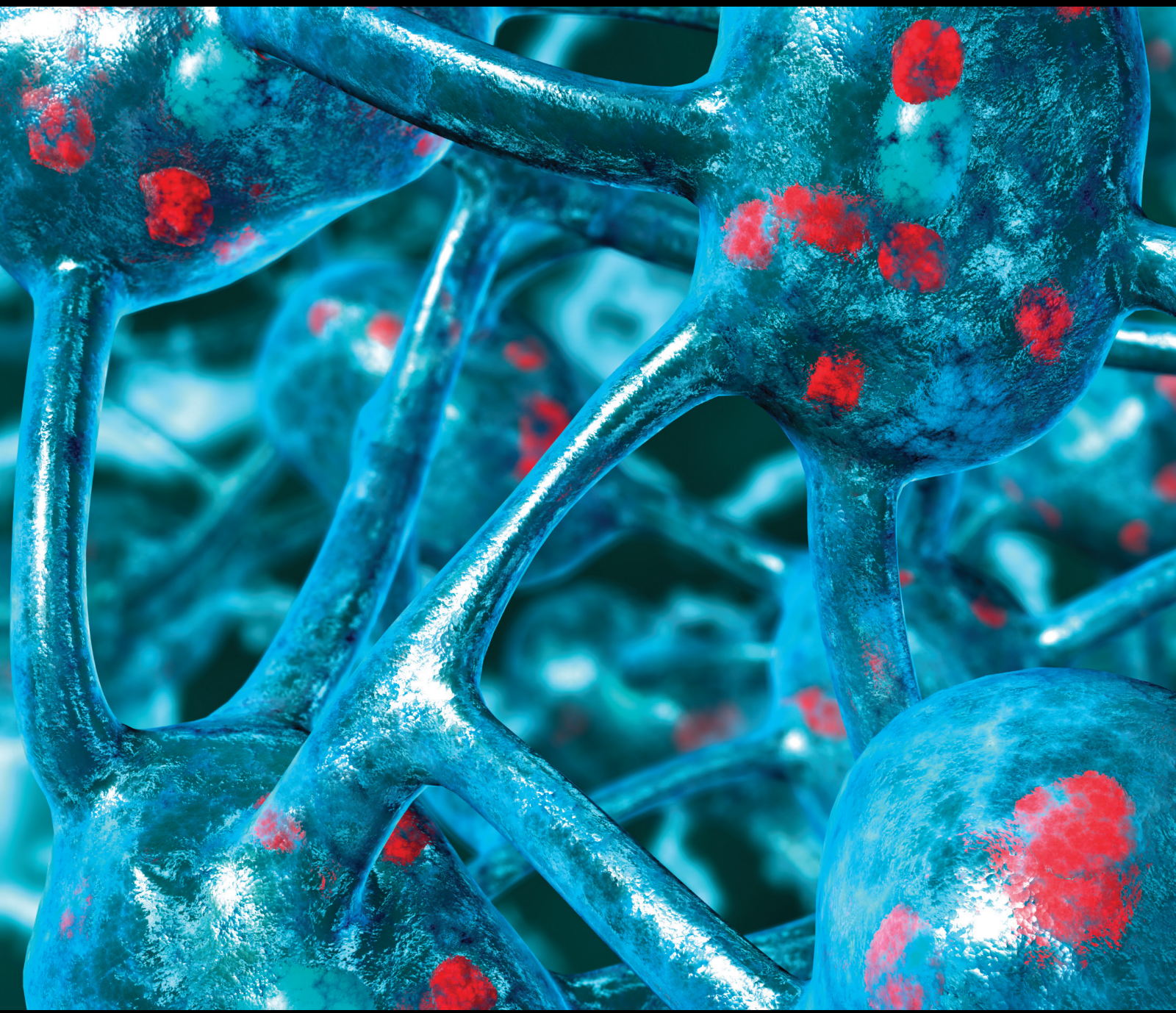
The Benefits of Exercise for Patients with Parkinson's Disease

Lead Guest Editor: Jose Maria Cancela
Guest Editors: Pedro Bezerra and Zachary Crowley-McHattan



The Benefits of Exercise for Patients with Parkinson's Disease

The Benefits of Exercise for Patients with Parkinson's Disease

Lead Guest Editor: Jose Maria Cancela
Guest Editors: Pedro Bezerra and Zachary Crowley-McHattan

Contents

Hindawi
Parkinson's Disease
Volume 2022, Article ID 7389658, 17 pages
https://doi.org/10.1155/2022/7389658

Review Article

How Cognitive Reserve should Influence Rehabilitation Choices using Virtual Reality in Parkinson's Disease

Letizia Pezzi,[1] **Andrea Di Matteo**,[2] **Roberta Insabella**,[3] **Sara Mastrogiacomo**,[4] **Carlo Baldari**,[5] **Victor Machado Reiss**,[6] **and Teresa Paolucci**[2]

[1]*Rehabilitation Unit, ASST Cremona–Ospedale di Cremona, Cremona, Italy*
[2]*Department of Oral and Biotechnological Biomedical Sciences, Physical Medicine and Rehabilitation, University of G. D'Annunzio of Chieti-Pescara, Chieti, Italy*
[3]*Department of Anatomical and Histological Sciences, Legal Medicine and Orthopedics, Sapienza University of Rome, Rome, Italy*
[4]*Fondazione Santa Lucia IRCCS, Rome, Italy*
[5]*Department of Theoretical and Applied Sciences, University eCampus, Novedrate, Italy*
[6]*Research Center for Sport, Health, and Human Development, University of Tras-Os-Monte and Alto Douro, Vila Real, Portugal*

Correspondence should be addressed to Teresa Paolucci; teresa.paolucci@unich.it

Received 14 April 2022; Revised 8 August 2022; Accepted 25 August 2022; Published 16 September 2022

Academic Editor: Eng King Tan

Virtual reality (VR) is used in the rehabilitation of patients with Parkinson's disease (PD) in several studies. In VR trials, the motor, physical characteristics, and the degree of the disease are often well defined, while PD cognitive reserve is not. This systematic review was performed to define a cognitive profile for patients with PD who could best benefit from using VR to enhance functional motor aspects during rehabilitation. PubMed, Cochrane Library, Scopus, and Web of Sciences databases were analysed to identify randomized clinical trials (RCT) and randomized pilot trials that addressed the rehabilitation of motor symptoms in subjects with PD using VR. The included studies used Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) to evaluate the cognitive aspect. Only articles written in English and with full texts were considered. The risk of bias from all included studies was assessed based on the Cochrane risk-of-bias tool and the PRISMA guideline was considered. Eighteen articles were eligible for review, including three randomized pilot trials. All studies aimed to evaluate the effect of VR on the motor aspects typically affected by PD (balance, postural control, risk of falls, walking, and reaching). The most widely adopted approach has been nonimmersive VR, except for one study that used immersive VR. Both the benefits of physical activity on the motor symptoms of patients with PD and the impact of cognitive reserve during the rehabilitation of these patients were highlighted. The analysis of the results allowed us to outline the ideal cognitive profile of patients with PD who can benefit from the effects of rehabilitation using VR.

1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease, characterized by the loss of dopaminergic neurons in the pars compacta of the substantia nigra and the accumulation of alpha-synuclein aggregates in specific regions of the brain stem, spinal cord, and cerebral cortex [1]. The estimated prevalence of PD in industrialized countries is 0.3% in the general population (1% in people over the age of 65 and 3% over 80 years), with incidence rates from 11 to 19 per 100,000 people each year [2, 3].

Patients with PD may also have affected cognitive functions, particularly global cognitive performance (as measured by the MMSE screening test) and behavioral deficits that affect aspects of social and community life [4]. The most common cognitive symptoms are deficit of attention and executive functions (working memory, planning, and inhibition), difficulties in episodic memory, verbal fluency, and visuospatial and visuoperceptual abilities [5].

Cognitive reserve (CR) is a theoretical construct that describes differences in individuals' susceptibility to cognitive, functional, or clinical decline due to ageing or neurological disease [6]. This concept is fundamental in neurodegenerative disorders such as PD, considering the severity of motor and cognitive disability and the functional impact on daily life [6]. Higher levels of CR are thought to be related to delayed disease onset and higher cognitive performance [7], and higher CR was associated with a better performance on the MMSE, thus confirming the protective role of CR on global cognitive functioning.

CR cannot be measured directly; it encompasses several different factors, including genetics, environment, education, occupational demands, lifetime experiences, and mental stimulation [8, 9].

Studies in the literature show that the level of education and physical activity, especially aerobic, and cognitive activities, reducing the loss of brain mass and strengthening compensatory circuits, have protective effects on the brain [10].

The study by Koerts et al. highlighted the relationship between CR and impairment of executive functions, that is, cognition skills; they pointed out that patients with PD who have high premorbid intellectual capacity show fewer cognitive deficits than patients with low premorbid capacity [11].

The complex management of PD can be achieved through a calibrated combination of drug therapy and rehabilitation. Physiotherapy aims to maximize the quality of movement and promote functional independence and general fitness in patients with PD, minimizing secondary complications of the disease [12].

From a rehabilitation perspective, virtual reality (VR) represents an alternative, noninvasive therapeutic modality, often used in association with conventional rehabilitation, to cope with the degenerative characteristics of PD. Furthermore, VR is more captivating for patients with high CR, as Pazzaglia et al. pointed, and the therapeutic exercise is perceived as more exciting and fun by having visual and auditory feedback contextual to the movement [13].

The following are the two main categories of VR: immersive, which allows a more direct experience of virtually generated environments, and nonimmersive, which allows a subject to observe, through a standard high-resolution monitor, a virtual environment with which he/she can interact through interfaces, such as keyboards and controllers [14].

Various studies, considering the premises to integrate cognitive and motor aspects, propose multimodal rehabilitation approaches that combine motor training with cognitive stimuli through technologies and virtual reality for patients with PD. The common goal is to create an enriched environment capable of stimulating different cognitive aspects, involving the subjects with a more playful approach [15–17].

Often, the physical characteristics and disease stage of PD patients, included in VR trials, are well defined; the same does not happen regarding their cognitive profiles. This could erroneously suggest that VR-associated motor rehabilitation may be useful to all patients with PD regardless of the degree of cognitive reserve. About 25% of patients with PD, especially after the age of 70, may experience mild cognitive impairment or dementia. In addition, in patients with PD, dual-task rehabilitation exercises or multimodal activities are not always recommended, especially in the presence of cognitive or complex tasks, which can lead to freezing of gait, loss of balance, and increased falls, all due to attention deficits and the reduction of automatisms and psychomotor speed in patients with PD [18].

From this premise, our hypothesis was that VR may be effective in patients with PD who respond to a specific neuro-cognitive profile. On the other hand, in PD patients with inadequate cognitive reserve, VR may not have the same therapeutic efficacy as suggested by Imbimbo et al., where patients with a higher cognitive reserve benefited more from the VR treatment. In contrast, patients with low cognitive reserve could achieve better results by following a traditional rehabilitation program [19].

Therefore, the cognitive reserve of PD patients could indicate the disease's evolution and help clinicians choose the most suitable rehabilitation strategy [14].

As a result, the considerations addressed so far lead to the goal of this systematic review, which is investigating to what extent neuro-motor rehabilitation with VR is useful for improving the motor aspects in patients with PD in relation to the cognitive reserve.

2. Materials and Methods

2.1. Search Strategy. This systematic review included articles published in the last 10 years (from 2011 to July 2021), according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20], and evaluated studies related to the rehabilitation of patients with PD using VR in the following databases: PubMed, Cochrane Library, Scopus, and Web of Science.

Different combinations of the following MeSH terms were used to select the articles: (Parkinson OR Parkinson's Disease) AND virtual reality AND (rehabilitation OR training OR exercise).

The reference lists for most of the relevant studies were scanned for additional citations. Country, author, affiliated institution, and enrolment period data were extracted and reviewed to identify and exclude duplicate publications using the same cohort. Any disagreement regarding accepting full-text articles was resolved by discussion until a consensus was reached.

2.2. Study Eligibility Criteria. Our target was randomized clinical trials (RCTs) and randomized pilot studies (full text in English) and studies evaluating cognitive aspects using the Mini Mental State Examination (MMSE) [21] or Montreal Cognitive Assessment (MoCA) [22] and that deal with the motor aspects of rehabilitation through virtual reality; the motor aspects were "balance," "falls," "ambulation," "postural control," and "reaching." MMSE is a short exam, used to evaluate the patient's neuro-cognitive performance by

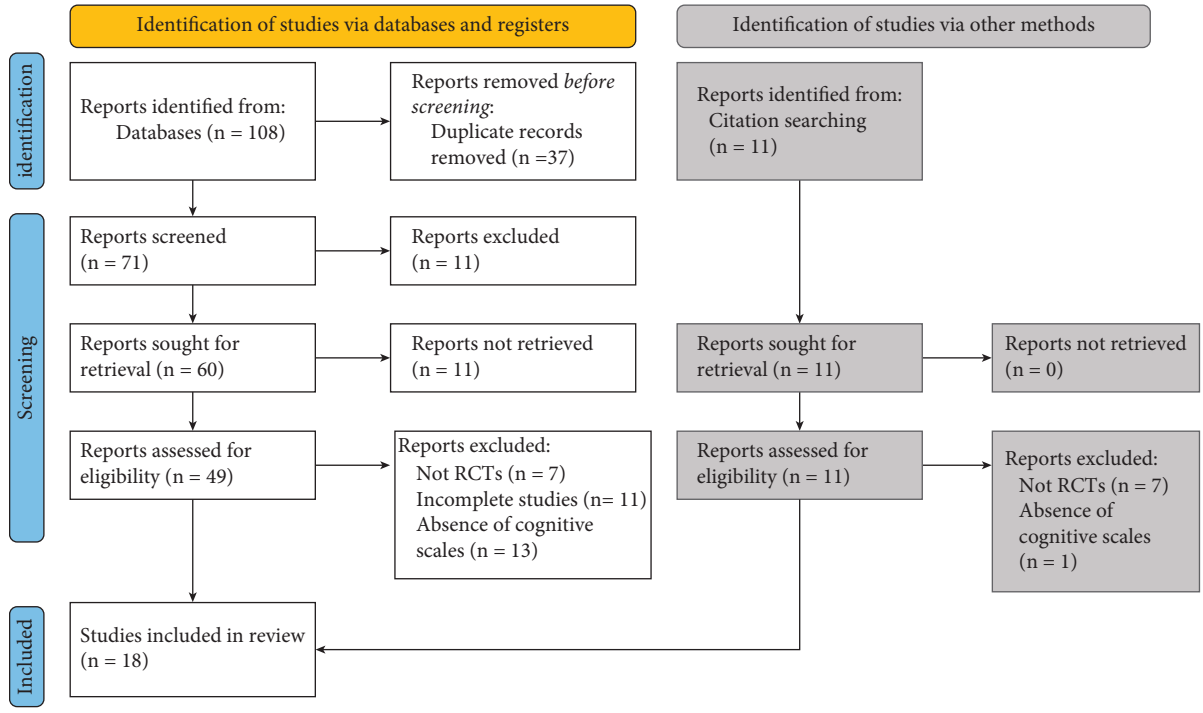


Figure 1: PRISMA flow-diagram.

administering a few questions to test orientation, memory, attention, calculation, and language. The total score is between 0 and 30; a score ≥ 24 indicates normal values. The MoCA acts as a quick screening for mild cognitive impairment. It evaluates different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructive skills, abstraction, calculation, and orientation. The maximum possible score is 30; a score ≥26 is considered normal.

Studies that adopted one or both of the previously mentioned scales were preferred to facilitate the analysis of the results. In this way, based on similar and comparable data, it was possible to consider the cognitive characteristics of the patients.

Studies other than RCTs and those that administered VR treatment to patients with neurological conditions other than PD (stroke and multiple sclerosis) were excluded.

2.3. Studies Quality Evaluation. The methodological quality of the studies was assessed using the PEDro scale [23]. Studies with scores ≥ 9 were of "excellent" quality. Studies with scores from 6 to 8 were considered "good," studies with scores from 4 to 5, "fair," and those with scores ≤4, "poor." The risk of bias was also assessed for each RCT using the Cochrane risk-of-bias tool [24]. The main domains were evaluated in the following sequence: (1) selection bias (generation of randomized sequences and allocation concealment); (2) reporting bias; (3) performance bias (blindness of participants and staff); (4) detection bias (blinding of the evaluation of results); (5) attrition bias (incomplete outcome data, such as those due to dropouts); (6) other sources of bias. The scores for each domain of bias and the final score for the risk of systematic bias were classified as low, high, or unclear risk.

3. Results

The initial search, carried out through electronic databases, produced 108 results. This search was complemented by a manual search of individual citations of systematic reviews and articles included in the review, identifying 11 additional studies. After duplicates were removed, the remaining 71 publications were reviewed according to their titles and abstracts. This led to the exclusion of 11 publications. Of the remaining 60, the full text of 11 studies could not be found (as they were posters and abstracts presented at conferences). The subsequent screening of the remaining complete texts allowed the identification of 15 publications relevant for the revision, and another three studies resulting from the selection of citations were added. Overall, 18 RCTs published in English were screened for inclusion (Figure 1).

The selected studies are shown in Table 1, which describes the type of VR and the protocols used, the results measured, the evaluation times, and the presence of adverse events during treatment.

According to the PEDro scale (Table 2), the mean methodological quality of the included RCTs was 6.1, indicating the overall good quality of the included studies. The risk of bias was considered low for 11 articles, while for the remaining seven articles, it was considered high (Table 3). The most frequent sources of potential bias were performance bias (related to participant and staff blinding), concealment of distribution in groups, the presence of uncompensated dropouts from analysis by intention to treat, and incomplete result data.

Table 1: Characteristics of the included studies.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Bekkers et al., 2020 [25] Do patients with Parkinson's disease with freezing of gait respond differently than those without to treadmill training augmented by virtual reality?	RCT, 6	No: 121 (FOG+ = 77, FOG− = 44) VRG: 62 TG: 59 Age VRG: 71.06 TG: 70.86 Disease duration, years VRG: 9.05 TG: 9.55	Nonimmersive VR	VRG: treadmill with simulated obstacles in a virtual environment TG: treadmill Both treatments, lasting 45 minutes, were carried out 3 times a week for 6 weeks	I.C: age 60–90; H&Y II-III; anti-Parkinson therapy; walking for 5 minutes without assistance; adequate vision and hearing; 2 or more falls in the previous 6 months E.C: psychiatric comorbidities; MMSE <24; history of stroke, head injury, or other neurological disease other than PD; orthopaedic or rheumatic diseases; acute lower back pain or pain in limbs, peripheral neuropathy, inability to participate in training.	—	VRG: 2.42 TG: 2.49	MMSE: VRG = 27.76 (1.7) TG = 28.34 (1.5) MoCA: VRG = 23.85 (4.5) TG = 24.27 (3.5)	Primary: balance and falls: mini-BEST Secondary: number of falls NFOG-Q TMT-B SPPB FSST FES-I PASE MMSE MoCA UPDRS-III	T0 (baseline); T1 (after 1 week); T2 (after 6 weeks) T3 (6 months follow up)	To show a reduction in falls and improvement in balance following training on the treadmill with virtual reality compared to the treadmill alone, highlighting any differences between patients with and without FOG.	FOG patients improved balance and risk of falls in treadmill training both with and without VR compared to non-FOG patients
Del Din et al., 2020 [26] Falls risk in relation to activity exposure in high-risk older adults	RCT, 5	No tot = 282, PD = 128 Age 71.68	Nonimmersive VR	VRG: treadmill associated with VR in elderly patients/ with MCI/PD TG: treadmill Both treatments, lasting 40 minutes, were carried out 3 times a week for 6 weeks.	I.C: age 60–90; able to walk for 5 minutes without assistance; stable therapy the month before; 2 or more falls in the previous six months E.C: psychiatric comorbidities; history of stroke, brain damage and other neurological disorders; acute lower back pain; rheumatic or orthopaedic diseases; MMSE <21	—	48%: 2 10%: 2.5 42%: 3 Mean MP = 2.47	MMSE (MP) 28.07 (1.68)	FRA index (Measure of the incidence of falls corrected for exposure)	T0 (pre-treatment); T1 (after 1 week) T2 (after 1 month) T3 (after 6 months)	To study the relationship between gait (exposure to falling risk) and fall rates before and after a treadmill exercise program with and without VR (V-TIME)	V-TIME intervention successfully reduced the risk of falling by maintaining walking activity levels in different groups of elderly people at risk of falling

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Feng et al., 2019 [27] Virtual reality rehabilitation versus conventional physical therapy for improving balance and gait in Parkinson's disease patients: a randomized controlled trial	RCT, 7	No: 28tot VRG: 14 TG: 14 Age VRG: 67.47 TG: 66.93	Nonimmersive VR	VRG: perform game-based actions with a standard VR device TG: conventional treatment 45 treatment, once a day, 5 times a week for 12 weeks	I.C: H&Y 2.5/4; age 50–70; signed informed consent E.C: other causes of tremor; severe bone or joint disease; visual or hearing disturbances; inability to cooperate in the study	—	VRG: 3.03 TG: 2.97	MMSE: VRG = 27.07 ± 2.09; TG = 26.29 ± 2.49 Education received (years) VRG: 10.47 TG: 9.93	BBS TUG UPDRS III FGA	T0 (baseline) T1 (after 12 weeks)	Studying the effects of virtual reality on balance and walking in patients with PD	Rehabilitation with VR improved outcomes compared to traditional treatment (except for UPDRS where no significant differences were noted)
Ferraz et al., 2018 [17] The effects of functional training, bicycle exercise, and exergaming on walking capacity of elderly patients with Parkinson disease: a pilot randomized controlled single-blinded trial	Pilot RCT, 7	No: 62 TG1: 22 TG2: 20 VRG: 20 Age: TG1: 71 TG2: 67 VRG: 67 Disease duration, years: G1: 4 G2: 6 G3: 4	Exergame (nonimmersive VR)	VRG: training with "Kinect Adventures" video game (Xbox 360) TG1: functional training TG2: cycling exercise. 50′ treatment, 3 times a week, for 8 weeks	I.C: age ≥ 60; regular use of therapy; H&Y II-III walking without aids E.C: visual and hearing impairment; parkinsonian syndromes other than PD; orthopaedic diseases limiting physical activity; chronic uncontrolled diseases; cardiovascular disease; use of alcohol or toxic substances; contraindications to physical activity; practiced physical activity programs in the past 6 months; or participate in endurance training in the previous 12 months	—	TG1: 2.50 (2.5–3) TG2: 2.50 (2-3) VRG: 2.50 (2–2.5)	MMSE TG1: 27.00 (24.75–28.00) TG2: 27.00 (25.00–29.00) VRG: 27.00 (25.00–28.00) Education received (years): TG1: 8.00 TG2: 9.50 VRG: 8.00	Primary: 6 MWT Secondary: 10 MWT SRT Body mass index MPQ-39 WHODAS 2.0 GDS	T0 (baseline) T1 (after 8 weeks)	Compare the effects of functional training, cycling and exergaming on walking ability in elderly patients with PD	Exergame training has achieved similar results to traditional treatments in improving gait; all three strategies are recommended, considering patients' motivation

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Gandolfi et al., 2017 [28] Virtual reality telerehabilitation for postural instability in Parkinson's disease: a multicenter, single-blind, randomized, controlled trial	RCT, 6	No: 76 VRG: 38 TG: 38 Age VRG: 67.45 TG: 69.84 Disease duration, (years) VRG: 6.16 TG: 7.47	VR nonimmersive	VRG: treatment with "Wii fit gaming system and balance board" at home, supervised via Skype by a physiotherapist TG: in-clinic sensory integration balance training (SIBT) 50′ treatment, 3 times a week for 7 consecutive weeks	I.C: age > 18; H&Y 2.5–3; stable therapy the month before; can perform postural transfer and stand for 10 minutes; presence of caregivers E.C: cardiovascular, orthopedic and otovestibular disorders; visual or neurological conditions interfering with balance; severe dyskinesia or on-off fluctuations; MMSE <24; depression	—	VRG: 2.5 TG: 2.5	MMSE VRG = 26.77 (1.48) TG = 28.64 (6.96)	Walking/balance Primary: BBS Secondary: ABC 10 MWT DGI MPQ-8	T0 (baseline) T1 (after treatment) T2 (after 1 month)	Compare the improvements in postural stability after balance training with VR at home remotely supervised and in-clinic. balance training with sensory integration	Use of VR at home (TeleWii) is a valid alternative to conventional rehabilitation to reduce postural instability in patients with PD (H&Y 2.5–3)
van den Heuvel et al., 2014 [29] Effects of augmented visual feedback during balance training in Parkinson's disease: a pilot randomized clinical trial	Pilot RCT, 8	No: 33 VRG: 17 TG: 16 Age: VRG: 66.3 (6.39) TG: 68.8 (9.68) Disease duration, (years) VRG: 9 TG: 8.8	Nonimmersive VR	VRG: interactive balance games with augmented visual feedback via an LCD monitor connected to a PC, a force plate, and an inertial sensor TG: conventional treatment 10 treatment sessions of 60′, for 5 weeks	I.C: H&Y 2–3; able to participate in both training programs; verbal and written informed consent E.C: other neurological, orthopaedic, or cardiopulmonary diseases that prevent participation in the study; MMSE <24; recent change in dopaminergic therapy; cognitive, visual or speech problems that prevent participation	—	VRG: 2.5 TG: 2.5	MMSE VRG: 29 TG: 28	Primary: FRT Secondary: BBS H&Y UPDRS (I, II, III, IV) FES MPQ-39 HAD Multidimensional Fatigue inventory	T0 (baseline) T1 (after 6 weeks) T2 (after 12 weeks follow up)	Investigate whether a balance training program that uses augmented visual feedback is feasible, safe, and more effective than conventional balance training in improving postural control in PD patients	The use of augmented visual feedback in a group setting is safe and feasible to provide therapeutic balance training for patients with PD, even if no more effective than conventional therapy
van der Kolk et al., 2019 [30] Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial	RCT, 7	No: 130 VRG:65 TG:65 Età VRG: 59.3 TG: 59.4 Disease duration, (years) VRG: 3.41 TG: 3.16	Nonimmersive VR	VRG: aerobic pedalling exercises at home (30′–45′at least 3 times a week) enriched with virtual reality software and real-life videos to create an exergaming experience TG: stretching and relaxation (30′, 3 times a week)	I.C: H&Y>/= 2; practice less than the recommended physical activity for older adults; age 30–75; stable dopaminergic therapy E.C: beta-blocker or antipsychotic drugs; neurological, orthopaedic or heart problems; psychiatric illness; MMSE <24	Arthralgia/ back pain (VRG = 2) Palpitations (VRG = 4)	VRG:4 TG: 3	MoCA VRG.: 26.3. (2.2) TG: 26.3 (2.5) Education received (years): VRG.: 15.1 (4.0) TG: 16.1 (4.5)	Primary: MSD-UPDRS III (off) Secondary: VO2 UPDRS III (on) UPDRS IV Number of falls, 6 MWT TUG mini-BEST Pegboard FTT MPQ-39 HADS SCOPA FSS TMT MoCA	T0 (baseline) T1(after 6 months)	Evaluate the effectiveness of aerobic exercise, gamified, and performed at home, to promote therapy adherence and relieve motor symptoms in patients with PD	The study provides level 1 evidence that aerobic exercise alleviates motor symptoms in Parkinson's disease and improves cardiovascular fitness

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Liao et al., 2015 [31] Virtual reality-based training to improve obstacle crossing performance and dynamic balance in patieshewidmernts with Parkinson's disease.	RCT, 7	No: 36 VRG: 12 TG: 12 GC:12 Age VRG: 67.3 TG: 65.1 CG: 64.6 Disease duration, (years): VRG: 7.9 TG: 6.9 CG: 6.4	Nonimmersive VR	VRG: VR exercises with Wii Fit Plus games and Wii Fit balance board TG: traditional treatment (stretching, strengthening, balance) CG: fall prevention education 12 treatment sessions of 45 '(+15' treadmill in VRG and TG), 2 times a week for 6 weeks	I.C: H&Y 1–3; autonomous walking without aids; stable therapy; MMSE>/= 24 E.C: unstable medical conditions; other neurological, cardiopulmonary, orthopaedic diseases; history of seizures; pacemaker; visual impairment	No adverse events	CG:1.9 TG: 2 VRG: 2	MMSE VRG: 29.5 (0.7) TG: 29.8 (0.3) CG:29.7 (0.6)	Primary: performance overcoming obstacles with "Liberty system" Dynamic balance with "balance master system" Secondary SOT MPQ-39 FES-I) TUG	T0 (baseline) T1(after 1 day) T2(30 days after treatment -follow up)	Examine the effects of virtual reality-based exercise on overcoming obstacles in patients with Parkinson's	VR with Wii, as part of a multi-faceted workout, is effective in improving performance when overcoming obstacles, dynamic balance, functional capacity, and quality of life in patients with PD
Liao et al., 2015 (b) [32] VR-based Wii fit training in improving muscle strength, sensory integration ability and walking abilities in patients with MP	RCT, 7	No = 36 VRG: 12 TG: 12 GC: 12 Age VRG: 67.3 TG: 65.1 CG: 64.6 Disease duration, (years) VRG: 7.9 TG: 6.9 CG: 6.4	Nonimmersive VR	VRG: exercises with Wii Fit and treadmill TG: conventional training and treadmill CG: fall prevention education 12 sessions, twice per week, for 6 weeks	I.C.: H&Y 1–3; autonomous walking without aids; stable therapy; MMSE ≥ 24 E.C: unstable medical conditions; other neurological, cardiopulmonary, orthopaedic diseases; pacemaker;	—	CG: 1.9 TG: 2 VRG: 2	MMSE VRG: 29.5 TG: 29.8 CG: 29.7	Gait: GAITRite FGA Muscle strength: dynamometer Sensory integration skills: SOT	T0 (baseline) T1 (after 6 weeks) T2 (after 1 month-follow up)	Examine the effects of virtual reality-based training in improving muscle strength, sensory integration capacity and walking in patients with PD	Wii training is as useful as traditional training in improving outcomes, and these improvements have persisted for at least a month. It is therefore suggested that Wii training be implemented in patients with PD
Ma et al., 2011 [33] Effects of virtual reality training on functional reaching movements in people with Parkinson's disease: a randomized controlled pilot trial	Pilot RCT, 5	No: 33 VRG: 17 TG: Age VRG: 64.77 TG: 68.13 Disease duration, (years) VRG: 5.32 TG: 5.16	Immersive VR	VRG: reach 60 moving balls with your right-hand using VR system and polarized glasses TG: roll 60 wooden cylinders with your left hand.	I.C: H&Y 2–3; Age 50–75; stable therapy; MMSE ≥ 24. Normal sight and hearing; right-handed to self-assessment E.C: other neurological conditions besides PD; musculoskeletal disorders impairing UL movements;	Fatigue (VRG = 1)	VRG: 2 TG: 2	MMSE VRG: 27.24 (3.09) TG: 26.31 (2.52)	Success rates of the required task (catching the ball) Kinematic data	T0 (baseline) T1 (After treatment)	To investigate whether practising with virtual moving targets would improve motor performance in people with Parkinson's disease	A short training program with VR improved speed of movement and accuracy in reaching real fixed objects. However, the transfer effect was minimal in reaching real moving objects

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Maidan et al., 2017 [34] Disparate effects of training on brain activation in Parkinson disease	RCT, 4	No: 34 VRG: 17 TG: 17 Age VRG: 71.2 TG: 71.5 Disease duration, (years) VRG: 7.9 TG: 11.6	Nonimmersive VR	VRG: VR associated treadmill TG: treadmill only 18 Sessions 3 times a week for 6 weeks	I.C: age 60–90; H&Y 1–3; ability to walk independently for at least 5 minutes; anti Parkinson therapy E.C: MRI contraindications; psychiatric comorbidities; MMSE <24; other neurological disorders besides PD; orthopaedic problems, unstable therapy	—	—	MMSE VRG: 27.8 (0.4) TG: 28.3 (0.5) MoCA VRG: 22.9 (0.9) TG: 21.9 (0.8) Global cognitive score VRG: 89.7 (2.7) TG: 88.4 (2.6) Attention VRG: 88 (4.2) TG: 84.1 (4.2) Executive functions VRG: 87.5 (2.2) TG: 83.4 (3.2)	fMRI assessment Step parameters MoCa Computerized cognitive test battery	T0 (baseline) T1 (after 7 weeks)	Compare the effects of treadmill training with virtual reality and treadmill training alone on brain activation in patients with Parkinson's disease	The results suggest that the task-specific exercise provided by VR led to experience-dependent neuroplasticity and reduced the usefulness of activating compensatory cognitive functions resulting in greater automaticity. Training with VR has improved both motor and cognitive aspects of the altered front-striatal circuit
Maidan et al., 2018 [16] Evidence for differential effects of 2 forms of exercise on prefrontal plasticity during walking in Parkinson's disease	RCT, 4	No: 64 VRG: 30 TG: 34 Age VRG: 70.1 TG: 73.1 Disease duration, (years) VRG: 8.9 TG: 9.7	Nonimmersive VR	VRG: treadmill training with virtual obstacles on a screen ahead TG: treadmill 45' treatment, 3 times a week for 6 weeks	I.C: age 60–90; H&Y 2–3; autonomous walking for at least 5 minutes; anti-Parkinson therapy E.C: psychiatric comorbidities; MMSE <24; performance-impairing neurological diseases; orthopaedic problems that could compromise walking; unstable medical conditions including cardiovascular instability	—	—	MMSE VRG: 28.2 (0.3) TG: 28.3 (0.3)	Deambulation (electronic gangway with pressure sensors) Prefrontal activation (functional near infrared spectroscopy—fNIRS)	—	Investigate whether the VR-paired treadmill and the treadmill alone differently affect prefrontal activation and whether this could explain the differences in fall rates after surgery	Providing a combined cognitive-motor training intervention may result in specific changes in prefrontal activation patterns that improve functional abilities, reduce falls and the risk of falling, which in turn could slow deterioration in patients with PD

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Mirelman et al., 2016 [35] Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial	RCT, 8	No: 302 (MP: 130) VRG: 154 TG: 148 Age (elderly and PD) VRG: 74.2 TG: 73.3	Nonimmersive VR	VRG: VR associated treadmill (elderly and with PD) TG: treadmill training 45' sessions, 3 times a week for 6 weeks	I.C: age 60–90; walking without assistance for at least 5 minutes; stable therapy in the previous month; 2 or more falls in the previous 6 months; clinical dementia rating scale = 0.5; H&Y 2-3; anti Parkinson therapy E.C: psychiatric comorbidities; history of stroke, brain damage and other neurological disorders; acute lower back pain; rheumatic or orthopaedic diseases; MMSE <24	Present but not related to the study	—	MMSE VRG: 27.8 (1.8) TG: 28.2 (1.7) Education received (years) VRG: 13.1 (4.0) TG: 12.9 (3.9)	Primary: rate of accidental falls Secondary: gait speed/ variability 2 MWT SPPB NeuroTrax Corp SF-36	T0 (baseline) T1 (after training) T3 (after 6 months)	Test the hypothesis that a treadmill intervention combined with non-immersive virtual reality, to address cognitive aspects, safe walking, and mobility, would lead to fewer falls than treadmill training alone	In a heterogeneous group of elderly people at high risk of falls, treadmill training associated with virtual reality led to lower fall rates than training with treadmill alone
Pelosin et al., 2020 [36] A multimodal training modulates short afferent inhibition and improves complex walking in a cohort of faller older adults with an increased prevalence of Parkinson's disease	RCT, 4	No: 39 (PD: 24) VRG: 17 TG: 22 Age (elderly and PD) VRG: 73.3 TG: 71.9	Nonimmersive VR	VRG: treadmill training with obstacles and distractors in VR (elderly patients and with PD) TG: treadmill training 45′ treatment, 3 times a week for 6 weeks	I.C: 2 or more falls in the previous six months; age 60–85; walk for 5 minutes without assistance; H&Y 2-3; stable therapy for at least a month E.C: MMSE <24; psychiatric comorbidities; stroke or other neurological disease; contraindications to TMS; use of anticholinergics or acetylcholinesterase inhibitors	—	—	MoCA (elderly and PD) VRG 23.5 (4.3) TG: 25 (3.2) Education received (years) (Elderly and PD) VRG: 11.1 (4.2) TG: 9.8 (4.7)	Primary: Number of falls SAI magnitude Secondary: Gait parameters during normal walking (GaitRite) Overcoming obstacles	T0 (baseline) T1 (after 1 week) T2 (after 6 months)	Evaluate whether virtual reality-based attention training modulates cholinergic activity (SAI-short-latency afferent inhibition) and affects obstacle negotiation performance in a cohort of elderly people with a history of falls and with a higher prevalence of PD	The multitasking training carried out modulated the SAI and allowed functional improvements in gait. Furthermore, the combination of such rehabilitation approach with cholinergic pharmacological agents may optimize the recovery induced by the rehabilitation

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Pompeu et al., 2012 [37] Effect of Nintendo Wii™-based motor and cognitive training on activities of daily living in patients with Parkinson's disease: a randomised clinical trial	RCT, 5	No: 32 VRG: 16 TG: 16	Nonimmersive VR	VRG: 10 games with Wii-Fit for motor and cognitive training TG: balance exercises without feedback or cognitive stimuli. 14 training sessions of 60′ (30′ stretching, strengthening + 30′ balance), 2 times a week for 7 weeks	I.C: age 60–85; H&Y 1–2; good visual and auditory acuity; 5–15 years of education; no other neurological or orthopaedic diseases; dementia (cut-off 23 MMSE) or depression (GDS cut-off 6) E.C: no other experiences in using the Wii fit; not having participated in other rehabilitation programs.	—	—	MoCA VRG: 20.6 (4.5) TG: 21.7 (4.6)	Primary: UPDRS II (ADL) Secondary: BBS UST MoCA	T0 (baseline) T1 (after treatment) T2 (after 60 days—follow up)	To study the effect of Nintendo Wii™-based cognitive-motor training compared to balance training on activities of daily living in patients with Parkinson's disease	Patients with PD showed better performance in daily life activities after 14 balance training sessions, without any additional benefits associated with motor and cognitive training with VR
Shih et al., 2016 [38] Effects of balance-based exergaming intervention using the Kinect sensor on posture stability in individuals with Parkinson's disease: a single-blinded randomized controlled trial	RCT, 6	No: 20 VRG: 10 TG: 10 Age VRG: 67.5 TG: 68.8 Disease duration, (years) VRG: 27.4 TG: 28.2	Exergaming/ nonimmersive VR	VRG: balance training with exergaming (Kinect sensor) TG: balance training 50′ sessions (30′ balance), 2 times a week for 8 weeks	I.C: H&Y 1–3; MMSE ≥ 24; stable therapy; can stand without help E.C: history of other neurological, cardiovascular, orthopaedic disease related to postural instability; uncontrolled chronic diseases	—	VRG: 1.6 TG: 1.4	MMSE VRG: 27.4 (2.59) TG: 28.2 (1.99).	Postural stability: LOS OLS balance: BBS TUG	T0 (baseline) T1 (after 8 weeks)	Examine the effects of balance-based exergaming training using the Kinect sensor on postural stability and balance in people with Parkinson's	Balance training with exergame resulted in a greater improvement in postural stability than conventional training. The results support the therapeutic use of exergaming with Kinect sensor in patients with PD
Yang et al., 2016 [39] Home-based virtual reality balance training and conventional balance training in Parkinson's disease: a randomized controlled trial	RCT, 7	No: 23 VRG: 11 TG: 12 Age VRG: 72.5 TG: 75.4 Disease duration, (years) VRG: 9.4 TG: 8.3	Nonimmersive VR	VRG: At home. balance training with VR via Wii and balance board TG: conventional balance training at home. 12 sessions of 50′, twice a week, for 6 weeks	I.C: age 55–85; MMSE >24; H&Y 2–3; no balance or step training in the previous 6 months; no other clinical conditions related to balance or walking C: E: untreated depression; major visual/hearing impairments	No adverse events. 1 VRG patient dropped out as he preferred conventional training	VRG:3 TG: 3	MMSE VRG: 27.5 ± 4.0 TG: 27.2 ± 2.5	Primary: BBS Secondary: DGI TUG MPQ-39 UPDRS-III	T0 (baseline) T1 (after 6 weeks) T2 (after 8 weeks-follow up)	Assess whether virtual reality home balance training is more effective than conventional home balance training in improving balance, walking and quality of life in patients with Parkinson's disease	The results do not show significant differences in the improvements in balance and walking in the two treatment groups. In any case, exercises with VR at home can represent a valid alternative for patients with PD with limited access to rehabilitation services

Table 1: Continued.

Author, year, Title	Study type, PEDro score	Participants	VR type	Device/software/ tools/protocol	Inclusion and exclusion criteria	Adverse events	H&Y score	Cognitive scales	Other outcomes	Evaluation times	Objective of the study	Conclusions
Yen et al., 2011 [40] Effects of virtual reality-augmented balance training on sensory organization and attentional demand for postural control in people with parkinson disease: a randomized controlled trial	RCT, 7	No: 42 VRG: 14 TG: 14 GC: 14 Age VRG: 70.4 TG: 70.1 GC: 71.6 Disease duration, (years) VRG: 6.0 TG: 6.1 GC: 7.8	Nonimmersive VR	VRG: balance training with dynamic balance board, LCD screen with 3D games (Virtools 3.5) TG: standing balance training. GC: no treatment. 30′ sessions, twice a week for 6 weeks	I.C: MMSE >24; H&Y 2–3; not having participated in other balance and gait training; ability to follow simple commands and the absence of chronic uncontrolled diseases E.C: history of other neurological, cardiovascular, orthopaedic diseases; on-off motor fluctuations and dyskinesia >3 on UPDRS	No adverse events, apart from the tendency to fall	VRG: 2.6 TG: 2.4 GC: 2.6	MMSE VRG: 28.5 (1.6) TG: 28.5 (1.2) GC: 28.1 (0.8)	SOT balance score	T0 (baseline) T1 (within 7 days after 6 weeks) T2 (after 10 weeks-follow up)	Examine the effects of balance training, associated with VR, on sensory integration of postural control and compare the results with those obtained from a conventional balance training group and an untrained control group	Both balance training with virtual reality and without could be considered valid for improving the sensory integration capacity for postural stability in people with PD

FOG: freezing of gait; VRG: virtual reality group; TG: treatment group; H&Y: Hoehn and Yahr scale; VR: virtual reality; MMSE: mini mental state examination; MoCA: montreal cognitive assessment; Mini-BEST: mini-balance evaluation systems test; NFOG-Q: new freezing of gait questionnaire; TMT-B: trail making test; SPPB: short physical performance battery; FSST: four square step test; FES-I: falls efficacy scale-international; PASE: physical activity scale for the elderly; UPDRS: unified Parkinson's disease rating scale; UL: upper limbs; MCI: mild cognitive impairment; BBS: Berg balance scale; TUG: timed up and go; FGA: functional gait assessment; 6 MWT: six minute walk test; SRT: sitting rising test; MPQ-39: multidimensional personality questionnaire; WHODAS 2.0: WHO disability assessment schedule; GDS: geriatric depression scale; ABC: activities-specific balance confidence scale; 10MWT: 10 meter walk test; DGI: dynamic gait index; FRT: functional reach test; HADS: hospital anxiety and depression scale; VO2max: maximum oxygen consumption; FTT: finger tapping test; SCOPA: scales for outcomes in Parkinson's disease; FSS: fatigue severity scale; SOT: sensory organization test; FMRI: functional magnetic resonance imaging; FNIRS: functional near infrared spectroscopy; 2 MWT: 2 minute walk test; SF-36: short form health survey 36; SAI: short-latency afferent inhibition; UST: unipedal stance test; LOS: limits of stability; OLS: one leg stand test.

Table 2: PEDro classification: methodological quality.

Author	1	2	3	4	5	6	7	8	9	10	11	Total score
Bekkers et al. [25]	N	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
Del Din et al. [26]	N	Y	N	Y	N	N	N	N	Y	Y	Y	5/10
Feng et al. [27]	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Ferraz et al. [17]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10
Gandolfi et al. [28]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
van den Heuvel et al. [29]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
van der Kolk et al. [30]	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7/10
Liao et al. [31]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10
Liao et al. [32]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10
Ma et al. [33]	N	Y	Y	Y	N	N	N	N	N	Y	Y	5/10
Maidan et al. [34]	N	Y	N	Y	N	N	Y	N	N	Y	N	4/10
Maidan et al. [16]	Y	Y	N	Y	N	N	Y	N	N	Y	N	4/10
Mirelman et al. [35]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
Pelosin et al. [36]	N	Y	N	Y	N	N	Y	N	N	Y	N	4/10
Pompeu et al. [37]	N	Y	N	Y	N	N	Y	N	N	Y	Y	5/10
Shih et al. [38]	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6/10
Yang et al. [39]	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Yen et al. [40]	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10

Y = yes; 1. Eligibility criteria; 2. random distribution of subjects in each group; 3. secret allocation of subjects; 4. similar groups regarding the most important prognosis; 5. blind participation of subjects; 6. Blind participation of therapists; 7. blind examiners; 8. at least one key result obtained in more than 85% of subjects; 9. subjects received treatment or control condition; 10. intergroup statistical comparisons have been performed for at least one key outcome; 11. presence of precision and variability measures.

It should be noted that, among the studies included in the review, Del Din et al. [26], Mirelman et al. [35], and Pelosin et al. [36] included elderly patients with mild cognitive impairment; therefore, of the 1393 patients analysed in the studies, only 1052 were PD patients, with a mean age of 68.8 years and a mean disease duration of 8.47 years.

In all studies, the cognitive level of the patients was assessed using the MMSE and/or the MoCA. The inclusion of patients in the trials, except in Del Din et al.'s study [26], was defined using the Hoehn and Yahr scale (H&Y) [41] relating to the progression of the disease (Figures 2 and 3).

A synthesis study was conducted on the patients included in the various protocols to observe under which conditions VR can be used effectively. None of the studies examined showed the influence of cognitive reserve (or the analysis of the patient's cognitive profile) on the results. However, no study planned the treatment protocol with VR by comparing subjects with high cognitive reserve and groups with poor cognitive reserve.

All the studies included in the review aimed to evaluate the effects of VR-associated rehabilitation on the motor characteristics typically affected by PD. More specifically, seven trials [25, 27–29, 31, 37, 39] focused on improving balance; five studies [15, 25, 26, 35, 36] addressed the risk of falls reduction and their incidence.; seven articles [17, 26–28, 32, 34, 39] aimed to evaluate the effects of rehabilitation treatment on walking; three articles [28, 38, 40] dealt with the problem of postural control in patients with PD; only one article [30] focused on motor symptoms (assessed through the third section of the UMPRS scale) and one article [33] dealt with motor performance during reaching exercises. Unfortunately, it is impossible to compare the individual studies' results as different outcome measures were used.

Among the studies listed, two [32, 40] evaluated the effects of VR on sensory integration, and three [16, 34, 36] examined the effect of VR on brain activation and cholinergic activity.

All studies adopted nonimmersive virtual reality systems [16, 25–32, 34–37, 39, 40] or exergaming [17, 38], except for one study [33], which used immersive VR.

4. Discussion

This review aims to investigate to what extent neuromotor rehabilitation with VR is useful for improving the motor aspects in PD patients in relation to the cognitive reserve.

Most of the studies analysed in this review stated that VR associated with conventional rehabilitation produced better results, compared with rehabilitation alone, in terms of increasing motor characteristics, such as walking, balance. and postural stability, typically affected by PD. VR is a good rehabilitation option, especially when combined with conventional therapy, and seems more suitable in patients with a good cognitive reserve, measured indirectly with mean MMSE and MoCA scores of 27.94 ± 0.86 and 23.43 ± 2.04, respectively. Working with VR can be stimulating in patients with a high cognitive reserve as it is challenging, as Pazzaglia et al. pointed, where the exercises are perceived as interesting, motivating, and funny, providing immediate visual and auditory feedback [13].

In the literature, several studies consider VR an efficient tool for the rehabilitation of patients with PD. Endurance training, especially exercises performed on the treadmill, can improve balance, reduce gait disturbances, improve speed, stride length, and walking [42–44]. VR offers the opportunity to simulate immersive and controllable environments,

Table 3: Risk of bias of the included studies.

		Random sequence generation	Allocation concealment	Selective reporting	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Other bias
Bekkers et al. 2020	High	?	−	+	−	+	−	?
Del Din et al. 2020	High	?	−	+	−	−	+	?
Feng et al. 2019	Low	?	−	+	−	+	+	?
Ferraz et al. 2018	Low	+	+	+	−	+	−	?
Gandolfi et al. 2017	Low	+	−	+	−	+	−	?
Heuvel et al. 2014	Low	?	+	+	−	+	+	?
Kolk et al. 2019	Low	+	+	+	−	+	−	?
Liao et al. 2015	Low	?	+	+	−	+	−	?
Liao et al. 2015 (b)	Low	?	+	+	−	+	−	?
Ma et al. 2011	High	+	+	+	−	−	−	?
Maidan et al. 2017	High	?	−	−	−	+	−	?
Maidan et al. 2018	High	?	−	−	−	+	−	?
Mirelman et al.2016	Low	+	+	−	−	+	+	?
Pelosin et al. 2020	Low	+	−	+	−	+	+	?
Pompeu et al. 2012	High	+	−	+	−	+	−	?
Shih et al. 2016	High	+	+	+	−	−	−	?
Yang et al. 2016	Low	+	−	+	?	+	+	?
Yen et al. 2011	Low	+	−	+	−	+	+	?

"+" means low risk of bias; "−" means high risk of bias; "?" means unclear risk of bias. Trials involving three or more high risks of bias were considered of poor methodological quality.

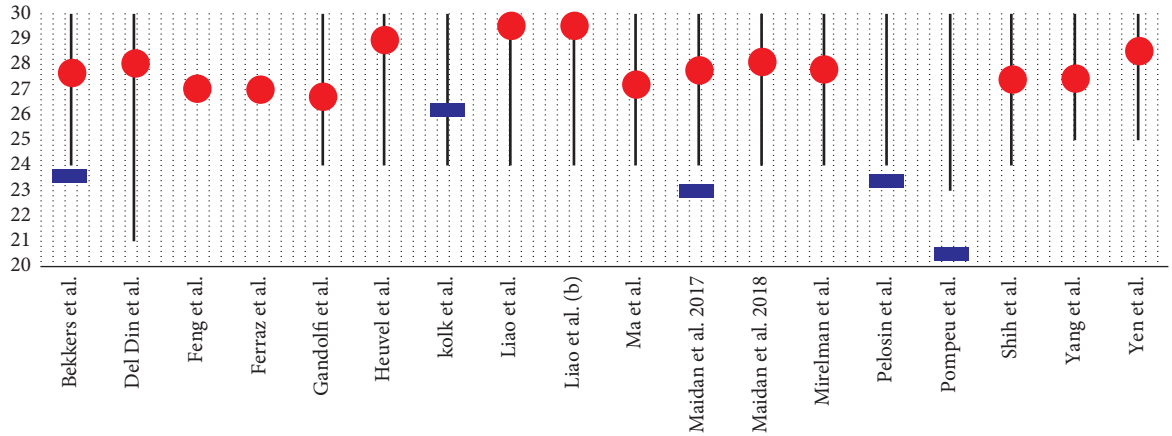


Figure 2: The mean of cognitive reserve score for each study included in the review. The grey line indicates the distribution of MMSE scores utilized as inclusion criteria for enrolled patients. The red spot indicates the mean MMSE score, and the blue tag, the mean MoCa score.

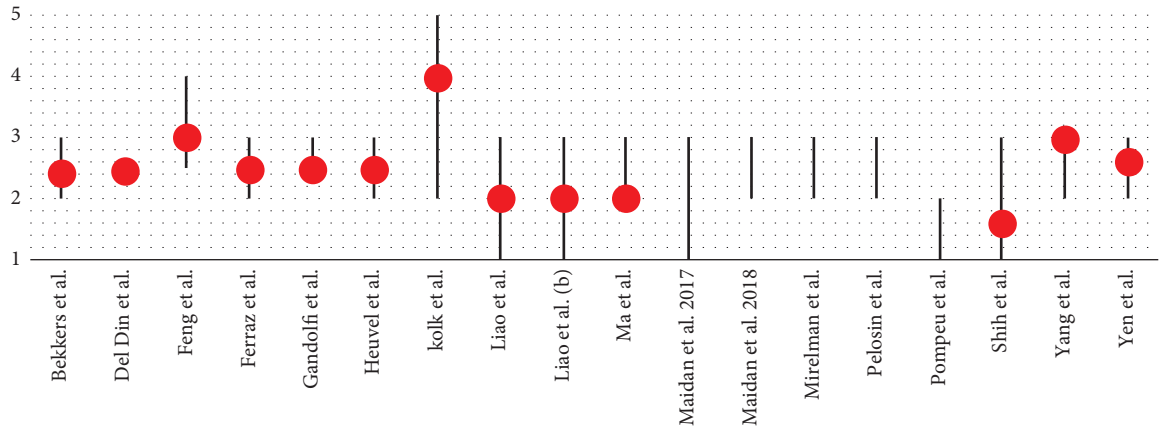


FIGURE 3: The grey line indicates the distribution of H&R scores of patients enrolled in the trials, and the red spot indicates the mean score of the H&R scale of patients who participated in the VR group.

with the possibility of customizing the rehabilitation treatment.

However, within the review, there are several articles, eight specifically [17, 25, 29, 32, 33, 37, 39, 40], which considered the effects of rehabilitation associated with VR on a par with those of conventional rehabilitation, suggesting that the use of VR could complement rehabilitation to increase motivation during treatment [17]. The home-based administration of VR could represent a valid alternative for subjects with PD with limited access to rehabilitation services [39].

Examples of exercises with VR carried out at home can be found in the studies of Gandolfi et al. [28] and van der Kolk et al. [30], which have associated VR with balance training and aerobic exercise, respectively.

It should be emphasized that the activity performed through VR guarantees good adherence to the treatment because, during the exercise, the integration of motor and cognitive skills is favored and reward circuits of the brain are stimulated [28, 45], which increases the possibility for patients to choose to train at any time of the day.

However, it is necessary to consider the cognitive aspects of patients with PD and their complex motor picture. Gandolfi et al. [28] admit that their results study should not be generalized and applied in patients with significant cognitive decline, as VR could be risky. Indeed, the European Physiotherapy Guideline for Parkinson's disease [18] says that dual-task or multimodal therapeutic exercises are not always indicated for parkinsonian patients because they can lead to freezing, loss of balance, and increased falls, especially during complex cognitive tasks. For this reason, VR could only be used with patients that respond to a specific cognitive profile since it may not have the same therapeutic efficacy in others with reduced cognitive reserve.

This is confirmed by the study of van der Kolk et al. [30], in which the participants' cognitive level, considered normal (MoCA = 26, 3), did not prevent the occurrence of adverse events, such as arthralgia, back pain, and palpitations, related to VR treatment, as well as falls, heart problems, and musculoskeletal damage, even if not related to exercise. In addition, the same authors state that several patients, from the VR treatment group, have left the study due to the onset of technical problems; this suggests that the presence of supervision or assistance can help in some circumstances to continue a training session with VR.

Although VR shows numerous advantages (related to learning motor skills through repetitive practice, performance feedback, and motivation) [46], it also presents some critical issues for patients: insufficient perception of depth and lack of tactile feedback (which, the latter, can cause difficulties when performing virtual tasks that simulate reality) [47, 48]. In addition, a recent systematic review results state that patients with advanced age may find VR games complicated or boring and may need supervision to complete the task undertaken [49].

Some of the studies described using VR rehabilitation programs have shown how resistance exercises, stretching, and cognitive rehabilitation can improve the patient's quality of life. This is because patient perceives themselves as an active part of treatment. However, the cognitive reserve was not considered, and its impact on rehabilitation was therefore not evaluated. However, we can infer from the review studies and the literature that the cognitive reserve should be considered in the evaluation phase of patients with PD to plan the optimal, tailored therapeutic approach.

Piccinini et al. [50] examined the influence of cognitive reserve on balance rehabilitation, using conventional therapy, in patients with PD. The results showed an improvement in balance, and regarding the relationship between the cognitive reserve and balance, the condition of patients with a lower cognitive reserve index (those with a lower level of education) improved more than that of patients with a high cognitive reserve index. It has been hypothesized that patients with better cognitive reserve should work on more stimulating mental tasks through approaches such as VR, dance, and technological tools. They found an inverse correlation between the level of cognitive reserve and the improvement of balance in patients with PD undergoing traditional rehabilitation, which highlights the important role that life experience, education, and recreational activities play on the individual's ability to cope with a brain pathology.

Imbimbo et al. [19] examined the relationship between VR and the cognitive reserve in patients with PD. The exercises proposed were intended to improve coordination and balance. At the end of the study, it was observed that, in relation to the cognitive reserve, some patients, unlike others, showed no improvement. VR showed better result in patients with a medium/high cognitive reserve index; these PD patients are accustomed to the use of technology, unlike subjects with a lower level of cognitive reserve who were uncomfortable with this tool and may felt less stimulated to learn. The results of our review may confirm Piccinini et al.'s results [50], which had suggested using a more complex rehabilitation approach for patients with a higher cognitive reserve.

This study had a few limitations: only four databases were searched, and we acknowledge the possibility that we did not identify all relevant studies.

5. Conclusion

Most of the studies analysed in this review included subjects with an MMSE score ≥ 24 and a H&Y stage between 2 and 3. Rehabilitation associated with VR was proposed for patients with PD with a mean score (mean of averages) of 27.94 (SD = 0.86) and 23.43 (SD = 2.04) for MMSE and MoCA, respectively, which shows a normal or slightly reduced cognitive level (if we consider the cut-off of 26 for MoCA).

According to the disease progression state, patients with PD who underwent treatment with VR had, on average (average of averages), an H&Y stage of 2.5 (SD = 0.60), indicating a slight bilateral involvement of the disease with recovery of balance on the pull test.

In conclusion, the results of these studies show that VR is a useful strategy that improves motor aspects mainly affected by PD and is feasible for patients with a normal cognitive level and an H&Y's stage less than three. This innovative approach, excluding excessively strenuous activities, is feasible at home and should preferably be performed in the presence of a caregiver or supervision.

Data Availability

The data supporting this systematic review are from previously published studies, which have been cited.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

References

[1] A. J. Lees, J. Hardy, and T. Revesz, "Parkinson's disease," *Lancet*, vol. 373, no. 9680, pp. 2055–2066, 2009.

[2] A. Lee and R. M. Gilbert, "Epidemiology of Parkinson disease," *Neurologic Clinics*, vol. 34, no. 4, pp. 955–965, 2016.

[3] R. Balestrino and A. H. V. Schapira, "Parkinson disease," *European Journal of Neurology*, vol. 27, no. 1, pp. 27–42, 2020.

[4] C. Papagno and L. Trojano, "Cognitive and behavioral disorders in Parkinson's disease: an update. I: cognitive impairments," *Neurological Sciences*, vol. 39, no. 2, pp. 215–223, 2018.

[5] D. Aarsland, K. Brønnick, J. P. Larsen, O. B. Tysnes, G. Alves, and Norwegian ParkWest Study Group, "Cognitive impairment in incident, untreated Parkinson disease: the Norwegian Parkwest study," *Neurology*, vol. 72, no. 13, pp. 1121–1126, 2009.

[6] Y. Stern, E. M. Arenaza-Urquijo, D. Bartrés-Faz et al., "The reserve, resilience and protective factors PIA empirical definitions and conceptual frameworks workgroup. whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance," *Alzheimers Dement*, vol. 16, no. 9, pp. 1305–1311, 2020.

[7] C. Pettigrew and A. Soldan, "Defining cognitive reserve and implications for cognitive aging," *Current Neurology and Neuroscience Reports*, vol. 19, no. 1, p. 1, 2019.

[8] J. V. Hindle, C. S. Hurt, D. J. Burn et al., "The effects of cognitive reserve and lifestyle on cognition and dementia in Parkinson's disease-a longitudinal cohort study," *International Journal of Geriatric Psychiatry*, vol. 31, no. 1, pp. 13–23, 2015.

[9] J. V. Hindle, A. Martyr, and L. Clare, "Cognitive reserve in Parkinson's disease: a systematic review and meta-analysis," *Parkinsonism & Related Disorders*, vol. 20, pp. 1–7, 2014.

[10] S. T. Cheng, "Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities," *Current Psychiatry Reports*, vol. 18, no. 9, p. 85, 2016.

[11] J. Koerts, L. Tucha, K. W. Lange, and O. Tucha, "The influence of cognitive reserve on cognition in Parkinson's disease," *Journal of Neural Transmission*, vol. 120, no. 4, pp. 593–596, 2013.

[12] C. E. Meek, *Improving the Clinical Effectiveness of Physiotherapy in Parkinson's Disease*, University of Birmingham, Birmingham, UK, 2011.

[13] C. Pazzaglia, I. Imbimbo, E. Tranchita et al., "Comparison of virtual reality rehabilitation and conventional rehabilitation in Parkinson's disease: a randomised controlled trial," *Physiotherapy*, vol. 106, pp. 36–42, 2020.

[14] B. Chau, S. Humbert, and A. Shou, "Systemic literature review of the use of virtual reality for rehabilitation in Parkinson disease," *Federal Practitioner: for the Health Care Professionals of the VA, DoD, and PHS*, vol. 38, no. 1, pp. S20–S27, 2021.

[15] I. Cikajlo and K. Peterlin Potisk, "Advantages of using 3D virtual reality based training in persons with Parkinson's disease: a parallel study," *Journal of NeuroEngineering and Rehabilitation*, vol. 16, no. 1, p. 119, 2019.

[16] I. Maidan, F. Nieuwhof, H. Bernad-Elazari et al., "Evidence for differential effects of 2 forms of exercise on prefrontal plasticity during walking in Parkinson's disease," *Neurorehabilitation and Neural Repair*, vol. 32, no. 3, pp. 200–208, 2018.

[17] D. D. Ferraz, K. V. Trippo, G. P. Duarte, M. G. Neto, K. O. Bernardes Santos, and J. O. Filho, "The effects of functional training, bicycle exercise, and exergaming on walking capacity of elderly patients with Parkinson disease: a pilot randomized controlled single-blinded trial," *Archives of Physical Medicine and Rehabilitation*, vol. 99, no. 5, pp. 826–833, 2018.

[18] S. H. J. Keus, M. Munneke, M. Graziano et al., "European Physiotherapy Guideline for Parkinson's Disease," 2014, https://www.parkinsonnet.nl/app/uploads/sites/3/2019/11/eu_guideline_parkinson_guideline_for_pt_s1.pdf.

[19] I. Imbimbo, D. Coraci, C. Santilli et al., "Parkinson's disease and virtual reality rehabilitation: cognitive reserve influences

the walking and balance outcome," *Neurological Sciences*, vol. 42, no. 11, pp. 4615–4621, 2021.

[20] M. J. Page, J. E. McKenzie, P. M. Bossuyt et al., "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews," *BMJ*, vol. 372, p. 71, 2021.

[21] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state"," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[22] Z. S. Nasreddine, N. A. Phillips, V. Bã©dirian et al., "The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[23] N. A. De Morton, "The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study," *Australian Journal of Physiotherapy*, vol. 55, no. 2, pp. 129–133, 2009.

[24] J. P. T. Higgins, D. G. Altman, P. C. Gotzsche et al., "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials," *BMJ*, vol. 343, no. 2, Article ID d5928, 2011.

[25] E. M. J. Bekkers, A. Mirelman, L. Alcock et al., "Do patients with Parkinson's disease with freezing of gait respond differently than those without to treadmill training augmented by virtual reality?" *Neurorehabilitation and Neural Repair*, vol. 34, no. 5, pp. 440–449, 2020.

[26] S. Del Din, B. Galna, S. Lord et al., "Falls risk in relation to activity exposure in high-risk older adults," *The journals of gerontology. Series A, Biological sciences and medical sciences*, vol. 75, no. 6, pp. 1198–1205, 2020.

[27] H. Feng, C. Li, J. Liu et al., "Virtual reality rehabilitation versus conventional physical therapy for improving balance and gait in Parkinson's disease patients: a randomized controlled trial," *Medical Science Monitor*, vol. 25, pp. 4186–4192, 2019.

[28] M. Gandolfi, C. Geroin, E. Dimitrova et al., "Virtual reality telerehabilitation for postural instability in Parkinson's disease: a multicenter, single-blind, randomized, controlled trial," *BioMed Research International*, vol. 201711 pages, Article ID 7962826, 2017.

[29] M. R. van den Heuvel, G. Kwakkel, P. J. Beek, H. W. Berendse, A. Daffertshofer, and E. E. van Wegen, "Effects of augmented visual feedback during balance training in Parkinson's disease: a pilot randomized clinical trial," *Parkinsonism & Related Disorders*, vol. 20, no. 12, pp. 1352–1358, 2014.

[30] N. M. van der Kolk, N. M. de Vries, R. P. C. Kessels et al., "Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial," *The Lancet Neurology*, vol. 18, no. 11, pp. 998–1008, 2019.

[31] Y. Y. Liao, Y. R. Yang, S. J. Cheng, Y. R. Wu, J. L. Fuh, and R. Y. Wang, "Virtual reality-based training to improve obstacle-crossing performance and dynamic balance in patients with Parkinson's disease," *Neurorehabilitation and Neural Repair*, vol. 29, no. 7, pp. 658–667, 2015.

[32] Y. Y. Liao, Y. R. Yang, Y. R. Wu, and R. Y. Wang, "Virtual reality-based wii fit training in improving muscle strength, sensory integration ability, and walking abilities in patients with Parkinson's disease: a randomized control trial," *International Journal of Gerontology*, vol. 9, no. 4, pp. 190–195, 2015.

[33] H. I. Ma, W. J. Hwang, J. J. Fang et al., "Effects of virtual reality training on functional reaching movements in people with Parkinson's disease: a randomized controlled pilot trial," *Clinical Rehabilitation*, vol. 25, no. 10, pp. 892–902, 2011.

[34] I. Maidan, K. Rosenberg-Katz, Y. Jacob, N. Giladi, J. M. Hausdorff, and A. Mirelman, "Disparate effects of training on brain activation in Parkinson disease," *Neurology*, vol. 89, no. 17, pp. 1804–1810, 2017.

[35] A. Mirelman, L. Rochester, I. Maidan et al., "Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial," *The Lancet*, vol. 388, no. 10050, pp. 1170–1182, 2016.

[36] E. Pelosin, C. Cerulli, C. Ogliastro et al., "A multimodal training modulates short afferent inhibition and improves complex walking in a cohort of faller older adults with an increased prevalence of Parkinson's disease," *The Journals of Gerontology. Series A, Biological sciences and medical sciences*, vol. 75, no. 4, pp. 722–728, 2020.

[37] J. E. Pompeu, F. A. d S. Mendes, K. G. d Silva et al., "Effect of Nintendo Wii™-based motor and cognitive training on activities of daily living in patients with Parkinson's disease: a randomised clinical trial," *Physiotherapy*, vol. 98, no. 3, pp. 196–204, 2012.

[38] M. C. Shih, R. Y. Wang, S. J. Cheng, and Y. R. Yang, "Effects of a balance-based exergaming inteVRention using the Kinect sensor on posture stability in individuals with Parkinson's disease: a single-blinded randomized controlled trial," *Journal of NeuroEngineering and Rehabilitation*, vol. 13, no. 1, p. 78, 2016.

[39] W. C. Yang, H. K. Wang, R. M. Wu, C. S. Lo, and K. H. Lin, "Home-based virtual reality balance training and conventional balance training in Parkinson's disease: a randomized controlled trial," *Journal of the Formosan Medical Association*, vol. 115, no. 9, pp. 734–743, 2016.

[40] C. Y. Yen, K. H. Lin, M. H. Hu, R. M. Wu, T. W. Lu, and C. H. Lin, "Effects of virtual reality-augmented balance training on sensory organization and attentional demand for postural control in people with Parkinson disease: a randomized controlled trial," *Physical Therapy*, vol. 91, no. 6, pp. 862–874, 2011.

[41] M. M. Hoehn and M. D. Yahr, "Parkinsonism: onset, progression and mortality," *Neurology*, vol. 17, no. 5, pp. 427–442, 1967.

[42] D. Cano Porras, P. Siemonsma, R. Inzelberg, G. Zeilig, and M. Plotnik, "Advantages of virtual reality in the rehabilitation of balance and gait: systematic review," *Neurology*, vol. 90, no. 22, pp. 1017–1025, 2018.

[43] K. Dockx, E. M. Bekkers, V. Van den Bergh et al., "Virtual reality for rehabilitation in Parkinson's disease," *Cochrane Database of Systematic Reviews*, vol. 12, no. 12, Article ID CD010760, 2016.

[44] W. Mrówczyński, "Health benefits of endurance training: implications of the brain-derived neurotrophic factor-A systematic review," *Neural Plasticity*, vol. 2019, Article ID 5413067, 2019.

[45] A. Mirelman, I. Maidan, and J. E. Deutsch, "Virtual reality and motor imagery: promising tools for assessment and therapy in Parkinson's disease," *Movement Disorders*, vol. 28, no. 11, pp. 1597–1608, 2013.

[46] M. K. Holden, "Virtual environments for motor rehabilitation: review," *CyberPsychology and Behavior*, vol. 8, no. 3, pp. 187–211, 2005.

[47] O. Martin, B. Julian, L. Boissieux, J. D. Gascuel, and C. Prablanc, "Evaluating online control of goal-directed arm movement while standing in virtual visual environment," *The Journal of Visualization and Computer Animation*, vol. 14, no. 5, pp. 253–260, 2003.

[48] A. Viau, A. G. Feldman, B. J. McFadyen, and M. F. Levin, "Reaching in reality and virtual reality: a comparison of movement kinematics in healthy subjects and in adults with hemiparesis," *Journal of NeuroEngineering and Rehabilitation*, vol. 1, pp. 11–17, 2004.

[49] P. H. Chau, Y. Y. J. Kwok, M. K. M. Chan et al., "Feasibility, acceptability, and efficacy of virtual reality training for older adults and people with disabilities: single-arm pre-post study," *Journal of Medical Internet Research*, vol. 23, no. 5, Article ID e27640, 2021.

[50] G. Piccinini, I. Imbimbo, D. Ricciardi et al., "The impact of cognitive reserve on the effectiveness of balance rehabilitation in Parkinson's disease," *European Journal of Physical and Rehabilitation Medicine*, vol. 54, no. 4, pp. 554–559, 2018.

Hindawi
Parkinson's Disease
Volume 2022, Article ID 2073068, 10 pages
https://doi.org/10.1155/2022/2073068

Research Article

Effects of an Aquatic Physical Exercise Program on Ventilatory Parameters in People with Parkinson's Disease

Bruna Yamaguchi, Dielise Debona Iucksch, Luis Henrique Paladini, and Vera Lúcia Israel

Federal University of Paraná, Curitiba, Brazil

Correspondence should be addressed to Luis Henrique Paladini; luishenriquepaladini@gmail.com

Received 20 April 2022; Accepted 8 August 2022; Published 31 August 2022

Academic Editor: Cristine Alves da Costa

Problems in the respiratory system are the main cause of death in Parkinson's disease (PD). Ventilatory limitations can also be part of a vicious cycle involving physical-functional limitations (e.g., walking difficulties) and the patients' perception of fatigue. The objective of this study was to analyze the effects of an aquatic physical exercise intervention program on ventilatory parameters, perception of fatigue, and gait capacity in participants with PD. This quasi-experimental study had a single group with repeated measures in four assessments, proposing an aquatic physical exercise intervention program. The inclusion criteria encompassed being in levels 1 to 4 on the Hoehn and Yahr scale and having a medical certificate for the activities. Assessments took place at 3-month intervals between them—the first period was the control, the second following the intervention, and the third period was the follow-up. The intervention had 25 biweekly sessions over 3 months. A total of 13 people (71.3 ± 5.61 years old) participated in the intervention, without significant differences in the control period. Between the intervention assessments, they had statistically significant differences in MIP, MEP, FVC, Tiffeneau index, MVV, and fatigue. The study demonstrated that the aquatic physical exercise intervention was effective for ventilatory outcomes and fatigue in people with PD.

1. Introduction

Possible respiratory impairments in Parkinson's disease (PD) were described in 1817 by James Parkinson, who defined it as "paralysis agitans" [1, 2]. It has been currently reported that more people in this population die from pneumonia than same-age older adults [3] and that respiratory problem share the main cause of death in PD [1, 2]. Besides the mortality rates, respiratory limitations also impair PD patients' overall functioning, causing them to progressively lose their independence and quality of life [2–4].

Results in the literature present different causal approaches regarding the characteristics of pulmonary function in PD. Studies indicate sharper respiratory changes than in healthy older people [1–5], which seem to be also related to PD progression [2]. Furthermore, ventilatory limitations can be part of a vicious cycle involving physical-functional limitations (e.g., walking difficulties) and the PD patients' perception of fatigue [6, 7]. However, studies do not unanimously define whether there are obstructions, restrictions, mixed limitations, or even respiratory muscle weakness in people with PD. Hence, the literature still lacks clarifications regarding pulmonary function in PD.

Regarding multi-professional treatments of possible respiratory disorders in PD, physical therapy and other exercise-based strategies are characterized as clinically helpful activities [8]. Physical exercises can stimulate neurotrophic factors, with neuroprotection and neuroplasticity effects [9]. However, few studies approach interventions based on physical activity programs, whose main outcomes are the limitations related to ventilatory variables [10, 11]. The existing ones use incentive spirometry [12, 13], while few studies approach physical activities and/or ventilatory patterns [4, 14–16].

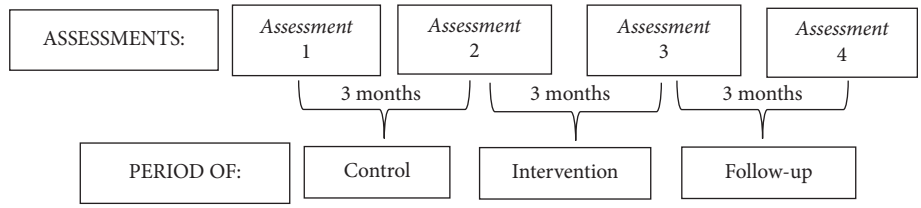


Figure 1: Outline of assessments and intervention.

No studies were found approaching aquatic physical therapy to improve respiratory parameters associated with the perception of fatigue and gait capacity in PD. On the other hand, successful experiences with aquatic physical therapy intervention have been reported, with motor and quality-of-life outcomes for this population [17–22]. Aquatic exercises, whose movements are safely made in the pool, have likewise been experienced for other neurological [23] and motor neuron diseases [24], which impair ventilation [25, 26].

Besides the positive effects of aerobic exercises performed on land, the aquatic environment further favors ventilation because it potentially increases inspiratory force. It also triggers the rearrangement of blood circulation and volume in the chest, due to hydrostatic pressure when immersed, in combination with water temperature and other physical properties, and adequately prescribed aquatic physical activities [16–26]

Thus, the objective of the present study was to analyze the effects of an intervention program with aquatic physical activities on the ventilatory parameters, perception of fatigue, and gait capacity in participants with PD.

2. Methodology

This is a quasi-experimental single-group study [27] with repeated measures. The research complied with the guidelines in Resolution 466/12, of the National Health Council [28], and the Declaration of Helsinki, and was approved by the Research Ethics Committee.

The assessments took place in four moments. The 3 months between assessments 1 and 2 were the control period when participants continued their everyday activities. In the second period (between assessments 2 and 3), the group not only maintained their everyday activities but also joined the heated pool intervention program. There was no intervention in the period between the last two assessments (3 and 4), i.e., follow-up, when the group only maintained their everyday activities. The flowchart (Figure 1) shows the periods, the four assessment moments, and the time between the assessments.

Participants were recruited from an association of people with PD in a capital city in Southern Brazil. They were invited to the research and joined it by signing an informed consent form. The inclusion criteria were as follows: participants of both sexes, clinically diagnosed with idiopathic PD, in stages 1 to 4 on the Hoehn and Yahr scale, and with a medical certificate for performing physical activities and attending heated pools.

The exclusion criteria were as follows: not being able to walk independently of help from other people; having other diseases that might interfere with the physical assessments (e.g., balance changes of vestibular origin), visual or auditory sensory deficits that hindered them from following verbal and visual instructions, or any uncontrolled respiratory or cardiovascular diseases; having a history of pulmonary surgery, recent respiratory tract infection, or any absolute contraindication to attend heated pools; being absent in more than 10% of the intervention; changing physical activities or L-dopa-based drug intake parameters during the research period.

Participants were assessed with the Hoehn & Yahr scale and Montreal Cognitive Assessment (MoCA) and had their data collected (age, sex, time since PD diagnosis) for sample characterization.

As intervention-dependent outcomes, participants were assessed with a duly calibrated analogic respiratory pressure meter manufactured by Wika to measure their maximum inspiratory (MIP) and expiratory pressure (MEP). The assessment followed the instructions of the American Thoracic Society and European Respiratory Society [29]. The spirometry was made with a portable spirometer (brand and model: MIR/Spirobank G). The forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), Tiffeneau index (i.e., the FEV1/FVC ratio), and maximum voluntary ventilation (MVV) were analyzed with criteria of the Brazilian Society of Pneumology [30]. Individual values below 80% of the expected per age, sex, height, and mass were inferred as at risk for obstructive, restrictive, or mixed respiratory disorders, as shown in Figure 2.

The Fatigue Severity Scale (FSS) was used for the perception of fatigue, with self-reported scores from 1 to 7—in which 1 indicated disagreement with the statement on fatigue, and 7 indicated strong agreement with it; higher values pointed to a greater perception of fatigue [31].

The 6-Minute Walk Test (6 MWT) was used to assess the physical capacity at submaximal effort [32].

2.1. Interventions. The aquatic environment interventions took place in small groups of participants in a 10.70 m long, 2.90 m wide, and 1.20 m deep pool, heated to approximately 33°C. There were 25 sessions over 3 months, held twice a week on non-consecutive days, lasting 50 minutes each. Every session had a warm-up, followed by specific exercises, and finished with a cooldown, following the recommendations of the European Physiotherapy Guideline for Parkinson's Disease [33]. The exercises approached the five

CHART1 – Composition for inference of ventilatory disorders.

< 80% of the expected = reduced	FVC	FEV1	FEV1/FVC
Obstructive	Ok	Reduced	Reduced
Restrictive	Reduced	Reduced	Ok
Mixed	Reduced	Reduced	Reduced

SOURCE: Modified from Pereira [30].

LEGEND: FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEV1/FVC: Tiffeneau index.

Figure 2: Composition for inference of ventilatory disorders.

Table 1: Phase of adjustment.

Exercise	Volume
1st month	
WARM-UP: Gait in circles, holding hands (to the right, left, forward, and backward)	2 min
Bucket handle: Standing; lower limbs apart and partially flexed. Inspiratory exercise combining upper limb abduction/adduction to the water surface; labial frenum prolonged expiration	2 × 5 repetitions, 1 min intervals
Pump lever: Standing; lower limbs apart and partially flexed. Inspiratory exercise combining upper limb flexion/extension; labial frenum prolonged expiration	2 × 5 repetitions, 1 min intervals
Floating with support	2 min
2nd month	
WARM-UP: Gait in circles, holding hands, with pool noodles between lower limbs (to the right, left, forward, and backward)	2 min
Respiratory exercises with short inspirations and prolonged expirations immersed in the water	2 × 5 repetitions, 1 min intervals
Respiratory exercises 2:1 with prolonged expiration immersed in the water	2 × 5 repetitions, 1 min intervals
Floating without support (w/ adaptations, if necessary)	2 min
3rd month	
Warm-up: Gait in circles, not holding hands but maintaining the circle pattern with a ball on the upper limbs and pool noodles between lower limbs; walk to the right, left, forward, in line, and backward	2 min
Respiratory exercises 3:1 with prolonged expiration immersed in the water	2 × 5 repetitions, 1 min intervals
Sliding in the prone position	—
Diving until touching the bottom of the pool	—

aquatic motor learning phases, as proposed by Israel and Pardo (2000) [34], with emphasis on specialized therapeutic exercises and global organic conditioning. The aquatic intervention program is described in detail in Tables 1–4 and Figure 3.

The Borg 6–20 scale was used during exercise to control the reported exercise intensity, which was kept between 12 and 16 on the scale. This range enables physiological adaptations of the physical activity balanced with good tolerance to them [35–37].

2.2. Data Analysis Procedures. The measures of central tendency and dispersion and the normality of the sample distribution were verified. The mean values of the four assessments were compared with the repeated-measure ANOVA for different times. Mauchly's sphericity test was applied, and the Greenhouse-Geisser correction was used in the case of data whose sphericity was not assumed [38]. Afterward, the Bonferroni post hoc test was applied to the variables with statistical differences to verify between which assessments there were differences [38]. The statistical significance value was set at $p < 0.05$; the SPSS 22.0 program for Windows [39] was used.

3. Results

3.1. Sample Characterization. Initially (Assessment1), 24 participants who met the inclusion and exclusion criteria were assessed. As shown in the flowchart, in Figure 4, there were sample losses, so only 12 subjects participated in the complete outcome analysis.

The characterization of subjects who finished the program is shown in Table 5.

3.2. Dependent Outcomes

3.2.1. Ventilatory Variables. The muscle strength respiratory assessments and the spirometry flow and volume outcomes are given in mean, standard deviation, 95% confidence interval, and p value. When the difference was significant, the effect size and statistical power for these comparisons were calculated (Table 6).

Table 2: Phase of familiarization with the liquid environment.

Volume (min)	1st month	2nd month	3rd month
4	Transversal rotation	Vertical position floatation	Rolling freely in the water
4	Sagittal rotation	Longitudinal rotation	Mixed/combined rotation

Table 3: Phase of specialized therapeutic exercises.

4 min each
1st month
Tandem gait forward and backward, holding a small ball
Trunk balance: Sitting on a pool noodle, not touching the feet on the bottom of the floor. Staying still or moving with upper limb movements
2nd month
Gait with an obstacle (up and down)
The upper spine: Extending the upper spine from a prone position, holding on to a bar or pool noodle with outstretched upper limbs; associated with respiratory training
The lower spine and gluteal muscles: Taking the lower limbs to the bottom of the pool from a supine position, contracting the abdomen, holding on to a bar with the upper limbs, and having a pool noodle in the lower limbs
3rd month
Tandem gait forward and backward, wearing ankle buoyancy cuffs to increase instability
Changing postures: kneeling, partially kneeling, and standing
Ball and bat: In a horizontal (supine or prone) position, embracing the knees (in ball position), then extending the spine and upper and lower limbs (in bat position)
Stretching at the end (2x 30 seconds for each member in each exercise)
Exercise
Stretching the ischiotibial and gastrocnemius muscles; one lower limb stretched forward, in unipedal support.
Stretching the quadriceps and iliopsoas muscles; one lower limb with the knee flexed and the hip extended, keeping the ankle behind the body, in unipedal support.
Stretching the quadriceps and iliopsoas muscles; one lower limb with the knee flexed and the hip extended, keeping the ankle behind the body, in unipedal support.
Stretching the large dorsal muscle, standing, hands together over the head, inclining the trunk sideways.
Stretching pectoral muscles; supporting an upper limb against the wall, twisting the trunk to the opposite side of the stretch

Table 4: Phase of global organic conditioning.

Exercise (≅12 min of exercise)	1st month	2nd month	3rd month
Stationary bicycle	x	x	x
Jump with upper and lower limb anteroposterior movement	x	x	x
Jumping jacks, taking the upper limbs to the water surface	x		
Swimming with a pool noodle under upper limbs, making front crawl lower limb movements	x		
Standing girdle dissociation, pool noodle under upper limbs, laterally pushing the water surface		x	x
"Swimming"; pool noodle between lower limbs, making displacement movements with upper limbs		x	
Free displacement (swimming), without any floating devices			x

Use the BORG scale every 4 minutes—the professional outside the pool times and takes notes regarding each participant.

The respiratory force variables had significant intervention-related differences. MIP increased significantly between Assessments 2 and 3 ($p = 0.026$); however, comparing Assessments 3 and 4, the intervention gains did not remain after follow-up ($p = 0.024$). There was also a statistical difference in MEP between Assessments 2 and 3 ($p \geq 0.001$), demonstrating a post-intervention gain in expiratory force, which decreased afterward between Assessments 3 and 4 ($p = 0.009$).

There were statistical differences in the spirometry means for FVC between Assessments 2 and 3 ($p = 0.015$)—FVC increased after the intervention. MVV had statistical differences between Assessments 2 and 3 ($p \geq 0.001$). MVV increased after the intervention and then significantly decreased between Assessments 3 and 4 ($p = 0.006$).

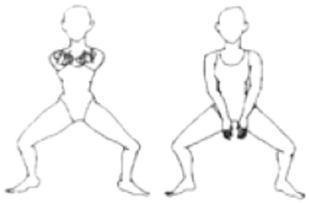
Regarding classification with spirometry, there were two cases of restrictive and two of mixed ventilatory disorders in the sample in Assessments 1, 2, and 3. In Assessment 4, there were two cases of mixed and one restrictive ventilatory disorder, according to the described inference criteria.

The secondary outcomes, perception of fatigue and gait capacity, are described in Table 7. There were statistical differences in fatigue between Assessments 2 and 3 ($p < 0.001$), indicating a decrease in complaints of fatigue after the intervention program. However, the reported

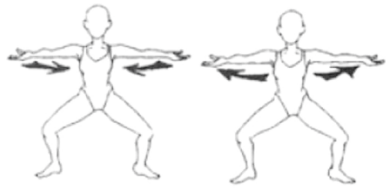
1st, 2nd, and 3rdmonth

Ai Chi: points 2 to 5, 2x each.

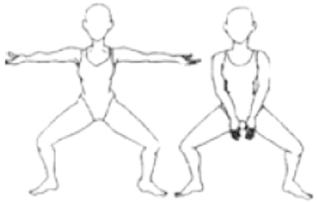
2. Floating
(inspiration: flexing; expiration: extending)



4. Closing
(inspiration: abducting horizontally;
expiration: adducting horizontally)



3. Raising
(inspiration: abducting; expiration: adducting)



5. Crossing
(inspiration: rotating inward;
expiration: rotating outward)

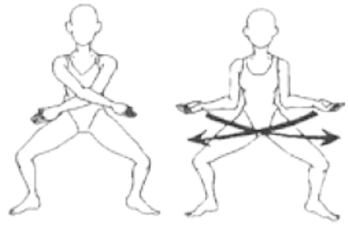


Figure 3: Phase of relaxation.

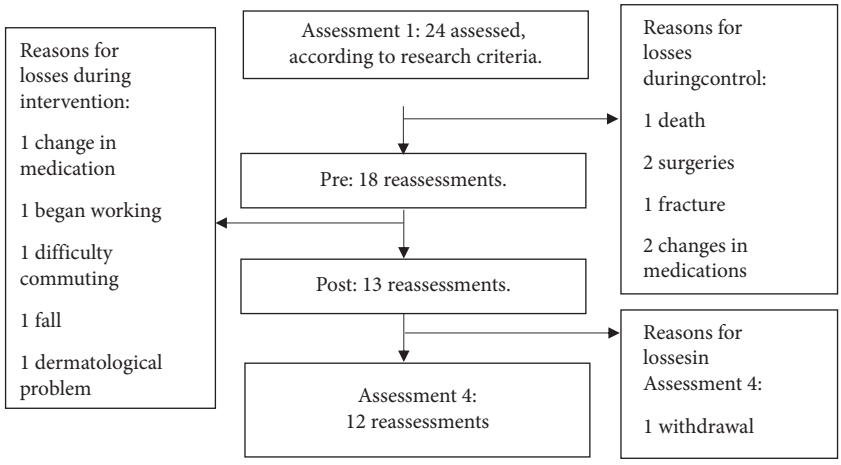


Figure 4: Flowchart of research sample losses.

Table 5: Sample characterization.

Sex (females, males) HY (I, II, III, IV)	5 men, 7 women 1, 4, 3, 4 Mean ± SD 95% CI (min-max)
Time since diagnosis (years)	8.5 ± 6.58 (3.782012–13.21)
Levodopa dose (mg/day)	570 ± 194.65 (430.75–709.24)
Age (years)	71.3 ± 5.61 (67.28–75.31)
Height (m)	1.61 ± 0.081 (1.55–1.67)
MoCA	21.3 ± 4.66 (17.96–24.63)

Source: the author (2020). Legend: HY: Hoehn & Yahr scale; SD: standard deviation; 95% CI: 95% confidence interval; mg: milligrams; m: meters; kg: kilograms.

fatigue increased between Assessments 3 and 4 ($p = 0.006$). Lastly, no difference was observed in the 6 MWT in the four research assessments.

4. Discussion

The proposed aquatic intervention had positive results in ventilatory variables and perception of fatigue, although it did not have a statistically significant increase in gait capacity assessed with 6 MWT. These results are relevant because respiratory impairments are greatly debilitating complications, expected in PD progression.

Table 6: Respiratory variables per assessment period.

Variables	Assessment 1 mean ± SD 95% CI (min-max)	Assessment 2 mean ± SD 95% CI (min-max)	Assessment 3 mean ± SD 95% CI (min-max)	Assessment 4 mean ± SD 95% CI (min-max)	p value
MIP (cmH_20)	44.1 ± 16.38 (32.38 55.81)	43 ± 15.47* (31.92–54.07)	52.6 ± 19.16*& (38.88–66.31)	46 ± 16.12& (34.46–57.53)	$p = 0.001^{(GG)}$ Effect size = 0.528 Power = 0.961
MEP (cmH_20)	37.9 ± 14.31 (27.65–48.14)	36.1 ± 11.72*(27.71–44.48)	45.8 ± 12.4*& (36.92–54.67)	41.7 ± 10.9& (33.89–49.5)	$p = 0.001$ Effect size = 0.567 Power = 0.998
FVC (%)	84.2 ± 19.64 (70.14–98.25)	79.2 ± 18.17*(66.2–92.19)	94.8 ± 21.25* (79.59–110)	87.4 ± 17.89 (74.59–100.2)	$p = 0.001$ Effect size = 0.374 Power = 0.954
FEV1 (%)	88.1 ± 22.46 (72.02–104.17)	86.09 ± 21.18 (71.85–100.32)	91.5 ± 23.21 (74.89–108.1)	85.8 ± 23.17 (69.21–102.38)	$p = 0.074$
FEV1/FVC	81.02 ± 10.04 (73.83–88.20)	82. ± 7.97* (77.18–88.6)	76.53 ± 7.53* (69.14–79.91)	77.1 ± 7.65 (71.62–82.57)	$p = 0.006$ Effect size = 0.308 Power = 0.872
MVV (%)	57.2 ± 24.74 (39.5–74.89)	55.95 ± 24.91* (38.12–73.77)	69.8 ± 18.85*& (56.31–83.28)	63.1 ± 21.47& (47.74–78.45)	$p \leq 0.001$ Effect size = 0.588 Power = 0.999

Source: the author (2020). Legend: SD: standard deviation; 95% CI: 95% confidence interval; min: minimum; max: maximum; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; cmH_2O: centimeters of the water column; %: percent; FVC: forced vital capacity; FEV1: forced expiratory volume; FEV1/FVC: tiffeneau index; MVV: maximum voluntary ventilation; [GG]: sphericity not assumed, greenhouse-Geisser correction used; *: astatistical difference between assessments 2 and 3; &: astatistical difference between assessments 3 and 4.

Table 7: Fatigue and 6-minute walk tests per assessment period.

	Assessment 1 mean ± SD 95% CI (min-max)	Assessment 2 mean ± SD 95% CI (min-max)	Assessment 3 mean ± SD 95% CI (min-max)	Assessment 4 mean ± SD 95% CI (min-max)	p value
Fatigue scale	4.49 ± 0.93 (3.82–5.16)	4.6 ± 0.58* 4.25–5.09	2.56 ± 0.93* (1.89–3.23)	4.81 ± 0.78& (4.25–5.38)	$p = 0.009$ Effect size = 0.736 Power = 0.999
6MWT (m)	400.7 ± 236.15 (231.76–569.63)	388.9 ± 206.08 (241.47–536.32)	433.1 ± 229.23 (269.11–597.08)	372.3 ± 151.54 (263.88–480.71)	$p = 0.144^{(GG)}$

Source: the author (2020). Legend: 6MWT: 6-minute walk test; SD: standard deviation; 95% CI: 95% confidence interval; *: astatistical difference between assessments 2 and 3; &: astatistical difference between assessments 3 and 4; [GG]: sphericity not assumed, greenhouse-Geisser correction used.

We determined the inclusion of participants with Hoehn and Yahr = 4, in order to include people with greater limitations in physical exercises, and we continue to recommend it for future studies. Few studies include severely ill patients, failing to propose activities that include this population. In addition, it seems that aquatic exercise is recommended more intensively for subjects with body balance disorders [40].

A review of aquatic exercise in PD included stages 1 to 4 of PD, showing no adverse effects in participants during aquatic therapy intervention. Our participants with Hoehn and Yahr = 4 also had no limitations in exercise participation and there were no issues related to unexpected submersion [41].

Respiratory muscle strength was one of the outcomes in this study that had positive results from the aquatic intervention in people with PD. On average, MIP increased by 18.25% and MEP, by 21.18% from pre- to post-intervention. Conducting the intervention in an aquatic environment possibly favored such gains because the water provides different ventilation stimuli from the land—the immersed chest suffers hydrostatic pressure, which creates inspiratory resistance and thus a type of overload [42]. The respiratory muscles responsible for inspiration need to surpass the overload, increasing respiratory strength [26]. Moreover, hydrostatic pressure is related to the depth and position of the body in the pool [26]. As the pool used for the intervention was 1.20 m deep, participants stayed with immersion between cervical (C2–C7) and upper thoracic (T1–T6) levels

when in the standing posture. This favored respiratory training, especially inspiratory.

Upper trunk immersion in water also causes acute ventilation adaptations, as it increases inner pressure [26]. Blood circulation is redistributed, and its central volume increases due to vasoconstriction in the limbs [42], especially in those more deeply immersed in the pool [26].

The gain in expiratory strength performance in aquatic intervention, though seemingly not grounded on hydrostatic pressure, may depend on other factors more related to the physical activity, which likely stimulate muscle groups that aid forced expiration. Muscles such as the abdominal ones are known to promote forced expiratory strength [43]. Thus, as the water changes body control—often without a base of support [44, 45]—recruiting core and abdominal muscle control and strength, the aquatic setting stimulates the person to seek body stabilization, activating especially the trunk muscles.

Lower FVC spirometry outcomes in PD patients have been reported in other cross-sectional studies [2–39, 42–47]. After aquatic exercises, we obtained a mean 16.45% FVC difference from pre-to post-intervention (Assessments 2 and 3).

Immersing the body in the water by the xiphoid process has a 7% to 9% difference in vital capacity in comparison with immersing to the neck [26], with possible negative consequences during immersion [48]. However, carefully planned clinical trials benefit the patients [40], using water resistance to the trunk as inspiratory resistance training. Since ventilation is performed by skeletal striated muscles, it responds to carefully planned intervention programs [49].

Muscle stiffness is one of the PD characteristics, especially in the trunk [5], stiffening the chest and impairing its expansibility [50]. Hence, the proposed exercises are associated with the benefits of heated water to stiffness. Heat transfer and temperature interaction are more intense in immersion [26]. The temperature used in the present study (approximately 33°C) influences muscle tone regulation and diminishes involuntary movements, which are recurrent in neurological cases [26]. Hence, it is believed that less stiff muscles aided more functional chest expansion, leading to higher FVC.

There was no statistically significant difference in FEV1 between the assessments in the present study. FEV1 is closely related to obstructive events and can be influenced by parasympathetic changes in PD. These may be the cause of reported obstructive disorders related to the upper airways [51]. The aquatic intervention program did not impact possible obstructions because it did not have approaches specifically aiming at upper airway obstruction [51].

In fact, FEV1 seems to be little responsive to other modalities of physical activity. Colgrove et al. [14] used yoga physical exercises in interventions, with FVC and FEV1 as outcomes. The yoga intervention lasted 12 weeks, with two sessions a week, which increased FVC after the exercise protocol. On the other hand, as in the present study, they obtained no differences in FEV1. Already the study of Silveira et al. [16] which used two forms of land exercise (functional and aerobic) and assessed chest expansibility, MIP, MEP, FVC, and FEV1–find any FEV1 improvements. The groups only differed in that the functional exercise one had a statistical difference in FVC.

Regarding MVV in the present study, 92.3% of the sample was individually below the recommended in Assessment 1 (MVV >80%). MVV indicates the endurance capacity of the ventilatory system [32]. After the aquatic intervention program, this variable not only significantly increased but also had a moderate effect size (0.596) and the greatest statistical power (0.999).

A cross-sectional study compared PD patients with healthy people and found a statistically significant difference in MVV [52]. On average, those in the PD group had 52.83% of the expected MVV, while the healthy ones had 91.52% of MVV [52]. In another cross-sectional study, Bonjorni et al. [32] demonstrated that MVV correlated in direct proportion with MEP and 6 MWT. These papers show the importance of considering together the respiratory and gait outcomes in PD. Particularly as hypoxic environments increase neurodegeneration, promoting an adequate ventilation volume may prevent neuronal loss [51].

In the present study, the subjective assessment of fatigue was one of the outcomes with the greatest difference before and after the heated pool intervention. There was a 45.18% mean difference in the subjective report of fatigue, with a 0.736 effect size and 0.999 statistical power. Thus, it corroborates the literature, which says that physical activity decreases fatigue and improves motor function and physical capacities in PD [53]. A positive aspect regarding fatigue in the studies on physical activities is the few reports of adverse effects, differently from medication use [54]. Nevertheless, in the present study, fatigue significantly worsened back in Assessment 4, i.e., 3 months after discontinuing the aquatic exercise program, participants reported statistically worse fatigue. Such worsening after finishing the aquatic interventions possibly reflects the progressive nature of PD. These combined results demonstrate firstly that the PD patients' fatigue condition can be changed with aquatic physical exercises and secondly that the stimuli must be continued to maintain the response.

Corroborating these fatigue findings, Ortiz-Rubio et al. addressed land exercises concerning fatigue outcomes in PD patients and the control group. The approach proved to effectively decrease reported fatigue, which was statistically different after the intervention both comparing the groups after the intervention and comparing before and after within the intervention group [55].

It is a complex issue to dissociate subjective fatigue from other findings in PD. Fatigue may be related to respiratory variables, which are much associated with peripheral vasoconstriction in the Metabo reflex mechanism [56]. Metabo reflex can be currently proven in milder land activities [56], reflecting everyday physical-motor difficulties [55]. Muscle stiffness may also be somehow related to the perception of fatigue. In the heated pool intervention, the temperature reduces such excessive tension [57], thus potentially influencing the reported fatigue.

Regarding exercise and gait capacity, PD patients have reportedly reached maximum O_2uptake and consumption earlier than healthy controls [58], possibly reporting fatigue

earlier and with less effort. This shows why PD patients tend to be more sedentary than same-age healthy people [58]. The literature has consolidated reports on the low self-effectiveness of people with PD [59]. Hence, professionals who prescribe physical activities and health administrators must individually identify the barriers to adherence to physical activity [59].

Gait capacity mean values did not reach, in any of the four 6 MWT assessments in the present study, the recommended for healthy older people in the community, which ranges from 392 m to 572 m on average, depending on their age and sex [60]. The body functions involved in the hypotheses that explain poorer 6 MWT performance are the pulmonary, cardiac, cognitive, and orthopedic functions and nutrition [37]. Since gait results from these various functions and structures, as well as other factors, gait intervention must address all these functional capacities. However, the proposed program did not provide significant differences after 3 months of aquatic exercises.

Greater gait distances in PD have been knowingly associated with better-preserved brain mass assessed 9 years later, which was also associated with a significantly lower risk of cognitive impairment [61]. In 6 MWT Assessment 3 (post-intervention), the mean distance was 44.2 m longer than in Assessment 2—which, on average, does not reach the minimum detectable difference for this test in PD, which is 83 m [60].

One hypothesis to explain difficulties in gait capacity is precisely related to ventilatory limitations found in this sample. The neural activity for respiratory muscles and other noble body functions may trigger neuromotor detachment, redirecting energy from peripheral motor activity to essential functions, such as breathing and heartbeat [62]. People with PD possibly have neuromotor detachment as well in situations that require a combined motor and cardiorespiratory responses, as in submaximal tests like 6 MWT. This occurs mainly due to cardiorespiratory complications, with inefficient gaseous exchange incapable of maintaining O_2 and CO_2 homeostasis—which commonly occurs in increased dead space, pulmonary hyperinflation, and chronic obstructive pulmonary disease [62].

The aquatic environment potentially provides neuromotor stimuli to trigger gait, with different efferent neuromotor actions from land. Thus, PD patients normally find it easier to walk in the water after adapting to it, due to the change in central pattern [17], which requires greater cortical recruitment—a circuit less dependent on dopamine.

As pointed out by Israel [45], interventions based on motor learning phases aiming at independence in the water enable participants to enjoy an environment with fewer limitations. They can even make movements that would not be possible on land because of the action of forces, especially gravity. Hence, in the therapeutic pool, PD patients explore and activate neuromotor pathways that aid in motor learning and compensation, especially when there are neurofunctional sequelae [40, 45–64].

Nonetheless, besides the slower motor learning rate in PD, they are seemingly dependent on the environment where the skill was trained [65]. This barrier is called set-shifting deficit or stuck-in-set perseveration [66]. A study reported the difficulty of transferring motor skills from the water to the land [67]. The neurophysiological mechanism demonstrating exactly how physical activities can compensate the motor pathways and counterbalance aging and sedentarism in PD is being studied [54].

Lastly, the literature [66] demonstrates that motor neurorehabilitation needs overlap with ventilatory needs in PD. The findings of the present study suggest that aquatic physical therapy stimulates the ventilatory function along with motor therapy in PD. When therapy needs are treated in combination with physical exercises, limitations are prevented or minimized—which is currently an emerging need in PD.

5. Conclusion

The aquatic physical exercise intervention program for people with PD positively increased respiratory strength (both inspiratory and expiratory), FVC, MVV, and fatigue. In the control period, no outcome presented differences; however, the respiratory strength, FVC, MVV, and fatigue statistically worsened after the follow-up period (3 months after intervention), receding to levels near those of Assessment 2 (pre-intervention).

Data Availability

Underlying data may be requested from the research authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) Finance t.Code 001

References

[1] G. Baille, A. M. De Jesus, T. Perez et al., "Ventilatory dysfunction in Parkinson's disease," *Journal of Parkinson's Disease*, vol. 6, no. 3, pp. 463–471, 2016.

[2] K. M. Torsney and D. Forsyth, "Respiratory dysfunction in Parkinson's disease," *The Journal of the Royal College of Physicians of Edinburgh*, vol. 47, no. 1, pp. 35–39, 2017.

[3] S. Pennington, K. Snell, M. Lee, and R. Walker, "The cause of death in idiopathic Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 16, no. 7, pp. 434–437, 2010.

[4] J. d. S. Thomé, L. Olmedo, F. M. d. Santos, K. L. Magnani, P. d. T. Müller, and G. Christofoletti, "Pacientes com doença de Parkinson sob assistênciafisioterapêutica apresentam parâmetros pulmonares melhores do que controlessedentários," *Fisioterapia e Pesquisa*, vol. 23, no. 1, pp. 30–37, 2016.

[5] G. Baille, T. Perez, D. Devos, V. Deken, L. Defebvre, and C. Moreau, "Early occurrence of inspiratory muscle weakness in Parkinson's disease," *PLoS One*, vol. 13, no. 1, Article ID e0190400, 2018.

[6] L. F. Owolabi, M. Nagoda, and M. Babashani, "Pulmonary function tests in patients with Parkinson's disease: a case control study," *Nigerian Journal of Clinical Practice*, vol. 19, no. 1, pp. 66–70, 2016.

[7] M. Siciliano, L. Trojano, G. Santangelo, R. Micco, G. Tedeschi, and A Tessitore, "Fatigue in Parkinson's disease, a systematic review and meta-analysis," *Movement Disorder*, vol. 33, no. 11, pp. 712–1723, 2018.

[8] S. H. Fox, R. Katzenschlager, S. Y. Lim et al., "International Parkinson and movement disorder society evidence-based medicine review: update on treatments forthe motor symptoms of Parkinson's disease," *Movement Disorders*, vol. 33, no. 8, pp. 1248–1266, 2018.

[9] A. R. Plecash and B. R. Leavitt, "Aquatherapy for neurodegenerative disorders," *Journal of Huntington's Disease*, vol. 3, no. 1, pp. 5–11, 2014.

[10] S. Vijayan, B. Singh, S. Ghosh, R. Stell, and F. L. Mastaglia, "Brainstem ventilatory dysfunction: a plausible mechanism for dyspnea in Parkinson's disease?" *Movement Disorders*, vol. 35, no. 3, pp. 379–388, 2020.

[11] B. Yamaguchi, D. D. Iucksch, and V. L. Israel, "Parâmetros ventilatórios naDoença de Parkinson revisão de literatura," *Revista Inspirar Movimento eSaúde*, vol. 19, no. 2, 2019.

[12] A. Reyes, A. Castillo, J. Castillo, and I. Cornejo, "The effects of respiratory muscle training on peak cough flow in patients with Parkinson's disease: a randomized controlled study," *Clinical Rehabilitation*, vol. 32, no. 10, pp. 1317–1327, 2018.

[13] Y. U Kuo, J. Chan, Y. U Wu, J. R. Bernard, and Y. I. Liao, "Effect of expiratory muscle strength training intervention on the maximum expiratory pressure and quality of life of patients with Parkinson disease," *Neuro Rehabilitation*, vol. 41, no. 1, pp. 219–226, 2017.

[14] Y. Colgrove, N. Sharma, K. Robbins, and K. Wagner, "A randomized controlled pilot study of the therapeutic effects of yoga in people with Parkinson's disease," *International Journal of Yoga*, vol. 8, no. 1, pp. 74–79, 2015.

[15] W. M. Alves, T. G. Alves, R. M. Ferreira et al., "Strength training improves there spiratory muscle strength and quality of life of elderly with Parkinson disease," *The Journal of Sports Medicine and Physical Fitness*, vol. 59, no. 10, pp. 1756–1762, 2019.

[16] R. A. D. Silveira, K. V. Trippo, G. P. Duarte, M. Gomes Neto, J. Oliveira Filho, and D. D. Ferraz, "The effects of functional training and stationary cycling on respiratory function of elderly with parkinson disease: a pilot study," *Fisioterapiaem Movimento*, vol. 31, Article ID e003119, 2018.

[17] E. E. Kurt, B. Büyükturan, Ö. Büyükturan, H. R. Erdem, and F. Tuncay, "Effects of Ai Chi on balance, quality of life, functional mobility, and motor impairment in patients with Parkinson's disease," *Disability & Rehabilitation*, vol. 40, no. 7, pp. 791–797, 2018.

[18] J. Vivas, P. Arias, and J. Cudeiro, "Aquatic therapy versus conventional land-based therapy for Parkinson's disease: an open-label pilot study," *Archives of Physical Medicine and Rehabilitation*, vol. 92, no. 8, pp. 1202–1210, 2011.

[19] D. Volpe, M. G. Giantin, R. Maestri, and G. Frazzitta, "Comparing the effects of hydrotherapy and land-based therapy on balance in patients with parkinson's disease: a randomized controlled pilot study," *Clinical Rehabilitation*, vol. 28, no. 12, pp. 1210–1217, 2014.

[20] C. Ayán and J. Cancela, "Feasibility of 2 different water-based exercise trainingprograms in patients with Parkinson's disease: a pilot study," *Archives of Physical Medicine and Rehabilitation*, vol. 93, no. 10, pp. 1709–1714, 2012.

[21] I. L. P. Villegas and V. L. Israel, "Effect of the AI-CHI method on functional activity, quality of life, and posture in patients with Parkinson disease," *Topicsin Geriatric Rehabilitation*, vol. 30, no. 4, pp. 282–289, 2014.

[22] J. Siega, D. D. Iucksch, A. Z. Da Silva, T. G. G. Zotz, and V. L. Israel, "Parkinson's disease and multicomponent aquatic exercise: effects on motor aspects, functional mobility, muscle function and aquatic motor skills," *Journal of Bodywork and Movement Therapies*, vol. 27, pp. 314–321, 2021.

[23] J. Jung, E. Chung, K. Kim, B. H. Lee, and J. Lee, "The effects of aquatic exercise on pulmonary function in patients with spinal cord injury," *Journal of Physical Therapy Science*, vol. 26, no. 5, pp. 707–709, 2014.

[24] S. Adams, S. Hutton, A. Janszen et al., "Effects of an individualized aquatic therapy program on respiratory muscle function in adolescents with muscular dystrophy," *Archives of Physical Medicine and Rehabilitation*, vol. 97, no. 10, pp. E130–E131, 2016.

[25] T. Karampitsakos, K. Dimakou, and D. Bouros, "Role of aquatic therapy andspeleotherapy as complementary therapies in the respiratory system," *Pneumon*, vol. 29, no. 4, pp. 269–273, 2016.

[26] D. A. Maniu, E. A. Maniu, and I. Benga, "Effects of an aquatic therapy program on vital capacity, quality of life and physical activity index in children with cerebral palsy," *HVM Bioflux*, vol. 5, no. 3, pp. 117–124, 2013.

[27] J. R. Thomas, J. K. Nelson, and S. J. Silverman, *Métodos de Pesquisa Ematividade Física*, Artmed, Porto Alegre, Brazil, 6 edition, 2012.

[28] Brasil—Conselho Nacional de Saúde, *Resolução No 466: Diretrizese Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos, de12 de Dezembro de 2012*, Brasil Conselho Nacional, Brasília, Brazil, 2012.

[29] M. R. Miller, J. Hankinson, V. Brusasco et al., "Standardisation of spirometry," *European Respiratory Journal*, vol. 26, no. 2, pp. 319–338, 2005.

[30] C. A. C. Pereira, "Espirometria," *Jornal Brasileiro de Pneumologia*, vol. 283 pages, 2002.

[31] S. Valderramas, A. C. Feres, and A. Melo, "Reliability and validity study of a Brazilian-Portuguese version of the fatigue severity scale in Parkinson's disease patients," *Arquivos de Neuro-Psiquiatria*, vol. 70, no. 7, pp. 497–500, 2012.

[32] L. A. Bonjorni, M. Jamami, V. A. P. Di Lorenzo, and B. V. Pessoa, "Influência da doença de Parkinson em capacidade física, função pulmonar eíndice de massa magra corporal," *Fisioterapia em Movimento*, vol. 25, no. 4, pp. 727–736, 2012.

[33] S. H. J. Keus, M. Munneke, and M. Graziano, *European Physiotherapy Guideline for Parkinson's Disease*, KNGF/ ParkinsonNet, Nijmegen, The Netherlands, 1 edition, 2014.

[34] V. L. Israel and M. B. L. Pardo, "Hydrotherapy: a teaching program to develop aquatic motor skills of injured spinal cord in thermal pool," *Revista Fisioterapia em Movimento*, vol. 1, no. 13, pp. 111–127, 2000.

[35] C. E. Garber, B. Blissmer, M. R. Deschenes et al., "American college of sports medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness inapparently healthy adults: guidance for prescribing exercise," *Medicine and Science in Sports and Exercise*, vol. 43, no. 7, pp. 1334–1359, 2011.

[36] E. A. Miranda, L. W. P. Pereira, P. M. Montserrat, and G. H. M. Oliveira, "Proceeding of the cardiac of the heart rate, perception subjective effort and blood pressure in walker of

two cities of Minas Gerais," *Revista Conexão Ciência*, vol. 11, no. 1, pp. 27–33, 2016.

[37] T. T. C. Capato, J. M. M. Domingos, and L. R. S. Almeida, *Versão Emportuguês da Diretriz Europeia de Fisioterapia para a Doença de Parkinson*, Omnifarma Editora e Eventos, São Paulo, Brazil, 1 edition, 2015.

[38] A. Field, *Descobrindo a Estatística Usando O SPSS. 2ª Edição. Tradução Lorí Viali*, Artmed, Porto Alegre, Brazil, 2009.

[39] IBM Corp Released, *IBM SPSS Statistic for Windows, Version 22*, IBM Corp, Armonk, NY, USA, 2013.

[40] L. Cugusi, A. Manca, M. Bergamin et al., "Aquatic exercise improves motor impairments inpeople with Parkinson's disease, with similar or greater benefits than land-based exercise:a systematic review," *Journal of Physiotherapy*, vol. 65, no. 2, pp. 65–74, 2019.

[41] L. M. Carroll, M. E. Morris, W. T. O'Connor, and A. M. Clifford, "Is aquatic therapy optimally prescribed for Parkinson's disease? A systematic review and meta-analysis," *Journal of Parkinson's Disease*, vol. 10, no. 1, pp. 59–76, 2020.

[42] A. D. de Andrade, J. C. Júnior, T. L. Lins de Barros Melo, C. S. F. Rattes Lima, D. C. Brandão, and J. de Melo Barcelar, "Influence of different levels of immersion in water on the pulmonary function and respiratory muscle pressure in healthy individuals: observational study," *Physiotherapy Research International*, vol. 19, no. 3, pp. 140–146, 2013.

[43] L. Ramos, D. R. Neves, V. P. Lima et al., "Análise de parâmetros pneumofuncionais empacientes com doença de Parkinson: estudo piloto," *Revista Brasileira de Neurologia*, vol. 50, no. 2, pp. 38–43, 2014.

[44] K. M. Porter, C. A. Hoglund, and S. Henry, "The difference in efficiency and pulmonary function while performing cycle ergometry on land and in water," *International Journal of Undergraduate Research and Creative Activities*, vol. 10, p. 1, 2018.

[45] V. L. Israel, "Aquatic physical therapy: the aquatic functional assessment scale (AFAS) in muscular dystrophy," *The Journal of Aquatic Physical Therapy*, vol. 26, no. 1, 2018.

[46] Y. Wang, W. B. Shao, L. Gao et al., "Abnormal pulmonary function and respiratory muscle strength findings in chinese patients with parkinson's disease and multiple system atrophy-comparison with normal elderly," *PLoS One*, vol. 9, no. 12, Article ID e116123, 2014.

[47] G. Baille, C. Chenivesse, T. Perez et al., "Dyspnea: an underestimated symptom in Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 60, pp. 162–166, 2019.

[48] K. H. Anstey and C. H. Roskell, "Detrimental or beneficial to the respiratory system?" *Physiotherapy*, vol. 86, pp. 5–13, 2000.

[49] G. M. d. Alvarenga, S. A. Charkovski, L. K. d. Santos, M. A. B. d. Silva, G. O. Tomaz, and H. R. Gamba, "The influence of inspiratory muscle training combined with the pilates method on lung function in elderly women: arandomized controlled trial," *Clinics*, vol. 73, p. e356, 2018.

[50] L. M. Oliveira, M. A. Oliveira, H. T. Moriya, T. S. Moreira, and A. C. Takakura, "Respiratory disturbances in a mouse model of Parkinson's disease," *Experimental Physiology*, vol. 104, no. 5, pp. 729–739, 2019.

[51] R. Ribeiro, D. Brandão, J. Noronha et al., "Breath-stacking and incentive spirometry in Parkinson's disease: randomized crossover clinical trial," *Respiratory Physiology & Neurobiology*, vol. 255, pp. 11–16, 2018.

[52] M. Polatli, A. Akyol, O. Cildag, and K. Bayulkem, "Pulmonary function tests in Parkinson's disease," *European Journal of Neurology*, vol. 8, no. 4, pp. 341–345, 2001.

[53] J. L. Sabino-Carvalho, A. L. Teixeira, M. Samora, M. Daher, and L. C. Vianna, "Blunted cardiovascular responses to exercise in Parkinson's disease patients: role of the muscle metaboreflex," *Journal of Neurophysiology*, vol. 120, no. 4, pp. 1516–1524, 2018.

[54] R. G. Elbers, J. Verhoef, E. E. H. Van Wegen, H. W. Berendse, and G. Kwakkel, "Interventions for fatigue in Parkinson's disease," *Cochrane Database of Systematic Reviews*, vol. 10, Article ID CD010925, 2015.

[55] A. Ortiz-Rubio, I. Cabrera-Martos, I. Torres-Sánchez, J. Casilda-López, L López-López, and M. C. Valenza, "Effects of a resistance training program on balance and fatigue perception in patients with parkinson's disease: a randomized controlled trial," *Medicina Clínica*, vol. 150, no. 12, pp. 460–464, 2018.

[56] D. B. Phillips and M. K. Stickland, "Respiratory limitations to exercise in health: a brief review," *Current Opinion in Physiology*, vol. 10, pp. 173–179, 2019.

[57] C. Pinto, A. P. Salazar, R. R. Marchese, C. Stein, and A. S. Pagnussat, "The effects of hydrotherapy on balance, functional mobility, motor status, and quality of life in patients with Parkinson disease: a systematic review and meta-analysis," *PM&R*, vol. 11, no. 3, pp. 278–291, 2019.

[58] A. D. Speelman, B. P. van de Warrenburg, M. van Nimwegen et al., "How might physical activity benefit patients with Parkinson disease?" *Nature Reviews Neurology*, vol. 7, no. 9, pp. 528–534, 2011.

[59] T. Ellis and L. Rochester, "Mobilizing parkinson's disease: the future of exercise," *Journal of Parkinson's Disease*, vol. 8, no. s1, pp. S95–S100, 2018.

[60] T. M. Steffen, T. A. Hacker, and L. Mollinger, "Age- and gender-related test performance in community-dwelling elderly people: six-minute walk test, berg balance scale, timed up & go test, and gait speeds," *Physical Therapy*, vol. 82, no. 2, pp. 128–137, 2002.

[61] J. E. Ahlskog, "Does vigorous exercise have a neuroprotective effect in Parkinson disease?" *Neurology*, vol. 77, no. 3, pp. 288–294, 2011.

[62] L. C. Aranda, J. L. C. Sabino-Carvalho, T. Miranda-Silva, and M. Paula-Ribeiro, "Abnormal muscle metaboreflex control of ventilation in patients with chronic obstructive pulmonary disease: what mechanisms should be blamed?" *The Journal of Physiology*, vol. 594, no. 24, pp. 7173-7174, 2016.

[63] V. L. Israel and M. B. L. Pardo, "Hydrotherapy: application of an aquatic functional assessment scale (AFAS) in aquatic motor skills learning," *American International Journal of Contemporary Research*, vol. 4, no. n2, pp. 42–52, 2014.

[64] A. Z. d. Silva and V. L. Israel, "Effects of dual-task aquatic exercises on functional mobility, balance and gait of individuals with Parkinson's disease: a randomized clinical trial with a 3-month follow-up," *Complementary Therapies in Medicine*, vol. 42, pp. 119–124, 2019.

[65] Z. Wang, Y. Guo, K. G. Myers, R. Heintz, and D. P. Holschneider, "Recruitment of the prefrontal cortex and cerebellum in Parkinsonian rats following skilled aerobic exercise," *Neurobiology of Disease*, vol. 77, pp. 71–87, 2015.

[66] S. Onla-Or and C. J. Winstein, "Determining the optimal challenge point for motor skill learning in adults with moderately severe Parkinson's disease," *Neurorehabilitation and Neural Repair*, vol. 22, no. 4, pp. 385–395, 2007.

[67] B. Yamaguchi, M. de Paula Ferreira, and V. L. Israel, "Aquatic physiotherapy and Parkinson's disease: effects on functional motor skills," *Advances in Parkinson's Disease*, vol. 9, no. 1, pp. 1–12, 2020.

Hindawi
Parkinson's Disease
Volume 2022, Article ID 8448638, 8 pages
https://doi.org/10.1155/2022/8448638

Research Article

Short-Term Motor Outcomes in Parkinson's Disease after Subthalamic Nucleus Deep Brain Stimulation Combined with Post-Operative Rehabilitation: A Pre-Post Comparison Study

Kazunori Sato,[1] **Yoshihide Hokari**,[2] **Eriko Kitahara**,[1] **Nana Izawa**,[1] **Kozo Hatori**,[3] **Kaoru Honaga**,[1] **Genko Oyama**,[4] **Taku Hatano**,[4] **Hirokazu Iwamuro**,[5,6] **Atsushi Umemura**,[5,6] **Yasushi Shimo**,[7] **Nobutaka Hattori**,[4,5] **and Toshiyuki Fujiwara**[1,8]

[1]*Department of Rehabilitation Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[2]*Department of Rehabilitation Medicine, Juntendo University Nerima Hospital, Tokyo, Japan*
[3]*Department of Rehabilitation Medicine, Juntendo University Urayasu Hospital, Tokyo, Japan*
[4]*Department of Neurology, Juntendo University Hospital, Tokyo, Japan*
[5]*Department of Research and Therapeutics for Movement Disorders, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[6]*Department of Neurosurgery, Juntendo University Hospital, Tokyo, Japan*
[7]*Department of Neurology, Juntendo University Nerima Hospital, Tokyo, Japan*
[8]*Department of Physical Therapy, Juntendo University Faculty of Health Science, Tokyo, Japan*

Correspondence should be addressed to Kazunori Sato; ksatoh@juntendo.ac.jp

Received 7 October 2021; Revised 1 June 2022; Accepted 21 June 2022; Published 12 August 2022

Academic Editor: Giuseppina Martella

Background. The effects of subthalamic nuclear deep brain stimulation therapy (STN-DBS) and combined postoperative rehabilitation for patients with Parkinson's disease with postural instability have yet to be well reported. This study investigated the effects of short-term postoperative rehabilitation with STN-DBS on physical function in patients with Parkinson's disease. *Methods*. Patients diagnosed with Parkinson's disease who were admitted to our hospital for STN-DBS surgery were included in this study. Data were prospectively collected and retrospectively analyzed. Postoperative rehabilitation consisted of muscle-strengthening exercises, stretching, and balance exercises for 40–60 minutes per day for approximately 14 days. The Mini-Balance Evaluation Systems Test (Mini-BESTest), Timed Up and Go test (TUG) seconds and steps, Trunk Impairment Scale (TIS), seconds for 10 times toe-tapping, lower limb extension torque using StrengthErgo240, and center of pressure sway in the quiet standing posture were evaluated preoperatively, postoperatively, and at discharge. Mini-BESTest changes were also evaluated in the two groups classified by the presence or absence of postural instability. One-way and two-way repeated measures analyses of variance were performed for each of the three periods of change, and paired *t*-tests with the Bonferroni method were performed as multiple comparison tests. A stepwise multiple regression model was used to identify factors associated with balance improvement. *Results*. A total of 60 patients with Parkinson's disease were included, and there were significant increases in Mini-BESTest, TIS, StrengthErgo240, and postural sway during closed-eye standing compared to pre- and postoperative conditions at discharge ($p < 0.05$), and they decreased significantly compared to the postoperative period ($p < 0.05$). On stepwise multiple regression analysis, decreased steps of TUG and improvement of TIS scores were related to improvement of the Mini-BESTest ($p < 0.05$). In addition, Mini-BESTest scores in both groups with and without postural instability were significantly increased at discharge compared to preoperative and postoperative conditions ($p < 0.01$). *Conclusion*. Postoperative rehabilitation combined with STN-DBS may provide short-term improvements in physical function compared with the preoperative medicated status. The improvements in gait step length and trunk function may be important factors for obtaining improvement of postoperative postural stability.

1. Background

Parkinson's disease (PD) is a neurodegenerative disease characterized by slowly progressive motor and nonmotor impairments caused by decreased dopamine neurons in the substantia nigra of the midbrain. In addition to the three major signs of resting tremor, muscle rigidity, and bradykinesia, PD patients present with a variety of manifestations, including postural instability and cognitive decline in the advanced stages of the disease [1, 2]. Since a quarter of a century ago, subthalamic nuclear stimulation therapy (STN-DBS) has been adopted worldwide to reduce motor complications and wearing-off symptoms in PD patients [3–6]. However, previous studies that reported the effect of STN-DBS on postural instability were limited. Some observational studies showed that STN-DBS did not improve postural stability after surgery compared to before on-medication status [7, 8]. The randomized, controlled trials showed that the effect of STN-DBS on balance function did not exceed the best-medicated state before surgery [3, 8–11]. In contrast, a few studies reported the effectiveness of STN-DBS for postural instability and postural deformity. A retrospective study suggested that the STN-DBS was effective for improving motor disability and balance performance [12]. Another retrospective study indicated the positive effect of STN-DBS for postural alignment [4]. A few studies, although very limited in number, have investigated the impact of combined post-operative rehabilitation therapy after STN-DBS [13–15]. Previous studies have reported that postoperative rehabilitation in conjunction with stimulation adjustment after STN-DBS improves activities of daily living (ADL), gait, and balance function. However, the improvement in balance function is still limited to cases of mild postural instability [13, 15], and which physical functions contribute to the improvement in postural instability has not been considered. Several studies have shown that background factors that contribute to balance function include trunk function, lower extremity muscle strength, bradykinesia, and walking ability [16–20]. Therefore, the following two points were examined in the present study. First, the effects of postoperative rehabilitation combined with STN-DBS on balance function in PD patients were examined. Which background factors (trunk function, gait speed, step counts, lower extremity bradykinesia, and lower extremity muscle strength) may be associated with changes in balance function was also investigated. Second, how balance function, which was considered to be poorly improved by STN-DBS, changed when patients were divided into two groups based on the presence or absence of postural instability before surgery was also examined.

2. Methods

2.1. Research Design. A pre- and postcomparison study was conducted at a single acute care hospital in Tokyo. The data were collected prospectively and analyzed retrospectively. Consecutive PD patients admitted to our hospital for STN-DBS surgery were included in the study. Based on the sample size calculation, the target number of patients was 66, when the results of each assessment parameter were assumed to be compared among the three groups of before, after, and at the time of discharge, with an effect size of 0.25, a significance level of 0.05, and power of 0.95. This study procedure was conducted with the approval of the ethics committee of Juntendo University Hospital (JHS18-276).

2.2. Study Subjects. Consecutive patients admitted to the Juntendo University Hospital between March 1, 2017, and December 31, 2018, for STN-DBS surgery and who underwent rehabilitation after surgery were included. The exclusion criteria were as follows: (1) those with complications (orthopedic diseases, such as osteoarthritis, or medical diseases, such as heart failure) that significantly reduced physical functioning before surgery; and (2) those who developed serious psychiatric symptoms as a complication of the surgery itself or who presented with delirium after surgery.

An interdisciplinary team including neurologists and neurosurgeons specialized in movement disorders evaluated the indications for STN-DBS a few months before STN-DBS surgery in all cases. The indications for STN-DBS followed our criteria [21]: (1) a clinical diagnosis of clinically established or clinically probable PD [1]; (2) severe diurnal fluctuations despite appropriate medication (e.g., dopamine-induced dyskinesia, wearing-off phenomenon, and on-off phenomenon) or inability to sufficiently increase the L-dopa medication dose due to side effects; (3) a good response to L-dopa medications (>30% improvement on the L-dopa challenge test); (4) no cognitive decline or psychiatric symptoms (Mini-Mental State Examination scores >24/30); (5) consented to and requested surgery; (6) no complications affecting electrode implantation (previous neurosurgery, tumors, calcification, etc.); (7) no cardiac pacemaker treatment; (8) an ability to tolerate general anesthesia; and (9) age less than 70 years desirable (age 70 years or older evaluated on an individual basis).

2.3. Postoperative Rehabilitation. Postoperative rehabilitation began on the third day after STN-DBS implantation surgery, and all patients received physical therapy for 40–60 minutes per day for approximately 14 days. The therapeutic intervention was carried out by a physical therapist skilled in movement disorders and was based on the neurological physical therapy guidelines for PD. It consisted of a general physical therapy program that included a combination of muscle-strengthening exercises, stretching, and balance exercises. STN-DBS stimulation began approximately 7 days after surgery, and the L-dopa medication dose was reduced as the intensity of the current increased and replaced the efficacy of the L-dopa medication. Approximately 2 weeks after surgery, the neurologist and neurosurgeon adjusted the amount of stimulation and dose reduction.

2.4. Clinical Assessment. At the time of admission for evaluation, the neurologist performed the L-dopa challenge test and assessed part III of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor items at the Off-state and Highest On-state. At the time of admission for surgery, physical function assessments were performed by a physical therapist at three points: preoperatively, three days after surgery, and immediately before discharge. All physical function assessments were performed between 60 and 120 minutes after oral medication, which is considered to be the On-state for PD medication.

2.4.1. Mini-Balance Evaluation Systems Test. The Mini-Balance Evaluation Systems Test (Mini-BESTest) is a balance assessment test reported by Franchignoni et al. in 2010 that has been widely used around the world [22]. This test consists of four different balance items (anticipatory postural adjustment, reactive postural control, sensory integration, and dynamic gait) to comprehensively evaluate standing balance and gait function. The lowest score is 0, and the highest scored is 28, with higher scores indicating higher balance ability. In recent years, it has become a commonly used balance assessment test for PD patients because it is less likely to produce a ceiling effect in assessing balance function in PD patients and can predict falls [23, 24].

2.4.2. Timed "Up and Go" Test. Gait function was assessed by the Timed "Up and Go" Test (TUG) used during the Mini-BESTest and the TUG-cognitive (TUG-cog) seconds and steps, respectively, in which the TUG is performed with a cognitive task [25]. The TUG is widely used worldwide to assess gait function in various neurological diseases, and more recently, it has been widely used to assess gait function in PD patients [26].

2.4.3. Trunk Impairment Scale. The Trunk Impairment Scale (TIS) was reported in 2004 by Fujiwara et al. and was created to assess trunk function in stroke [27]. It consists of seven different items (vertical axis perception, left-right rotator strength, right-right turn reflex, left-right righting reflex, verticality, and forward abdominal muscle strength) and can assess various characteristics of the trunk individually.

2.4.4. Evaluation of General Lower Extremity Extension Torque Using the StrengthErgo240. General lower limb extension muscle strength (Newton-meter) was evaluated using the StrengthErgo240 (SE240 : Mitsubishi Electric Engineering Corporation, Tokyo, Japan) [28]. Measurements were made in isokinetic mode with five consecutive drives at a rotational speed of 50 rotations/minute, and the peak left-right extension torque was measured during the lower limb's extension movement. The backrest angle was set at 110°, and the seat position was set, so that the knee joint was at 30° flexion and the ankle joint was at 0° dorsiflexion during maximum unilateral lower limb extension. Measurements were taken as the average of the right and left lower limb extension muscle forces.

2.4.5. Lower Limb Bradykinesia Test (10 Toe-Tapping Seconds). Lower extremity bradykinesia was assessed with MDS-UPDRS part III, item 7, toe-tapping (10 taps, as large and as fast as possible, with the toe) [29], and the seconds of tapping was measured. The measurements were averaged over the left and right sides.

2.4.6. Postural Sway Test. Postural sway during opening and closing of the eyes in the standing posture was measured using Noraxon's myoPressure™ (Noraxon Inc., USA). The center of pressure (COP) 95% range circle, COP path length, and COP mean velocity were measured during both eye-opened and eye-closed standing postures for 30 seconds.

2.4.7. Levodopa Daily Dose and Levodopa Equivalent Daily Dose. The levodopa daily dose (LDD) and levodopa equivalent daily dose (LEDD) were recorded based on the worldwide conversion method proposed by Tomlinson et al. to ensure the appropriateness of STN-DBS therapy [30].

2.5. Statistical Analysis

2.5.1. Statistical Analysis for Study 1. The Mini-BESTest, TUG, TIS, SE240, 10 toe-tapping in seconds, gravity sway during eye-opening/closed standing, LDD, and LEDD at three time-points (before surgery, three days after surgery, and just before discharge) were calculated, and one-way repeated measures analysis of variance (ANOVA) was used to detect significant differences among the three 3 temporal moments. If there were significant differences, Bonferroni's paired *t*-tests were performed as post hoc multiple comparison tests. The correlations between the Mini-BESTest and other changed parameters of the assessments were analyzed by Spearman's correlation coefficients. The variance inflation factor was calculated to detect multicollinearity among dependent variables. After the determination of multicollinearity, multiple regression analysis was used to identify which improvements of physical functions were predictors of improvement of Mini-BESTest scores. The improvements were defined as the differences between the before surgery and the discharge-period scores.

2.5.2. Statistical Analysis for Study 2. To analyze therapeutic effects in the patients with PD both who have postural instability or not before operation, number 12 of the MDS-UPDRS part III, postural stability item, were performed at the time of the assessment admission. A score of 3 or more on the PS item in the MDS-UPDRS indicates the absence of postural response [29]. According to this classification, we divided the patients into two groups: those with a postural

stability score of 3 or more (with moderate or greater postural instability) and a mild case group with less than 3 points. Welch's t-test was used to test for significant differences between the two groups in basic information. In addition, the Mini-BESTest scores of the two groups were measured at three time-points (preoperatively, three days after surgery, and just before discharge) to detect significant differences among the three groups by two-way repeated measures ANOVA, and if there was a significant difference, post hoc paired t-tests using the Bonferroni method were performed as multiple comparison tests.

All statistical analyses were performed using the statistical software R (ver. 3.6.2), and the significance level was set at $p < 0.05$. Randomly occurring missing values were complemented by the multiple imputation method.

3. Results

Sixty-six patients were included in the study. Five patients were excluded due to postoperative delirium or worsening of psychiatric symptoms, and one patient was excluded due to complications of spinal canal stenosis, which had a strong impact on physical function. Thus, 60 of the 66 patients were included in this study. Table 1 shows the demographic data of the total eligible cases and the basic attributes of the MDS-UPDRS part III postural stability items at the time of admission for evaluation, with the cases divided into those with a score of 3 or more and a score of less than 3.

3.1. Results of Study 1. The results of each clinical assessment are shown in Table 2. On ANOVA, there were significant differences in Mini-BESTest, TUG steps, TUG-cog steps, TIS, 10 toe taps, SE240, gravitational sway during closed-eyed standing, and LEDD. There were no significant differences in gait speed or center of gravity sway during open-eyed quiet stance. Multiple comparisons of the above clinical assessments, which were significantly different by ANOVA analysis, were performed using the Bonferroni method of paired t-tests, and the results showed that Mini-BESTest, TIS, SE240, 95% circle of the center of gravity (COP) during the closed-eyed stance, COP pass length, and COP mean speed were significantly increased at discharge compared to preoperative and postoperative; in TUG/TUG-cog steps, LDD, and LEDD, there were significant decreases at discharge status compared to preoperative and postoperative; in 10 toe taps, there was a significant decrease in time at discharge compared to preoperative and postoperative. Spearman's correlation coefficients showed the correlations between the Mini-BESTest and TUG seconds ($r = -0.54$, $p < 0.01$), TUG steps ($r = -0.54$, $p < 0.01$), TUG-cog seconds ($r = -0.51$, $p < 0.01$), TUG-cog steps ($r = -0.41$, $p < 0.01$), TIS ($r = 0.25$, $p = 0.05$), 10 toe taps ($r = -0.04$, $p = 0.79$), SE240 ($r = 0.06$, $p = 0.63$), eye-opened COP 95% range circle ($r = 0.20$, $p = 0.11$), eye-opened COP path length ($r = 0.35$, $p < 0.01$), eye-opened COP mean velocity ($r = 0.34$, $p < 0.01$), eye-closed COP 95% range circle ($r = 0.21$, $p = 0.09$), eye-closed COP path length ($r = 0.29$, $p = 0.03$), and eye-closed COP mean velocity ($r = 0.33$, $p < 0.01$). On multiple regression analysis, decreased steps of TUG and increased TIS scores were identified as predictors of improvement on the Mini-BESTest ($p < 0.05$) in Table 3.

3.2. Results of Study 2. Two-way repeated ANOVA showed significant differences in the Mini-BESTest in both groups ($p < 0.01$), with no interaction ($p = 0.41$). Multiple comparisons with the Bonferroni method of paired t-tests showed a significant increase in condition at discharge from the hospital in both groups compared to preoperative and postoperative ($p < 0.01$) (Figure 1).

4. Discussion

In this study, we observed the combined effect of STN-DBS and postoperative acute rehabilitation on balance function, which had not been previously clarified, and what these changes contributed to, as well as whether there was a combined effect of STN-DBS with postoperative rehabilitation on patients with PD who had postural instability from before surgery, was investigated. The results suggested that patients with PD who underwent early postoperative rehabilitation after STN-DBS improved their On-state balance and gait function compared with those who received the best medication before surgery, and the balance function was also improved in the group of patients who had postural instability before surgery.

Previous studies reporting the effects of STN-DBS postoperative rehabilitation reported improvements in scores of the Unified Parkinson's disease rating scale, Activities of Daily Living, and balance function, but it is not clear what contributed to the improvements in balance function [13, 15]. In the present study, postoperative rehabilitation combined with adjustment of stimulation settings and medications improved balance function, trunk function, lower limb muscle strength, and the number of steps during gait. It has been reported that trunk function, lower limb muscle strength, and stride length are related to balance function in PD [16–19]. Therefore, it is necessary to take into account the possibility that improvements in trunk function, lower limb muscle strength, and stride length contributed to the improvement of balance function. Multiple regression analysis suggested that a decrease in the number of steps taken, especially during walking, and improvements in trunk function may contribute to the improvement of balance function. Therefore, in the short term, the improvement of walking stride and trunk function may contribute more to the improvement of balance function than the improvement of lower limb muscle strength.

According to a previous study that reported the effects of early postoperative rehabilitation after STN-DBS, the balance function and gait ability may be improved in the short term when the subject has postural instability [15], but the present study, regardless of the presence or absence of postural instability, showed the possibility of improvement in balance and gait functions. Therefore, even in the short term, combining rehabilitation with adjustment of stimulation and medication after STN-DBS surgery in all cases

Table 1: Demographic data of the participants.

	Total ($n = 60$)	PI ≥ 3 ($n = 18$)	PI < 3 ($n = 42$)	p value between PI ≥ 3, PI < 3
Age, years	60.7 (8.9)	61.2 (9.9)	60.5 (8.6)	0.81
Sex, female/male	28 (47%)/32 (53%)	13 (72%)/5 (28%)	15 (36%)/27 (64%)	—
Duration of disease, years	12.2 (4.6)	12.8 (4.3)	11.9 (4.8)	0.49
Duration of medication, years	10.6 (4.1)	10.1 (4.1)	11.9 (4.0)	0.12
H & Y stage (on-state)	2.4 (0.7)	2.8 (0.5)	2.2 (0.7)	<0.001**
MDS-UPDRS part III score of preoperation (on-state)	18.1 (8.6)	24.9 (6.9)	15.1 (7.6)	<0.001**
MDS-UPDRS part III 12 postural stability score of preoperation (on-state)	1.2 (1.3)	3.0 (0)	0.4 (0.6)	<0.001**
Final stimulation setting				
Pulse, microseconds	58.8 (4.9)	57.2 (7.3)	59.4 (3.3)	0.24
Hz	131.2 (6.5)	131.0 (7.1)	131.2 (6.3)	0.90
mA	1.8 (0.5)	1.8 (0.5)	1.8 (0.5)	0.97
Preoperative LDD	740 (272)	806 (275)	712 (269)	0.22
Discharge LDD	332 (218)	300 (227)	345 (216)	0.46
Preoperative LEDD	1464 (490)	1549 (456)	1439 (496)	0.43
Discharge LEDD	847 (456)	846 (502)	844 (444)	0.99
Duration of hospitalization, days	25.2 (16.9)	24.7 (14.3)	25.4 (18.1)	0.88

Data are means (SD), n (%). abbreviations: H & Y, Hoehn and Yahr; MDS-UPDRS, movement disorders society-unified Parkinson's disease rating scale; PI, MDS-UPDRS part III 12 postural instability score; LDD, levodopa daily dose; LEDD, levodopa equivalent daily dose.

Table 2: Results of post-operative rehabilitation with STN-DBS.

		PRE	POST	DISC	p value ANOVA	F value	p value (PRE-POST)	p value (PRE-DISC)	p value (POST-DISC)
Mini-BESTest		19.8 (5.1)	20.3 (4.8)	23.1 (4.3)	<0.0001**	32.2	N.S	**	**
TUG seconds		10.4 (4.0)	11.3 (6.0)	9.7 (3.3)	0.053	3.0	N.S	N.S	N.S
TUG steps		17.1 (7.2)	17.1 (6.5)	14.7 (3.7)	0.003**	6.1	N.S	**	**
TUG-cog seconds		14.4 (7.3)	15.9 (14.1)	12.2 (4.7)	0.046*	3.2	N.S	N.S	*
TUG-cog steps		23.2 (15.8)	22.1 (10.9)	17.5 (5.3)	0.005**	5.6	N.S	**	*
TIS		17.3 (3.8)	17.5 (3.1)	18.8 (2.5)	<0.0001**	11.8	N.S	**	**
10 times toe-tapping time (seconds)		4.4 (1.4)	4.0 (0.8)	3.8 (0.8)	0.0008**	7.7	*	**	N.S
StrengthErgo240 (Newton-meter)		143.1 (71.6)	142.9 (73.5)	157.9 (74.8)	<0.0001**	15.0	N.S	**	**
Eyes opened standing	COP 95% range circle (mm^2)	1175.5 (2206.3)	1077.9 (1274.7)	1293.3 (1906.7)	0.80	0.2	N.S	N.S	N.S
	COP path length (mm)	632 (587.9)	705.5 (654.7)	794.6 (687.0)	0.41	0.9	N.S	N.S	N.S
	COP average speed (mm/sec)	21.7 (18.6)	22.8 (21.0)	24.0 (21.0)	0.89	0.1	N.S	N.S	N.S
Eyes closed standing	COP 95% range circle (mm^2)	1029.2 (1162.9)	1150.1 (1588.5)	2027.4 (2835.6)	0.011*	4.7	N.S	**	*
	COP path length (mm)	880.9 (726.7)	926.0 (811.8)	1200.4 (1174.8)	0.04*	3.4	N.S	*	*
	COP average speed (mm/sec)	22.8 (20.3)	28.2 (25.6)	36.7 (35.8)	0.007**	5.2	N.S	*	*
LDD		740 (272)	767 (240)	332 (218)	<0.0001**	109.2	N.S	**	**
LEDD		1464 (490)	1462 (516)	847 (456)	<0.0001**	208.8	N.S	**	**

Data are mean (SD), * $p < 0.05$, ** $p < 0.01$. abbreviations: PRE, preoperation; POST, postoperation; DISC, discharge; TUG, timed up and go test; TUG-cog, timed up and go test cognitive tasking; TIS, trunk impairment scale; mini-BESTest, mini-balance evaluation systems test; LDD, levodopa daily dose; LEDD, levodopa equivalent daily dose; COP, center of pressure.

Table 3: Multiple regression analysis for the prediction of mini-BESTest score improvements.

	β	p value	VIF	R^2
TUG steps	−0.544	<0.0001**	1.41	0.4425
TIS	0.2859	0.023*	1.07	

Data are means (SD), *$p < 0.05$, **$p < 0.01$. abbreviations: β, standardised partial regression coefficient; VIF, variance inflation factor; R^2, multiple coefficient of determination; TUG, timed up and go test; TIS, trunk impairment scale.

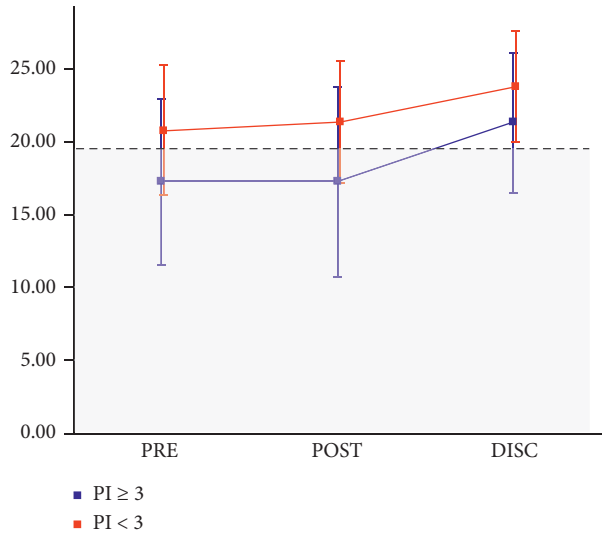


Figure 1: Mini-BESTest score changes in patients with and without postural instability. *gray field indicates the risk of falls (mini-BESTest < 19 points). abbreviations: mini-BESTest, mini-balance evaluation systems test; PI, the point of movement disorder society unified Parkinson's disease rating scale-part III 12 (postural stability score); PRE, preoperation period; POST, postoperation period; DISC, discharge period.

may bring some benefits. Indeed, the present result showed that the short-term improvement in the mean Mini-BESTest value was above the cutoff value (Figure 1 and Table 3), which is 19 points, as shown in our previous study [23]. In addition, the changes in the Mini-BESTest in the present study were also clinically meaningful compared to the previous study of neurological diseases including PD, which has been reported to be 4 points [31].

As stated in research reports investigating the mid-to-long-term physical performance after STN-DBS surgery, the effect of STN-DBS surgery on axial symptoms was said to be poor [7, 32]. However, due to the scarcity of studies that have investigated the short-term effects of STN-DBS on physical function, it is not possible to provide a definitive answer about the short-term effects of STN-DBS monotherapy on physical performance. A double-blind study reported that STN-DBS had no significant effect on postural stability assessed with Mini-BESTest, whereas STN-DBS improved overall motor performance assessed by UPDRS motor examination [33]. If stimulation of STN-DBS had no direct effect on postural stability, postoperative rehabilitation with stimulation would have some positive effect on the learning of postural stability. In this study, since the effects of rehabilitation after STN-DBS surgery were not directly compared with those of rehabilitation combined with drug treatment, it is difficult to give a clear answer regarding the difference in effects. However, there is a possibility that the combined use of rehabilitation after STN-DBS surgery can be expected to have an effect on the physical function that exceeds the maximum physical function during preoperative drug treatment, and we can recommend the use of postoperative rehabilitation in a clinical setting.

In the present study, there was no change in gravitational sway during open-eye standing, but gravitational sway during eye closure was significantly increased at discharge. Previous studies have reported a concern that STN-DBS was less effective in reducing center of gravity sway, namely, static balance [34], and the present results agreed with this. Another study reported the opposite result to the present study, that STN-DBS reduces center of gravity sway but does not improve dynamic balance [32]. In the present study, center of gravity sway was increased during eye closure even though overall balance function was improved. This suggests that postoperative rehabilitation with STN-DBS was not effective for keeping quiet standing without visual sensory input, and this might reflect acutely changed sensory integration of proprioceptive and vestibular inputs. It is unclear whether these changes represent a novel motor learning process or just a short-term postoperative complication, and further research is needed.

4.1. Limitations. There are many limitations to this study. One is the weakness of the study design. Because medical guidelines recommend rehabilitation of patients with PD, it would be unethical to design a study in which postoperative rehabilitation of STN-DBS patients was not performed. Therefore, it was difficult to design a case-control study design with a control group. In addition, because this study had no control group, it was difficult to investigate the effects of STN-DBS treatment and postoperative neurological physical therapy separately. Furthermore, it is difficult to determine the long-term effects of postoperative rehabilitation. In the present study, there was an improvement in trunk function and lower extremity muscle strength, as well as balance function, but a direct causal relationship between trunk function and lower extremity muscle strength and improvement in balance function cannot be directly addressed due to the study design. In addition, further study is needed to determine what kind of postoperative physical therapy is most appropriate for the patient. In light of the above, case-control studies by intervention type and randomized, controlled trials with target groups need to be performed in the future to better understand the effects of postoperative rehabilitation.

5. Conclusion

The combination of STN-DBS postoperative stimulation therapy with rehabilitation may provide short-term

improvements in physical function that cannot be achieved with preoperative drug therapy alone. In addition, the effects of postoperative rehabilitation may also be reflected in postural stability, which has been considered to be difficult to achieve with STN-DBS.

Abbreviations

STN-DBS:	Subthalamic nuclear stimulation therapy
MDS-UPDRS:	Movement disorder society-unified Parkinson's disease rating scale
Mini-BESTest:	Mini-balance evaluation systems test
TUG:	Timed up and go test
TIS:	Trunk impairment scale
LDD:	Levodopa daily dose
LEDD:	Levodopa equivalent daily dose.

Data Availability

The data used in the current study to support the findings are included within this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

KS and TF conceived the study. KS led the statistical analyses. KS and NI drafted the manuscript. YH, EK, KH, GO, TH, KI, AU, and YS reviewed and critiqued the manuscript. NH and TF edited the manuscript. All authors have read and approved the manuscript.

Acknowledgments

The medical staff of the Laboratory of Rehabilitation Medicine, Juntendo University Graduate School of Medicine supported this study.

References

[1] R. B. Postuma, D. Berg, M. Stern et al., "MDS clinical diagnostic criteria for Parkinson's disease," *Movement Disorders*, vol. 30, no. 12, pp. 1591–1601, 2015.

[2] L. V. Kalia and A. E. Lang, "Parkinson's disease," *The Lancet*, vol. 386, no. 9996, pp. 896–912, 2015.

[3] V. J. Odekerken, T. van Laar, M. J. Staal et al., "Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial," *The Lancet Neurology*, vol. 12, no. 1, pp. 37–44, 2013.

[4] A. Umemura, Y. Oka, K. Ohkita, T. Yamawaki, and K. Yamada, "Effect of subthalamic deep brain stimulation on postural abnormality in Parkinson disease," *Journal of Neurosurgery*, vol. 112, no. 6, pp. 1283–1288, 2010.

[5] J. A. Vizcarra, M. Situ-Kcomt, C. A. Artusi et al., "Subthalamic deep brain stimulation and levodopa in Parkinson's disease: a meta-analysis of combined effects," *Journal of Neurology*, vol. 266, no. 2, pp. 289–297, 2019.

[6] K. J. Lizarraga and A. Fasano, "Effects of deep brain stimulation on postural trunk deformities: a systematic review," *Movement Disorders Clinical Practice*, vol. 6, no. 8, pp. 627–638, 2019.

[7] P. Krack, A. Batir, N. van Blercom et al., "Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease," *New England Journal of Medicine*, vol. 349, no. 20, pp. 1925–1934, 2003.

[8] S. Szlufik, M. Kloda, A. Friedman et al., "The neuromodulatory impact of subthalamic nucleus deep brain stimulation on gait and postural instability in Parkinson's disease patients: a prospective case controlled study," *Frontiers in Neurology*, vol. 9, 2018.

[9] R. J. St George, P. Carlson-Kuhta, J. G. Nutt, P. Hogarth, K. J. Burchiel, and F. B. Horak, "The effect of deep brain stimulation randomized by site on balance in Parkinson's disease," *Movement Disorders*, vol. 29, no. 7, pp. 949–953, 2014.

[10] R. J. St George, P. Carlson-Kuhta, L. A. King, K. J. Burchiel, and F. B. Horak, "Compensatory stepping in Parkinson's disease is still a problem after deep brain stimulation randomized to STN or GPi," *Journal of Neurophysiology*, vol. 114, no. 3, pp. 1417–1423, 2015.

[11] P. H. Weiss, J. Herzog, M. Potter-Nerger et al., "Subthalamic nucleus stimulation improves Parkinsonian gait via brainstem locomotor centers," *Movement Disorders*, vol. 30, no. 8, pp. 1121–1125, 2015.

[12] H. Li, S. Liang, Y. Yu et al., "Effect of subthalamic nucleus deep brain stimulation (STN-DBS) on balance performance in Parkinson's disease," *PLoS One*, vol. 15, no. 9, Article ID e0238936, 2020.

[13] C. Tassorelli, S. Buscone, G. Sandrini et al., "The role of rehabilitation in deep brain stimulation of the subthalamic nucleus for Parkinson's disease: a pilot study," *Parkinsonism & Related Disorders*, vol. 15, no. 9, pp. 675–681, 2009.

[14] N. Allert, B. Cheeran, G. Deuschl et al., "Postoperative rehabilitation after deep brain stimulation surgery for movement disorders," *Clinical Neurophysiology*, vol. 129, no. 3, pp. 592–601, 2018.

[15] K. Sato, N. Aita, Y. Hokari et al., "Balance and gait improvements of postoperative rehabilitation in patients with Parkinson's disease treated with subthalamic nucleus deep brain stimulation (STN-DBS)," *Parkinson's Disease*, vol. 2019, Article ID 7104071, 5 pages, 2019.

[16] B. R. Bloem, "Postural instability in Parkinson's disease," *Clinical Neurology and Neurosurgery*, vol. 94, pp. S41–S45, 1992.

[17] M. K. Y. Mak, M. Y. C. Pang, and V. Mok, "Gait difficulty, postural instability, and muscle weakness are associated with fear of falling in people with Parkinson's disease," *Parkinson's Disease*, vol. 2012, Article ID 901721, 5 pages, 2012.

[18] T. Gazibara, D. Kisic-Tepavcevic, M. Svetel et al., "Indoor and outdoor falls in persons with Parkinson's disease after 1 year follow-up study: differences and consequences," *Neurological Sciences*, vol. 37, no. 4, pp. 597–602, 2016.

[19] N. R. Artigas, C. Franco, P. Leao, and C. R. M. Rieder, "Postural instability and falls are more frequent in Parkinson's disease patients with worse trunk mobility," *Arquivos de Neuro-Psiquiatria*, vol. 74, no. 7, pp. 519–523, 2016.

[20] J. H. Park, Y. J. Kang, and F. B. Horak, "What is wrong with balance in Parkinson's disease?" *Journal of Movement Disorders*, vol. 8, no. 3, pp. 109–114, 2015.

[21] G. Oyama, Y. Shimo, S. Natori et al., "Acute effects of bilateral subthalamic stimulation on decision-making in Parkinson's

disease," *Parkinsonism & Related Disorders*, vol. 17, no. 3, pp. 189–193, 2011.

[22] F. Franchignoni, F. Horak, M. Godi, A. Nardone, and A. Giordano, "Using psychometric techniques to improve the balance evaluation systems test: the mini-BESTest," *Journal of Rehabilitation Medicine*, vol. 42, no. 4, pp. 323–331, 2010.

[23] M. K. Mak and M. M. Auyeung, "The mini-BESTest can predict Parkinsonian recurrent fallers: a 6-month prospective study," *Journal of Rehabilitation Medicine*, vol. 45, no. 6, pp. 565–571, 2013.

[24] L. K. R. Lopes, A. A. Scianni, L. O. Lima, R. de Carvalho Lana, and F. Rodrigues-de-Paula, "The mini-BESTest is an independent predictor of falls in Parkinson disease," *Brazilian Journal of Physical Therapy*, vol. 24, no. 5, pp. 433–440, 2020.

[25] D. Podsiadlo and S. Richardson, "The timed "up & go": a test of basic functional mobility for frail elderly persons," *Journal of the American Geriatrics Society*, vol. 39, no. 2, pp. 142–148, 1991.

[26] R. C. Vance, D. G. Healy, R. Galvin, and H. P. French, "Dual tasking with the timed "up & go" test improves detection of risk of falls in people with Parkinson disease," *Physical Therapy*, vol. 95, no. 1, pp. 95–102, 2015.

[27] T. Fujiwara, M. Liu, T. Tsuji et al., "Development of a new measure to assess trunk impairment after stroke (trunk impairment scale): its psychometric properties," *American Journal of Physical Medicine & Rehabilitation*, vol. 83, no. 9, pp. 681–688, 2004.

[28] K. Tateisi, S. Yamada, Y. Omori, T. Kobayashi, Y. Morio, and H. Aoki, "Reliability of strength Ergo 240 for leg extension strength," *Physical Therapy*, vol. 28, no. 7, pp. 329–331, 2001.

[29] C. G. Goetz, B. C. Tilley, S. R. Shaftman et al., "Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results," *Movement Disorders*, vol. 23, no. 15, pp. 2129–2170, 2008.

[30] C. L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, and C. E. Clarke, "Systematic review of levodopa dose equivalency reporting in Parkinson's disease," *Movement Disorders*, vol. 25, no. 15, pp. 2649–2653, 2010.

[31] M. Godi, F. Franchignoni, M. Caligari, A. Giordano, A. M. Turcato, and A. Nardone, "Comparison of reliability, validity, and responsiveness of the mini-BESTest and berg balance scale in patients with balance disorders," *Physical Therapy*, vol. 93, no. 2, pp. 158–167, 2013.

[32] A. Collomb-Clerc and M. L. Welter, "Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: a systematic neurophysiological review," *Neurophysiologie Clinique/Clinical Neurophysiology*, vol. 45, no. 4-5, pp. 371–388, 2015.

[33] M. E. McNeely, T. Hershey, M. C. Campbell et al., "Effects of deep brain stimulation of dorsal versus ventral subthalamic nucleus regions on gait and balance in Parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 82, no. 11, pp. 1250–1255, 2011.

[34] J. Nantel, J. C. McDonald, and H. Bronte-Stewart, "Effect of medication and STN-DBS on postural control in subjects with Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 18, no. 3, pp. 285–289, 2012.

Hindawi
Parkinson's Disease
Volume 2022, Article ID 3191598, 6 pages
https://doi.org/10.1155/2022/3191598

Research Article

Daily Exercise Patterns and Their Differences between Parkinson's Disease Patients with and without Postural Instability

Joomee Song[1,2], **Jun Kyu Mun**[1,2], **Jong Hyeon Ahn**[1,2], **Jinyoung Youn**[1,2], **Inyoung Choi**[1,2] and **Jin Whan Cho**[1,2]

[1]*Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[2]*Neuroscience Center, Samsung Medical Center, Seoul, Republic of Korea*

Correspondence should be addressed to Jin Whan Cho; jinwhan.cho@samsung.com

Received 14 January 2022; Accepted 9 May 2022; Published 19 May 2022

Academic Editor: Carlo Colosimo

Background. Due to the clinical impact of exercise in patients with Parkinson's disease (PD), management should include personalized and effective exercises according to patient's PD stage. We investigated the detailed exercise behaviors of patients with mild to advanced PD and compared their patterns between PD with and without postural instability (PI). *Methods*. We enrolled PD patients from September to December 2019. Clinical data on parkinsonism, exercise behaviors, and Physical Activity Scale of the Elderly (PASE) scores were collected and compared between mild PD without PI (Hoehn–Yahr (HY) stages 1 and 2) and advanced PD with PI (HY stages 3 and 4). *Results*. In total, 263 PD patients were recruited. The mean exercise frequency was 4.7 ± 2.1 times/week, and the average duration was 7.8 ± 6.7 hours/week. The most common exercise was an aerobic exercise (71.9%) of mild-to-moderate intensity, with active walking being the most common (49.0%). The mild PD patients demonstrated a higher duration and intensity of exercise and more physical activity than the advanced PD patients. However, the frequency of exercise was not significantly different between the two groups. The PASE score was significantly higher in mild PD patients than in advanced PD patients ($p < 0.001$). *Conclusion*. PD patients focused mostly on aerobic exercises, especially active walking. With the disease progression, the amount and intensity of exercise decreased while frequency remained. Higher intensity of exercise is needed in the mild PD group, while the advanced PD group requires the increment of duration for each exercise session.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder, and its treatment has traditionally focused on symptomatic management along with dopamine replacement therapy [1]. Unlike pharmacological treatment, exercise improves various motor and nonmotor symptoms in PD without worsening dyskinesia or producing significant side effects [2–5]. In addition, previous studies have revealed a possible disease-modifying effect from exercise in PD patients [4, 6]. Despite some guidelines for exercise in PD patients [7, 8], much controversy remains regarding the detailed protocols for exercise in PD patients. While standardized aerobic exercises were the primary method in most of the previous studies, several studies have approached various kinds of exercises such as land and water-based exercise [9] or mat Pilates [10] and showed positive effects on motor function and quality of life. High-intensity aerobic workouts with a lower extremity cycle ergometer were feasible in PD patients and improved motor symptoms [11]. Still, the exercise is a tremendously complicated behavior depending on various environmental and personal factors. The exercise recommendations should be based on the patients' condition, such as the living area, any comorbidities, and the patient's confidence for exercise.

More importantly, as PD progresses, exercise recommendations should also evolve to adapt to the symptom severity of the patients. Among the motor symptoms of PD, postural instability (PI), which develops as the disease

progresses, has been reported to contribute significantly to both physical inactivity and decreased ADL than other motor symptoms [12–14]. Therefore, it is necessary to understand the exercise behaviors of patients in various stages of PD because these data would be the first step to personalize exercise programs for specific stages of PD and to establish guidelines for effective exercises as part of a treatment plan for PD patients. As part of the exercise behaviors, the exercise type, frequency, and intensity are the most basic parameters, but there is a paucity of knowledge on the best exercise patterns to recommend depending on PD severity.

In this study, we investigated the exercise patterns which include exercise type, frequency, and intensity of PD patients and compared it between PD without PI and PD with PI patients. While investigating the exercise patterns, we also investigated physical activity levels of the patients including intensity of work or household chores. The aim was to identify a baseline for exercise recommendations in PD patients and also to establish necessary changes for PD progression, which could serve as a reference for personalized exercise recommendations for PD patients in the future.

2. Methods

2.1. Participants and Clinical Assessments. We enrolled PD patients who were able to walk independently (Hoehn–Yahr (HY) stage ≤4) [15] from September to December 2019 at the Movement Disorders Clinic of Samsung Medical Center in Seoul, Korea. PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria [16]. We excluded patients with Parkinson-plus syndromes, including multiple systemic atrophy, progressive supranuclear palsy, and corticobasal syndrome, vascular parkinsonism, drug-induced parkinsonism, or normal pressure hydrocephalus; structural brain lesions, including stroke or tumor; cardiopulmonary, musculoskeletal problems, or other neurological conditions (e.g., myelopathy, known neuropathy, and chronic vestibular dysfunction) that preclude any exercise; severe cognitive impairment (4 ≤ Global Deterioration Scale (GDS) score) [17, 18]; and psychiatric diseases requiring medical treatment, including major depressive disorder, bipolar and related disorders, and schizoaffective disorders diagnosed according to DSM-V criteria [19].

Parkinsonian motor symptoms were evaluated using the unified Parkinson's disease rating scale (UPDRS) part 3 and the Hoehn–Yahr (HY) stage in the medication "on" state [15]. The dose of dopaminergic medications was checked using the levodopa equivalent daily dose (LEDD) based on previous literature [20]. We divided all recruited patients into either the mild PD group (HY stages 1-2) who did not have PI or the advanced PD group (HY stages 3-4) who have PI.

2.2. Exercise Behavior and Physical Activity Level Evaluation. We interviewed all the enrolled participants, and they reported the types, duration (hours/session), and frequency (times/week) of recently completed exercises. When they reported multiple exercises, the most frequently preformed exercise was designated as the primary exercise, followed by any secondary and tertiary exercises. The primary exercises were categorized as follows based on the physiology of exercise: aerobic exercise/resistance exercise/stretching [21]. We classified exercises into categories corresponding to their major components. When the major component was obscure, we followed previous studies' classifications which utilized the exercises. Also, we classified the exercises according to home-based (indoor or outdoor)/at sports facilities and solo/group exercise. The types of exercises corresponding to each category are summarized in Supplementary Table 1. The intensity of the primary exercises done by patients was measured using metabolic equivalents (METs), and the exercises were classified as mild (METs ≤ 3), moderate (4 ≤ METs ≤ 6), or high-intensity (7 ≤ METs) exercise [22].

The amount of physical activity undertaken by the included PD patients was evaluated using the Korean version of the Physical Activity Scale of the Elderly (PASE), a validated, self-reported questionnaire that assesses the level of activity over the prior week [23, 24]. Higher PASE scores indicate more physical activity, with scores ranging from 0 to 365 in the validated sample. The final score is calculated by adding up three sections: leisure exercise, work/volunteering, and household chores.

Finally, we classified patients into either the mild PD group (HY stages 1-2) or the advanced PD group (HY stages 3-4) based on the presence of postural instability and compared the exercise patterns between these two groups.

2.3. Statistical Analysis. All data are presented as the mean ± standard deviation. The demographic and clinical data of the mild PD and moderate-to-severe PD groups were compared using Student's *t*-tests or Mann–Whitney *U*-tests for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables. A p value <0.05 was considered significant. Statistical analyses were performed using a commercially available software package (SPSS, Version 25.0., IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic and Clinical Characteristics of Recruited Participants. We screened 323 eligible patients based on our movement clinic records, and 309 were assessed for eligibility in person (Figure 1). In total of 263 PD patients finally enrolled, 210 (79.8%) participants were classified into the mild PD group, while 53 (20.2%) were placed in the advanced PD group. Their mean age was 67.7 ± 29.2 years, and the average disease duration was 8.3 ± 5.2 years. All the demographics, clinical data, and exercise characteristics are given in Table 1.

3.2. Exercise Patterns of PD Patients. The mean exercise frequency and hours were 4.7 ± 2.1 times/week and 7.8 ± 6.7 hours/week, respectively. In total, 24 kinds of

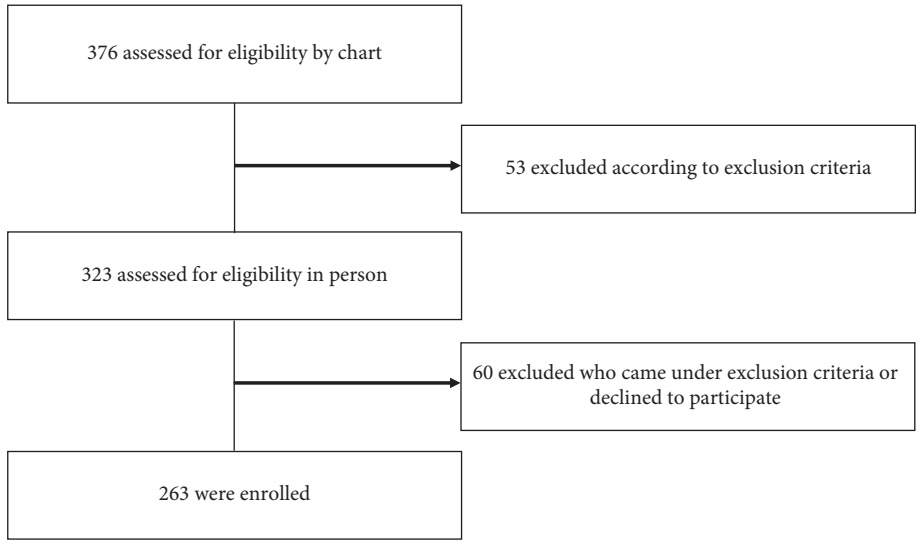


Figure 1: Flowchart to describe the enrolled study population.

Table 1: Demographics, exercise patterns, and PASE scores of Parkinson's disease patients.

	Total ($n = 263$)	HY 1-2 ($n = 210$)	HY 3-4 ($n = 53$)	P value
Demographics				
Age (years)	67.7 ± 29.2	66.5 ± 9.2	72.3 ± 7.1	<0.001
Male, n (%)	129 (49.0)	104 (49.5)	25 (47.2)	0.759
BMI (kg/m^2)	24.8 ± 5.8	24.6 ± 3.3	25.5 ± 11.2	0.276
Disease duration (years)	8.3 ± 5.2	7.4 ± 4.6	11.5 ± 6.1	<0.001
UPDRS part 3	17.6 ± 8.2	15.9 ± 8.2	24.1 ± 8.6	<0.001
LEDD (mg/day)	610.8 ± 400.4	535.9 ± 354.2	907.6 ± 437.0	<0.001
Exercise behaviors				
Frequency (times/week)	4.7 ± 2.1	4.8 ± 2.1	4.3 ± 2.2	0.281
Exercise amount (hours/week)	7.8 ± 6.7	8.5 ± 6.9	5.0 ± 4.9	<0.001
Exercise intensity (mild/moderate/high), n (%)	120 (45.6)/93 (35.4)/43 (16.3)	88 (41.9)/82 (39.0)/39 (18.6)	32 (60.4)/11 (20.8)/4 (7.5)	<0.001
Categories of primary exercise, n (%)				
None	7 (2.7)	1 (0.5)	6 (11.3)	—
Aerobic/resistance/stretching	189 (71.9)/43 (16.3)/24 (9.1)	152 (72.4)/39 (18.6)/18 (8.6)	37 (69.8)/4 (7.5)/6 (11.3)	—
Home-based/ sports facility-based	207 (78.7)/49 (18.6)	164 (78.1)/45 (21.4)	43 (81.1)/4 (7.5)	0.020
Group exercise	22 (8.4)	22 (10.5)	0	0.010
PASE (total score)	51.5 ± 45.4	55.9 ± 47.1	34.1 ± 32.8	<0.001
Leisure exercise	25.7 ± 22.0	28.2 ± 22.7	16.2 ± 16.2	<0.001
Work/volunteering	6.8 ± 25.9	7.5 ± 27.1	4.0 ± 20.2	0.368
Household	19.0 ± 21.4	20.3 ± 22.3	13.9 ± 17.0	0.092

HY, Hoehn–Yahr stage; BMI, body mass index; UPDRS, unified Parkinson's disease rating sale; LEDD, levodopa equivalent daily dose; PASE, Physical Activity Scale of the Elderly.

exercise were reported, and 169 (69.8%) patients noted more than one type of exercise. Among the 24 kinds of primary exercises, the most common exercise was active walking ($n = 129$, 49.0%), followed by stretching (Table 2). When we classified all the exercises into superior categories (i.e., aerobic, resistance, and stretching), aerobic exercise was the most common (71.9%). Additionally, 78.7% of the participants exercised at home, and solo exercise was reported by more than 90% (91.5%). In terms of exercise intensity, exercise with a mild intensity was the most common (45.6%), followed by moderate intensity exercise.

3.3. Comparison of Exercise Patterns between Mild and Advanced PD Patients. When we compared exercise patterns between the two groups, the amount of exercise was significantly lower in the advanced PD group than in the mild PD group, while there was no difference in the frequency of exercise (Table 1). Regarding the exercise intensity, moderate-to-high intensity exercise was performed by 57.6% of the mild PD participants, but only 28.3% of the moderate-to-severe PD patients. While a wide variety of exercises (a total of 24 kinds) was reported by the mild PD group, only 8 types of exercises were reported in the advanced PD group (Table 2). Active walking was the most frequently reported

Table 2: Rank of the specific exercises reported by patients.

Rank	Specific exercises			
	Total	Patients	HY 3-4	Patients
1	Active walking	129	Active walking	32
2	Stretching	21	Stretching	5
3	Table tennis	12	Climbing stairs	3
4	Push-ups, squatting, stationary bike, working out at fitness clubs	10	Stationary bike, squatting	2
6	Yoga	9		
7	Climbing stairs	6		
8	Outside biking, running	5	Physical therapy, weight training, yoga	1
9	Climbing mountains, golf, swimming	4		
10	Badminton, lifting dumbbells, Tai Chi, water aerobics	2		
Else	Basketball, billiards, bowling, dancing (ball room, aerobics), football, physical therapy, Pilates, pull-ups	1		

primary exercise in both groups (50% and 45.2% in the mild and advanced PD groups, respectively). There was no difference in the category of exercise between the two groups, but more patients in the advanced group did home-based exercise and solo exercise compared to the mild PD group.

3.4. Physical Activity Level of PD Patients. The mean K-PASE score of all PD patients was 51.52 ± 45.36, and the mean subscores for each section were 25.7 ± 22.1, 6.8 ± 25.9, and 19.0 ± 21.4 for leisure exercise, work or volunteering, and household chores, respectively (Table 1). When we compared the mean PASE scores between the two groups, the advanced PD group showed a significantly lower total PASE score ($p < 0.001$) and leisure exercise subscore ($p < 0.001$) than the mild PD group. There was no significant difference in PASE work/volunteering and household chores between the two groups.

4. Discussion

To our knowledge, this is the first study to examine the detailed daily exercise patterns and physical activity levels of PD patients in the mild to advanced stages. The advanced PD group reported a lower amount and intensity of exercise and less physical activity compared to the mild PD group. Considering there was no significant difference in the frequency of exercise, advanced PD patients tended to spend less time completing each type of exercise. Based on our results, the exercise recommendations for advanced PD patients should focus on how to increase the duration of each session of exercise and to increase the exercise intensity due to limited mobility.

Not only the decrement of amount and intensity in exercise but also the loss of diversity of exercise was observed in the advanced group. Only 8 kinds of exercise were done in the advanced PD group, whereas 24 types were reported by patients in the mild PD group. Exercises requiring a higher level of balance, like ball games, yoga, or mountain hiking, were not reported in the advanced PD group.

Still, it is encouraging that both mild and advanced PD patients in this study were exercising properly with regards to the duration and frequency of exercise that is recommended by current guidelines [7, 8]. PD patients did exercise regularly (4.7 times a week on average), and the most common exercise pattern was aerobic exercise with a mild-to-moderate intensity. Although there has been no head-to-head comparison study between elderly controls and PD patients, PD patients exercise as much as healthy Korean elderly individuals based on the K-PASE score of healthy Korean elderly people from a previous study [24]. There was no significant difference (according to Mann–Whitney *U*-tests) between the mean PASE leisure exercise score of PD patients (25.7 ± 22.0) and that of healthy Korean elderly individuals (24.6 ± 24.6).

However, the household chores or working scores of PD patients were significantly lower than those of healthy elderly individuals ($p = 0.008$). In addition, compared to the PASE scores of PD patients from the United States (US) [6, 25], our South Korean PD patients did substantially fewer household chores and work/volunteering activities, making their total PASE scores lower. This finding implies that exercise contributes to a large portion of physical activity compared to household chores or working in Korean PD patients.

The most frequently performed exercise in both groups was active walking, which is easily accessible and does not require any equipment or specific places. It is difficult to directly compare our results with PD patients in other countries due to the lack of similar studies, but active walking is a popular exercise not only in PD patients but in the general population in South Korea. Accordingly, a previous study revealed the mean number of daily steps was 5,755 (8^{th}) in South Korea, while the US ranked 29^{th} with 4,774 steps out of 46 countries [26]. Since PD can present with various gait symptoms, active walking is often regarded as an effective exercise for PD patients. However, combined exercises from various categories are typically recommended for PD patients [7, 8]. Therefore, it is also important to recommend that PD patients combine other resistance exercises or stretching for flexibility with walking.

Our study showed most PD patients performed solo exercise, and this tendency was stronger in advanced PD patients. Group exercise offers social support and bonding with other patients, which is important to motivate PD patients to continue exercising. Additionally, most PD patients did home-based exercise, which indicates that it is not easy for PD patients to access sports facilities and perform

sophisticated exercises [27]. Sports facilities are equipped with exercise coaches and various exercising equipment, which allow people to take part in exercise of a higher intensity. Therefore, these higher intensity exercises should be recommended to patients in the mild PD group who already took part in a fair amount of low-intensity exercise.

Our study has strong points. We not only cataloged information about the duration, frequency, and specific type of exercise done by mild to advanced PD patients in their daily lives but also objectively supported and quantified those exercise patterns using the PASE scores. Still this study has some limitations. First, while investigating the exercise patterns of PD patients, we relied on subjective patient reports, which may have introduced reporting and recall biases. However, to address this potential limitation, we used PASE, a validated measurement tool of physical activity that has been demonstrated to correlate with objective measures of aerobic capacity [23]. The PASE was used in a previous study to evaluate physical activity in patients with early PD [6, 25]. Second, the presence of nonmotor symptoms, which may affect the quality and amount of exercise performed, was not investigated. Instead, while enrolling patients, we excluded people who reported dementia or psychiatric problems that could have significantly influenced their exercise patterns. At the same time, however, it is possible that the amount of exercise and physical activity of the advanced PD patients might have been overestimated. Third, we did not enroll a normal matched elderly population to use as a control group and compare with the PD participants. However, a report of the physical activity of a normal elderly population in South Korea using the same scale (K-PASE) has already been published; thus, we were able to use those results indirectly. Last, this was a cross-sectional observational study, so it was difficult to investigate direct changes associated with disease progression and also to show the prognosis based on the exercise level alone in PD patients.

In conclusion, our study demonstrated the real-life exercise patterns of PD patients and the differences between mild and advanced PD patients, which can serve as baseline data for clinicians to plan well-organized, practical exercise regimens for PD patients. The exercise activities reported by PD patients mainly included aerobic exercise with a mild-to-moderate intensity. Based on our results, a greater emphasis on a higher intensity of exercise is needed in the mild PD group, while the advanced PD group requires an increasing amount of time for each exercise session. Future studies will be needed to determine more personalized exercise recommendations for these PD patients.

Data Availability

All data generated or analysed during this study are included in this published article (and its supplementary information files).

Ethical Approval

This study was approved by the Institutional Review Board (IRB) of the Samsung Medical Center.

Consent

Written informed consent was obtained from all participants (IRB number: 2020-09-214).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary Table 1. Specific exercises reported by patients and their exercise categories. (*Supplementary Materials*)

References

[1] M. van Nimwegen, A. D. Speelman, E. J. M. Hofman-van Rossum et al., "Physical inactivity in Parkinson's disease," *Journal of Neurology*, vol. 258, pp. 2214–2221, 2011.

[2] L. J. P. Altmann, E. Stegemöller, A. A. Hazamy et al., "Aerobic exercise improves mood, cognition, and language function in Parkinson's disease: results of a controlled study," *Journal of the International Neuropsychological Society*, vol. 22, no. 9, pp. 878–889, 2016.

[3] M. Schenkman, C. G. Moore, W. M. Kohrt et al., "Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease: a phase 2 randomized clinical trial," *JAMA Neurology*, vol. 75, pp. 219–226, 2018.

[4] N. M. van der Kolk, N. M. de Vries, R. P. C. Kessels et al., "Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial," *The Lancet Neurology*, vol. 18, no. 11, pp. 998–1008, 2019.

[5] J. Marusiak, B. E. Fisher, A. Jaskólska et al., "Eight weeks of aerobic interval training improves psychomotor function in patients with Parkinson's disease—randomized controlled trial," *International Journal of Environmental Research and Public Health*, vol. 16, no. 5, p. 880, 2019.

[6] A. W. Amara, L. Chahine, N. Seedorff, C. J. Caspell-Garcia, C. Coffey, and T. Simuni, "Self-reported physical activity levels and clinical progression in early Parkinson's disease," *Parkinsonism and Related Disorders*, vol. 61, pp. 118–125, 2019.

[7] S. Keus, M. Munneke, M. Graziano et al., "European guidelines for physiotherapy in Parkinson's disease," in *Proceedings of the 17th international Congress of Parkinson's Disease and Movement Disorders*, Sydney, Australia, June 2013.

[8] Parkinson's Foundation, *Exericse Guidelines for Professionals*, Parkinson's Foundation, Miami, FL, USA, 2021.

[9] C. Ayán, J. M. Cancela, A. Gutiérrez-Santiago, and I. Prieto, "Effects of two different exercise programs on gait parameters in individuals with Parkinson's disease: a pilot study," *Gait and Posture*, vol. 39, no. 1, pp. 648–651, 2014.

[10] J. M. Cancela, I. Mollinedo Cardalda, C. Ayán, and I. M. de Oliveira, "Feasibility and efficacy of mat pilates on people with mild-to-moderate Parkinson's disease: a preliminary study," *Rejuvenation Research*, vol. 21, no. 2, pp. 109–116, 2018.

[11] J. M. Cancela, I. Mollinedo, S. Montalvo, and M. E. Vila Suárez, "Effects of a high-intensity progressive-cycle program on quality of life and motor symptomatology in a Parkinson's

disease population: a pilot randomized controlled trial," *Rejuvenation Research*, vol. 23, no. 6, pp. 508–515, 2020.

[12] M. S. Bryant, J. G. Hou, R. L. Collins, and E. J. Protas, "Contribution of axial motor impairment to physical inactivity in Parkinson disease," *American Journal of Physical Medicine and Rehabilitation*, vol. 95, no. 5, pp. 348–354, 2016.

[13] N. E. Allen, A. K. Schwarzel, and C. G. Canning, "Recurrent falls in Parkinson's disease: A systematic review," *Parkinson's Disease*, vol. 2013, Article ID 906274, 16 pages, 2013.

[14] B. Palakurthi and S. P. Burugupally, "Postural instability in Parkinson's disease: a review," *Brain Sciences*, vol. 9, p. 239, 2019.

[15] M. M. Hoehn and M. D. Yahr, "Parkinsonism: onset, progression and mortality," *Neurology*, vol. 17, no. 5, pp. 427–442, 1967.

[16] A. J. Hughes, S. E. Daniel, L. Kilford, and A. J. Lees, "Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 55, no. 3, pp. 181–184, 1992.

[17] S. H. Choi, D. L. Na, B. H. Lee et al., "The validity of the Korean version of global deterioration scale," *Journal of Korean Neurological Association*, vol. 20, pp. 612–617, 2002.

[18] B. Reisberg, S. H. Ferris, M. J. de Leon, and T. Crook, "The Global Deterioration Scale for assessment of primary degenerative dementia," *American Journal of Psychiatry*, vol. 139, pp. 1136–1139, 1982.

[19] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, American Psychiatric Association, Richmond, VA, USA, 5th edition, 2013.

[20] C. L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, and C. E. Clarke, "Systematic review of levodopa dose equivalency reporting in Parkinson's disease," *Movement Disorders*, vol. 25, no. 15, pp. 2649–2653, 2010.

[21] S. K. Powers, E. T. Howley, and J. Quindry, *Exercise Physiology: Theory and Application to Fitness and Performance*, McGrow Hill, New York, NY, USA, 11th edition, 2021.

[22] B. E. Ainsworth, W. L. Haskell, A. S. Leon et al., "Compendium of physical activities: classification of energy costs of human physical activities," *Medicine and Science in Sports and Exercise*, vol. 25, no. 1, pp. 71–80, 1993.

[23] R. A. Washburn, E. McAuley, J. Katula, S. L. Mihalko, and R. A. Boileau, "The physical activity scale for the elderly (PASE): evidence for validity," *Journal of Clinical Epidemiology*, vol. 52, pp. 643–651, 1999.

[24] J. K. Myoung-Ae Choe, J. Kim, M.-Y. Jeon, Y.-R. Chae, and Y. R. Chae, "Evaluation of the Korean version of physical activity scale for the elderly (K-PASE)," *Korean Journal of Women Health Nursing*, vol. 16, no. 1, pp. 47–59, 2010.

[25] S. Mantri, M. E. Fullard, J. E. Duda, and J. F. Morley, "Physical activity in early Parkinson disease," *Journal of Parkinson's Disease*, vol. 8, no. 1, pp. 107–111, 2018.

[26] T. Althoff, R. Sosič, J. L. Hicks, A. C. King, S. L. Delp, and J. Leskovec, "Large-scale physical activity data reveal worldwide activity inequality," *Nature*, vol. 547, no. 7663, pp. 336–339, 2017.

[27] Sport England, *Active People Survey*, Sport England, London, UK, 2014.