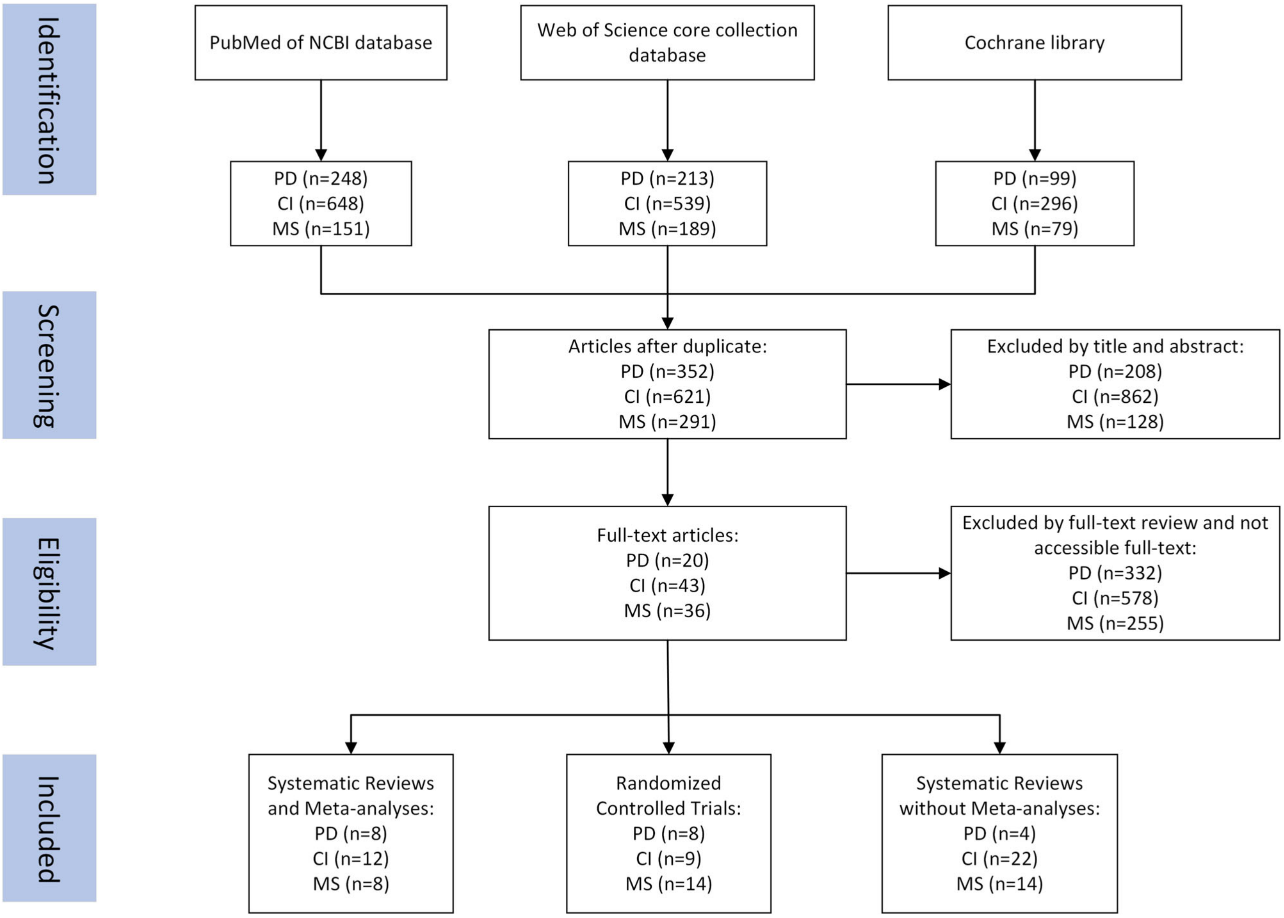

Fig. 1 | Flowchart of article search, exclusion, and analyses. PD Parkinson's disease, CI cognitive impairment, MS multiple sclerosis.

intervention combined with the treadmill training group demonstrated significant advantages in multiple domains, including running speed, obstacle crossing ability, attention, executive function, lower limb function, and balance ability[20]. VR cognitive training group exhibited superior cognitive flexibility, visual–motor tracking ability (MD = 2.70, $P = 0.045$), information processing ability, visual attention ability (MD = -6.10, $P = 0.039$), information execution ability, task switching ability (MD = −6.20, $P = 0.04$), and short-term auditory memory capacity and attention span (MD = 1.10, $P = 0.011$) compared with the traditional cognitive training group[41].

In patients with MS, the principal measures for evaluating the efficacy of semi-immersive VR therapy were Beck Depression Inventory, TUG, and MoCA. Seven semi-immersive RCTs and nine meta-analyses were included in the analysis. Compared with the conventional physical rehabilitation group, the semi-immersive VR rehabilitation group exhibited superior outcomes in terms of overall balance ability (MD = 6.28, $P < 0.05$), vestibular system function (MD = 16.31, $P < 0.05$), motor control ability, and response to sudden disturbances (MD = 13.16, $P < 0.05$)[42]. The benefits of semi-immersive VR rehabilitation were remarkably evident in specific balance assessments (MD = 2.13, $P = 0.03$)[43] and fall risk management (MD = 2.10, $P = 0.009$)[44]. Patients receiving VR intervention reduced fall anxiety (MD = 2.70, $P = 0.021$)[44], and accelerated upper limb muscle strength recovery (MD = 1.68, $P = 0.004$) compared with those receiving conventional cognitive rehabilitation[45]. In addition, the semi-immersive VR group exhibited marked benefits in the improvement of cognitive dysfunction (MD = 1.50, $P < 0.001$), depression risk (MD = −2.00, $P < 0.001$), and visual memory retention (MD = 2.80, $P = 0.008$)[46]. There are two additional studies that support this conclusion[47,48]. A meta-analyses suggested that the balance improvement of the VR intervention group was superior to that of the conventional exercise group[49]. Another study reported that VR intervention was more effective in enhancing balance ability compared with no intervention (SMD = 0.94, 95% CI [0.21, 1.87], $P = 0.02$), and also indicated that the enhancement in walking ability of the VR rehabilitation group were superior to those of the conventional exercise group[50].

Non-immersive VR intervention for neurodegenerative diseases

The effectiveness of non-immersive VR therapy on patients with PD was evaluated using multiple standardized measures: UPDRS for motor symptoms, BBS for daily living activities, TUG for mobility, Parkinson's disease quality of life questionnaire for the assessment of quality of life, and 6-minute walk test for walking capacity. This evaluation incorporated data from three RCTs that investigated non-immersive VR interventions, the results revealed that VR rehabilitation was superior to traditional training in improving both static and dynamic balance and reducing fall risk[51–53].

In patients with CI, the effectiveness of non-immersive VR rehabilitation for cognitive impairment was primarily assessed through two key measures: Korean-Executive Function Performance Test and Korean-Instrumental Activities of Daily Living Scale, which evaluate cognitive function and daily living activities respectively. Findings from two RCTs examining these outcomes were included in the analysis. Choi et al[54]. found that VR-based yoga exercises significantly enhanced walking function (MD = 1.05, $P < 0.001$) and balance function (MD = 3.83, $P < 0.001$) compared with the conventional yoga exercises. The magnitude of these effects was substantial with large effect sizes ($\eta^2_p > 0.14$). Furthermore, the VR-based traditional exercise group showed superior performance in independent living ability (MD = 2.68, $P < 0.001$) and executive function (MD = 9.94, $P < 0.001$) compared with the no-intervention control group[55].

Table 1 | Summary of systematic reviews and meta-analyses of virtual reality for neurodegenerative diseases

First author (year) [ref]	Quality score	Included sample	Patients (number)	Outcomes	Main results
Chen et al., 2020[34]	9, high	14 RCT	PD (574)	(1) BBS (2) Activities-specific balance confidence scale (3) TUG (4) Dynamic gait index	(1) MD = 1.23, 95% CI (0.15, 2.31), $P = 0.03$ (2) NS ($P = 0.44$) (3) NS ($P = 0.76$) (4) NS ($P = 0.48$)
Kwon et al., 2023[35]	10, high	14 RCT	PD (524)	(1) BBS (2) Activities-specific balance confidence scale (3) Dynamic gait index (4) TUG (5) 10-metre walk test (6) 6-minute walk Test (7) Unified Parkinson's disease rating scale (8) Unified Parkinson's disease rating scale-III (9) Parkinson's disease questionnaire	(1) MD = 2.32, 95% CI (1.13, 3.52), $P < 0.001$ (2) MD = 9.43, 95% CI (5.67, 13.19), $P < 0.001$ (3) NS ($P = 0.14$) (4) NS ($P = 0.41$) (5) MD = 0.09, 95% CI (0.01, 0.18), $P = 0.04$ (6) NS ($P = 0.29$) (7) NS ($P = 0.42$) (8) NS ($P = 0.20$) (9) NS ($P = 0.42$)
Wang et al., 2021[36]	10, high	15 studies	PD (569)	(1) BBS (2) TUG	(1) SMD = 0.52, 95% CI (0.31, 0.73), $P < 0.001$ (2) NS ($P = 0.16$)
Wu et al.,2022[37]	10, high	16 RCT	PD (583)	(1) BBS	(1) SMD = 2.13, 95% CI (1.20, 3.05), $P < 0.001$
Sarasso et al., 2021[38]	11, high	22 studies	PD (901)	(1) BBS (2) TUG (3) Walking speed	(1) MD = 2.09,95% CI (0.86, 3.33), $P < 0.001$ (2) MD = 1.55, 95% CI (0.04, 3.06), $P = 0.04$ (3) NS ($P = 0.16$)
Wang et al., 2019[39]	10, high	12 studies	PD (419)	(1) BBS (2) TUG	(1) MD = 2.69, 95% CI (1.37, 4.02), $P < 0.001$ (2) MD = −2.86, 95% CI (− 5.60, −0.12), $P = 0.04$
Lina et al., 2020[40]	8, high	12 RCT	PD (360)	(1) BBS (2) TUG (3) 10-metre walk test (4) Modified Barthel index	(1) MD = 2.28, 95% CI (1.39, 3.16), $P < 0.001$ (2) MD = −1.66, 95% CI (− 2.74, −0.58), $P = 0.003$ (3) MD = 0.13, 95% CI (0.02, 0.24), $P = 0.02$ (4) MD = 2.93, 95% CI (0.8, 5.06), $P = 0.007$
Dockx et al., 2016[23]	9, high	8 trials	PD (263)	(1) Gait (2) Gait speed (3) Step and stride length (4) Balance (5) BBS (6) Parkinson's disease questionnaire	(1) NS ($P = 0.25$) (2) NS ($P = 0.35$) (3) MD = 0.69, 95% CI (0.3, 1.08), $P < 0.01$ (4) NS ($P = 0.08$) (5) NS ($P = 0.30$) (6) NS ($P = 0.21$)
Papaioannou et al., 2022[94]	10, high	15 RCT	MCI (612)	(1) Combined cognitive functioning (2) General cognition memory (3) Memory (4) Attention, processing speed and working memory (5) Executive function (6) Construction and motor performance (7) Verbal function and language	(1) Hedges's g = 1.077, 95%CI (0.71, 1.45), $P < 0.001$ (2) Hedges's g = 0.531, 95%CI (0.26, 0.80), $P < 0.001$ (3) Hedges's g = 1.009, 95%CI (0.27, 1.75), $P = 0.008$ (4) Hedges's g = 1.423, 95%CI (0.92, 1.92), $P < 0.001$ (5) NS ($P = 0.102$) (6) Hedges's g = 1.164, 95%CI (0.03, 2.30), $P = 0.044$ (7) NS ($P = 0.253$)
Hill et al., 2016[95]	11, high	MCI: 17 studies Dementia: 12 studies	MCI (686) Dementia (389)	MCI: (1) Overall cognitive (2) Global cognition (3) Dementia: Overall cognitive	(1) Hedges's g = 0.35, 95%CI (0.20, 0.51), $P < 0.001$ (2) Hedges's g = 0.38, 95%CI (0.14, 0.62), $P = 0.002$ (3) Hedges's g = 0.26, 95%CI (0.01, 0.52), $P = 0.045$
Zuschnegg et al., 2023[96]	11, high	MCI: 18 RCT Dementia: 6 RCT	MCI (924) Dementia (273)	(1) Global cognition	(1) NS ($P = 0.12$)
Wu et al., 2020[30]	10, high	15 RCT	MCI (612)	(1) Overall cognitive function (2) Executive functions (3) Short-term memory (4) Long-term memory	(1) SMD = 0.87, 95%CI (0.33, 1.40), $P = 0.002$ (2) SMD = 1.08, 95%CI (0.13, 2.03), $P = 0.025$ (3) NS ($P = 0.109$) (4) NS ($P = 0.214$)

Table 1 (continued) | Summary of systematic reviews and meta-analyses of virtual reality for neurodegenerative diseases

First author (year) [ref]	Quality score	Included sample	Patients (number)	Outcomes	Main results
Kim et al., 2022[97]	10, high	6 studies	MCI (279)	(1) Global cognition (2) Executive function (3) Working memory (4) Memory (5) Attention	(1) NS ($P = 0.18$) (2) NS ($P = 0.43$) (3) NS ($P = 0.87$) (4) NS ($P = 0.29$) (5) NS ($P = 0.07$)
Yu et al., 2023[29]	9, high	14 RCT	MCI (518)	(1) Working memory (2) Cognitive flexibility (3) Global cognitive function (4) Attention (5) Short-term memory	(1) NS ($P = 0.20$) (2) MD = −42.48, 95%CI (−84.03, −0.92), $P = 0.05$ (3) MD = 0.63, 95%CI (0.06, 1.20), $P = 0.03$ (4) MD = −12.31, 95%CI (− 24.59, −0.04), $P = 0.05$ (5) MD = 0.64, 95%CI (0.25, 1.03), $P = 0.001$
Son et al., 2022[24]	10, high	5 RCT	MCI/ Alzheimer's disease (74)	(1) Instrumental activities of daily living	(1) Hedges's g = 0.558, 95%CI (0.22, 0.90), $P = 0.001$
Zhong et al., 2021[98]	10, high	17 studies	MCI (744)	(1) MoCA (2) Mini-mental state examination (3) Delayed memory (4) Immediately memory (5) Executive function (Trail A) (6) Executive function (Trail B) (7) Attention (Digit Span Forward) (8) Attention (Digit Span Backward) (9) Instrumental activities of daily living	(1) SMD = 1.17, 95%CI (0.93, 1.41), $P < 0.001$ (2) SMD = 0.93, 95%CI (0.64, 1.22), $P < 0.001$ (3) NS ($P = 0.09$) (4) NS ($P = 0.06$) (5) SMD = −0.58, 95%CI (−0.80, −0.35), $P < 0.001$ (6) SMD = −0.33, 95%CI (−0.54, −0.13), $P = 0.002$ (7) SMD = 0.60, 95%CI (0.25, 0.96), $P < 0.001$ (8) SMD = 0.78, 95%CI (0.42, 1.13), $P < 0.001$ (9) NS ($P = 0.96$)
Yan et al., 2022[99]	11, high	7 RCT	MCI (195)	(1) Global cognition (2) Memory (3) Executive function	(1) MD = 2.66, 95%CI (1.79, 3.54), $P < 0.001$ (2) NS ($P = 0.93$) (3) NS ($P = 0.50$)
Ren et al., 2024[31]	10, high	21 RCT	MCI (1138)	(1) Mini-mental State (2) MoCA (3) Trail Making Test A (4) Trail Making Test B (5) Forward Digital Span Test (6) Backward Digital Span Test (7) Gait Speed (8) TUG (9) BBS (10) Hand Grip strength test (11) Instrumental Activity of Daily Living Scale	(1) NS ($P = 0.06$) (2) SMD = 0.50, 95%CI (0.05, 0.95), $P = 0.03$ (3) SMD = −0.38, 95%CI (− 0.61, −0.14), $P = 0.002$ (4) NS ($P = 0.52$) (5) SMD = 1.17, 95%CI (0.46, 1.88), $P = 0.001$ (6) NS ($P = 0.16$) (7) NS ($P = 0.90$) (8) NS ($P = 0.52$) (9) SMD = 0.79, 95%CI (0.13, 1.45), $P = 0.02$ (10) SMD = 0.35, 95%CI (0.01, 0.69), $P = 0.05$ (11) NS ($P = 0.09$)
Mura et al., 2017[100]	11, high	1 RCT	MCI (20)	(1) Global cognitive functioning (2) Attention (3) Executive function (4) Perception (visuo-spatial abilities)	(1) NS ($P = 0.80$) (2) NS ($P = 0.07$) (3) SMD = 0.53, 95%CI (0.16, 0.90), $P = 0.005$ (4) SMD = 0.65, 95%CI (0.37, 0.93), $P < 0.001$
Gómez-Cáceres et al., 2022[15]	9, high	13 RCT	MCI (438)	(1) Global cognitive function (2) Attention (3) Executive function (4) Working memory (5) Immediate memory (6) Delayed memory (7) Language (8) Visuo construction	(1) SMD = 0.30, 95%CI (0.05, 0.56), $P = 0.02$ (2) SMD = 0.27, 95%CI (0.04, 0.49), $P = 0.02$ (3) SMD = 0.60, 95%CI (0.38, 0.81), $P < 0.001$ (4) NS ($P = 0.22$) (5) NS ($P = 0.29$) (6) NS ($P = 0.16$) (7) NS ($P = 0.78$) (8) NS ($P = 0.15$)
Castellano-Aguilera et al., 2022[50]	11, high	16 studies	MS (663)	(1) BBS (2) TUG	(1) Compared to conventional treatment: NS ($P = 0.28$); compared to no-treatment: SMD = 0.94, 95%CI (0.21, 1.87), $P = 0.02$ (2) Compared to conventional treatment: SMD = −0.55,95% CI (−1.07, −0.04), $P < 0.001$; compared to no-treatment: SMD = −0.87, 95% CI (−1.52, −0.23), $P < 0.001$

Table 1 (continued) | Summary of systematic reviews and meta-analyses of virtual reality for neurodegenerative diseases

First author (year) [ref]	Quality score	Included sample	Patients (number)	Outcomes	Main results
Casuso-Holgado et al., 2018[101]	9, high	11 studies	MS (466)	(1) Postural control (2) BBS (3) Tinetti Test (4) Walking speed (5) TUG (6) Four-step square test	(1) Compared to no intervention (bipedal eyes opened): SMD = −0.64, 95%CI (−1.05, −0.24), $P = 0.002$; compared to standard therapy (bipedal eyes opened): NS ($P = 0.90$); Compared to standard therapy (bipedal eyes closed): NS ($P = 0.22$); compared to standard therapy (monopedal eyes opened): NS ($P = 0.54$) (2) Compared to standard therapy: NS (P = 0.55) (3) Compared to standard therapy: MD = −1.98, 95%CI (− 3.17, −0.79), $P = 0.001$ (4) Compared to standard therapy: NS ($P = 0.79$); compared to no intervention: NS ($P = 0.64$) (5) Compared to standard therapy: NS ($P = 0.07$); compared to no intervention: NS ($P = 0.69$) (6) Compared to standard therapy: NS ($P = 0.38$); compared to no intervention: NS ($P = 0.49$)
Keersmaecker et al., 2019[102]	9, high	4 studies	MS (86)	(1) Walking speed (2) Cadence (3) Stride length (4) TUG (5) BBS (6) 6-minute walk test (7) 10-meter walk test	(1) NS ($P = 0.74$) (2) NS ($P = 0.85$) (3) NS ($P = 0.86$) (4) NS ($P = 0.95$) (5) MD = 3.62, 95%CI (1.90, 5.33), $P < 0.001$ (6) NS ($P = 0.56$) (7) NS ($P = 0.19$)
Nascimento et al., 2021[103]	10, high	9 RCT	MS (424)	(1) TUG (2) Multiple sclerosis walking scale (3) Modified fatigue impact scale (4) BBS	(1) VR games associated with exercises compared to traditional exercises: NS ($P = 0.19$); VR games compared to without exercises: NS ($P = 0.91$) (2) VR games compared to traditional exercises: NS ($P = 0.14$); VR games compared to without exercises: NS ($P = 0.69$) (3) VR games compared to traditional exercises: NS ($P = 0.44$); VR games compared to without exercises: NS ($P = 0.93$) (4) VR games compared to traditional exercises: NS ($P = 0.35$); VR games associated with exercises compared to traditional exercises: NS (P = 0.12); VR games associated with exercises compared to without exercises: NS ($P = 0.47$)
Cortés-Pérez et al., 2023[104]	11, high	19 RCT	MS (858)	(1) Function (2) Dynamic balance (3) Therapy on sway area with eyes closed (4) Therapy on CoP with eyes open (5) Confidence of balance (6) Fear of falling (7) Gait speed	(1) SMD = 0.80, 95%CI (0.47, 1.14), $P < 0.001$ (2) SMD = −0.30, 95%CI (−4.83, −0.11), $P = 0.002$ (3) SMD = −0.54, 95%CI (−0.99, −0.10), $P = 0.017$ (4) SMD = −0.25, 95%CI (−0.50, −0.00), $P = 0.048$ (5) SMD = 0.43, 95%CI (0.15, 0.71), $P = 0.003$ (6) SMD = −1.07, 95%CI (−2.00, −0.07), $P = 0.035$ (7) NS ($P = 0.393$)
Calafiore et al., 2021[49]	10, high	7 RCT	MS (209)	(1) BBS	(1) MD = 4.25, 95%CI (3.14, 5.36), $P < 0.001$
Zhang et al., 2024[105]	11, high	10 RCT	MS (461)	(1) Symbol digit modalities test (2) Paced auditory serial addition test (3) MoCA (4) Selective reminding test	(1) NS ($P = 0.841$) (2) SMD = 0.34, 95%CI (-0.26,0.95), $P = 0.018$ (3) WMD = 1.93, 95%CI (0.51, 3.36), $P = 0.007$ (4) NS ($P = 0.571$)
Doherty et al., 2024[106]	9, high	5 RCT	MS (434)	(1) Mobility (2) Balance	(1) SMD = 0.41, 95%CI (0.05, 0.77), $P = 0.02$ (2) SMD = 0.64, 95%CI (0.31, 0.97), $P < 0.001$

RCT randomized controlled trial, *PD* Parkinson's disease, *BBS* berg balance scale, *TUG* timed up and go test, *MoCA* Montreal cognitive assessment, *MCI* mild cognitive impairment, *MS* multiple sclerosis, *MD* mean difference, *SMD* standardized mean difference, 95% *CI* 95% confidence interval, *VR* virtual reality, *NS* No statistical significance.

Table 2 | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
Feng et al., 2019[32]	RCT (6/11)	PD (28)	VR training (45 min, five times/week, 12 weeks)	Conventional physical therapy (45 min, five times/week, 12 weeks)	(1) BBS (2) TUG (3) Functional gait assessment (4) Unified Parkinson's disease rating scale part III	(1) $P < 0.05$ (2) $P < 0.05$ (3) $P < 0.05$ (4) NS (no significant difference)
GoffrEdo et al., 2023[51]	RCT (9/11)	PD (97)	Non-immersive virtual reality-based telerehabilitation (45 min, three-five times/week, 6-10 weeks)	Self-administered structured conventional motor activities at-home (45 min, three-five times/week, 6-10 weeks)	(1) TUG (2) 6MWT (3) Unified Parkinson's disease rating scale part III (4) Mini-BESTest primary outcome (5) Mini-BESTest anticipatory postural control (6) Mini-BESTest reactive postural control (7) Mini-BESTest somatosensory orientation (8) Mini-BESTest dynamic walking	(1) NS (did not differ between groups) (2) NS (did not differ between groups) (3) $P = 0.02$ (4) NS (did not differ between groups) (5) NS (did not differ between groups) (6) NS (did not differ between groups) (7) NS (did not differ between groups) (8) NS (did not differ between groups)
Yang et al., 2016[107]	RCT (8/11)	PD (23)	Custom-made virtual reality balance training (50 min, two times/week, 6 weeks)	Physical rehabilitation (50 min, two times/week, 6 weeks)	(1) BBS (2) Dynamic gait index (3) TUG (4) Parkinson's disease questionnaire-39 (5) Unified Parkinson's disease rating scale part III	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference)
Lee et al., 2015[33]	RCT (6/11)	PD (20)	Virtual reality dance exercise (30 min), neurodevelopment treatment (30 min), functional electrical stimulation (15 min), (five times/week, 6 weeks)	Neurodevelopment treatment (30 min), functional electrical stimulation (15 min) (five times/week, 6 weeks)	(1) BBS (2) Modified barthel index (3) BDI	(1) $P < 0.05$ (2) $P < 0.05$ (3) $P < 0.05$
Gandolfi et al., 2017[52]	RCT (9/11)	PD (76)	Remotely supervised in home VR balance training (50 min, three times /week, 7 weeks)	Sensory integration balance training in-clinic (50 min, three times /week, 7 weeks)	(1) BBS (2) Dynamic gait index (3) Activities-specific balance confidence scale (4) 10MWT (5) Falls (6) Parkinson's Disease questionnaire-8	(1) $P = 0.02$ (2) NS (did not differ between groups) (3) NS (did not differ between groups) (4) NS (did not differ between groups) (5) NS (did not differ between groups) (6) NS (did not differ between groups)
Kashif et al., 2024[108]	RCT (8/11)	PD (60)	VR training and physical therapy (60 min, three times /week, 12 weeks)	Routine physical therapy (60 min, three times /week, 12 weeks)	(1) Unified Parkinson's disease rating scale part III (2) BBS (3) Activities-specific balance confidence scale (4) Unified Parkinson's disease rating scale-part II	(1) as the Mean ± SD at 12th week was 17.20 ± 9.451 with a P-value < 0.001 (2) as the Mean ± SD at 12th week was 50.10 ± 4.897 with a P-value < 0.001 (3) as the Mean ± SD at 12th week was 78.59 ± 6.386 with a P-value < 0.001 (4) as the Mean ± SD at 12th week was 15.30 ± 2.364 with a P-value < 0.001
Liao et al., 2015[109]	RCT (8/11)	PD (36)	VR-based Wii Fit exercise (60 min, two times /week, 6 weeks)	Traditional exercise (60 min, two times /week, 6 weeks)	(1) TUG (2) Parkinson's Disease questionnaire-39 (3) FES-I scores (4) Stride length	(1) $P < 0.001$ (2) $P = 0.004$ (3) $P < 0.001$ (4) $P = 0.003$ (5) $P = 0.011$

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
					(5) Stride velocity (6) Forward movement velocity (7) Sideward movement velocity (8) Sensory organization test (9) Forward maximum excursion (10) Sideward maximum excursion (11) Forward directional control (12) Sideward directional control	(6) $P < 0.001$ (7) $P < 0.001$ (8) $P < 0.001$ (9) $P = 0.023$ (10) $P = 0.011$ (11) $P = 0.001$ (12) $P = 0.006$
Maranesi et al., 2022[53]	RCT (7/11)	PD (30)	Traditional therapy and treatment with the system (50 min, two times/week, 5 weeks)	Traditional therapy (50 min, two times/week, 5 weeks)	(1) Barthel index (2) Performance-oriented mobility assessment total (3) Performance-oriented mobility assessment gait (4) Performance-oriented mobility assessment balance (5) Short Form-12 health survey -To (6) Physical component summary of short form-12 health survey (7) Mental component summary of short form-12 health survey (8) FES-I (9) Gait speed	(1) NS (did not differ between groups) (2) $P = 0.034$ (3) $P = 0.003$ (4) $P = 0.034$ (5) NS (did not differ between groups) (6) NS (did not differ between groups) (7) $P = 0.034$ (8) NS (did not differ between groups) (9) NS (did not differ between groups)
Mirelman et al., 2016[20]	RCT (9/11)	MCI (43)	Treadmill training plus VR (45 min, three times/week, 6 weeks)	Treadmill training alone (45 min, three times/week, 6 weeks)	(1) Gait speed usual walking (2) Gait speed variability usual walking (3) Gait speed obstacle negotiation (4) Gait speed variability obstacle negotiation (5) Leading foot clearance from obstacle during walking (6) 2-minute walk test (7) Executive function index (8) Attention index score (9) SPPB total (10) SPPB chair rise (11) SPPB balance (12) SPPB gait (13) Physical activity scale for the elderly (14) Short form-36 physical total	(1) $P = 0.005$ (2) $P = 0.003$ (3) $P = 0.023$ (4) $P = 0.02$ (5) NS (intergroup difference) (6) NS (intergroup difference) (7) $P = 0.042$ (8) $P = 0.034$ (9) NS (intergroup difference) (10) $P = 0.017$ (11) $P = 0.032$ (12) NS (intergroup difference) (13) NS (intergroup difference) (14) $P = 0.008$ (15) NS (intergroup difference)

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
					(15) Short form-36 mental total	
Park et al., 2020[41]	RCT (7/11)	MCI (40)	Virtual reality-based cognitive–motor rehabilitation (30 min, five times/week, 6 weeks)	Conventional cognitive rehabilitation (30 min, five times/week, 6 weeks)	(1) MoCA trail making test (2) Trail making test part A (3) Trail making test part B (4) Digit span test-forward (5) Digit span test-backward	(1) $P = 0.045$ (2) $P = 0.039$ (3) $P = 0.04$ (4) $P = 0.011$ (5) NS (intergroup difference)
Hsieh et al., 2018[92]	RCT (6/11)	MCI (60)	VR-based Tai Chi (60 min, two times/week, 24 weeks)	No exercise or specific behavioural management training (60 min, two times/week, 24 weeks)	From baseline (T0) to the 3-month intervention (T1) Assessment: (1) 30-s sit-to-stand test (2) Functional reach test From baseline (T0) to the 6-month intervention (T2) Assessment: (1) 6MWT (2) 30-s sit-to-stand test (3) Functional reach test (4) 5-m gait speed	From baseline (T0) to the 3-month intervention (T1) assessment: (1) $P = 0.01$ (2) $P = 0.048$ From baseline (T0) to the 6-month intervention (T2) assessment: (1) $P = 0.001$ (2) $P = 0.002$ (3) $P < 0.001$ (4) $P = 0.009$
Choi et al., 2019[54]	RCT (8/11)	MCI (60)	Virtual kayak paddling exercise (60 min, two times/week, 6 weeks)	Home exercises (60 min, two times/week, 6 weeks)	(1) Medial–lateral sway (i) Eyes open (ii) Eyes closed (2) Anterior–posterior sway (i) Eyes open (ii) Eyes closed (3) Velocity moment (i) Eyes open (ii) Eyes closed (4) Right one-leg stance (5) Left one-leg stance (6) TUG (7) Functional reach test (8) BBS (9) Four-step square test (10) Arm curl test (11) Right handgrip strength (12) Left handgrip strength (13) MoCA (14) General practitioner assessment of cognition	(1) (i) $P = 0.001$ (ii) $P = 0.007$ (2) (i) $P = 0.005$ (ii) $P = 0.008$ (3) (i) $P = 0.046$ (ii) $P = 0.003$ (4) $P = 0.004$ (5) $P = 0.04$ (6) $P < 0.001$ (7) $P = 0.003$ (8) $P < 0.001$ (9) $P < 0.001$ (10) $P < 0.001$ (11) $P < 0.001$ (12) $P = 0.05$ (13) $P = 0.001$ (14) $P = 0.007$
Park et al., 2022[55]	RCT (7/11)	MCI (32)	Virtual shopping training (two times/week, 8 weeks)	No intervention (two times/week, 8 weeks)	(1) Executive function performance test-korean version (2) Korean version of the instrumental activities of daily living	(1) $P < 0.001$ (2) $P < 0.001$
Kim et al., 2023[26]	RCT (6/11)	MCI (60)	VR-based cognitive training program (30 min, two times/week, 12 weeks)	Regular daily activities (30 min, two times/week, 12 weeks)	(1) Korean version of the montreal cognitive assessment (2) Digit span test forward (points) (3) Digit span test backward (points)	(1) $P = 0.01$ (2) $P = 0.01$ (3) $P = 0.01$ (4) NS (intergroup difference) (5) NS (intergroup difference) (6) $P < 0.001$

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
					(4) Korean-Colour word stroop word reading test (points) (5) Korean-Colour word stroop word colour (points) (6) Short geriatric depression scale-korean version (points)	
Liao et al., 2020[25]	RCT (7/11)	MCI (34)	VR-based physical and cognitive training (60 min, three times/week, 12 weeks)	Combined physical and cognitive training (60 min, three times/week, 12 weeks)	(1) MoCA (2) Executive interview-25 (3) Conant visual verbal learning test (4) Immediate recall (5) Delayed recall (6) Instrumental activities of daily living	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) $P = 0.006$
Liao et al., 2019[27]	RCT (8/11)	MCI (42)	VR-based physical and cognitive training (60 min, three times/week, 12 weeks)	Traditional physical and cognitive training (60 min, three times/week, 12 weeks)	(1) Trail making test part A (2) Trail making test part B (3) Change in trail making test time (4) Stroop colour and word Test (5) Single-task gait (6) Speed (7) Dual-task costs: speed (8) Stride length (9) Dual-task costs: stride length (10) Cadence (11) Dual-task costs: cadence (12) Motor dual-task gait	(1) NS (intergroup difference) (2) $P = 0.032$ (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) NS (intergroup difference) (7) NS (intergroup difference) (8) NS (intergroup difference) (9) NS (intergroup difference) (10) NS (intergroup difference) (11) $P = 0.018$ (12) NS (intergroup difference)
Baldimtsi et al., 2023[28]	RCT (6/11)	MCI (122)	Virtual reality training system (45 min, two or three times/week, 12 weeks)	Group 1: bike (45 min, two or three times/week, 12 weeks), Group 2: physical exercise (45 min, two or three times/week, 12 weeks) Group 3: mixed group (physical and cognitive exercise) (45 min, two or three times/week, 12 weeks) Group 4: non-contact control group (patients who did not participate in any intervention program and were passive) (45 min, two or three times/week, 12 weeks)	(1) Mini-Mental state examination (2) Rey auditory verbal learning test-IV (3) Wechsler adult intelligence scale forward (4) Trail making test part B	(1) VR VS CG1: $P = 0.006$, VR VS CG2: NS (intergroup difference), VR VS CG3: NS (intergroup difference), VR VS CG4: NS (intergroup difference) (2) VR VS CG1: $P = 0.007$, VR VS CG2: NS (intergroup difference), VR VS CG3: NS (intergroup difference), VR VS CG4: NS (intergroup difference) (3) VR VS CG1: $P = 0.003$, VR VS CG2: NS (intergroup difference), VR VS CG3: NS (intergroup difference), VR VS CG4: NS (intergroup difference) (4) VR VS CG1: NS (intergroup difference), VR VS CG2: NS (intergroup difference), VR VS CG3: NS (intergroup difference), VR VS CG4: $P = 0.016$
Gutiérrez et al., 2013[110]	RCT (7/11)	MS (50)	Telerehabilitation treatment (20 min, four times/week, 10 weeks)	Physiotherapy treatment (40 min, two times/week, 10 weeks)	(1) Comprehensive evaluation Scale (2) Virtual interaction room (3) Patient-Reported experience of function (4) Virtual environment for stroke therapy (5) Satisfaction rating (6) Motor control test	(1) $P < 0.05$ (2) NS (intergroup difference) (3) $P < 0.05$ (4) $P < 0.05$ (5) NS (intergroup difference) (6) $P < 0.05$

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
Gutiérrez et al., 2013[42]	RCT (6/11)	MS (50)	Monitored telerehabilitation treatment (20 min, four times/week, 10 weeks)	Physiotherapy treatment (40 min, two times/week, 10 weeks)	(1) Comprehensive evaluation Scale (2) Virtual interaction room (3) Patient-Reported experience of function (4) Virtual environment for stroke therapy (5) Satisfaction rating	(1) $P < 0.05$ (2) NS (intergroup difference) (3) $P < 0.05$ (4) $P < 0.05$ (5) NS (intergroup difference)
Lozano et al., 2014[43]	RCT (7/11)	MS (11)	Virtual rehabilitation exercises (60 min, one time /week, 10weeks)	Standard balance and gait rehabilitation exercises (60 min, one time/week, 10weeks)	(1) BBS (2) Tinetti (3) Step length balance left foot (4) Step length balance right foot (5) TUG (6) 10MWT	(1) $P = 0.03$ (2) NS (intergroup difference) (3) NS (intergroup difference) (4) $P = 0.033$ (5) NS (intergroup difference) (6) NS (intergroup difference)
Kalron et al., 2016[44]	RCT (8/11)	MS (32)	VR intervention (30 min, two times/week, 6 weeks)	Conventional exercise program (30 min, two times/week, 6 weeks)	(1) Center of pressure path length (i) Posturography-eyes open (ii) Posturography-eyes closed (2) Sway rate (i) Posturography-eyes open (ii) Posturography-eyes closed (3) Ellipse sway area (i) Posturography-eyes open (ii) Posturography-eyes closed (4) Pressure distribution difference (i) Posturography-eyes open (ii) Posturography-eyes closed (5) Functional reach test (6) BBT (7) The four square step test (8) FES-I questionnaire	(1) (i) NS (intergroup difference) (ii) NS (intergroup difference) (2) (i) NS (intergroup difference) (ii) NS (intergroup difference) (3) (i) NS (intergroup difference) (ii) NS (intergroup difference) (4) (i) NS (intergroup difference) (ii) NS (intergroup difference) (5) $P = 0.009$ (6) NS (intergroup difference) (7) NS (intergroup difference) (8) $P = 0.021$
Peruzzi et al., 2016[111]	RCT (6/11)	MS (25)	Virtual reality treadmill training (45 min, three times/ week, 6 weeks)	Treadmill training (45 min, three times/week, 6 weeks)	(1) Expanded disability status scale score (2) 6MWT (3) 10MWT (4) TUG (5) The four square step test (6) Berg	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) NS (intergroup difference)
Marcos et al., 2023[45]	RCT (10/11)	MS (30)	Treatment based on upper limb serious games and conventional rehabilitation (60 min, two times/week, 8 weeks)	Same conventional rehabilitation for the upper limb (60 min, two times/week, 8 weeks)	(1) Jamar hand dynamometer (2) BBT modified ashworth Scale (3) FSS (4) Abilhand questionnaire (5) MSIS-29 physical impact score (6) Psychological impact score	(1) $P = 0.004$ (2) NS (intergroup difference) (3) NS (intergroup difference) (4) NS (intergroup difference) (5) NS (intergroup difference) (6) NS (intergroup difference)

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
Waliño et al., 2019[112]	RCT (6/11)	MS (16)	Occupational therapy and VR (30 min, two times/week, 10 weeks)	Occupational therapy (30 min, two times/week, 10 weeks)	(1) PPT (2) Jebsen-taylor hand function test (3) Grooved pegboard test	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) NS (intergroup difference)
Cuesta et al., 2020[56]	RCT (7/11)	MS (30)	Conventional motor rehabilitation therapy and leap motion controller (60 min, two times/week, 10 weeks)	Conventional motor rehabilitation therapy (60 min, two times/week, 10 weeks)	(1) Jamar hand dynamometer more affected (2) Jamar hand dynamometer less affected (3) PPT more affected (4) PPT less affected (5) PPT both hands (6) PPT assembly (7) BBT more affected (8) BBT less affected (9) Nine-Hole peg test more affected (10) Nine-Hole peg test less affected (11) MSIS-29 physical score (12) MSIS-29 psychological score (13) FSS	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) $P = 0.032$ (4) NS (intergroup difference) (5) $P = 0.019$ (6) $P = 0.008$ (7) $P = 0.036$ (8) NS (intergroup difference) (9) NS (intergroup difference) (10) NS (intergroup difference) (11) NS (intergroup difference) (12) NS (intergroup difference) (13) NS (intergroup difference)
Goffredo et al., 2023[57]	RCT (9/11)	MS (60)	Motor and cognitive rehabilitation exercises with home telerehabilitation system (45 min, five times/week, 6-8 weeks)	Treatments without the use of any technological devices at home (45 min, five times/week, 6–8 weeks)	(1) Mini-BESTest reactive postural control (2) Mini-BESTest somatosensory orientation (3) Mini-BESTest dynamic walking (4) TUG (5) Timed up and go with dual task (6) MoCA	(1) NS (intergroup difference) (2) NS (intergroup difference) (3) $P = 0.011$ (4) NS (intergroup difference) (5) $P = 0.048$ (6) NS (intergroup difference)
Maggio et al., 2022[47]	RCT (9/11)	MS (60)	Semi-immersive virtual reality training (60 min, three times/week, 8 weeks)	Conventional cognitive training (60 min, three times/week, 8 weeks)	(1) MOCA (2) BDI (3) ROCF copy condition; (4) ROCF immediate recall (5) ROCF delayed recall (6) Selective reminding test (7) PASAT 3 (8) PASAT 2 (9) Contralateral tapping (10) Timed up and go with sit-to-stand (11) Timed up and go with dual task (12) Tinetti balance scale (13) Tinetti gait scale (14) Multiple sclerosis quality of life physical health	(1) $P < 0.001$ (2) $P < 0.001$ (3) $P < 0.001$ (4) $P < 0.001$ (5) $P < 0.001$ (6) $P < 0.001$ (7) $P < 0.001$ (8) $P < 0.001$ (9) NS (intergroup difference) (10) NS (intergroup difference) (11) $P < 0.001$ (12) $P < 0.001$ (13) $P < 0.001$ (14) $P < 0.001$ (15) $P < 0.001$

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
					(15) Multiple sclerosis quality of life mental health	
Pagliari et al., 2021[113]	RCT (9/11)	MS (70)	Home-based virtual reality rehabilitation system training (45 min, five times/week, 10 weeks)	Usual care (30 min, five times/week, 10 weeks)	(1) Mini-BESTest global (2) Anticipatory postural control (3) Reactive postural control (4) Somatosensory orientation (5) Dynamic walking (6) BBT dominant hand (7) BBT non-dominant hand (8) MoCA (9) SDMT (10) Multiple sclerosis quality of life-54 physical health composite score (11) Multiple sclerosis quality of life-54 mental health composite score (12) 9-Hole peg test dominant hand (13) 9-Hole peg test non-dominant hand (14) SDMT-long term storage (15) SDMT-controlled learning and transfer of retrieval (16) 10/36 Selective reminding test (17) PASAT 3 (18) selective reminding test-delayed recall (19) D-10/36-spatial recall test-delayed recall (20) Word list generation (21) 12-Item multiple sclerosis walking scale (22) BDI (23) FSS (24) Resilience scale positive (25) Resilience scale negative (26) State-Trait anxiety inventory form Y1 (27) State-Trait anxiety inventory form Y2	(1) $P = 0.014$ (2) $P = 0.024$ (3) NS (intergroup difference) (4) NS (intergroup difference) (5) $P = 0.020$ (6) NS (intergroup difference) (7) NS (intergroup difference) (8) NS (intergroup difference) (9) NS (intergroup difference) (10) $P = 0.045$ (11) NS (intergroup difference) (12) NS (intergroup difference) (13) NS (intergroup difference) (14) NS (intergroup difference) (15) NS (intergroup difference) (16) NS (intergroup difference) (17) NS (intergroup difference) (18) NS (intergroup difference) (19) NS (intergroup difference) (20) NS (intergroup difference) (21) NS (intergroup difference) (22) NS (intergroup difference) (23) NS (intergroup difference) (24) NS (intergroup difference) (25) NS (intergroup difference) (26) NS (intergroup difference) (27) NS (intergroup difference)
Maggio et al., 2023[46]	RCT (9/11)	MS (106)	Training using semi-immersive VR (60 min, three times/week, 8 weeks)	Traditional therapy (60 min, three times/week, 8 weeks)	(1) MOCA (2) BDI (3) Hamilton anxiety rating scale-anxiety	(1) $P < 0.001$ (2) $P < 0.001$ (3) NS (intergroup difference) (4) $P < 0.001$

Table 2 (continued) | Summary of clinical trials of virtual reality for neurodegenerative diseases

First author (year) [ref]	Design (quality score)	Participants (sample size)	Compare		Outcomes	Main results
			VR group (regimen)	Control group (regimen)		
					(4) Internet addiction test (5) Rey-Osterrieth complex Figure-copy condition (6) Rey-Osterrieth complex Figure-immediate recall (7) Rey-Osterrieth complex Figure-delayed recall	(5) $P < 0.001$ (6) $P < 0.001$ (7) $P < 0.001$
Leonardi et al., 2021[48]	RCT (7/11)	MS (30)	Rehabilitation training with the virtual reality rehabilitation (45 min, three times/week, 8 weeks)	Conventional cognitive rehabilitation (45 min, three times/week, 8 weeks)	(1) MOCA (2) BDI (3) SDMT-long term storage (4) SDMT-controlled learning and transfer of retrieval (5) Selective reminding test (6) SDMT (7) PASAT 3 (8) PASAT 2 (9) SDMT-discrimination (10) Selective reminding test - delayed recall (11) Word list generation (12) Multiple sclerosis quality of life physical health (13) Multiple sclerosis quality of life mental health	(1) $P < 0.001$ (2) NS (intergroup difference) (3) $P < 0.001$ (4) NS (intergroup difference) (5) NS (intergroup difference) (6) NS (intergroup difference) (7) NS (intergroup difference) (8) NS (intergroup difference) (9) NS (intergroup difference) (10) NS (intergroup difference) (11) $P < 0.001$ (12) NS (intergroup difference) (13) $P < 0.001$
Doğan et al., 2023[58]	RCT (7/11)	MS (34)	Virtual reality supported task oriented circuit therapy (60 min, three times/week, 8 weeks)	Mobile application based telerehabilitation (60 min, three times/week, 8 weeks)	(1) TIS-Static sitting balance (2) TIS-Dynamic sitting balance (3) TIS-Coordination (4) TIS-Total (5) International cooperative ataxia rating scale-Kinetic Functions (6) Manual dexterity-dominant hand (7) Manual dexterity-non-dominant hand (8) Mobility-turning (9) Abilhand questionnaire	(1) NS (intergroup difference) (2) $P = 0.001$ (3) NS (intergroup difference) (4) NS (intergroup difference) (5) $P = 0.02$ (6) NS (intergroup difference) (7) NS (intergroup difference) (8) NS (intergroup difference) (9) NS (intergroup difference)

RCT randomized controlled trial, PD Parkinson's disease, *MS* multiple sclerosis, *VR* virtual reality, *BBS* berg balance scale, *TUG* timed up and go test, *6MWT* 6-minute walk test, *10MWT* 10-minute walk test, *Mini-BESTest* mini-balance evaluation systems test, *FES-I* falls efficacy scale-international, *MoCA* Montreal cognitive assessment, *BBT* box and block test, *BDI* beck depression inventory, *FSS* fatigue severity scale, *MSIS-29* multiple sclerosis impact scale-29, *PPT* Purdue pegboard test, *ROCF* Rey-osterrieth complex figure, *PASAT* paced auditory serial addition test, *TIS* trunk impairment scale, *SPPB* short physical performance battery, *SDMT* symbol digit modalities test, *NS* No statistical significance, *CG* control group.

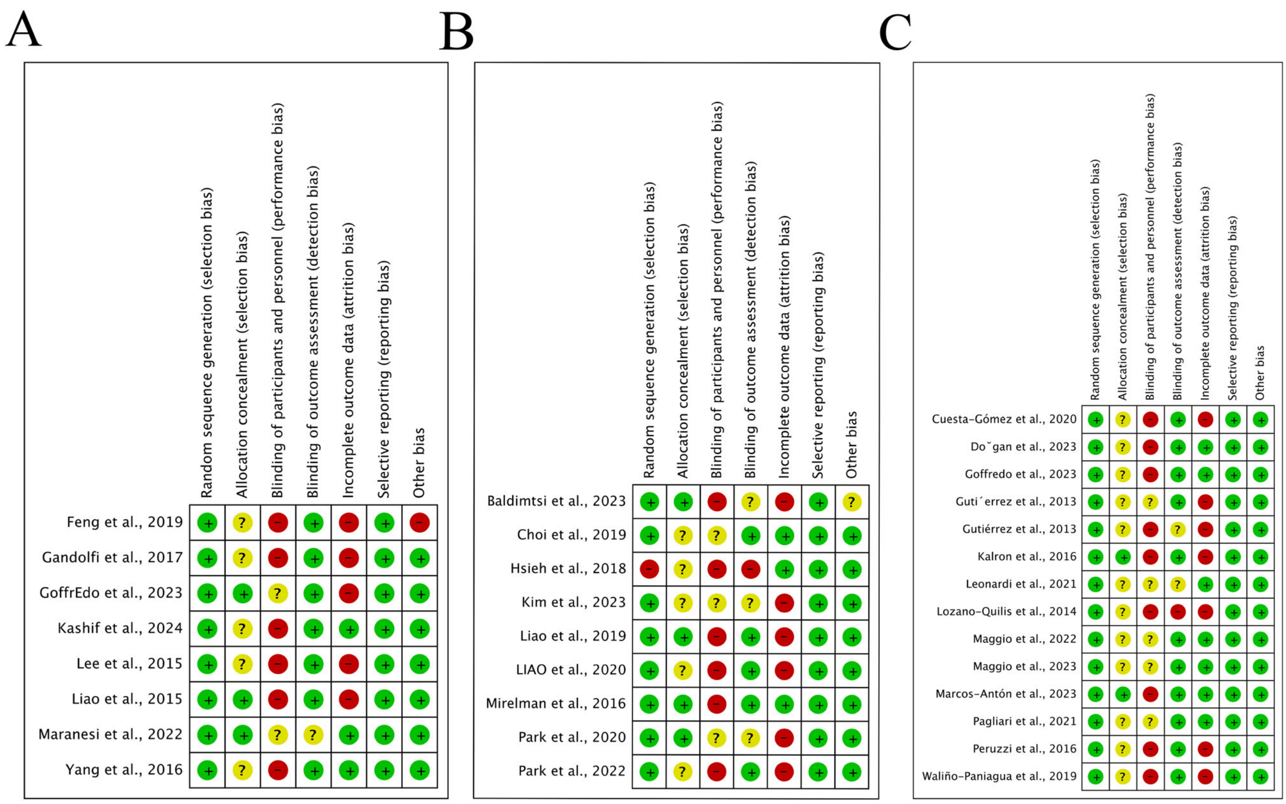

Fig. 2 | Risk of bias in the included randomized controlled trials. **A** Trials included participants with Parkinson's disease. **B** Trials included participants with cognitive impairment. **C** Trials included participants with multiple sclerosis.

In patients with MS, the primary measures for evaluating the efficacy of non-immersive VR therapy included the Purcell–Purcell Test (PPT) for hand fine motor coordination, Center for Depression and Anxiety Scale (CES) for depressive symptoms, and Mini-Balance Evaluation Systems Test for balance function. Seven RCTs were included in the analysis. Two RCTs studies demonstrated that VR-based rehabilitation training exhibited significant advantages in multiple hand function indicators over traditional rehabilitation training[56,57]. The VR intervention group demonstrated enhanced fine motor ability in the affected hand (MD = 1.67, $P = 0.032$)[56]. Compared to the control group, the experimental group showed significant improvements in the following domains: bilateral coordination and cooperative work ability (MD = 5.34, $P = 0.019$), hand function and cognitive–motor integration ability in complex assembly tasks (MD = 7.01, $P = 0.008$), and dexterity and movement speed of the affected hand (MD = 6.00, $P = 0.036$)[56]. Another study established that the VR traditional rehabilitation group exhibited superior outcomes in dynamic sitting balance and trunk adjustment ability, and motor coordination ability compared with the telephone-based remote rehabilitation group[58]. These findings collectively support the promotional role of VR technology in motor function rehabilitation from multiple perspectives, highlighting its consistent advantages across critical functional indicators, including fine motor skills, coordination, and balance.

Reporting bias assessment

A total of 31 RCTs were included in this study, and their methodological quality was evaluated using the PEDro scale (Supplementary Information). The results showed that 23 studies (74.2%) were rated as high quality (score ≥ 7), and 8 studies (25.8%) were rated as moderate quality (score 4–6). No studies were identified as low quality (score ≤ 3). Overall, the methodological quality of the included RCTs was relatively high, indicating satisfactory performance in aspects such as random allocation, baseline comparability, and outcome reporting. However, the main reasons for lower scores in some studies included: lack of implementation or reporting of allocation concealment, inadequate blinding (particularly of subjects and therapists), and absence of intention-to-treat analysis. These factors are common in rehabilitation-related RCTs, where the nature of the interventions (e.g., physical therapy, exercise training) presents practical challenges to implementing complete blinding[59]. Figure 2 shows visually presents the risk of bias in the included RCTs.

This study employed the AMSTAR tool to assess systematic reviews and meta-analyses. A total of 28 studies were included and rated as high quality with AMSTAR scores ranging from 8 to 11 (the highest score). The details are provided in Supplementary Information. Most studies that scored below 11 lost points in the item related to grey literature search, which was rated as "No" or "Can't Answer". The absence of grey literature may lead to publication bias, affecting the comprehensiveness and representativeness of the results. In addition, some studies did not use methods such as funnel plots or Egger's regression to assess publication bias, which may result in an overestimation of the intervention effects.

Discussion

This review evaluated the effectiveness of VR rehabilitation in patients with neurodegenerative diseases, providing a comprehensive analysis of the application of VR rehabilitation in neurodegenerative diseases. A total of 99 studies were included, and VR rehabilitation was mainly applied to patients with PD, CI, or MS. This study demonstrates that immersive VR rehabilitation has benefits in improving cognitive function, alleviating depression risk, and enhancing task execution ability and short-term memory capacity in patients with CI. Semi-immersive VR rehabilitation improves dynamic balance and gait in patients with PD or MS, reduces depression risk in patients with MS, and enhances attention and information-processing ability in patients with CI. Non-immersive VR rehabilitation also improves balance and gait in patients with PD or CI, and enhances physical coordination in patients with MS. Collectively, VR-based interventions exert clinically meaningful benefits across neurodegenerative conditions.

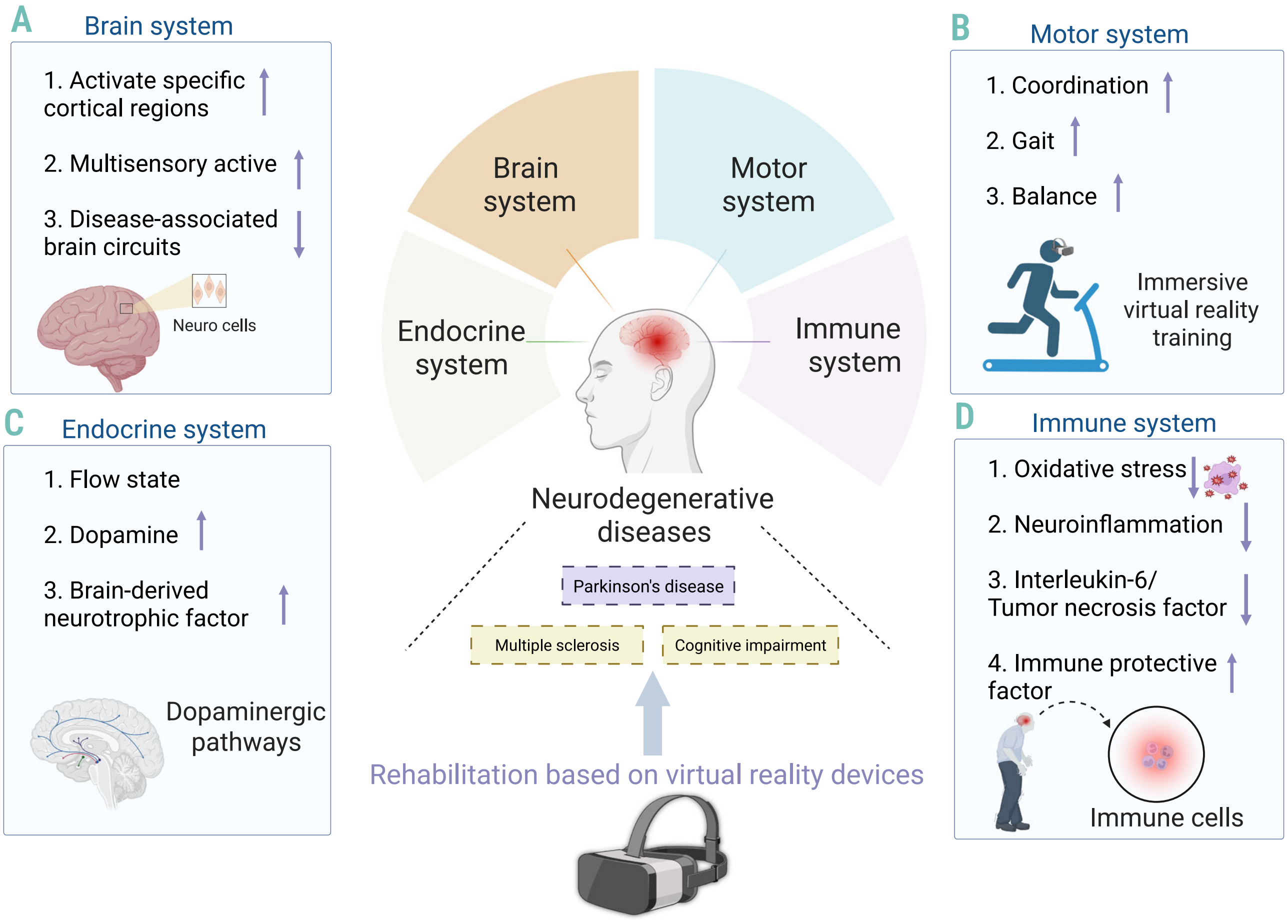

Fig. 3 | Potential therapeutic mechanisms of virtual reality rehabilitation on neurodegenerative diseases.

Our study summarized the four most important mechanisms of VR intervention in the treatment of neurodegenerative diseases, as illustrated in Fig. 3. Based on the functional neuroimaging techniques, long-term cognitive training through VR interventions has been proven to effectively activate specific cortical regions involved in cognitive function[60]. In addition, semi-immersive VR systems can simulate visual and proprioceptive feedback during actual gait. This intervention method has been shown to improve the brain circuit function associated with neurodegenerative diseases (Fig. 3A), including the mesocortical, limbic, and corticobasal ganglia circuits[61]. Calabrò et al. used electroencephalographic technology to demonstrate that VR rehabilitation can engage several brain areas involved in motor planning and learning, thereby enhancing motor performance[62].

Immersive VR intervention provides real-time stimulation through multisensory modalities (including visual, auditory, tactile, olfactory, and gustatory inputs), enhancing participants' sense of reality within the VR environment. This technology can accurately discern the interaction between visual and vestibular systems, thereby facilitating precise evaluations of balance ability[63,64]. The utilization of visual or auditory stimuli in a VR context has alleviated symptoms of freezing gait in patients with PD. Patients with PD exhibit a high degree of dependence on visual cues. The utilization of visual and auditory stimuli has been demonstrated to enhance patients' attention, bringing to an improvement in motor function[65].

In VR rehabilitation, the incorporation of gamified design and multisensory feedback has been instrumental in creating a rehabilitation experience that is enjoyable and challenging for patients with neurodegenerative diseases. VR-based rehabilitation training can substantially enhance coordination, balance, and gait in patients with neurodegenerative diseases (Fig. 3B). Through high-precision motion capture and real-time feedback systems, VR technology can provide personalized training that target core motor deficits such as gait and balance[61,66–69]. Immersive VR environments can simulate walking on different terrains to assist patients in restoring normal gait patterns, thereby significantly enhancing lower limb coordination in patients with moderate-to-severe balance disorders. Grounded in its immersive training scenarios, VR rehabilitation can customize training scenarios (e.g., obstacle avoidance and dual-task training) for patients with neurological disorders to enhance motor–cognitive coordination[70,71]. Clinical studies demonstrated that this adjustable-scenario VR training model is more effective than fixed-mode or single-scenario task training[71–73].

Emotional factors represent a pivotal class of internal factors that significantly influence the mental state of patients diagnosed with PD. Negative emotions exert a substantial detrimental influence on the rehabilitation of patients with neurodegenerative diseases. Highly immersive VR systems effectively modulate emotions, reducing maladaptive negative affects like anxiety and fear while enhancing motivation and engagement in rehabilitation training[74]. This enhanced sense of reality promotes emotional expression, thereby enhancing patients' motivation to engage in training[63]. The flow state holds particular significance in the rehabilitation of patients diagnosed with PD. In the flow state, patients experience intrinsic pleasure and satisfaction, which stimulates dopamine release[75]. As a key neurotransmitter, dopamine regulates emotions and maintains dynamic balance in patients with PD[76]. The occurrence of flow state depends on task complexity and individual skill, and VR technology precisely adjusts difficulty to keep patients in an optimal flow state and boost compliance, especially in older or reluctant patients[77].

The regulation of the dopamine system is closely related to the treatment of PD. Current pharmacological treatment for PD centers on dopaminergic drugs that increase brain dopamine levels[78]. Dysregulation of the

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dopaminergic system is associated with poor prognosis in patients with MS[79]. Reduced dopamine transporter availability is linked to cognitive decline in patients with CI[80]. Therefore, dopamine levels play a crucial role in the prognosis of neurodegenerative diseases. Positive emotions can promote the generation of dopamine neurons, thereby increasing dopamine levels in the brain[81]. Cycling exercise has been found to stimulate dopamine release in the caudate nucleus of patients with PD[82]. Treadmill training can enhance neuroplasticity in dopaminergic signalling, thus improve early symptoms of PD[83]. Researchers have also observed enhanced dopaminergic signalling in mice subjected to moderate-intensity treadmill exercise[84]. Therefore, VR-based training could also benefit neurodegenerative diseases by increasing dopamine levels (Fig. 3C). VR integrated with exercise training is pivotal in enhancing neuroprotection and neuroplasticity. One study revealed that VR-based exercise elicits significantly greater increases in brain-derived neurotrophic factor to promote neuroplasticity and the survival of dopamine neurons compared with conventional physical training[85].

Neuroinflammation mechanisms are a common pathological basis for various neurodegenerative diseases. Aberrant microglial activation can instigate a sustained neuroinflammatory cascade reaction[86]. This chronic inflammatory state results in neuronal dysfunction and structural damage to the blood–brain barrier[87]. Within this pathological milieu, abnormal protein aggregation and mitochondrial dysfunction occur and form a vicious cycle that ultimately results in irreversible neuronal damage[88]. Immunomodulatory therapy can notably delay disease progression[89].

Exercise alleviates oxidative stress and neuroinflammation while promoting protective factors to regulate microglia activity and reduce β-amyloid deposition, thereby exerting neuroprotective effects[90]. The regular undertaking of rehabilitation exercises can assist in the reduction of systemic inflammatory factors, including interleukin-6 and tumour necrosis factor (Fig. 3D)[91]. Appropriate exercise benefits the immune system. VR-based rehabilitation allows precise control of exercise intensity, maximizing therapeutic gains while eliminating the overexertion risks common in conventional training.

Despite the continuous growth in the number of clinical studies exploring VR rehabilitation for neurodegenerative diseases, there are limitations that need to be taken into account. Firstly, the effectiveness of VR rehabilitation possibly depends on the disease stage, with early intervention offering good functional outcomes. However, the ideal timing and intensity of VR therapy remain unclear. Secondly, meta-analyses sometimes include low-quality clinical trials, which may weaken the reliability of the findings. This phenomenon highlights the need for strict study designs and high research standards. Thirdly, studies often use different VR devices, introducing technical variability that hampers the generalizability of results. Standardizing VR equipment and intervention protocols would improve consistency across research. Fourthly, the rehabilitation methods based on VR are limited. Future research could consider incorporating some distinctive training modalities with VR devices, such as Tai Chi, rhythmic auditory cueing, and sensorimotor training with proprioceptive enhancement, which have been proven to have therapeutic effects on neurodegenerative diseases[10,22,92,93]. Finally, sufficient evidence on the mechanisms underlying the therapeutic effects of VR rehabilitation is lacking. Future research could explore the health benefits of VR rehabilitation at the cellular and molecular levels and elucidate its potential neurotic mechanisms through advanced neuroimaging techniques. Addressing these limitations is imperative to enhance the credibility and clinical applicability of VR rehabilitation as a treatment intervention for neurodegenerative diseases.

Overall, VR rehabilitation has demonstrated some benefits in motor performance, cognitive function, and quality of life for people with neurodegenerative diseases. Both immersive and non-immersive VR modalities offer distinct benefits, yet inconsistencies in study designs underscore the need for standardized protocols. The functional improvements brought by VR may be achieved by promoting neural plasticity, integrating sensory-motor functions, regulating emotions and dopaminergic pathways, and controlling neuroinflammation.

Methods

Eligibility criteria

The initial search results indicated that virtual reality rehabilitation is mainly applied to patients with PD, CI, and MS. The inclusion criteria for the literature were as follows: (1) study designs must be restricted to systematic reviews, meta-analyses, and clinical trials (randomized or nonrandomized designs); (2) participants must be diagnosed with PD, CI, or MS included without restrictions on age or disease progression, and CI refers broadly to cognitive impairment; (3) interventions in clinical trials must incorporate VR-based rehabilitation as a therapeutic approach for the specified conditions; (4) only English publications were considered. The exclusion criteria involved the removal of review articles, study protocols, case reports, editorial communications, clinical guidelines, irrelevant data, and inaccessible studies.

Data sources and search strategy

A systematic search was performed on the PubMed database, the Cochrane Library, and the Web of Science Core Collection database as of October 9, 2024. The search terms included “Virtual reality”, “Rehabilitation”, and specific disease terms (“Parkinson’s disease”, “dementia”, “Alzheimer’s disease”, “cognitive impairment”, and “multiple sclerosis”), using appropriate Boolean operators and database-specific syntax. The detailed search strategy is available in the Supplementary Information.

Study selection and data extraction

The study selection process adhered to the PRISMA 2020 statement. Two independent researchers screened titles, abstracts, and full-texts with disagreements resolved through discussion. The selection process is illustrated in Fig. 1. Two researchers independently extracted data on the therapeutic effects of VR rehabilitation for neurodegenerative diseases from the selected meta-analyses and clinical trials. The extracted data included study basic information (authors and year), participant information (disease types and sample size), intervention details (VR type, duration, frequency, and total volume), assessment indicators, and main results. Some specific statistical values, such as standardized mean difference (SMD), mean difference (MD), partial eta squared (η^2_p), 95% confidence interval (95% CI) with p value, were used to present the therapeutic effect of VR rehabilitation. In addition, our research did not include articles with missing data.

Synthesis methods

We stratified all studies into three VR system types, i.e., immersive, semi-immersive, and non-immersive platforms, and then systematically evaluated the therapeutic effects of VR rehabilitation on various outcomes in different neurodegenerative diseases. The comparative results were quantified using multiple statistical values, including MD, SMD, η^2_p, and 95% CI. All remarkable findings were reported in the results section. Data were qualitatively described and summarized in tabular form. This study integrated findings from previous literature and provided a systematic synthesis.

Study risk of bias assessment

Two researchers independently conducted quality assessments of these included studies to ensure methodological rigour. Any discrepancies were resolved through consensus discussions. The Assessment of Multiple Systematic Reviews tool (AMSTAR) was applied to appraise systematic reviews and meta-analyses, and the PEDro Scale was used for randomized controlled trials (RCTs). Both instruments comprise 11 criteria, and the total score is 11 points. Studies scoring ≥ 7 points were rated as high-quality evidence, those scoring ≤ 3 points as low-quality evidence, and those scoring 4 ~ 6 points as medium-quality evidence. Furthermore, the Review Manager 5.3 software was used to create the traffic-light plot for visually assessing the risk of bias in the included RCTs.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, and was retrospectively registered on the Open Science Framework platform (registration DOI: 10.17605/OSF.IO/UXY5Z).

Ethics approval and consent to participate

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

W.R. and T.T.T.X. conceived and designed the study. T.T.T.X., Y.Y., Z.T.T., and L.H.Q. performed the majority of the analyses and visualizations and drafted the manuscript. T.T.T.X., Y.Y., Z.T.T., and L.H.Q. contributed to the development of the analysis strategy. W.W.M. and F.L.L. were responsible for data collection and data management. W.R. and J.S.H. provided guidance during the analysis. T.T.T.X. drafted the manuscript, and W.R. revised the manuscript. All authors reviewed the final version of the manuscript and approved it for publication.

Competing interests

The authors declare no competing interests.

Additional information

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