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ORIGINAL ARTICLE

Efficacy of non-immersive virtual reality-based telerehabilitation on postural stability in Parkinson's disease: a multicenter randomized controlled trial

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ABSTRACT

BACKGROUND: The implementation of regular prolonged, and effective rehabilitation in people with Parkinson's disease is essential for ensuring a good quality of life. However, the continuity of rehabilitation care may find barriers related to economic, geographic, and social issues. In these scenarios, telerehabilitation could be a possible solution to guarantee the continuity of care.
AIM: To investigate the efficacy of non-immersive virtual reality-based telerehabilitation on postural stability in people with Parkinson's disease, compared to at-home self-administered structured conventional motor activities.
DESIGN: Multicenter randomized controlled trial.
SETTING: Five rehabilitation hospitals of the Italian Neuroscience and Rehabilitation Network.
POPULATION: individuals diagnosed with Parkinson's disease.
METHODS: Ninety-seven participants were randomized into two groups: 49 in the telerehabilitation group (non-immersive virtual reality-based telerehabilitation) and 48 in the control group (at-home self-administered structured conventional motor activities). Both treatments lasted 30 sessions (3-5 days/week for, 6-10 weeks). Static and dynamic balance, gait, and functional motor outcomes were registered before and after the treatments.
RESULTS: All participants improved the outcomes at the end of the treatments. The primary outcome (mini-Balance Evaluation Systems Test) registered a greater significant improvement in the telerehabilitation group than in the control group. The gait and endurance significantly improved in the telerehabilitation group only, with significant within-group and between-group differences.
CONCLUSIONS: Our results showed that non-immersive virtual reality-based telerehabilitation is feasible, improves static and dynamic balance, and is a reasonably valuable alternative for reducing postural instability in people with Parkinson's disease.
CLINICAL REHABILITATION IMPACT: Non-immersive virtual reality-based telerehabilitation is an effective and well-tolerated modality of rehabilitation which may help to improve access and scale up rehabilitation services as suggested by the World Health Organization's Rehabilitation 2030 agenda.

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KEY WORDS: Telerehabilitation; Parkinson disease; Continuity of patient care.

Parkinson's disease (PD) is a chronic degenerative pathology characterized by both motor and non-motor symptoms that may have a significant long-term impact on activities of daily living (ADL).[1] Subjects with PD need continuous, intensive, and tailored rehabilitation in order to improve motor function as well as their Quality of Life (QoL), and to reduce the risk of balance impairment and falls.[2, 3] To this extent, the implementation of regular prolonged, and effective rehabilitation in people with PD is essential for ensuring well-being.[4-6] However, the continuity of rehabilitation care may find barriers related to economic, geographic, and social issues.[7] The latter has become more evident during the recent COVID-19 pandemic-related quarantine measures.[8] Recent studies have shown that pandemic-related sedentariness decreased functional mobility, postural control, and QoL in people with PD.[9-11] In this scenario, the delivery of rehabilitation services at distance, namely telerehabilitation (TR), is a possible solution to guarantee the continuity of care and physical exercise at home *via* digital healthcare.[12, 13]

TR allows clinicians to set exercise plans, remotely monitor the patient, and continuously adapt and tailor the rehabilitation treatment. The literature of the last decade demonstrated the feasibility, acceptability, and cost-benefit of TR in individuals with PD.[14-18] Vellata *et al.*[19] found that TR improves a subset of motor (balance, gait performance, and postural stability) parameters and non-motor (speech and dysphagia) functions in PD, comparably to the conventional treatments. The randomized controlled trial (RCT) by Gandolfi *et al.*[20] evidenced that TR with a virtual reality (VR) system is a feasible alternative to in-clinic sensory integration balance training for reducing postural instability in people with PD having a caregiver.

Although the TR intervention has been proposed as a sustainable and innovative approach in people with PD, there are still conflicting results in the literature about its efficacy, as concluded by recent systematic reviews.[21-23] Specifically, Lei *et al.*[22] and Truijen *et al.*[23] reviewed the existing literature focusing on gait and balance, and found that, despite the small sample sizes, TR associated with VR seems to achieve the same effect as conventional rehabilitation training and it can therefore be used as an alternative approach. However, larger trials are needed, considering the importance of balance rehabilitation to reduce the risk of falls and fractures,[24] and the potential impact of VR in PD rehabilitation.[25]

This study aims to investigate the efficacy of non-immersive VR-based TR on postural stability in people with PD, compared to at-home conventional rehabilitation in a multicenter trial conducted in a network of neurorehabilitation units. The hypothesis of the study is that physical therapy delivered *via* TR may have positive effects in improving static and dynamic balance compared to at-home self-administered structured conventional motor activities.

Materials and methods

The study was a multicentre randomized controlled trial that involved five Italian rehabilitation hospitals (Istituti di Ricovero e Cura a Carattere Scientifico - IRCCS) of the Italian Neuroscience and Rehabilitation Network (https://www.reteneuroscienze.it/en). All investigators and outcome assessors were blinded to the type of treatment.

Participants

A sample of individuals diagnosed with PD (according to the UK PD Society Brain Bank criteria)[26] was recruited between 2018 and 2020. The subjects were enrolled if they met the following eligibility inclusion criteria:

- Hoehn & Yahr (H&Y) score between ≤3 (ON-state);
- absence of moderate and severe dyskinesias assessed by the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) with a score of items 4.1 and 4.2 <3;
- absence of moderate and severe freezing episodes assessed by the MDS-UPDRS with a score of items 2.13 and 3.11 <3;
- ability to perform the 6 Minutes Walking Test (6MWT) between 200 m and 600 m;
- age ≤80 years;
- absence of cognitive impairment measured by the Montreal Cognitive Assessment (MoCA) total score ≥17.54;[27]
- stabilized drug treatment;
- sufficient cognitive and linguistic level to understand and comply with study procedures;
- sign informed consent.

Subjects were excluded if having:

- other neurological pathologies, psychiatric complications or personality disorders;
- blurred or low vision problems;
- hearing and speech impairment affecting participation in the study.
- Written and informed consent was obtained for all participants. None of the participants were involved in other experimental trials during the entire duration of the present study.

Rehabilitation procedures

All enrolled subjects were randomized into two groups: 1) the telerehabilitation group (TG) which received non-immersive VR-based TR; 2) the control group (CG) which received at-home conventional rehabilitation. All treatments were always performed under the effect of stable anti-parkinsonian therapy (*i.e.*, in the best motor condition ["ON" phase]). Participants in both groups were excluded from the study if they missed three consecutive sessions.

Supplementary Digital Material 1 (Supplementary Table I) shows an overview of an intervention session in TG and CG according to the Template for Intervention Description and Replication (TIDieR) checklist and guide.

Telerehabilitation group

The TG consisted of 30 sessions lasting approximately 45 minutes (3-5/week for 6-10 weeks) of motor, and cognitive rehabilitation exercises in non-immersive VR-based TR modality using the VRRS Tablet system (Khymeia Srl, Noventa Padovana, Padua, Italy). The VRRS Tablet system is a medical device approved by the Italian Ministry of Health for the rehabilitation of neurological patients. The motor exercises were performed using inertial sensors for the acquisition and processing of the movement performed by the patient. The patient was trained to perform these exercises using visual and auditory feedback in a serious game environment. The exercises were aimed at the rehabilitation of balance and at the improvement of motor performance in lower limbs (*e.g.*, maintaining balance on one leg, marching in place, standing on tiptoe, squatting, etc.), as detailed in Supplementary Digital Material 2 (Supplementary Table II).

The therapists involved in the study customized the protocol of exercises in TR mode according to the characteristics and needs of the subject. The TR treatments were asynchronous and the difficulty of the exercise was gradually modified by varying a set of parameters in the software (*e.g.*, speed of the visualized target, number of virtual objects, etc.) with a weekly synchronous session with the physiotherapist. The weekly session also ensured the monitoring of adherence to the program in the TG. Adherence was also ensured by the physiotherapist by checking the daily reports from the tablets at the end of the treatment.

Control group

The CG carried consisted of 30 sessions lasting approximately 45 minutes (3-5 days/week for, 6-10 weeks) of at-home self-administered structured conventional exercises without the use of any technological devices. The CG rehabilitation was an active comparator treatment and consisted of a written home-based self-administered booklet with conventional motor activities tailored for each subject. The motor activities were chosen and adapted from a specialized manual.[28] The motor exercises were aimed at the rehabilitation of balance and at the improvement of motor performance in lower limbs (*e.g.*, maintaining balance on one leg, marching in place, standing on tiptoe, squatting, etc.), as detailed in Supplementary Digital Material 3 (Supplementary Table III). The intensity and duration of the CG were the same as the TG. Monitoring of adherence to the program was ensured with a paper diary drawn up daily by the patient (with the help of a caregiver) and checked by the physiotherapist at the end of the treatment.

All patients were sequentially assigned to either the TG or CG subsequent to enrolment in the study by using an envelope randomization technique. The randomization was performed in a 1:1 equal allocation ratio. The opaque, sealed, and sequentially numbered randomization envelopes were mixed and distributed to the research hospitals by the main research center. A randomization envelope was opened at the time of recruitment for each patient who met the inclusion criteria.

Outcome measures

Clinical assessment was performed at baseline (T1) and at the end of the treatment (T2). The following outcome measures were administered by an assessor blinded to the intervention groups (all assessors involved in the study underwent a preliminary course to harmonize methods and increase inter-rater reliability).

Primary outcome measure:

• the mini-Balance Evaluation Systems Test (mini-BESTest) is a shortened version of the Balance Evaluation Systems Test. It is composed of 14 items scale that evaluates balance with a total score of 28. Items are grouped into the following four subcomponents: anticipatory postural control (max score = 6), reactive postural control (max score = 6), somatosensory orientation (max score = 6), and dynamic walking (max score = 10). The mini-BESTest has been shown to have good psychometric properties in people with PD,[29] with a Minimal Clinically Important Difference (MCID) of 4 points.[30]

Secondary outcome measures:

• the Timed Up-and-Go (TUG) test which involves rising from a seated position, walking to a pre-defined location, turning, and returning to a seated position, is a

common test used to assess functional mobility, dynamic balance, and walking ability. The score is the time required to perform the following tasks: standing up from a chair, walking three meters: turning around, walking back to the chair, and sitting down. The validity and reliability of the TUG in people with PD have been published;[31, 32]

- the 6-Minute Walking Test (6MWT) was employed as a sub-maximal test of aerobic capacity or endurance during gait.[33] The score is the distance (m) walked over a time of 6 minutes;
- the motor section of the MDS-UPDRS (part III) is composed of 18 items with a total score of 132. The MDS-UPDRS was scored by clinicians specialized in movement disorders and trained for its administration and interpretation.[34, 35]

All outcome measures were collected in the "ON medication" phase (*i.e.*, 1 h after oral consumption of the usual Levodopa dose and always in the morning to minimize variability).

All outcome measures were evaluated at T1 and at T2.

Ethical aspects

Reporting of this controlled clinical trial follows the statement CONSORT. The study protocol was approved by the Ethics Committee (protocol code RP2018; date of approval: 20/06/2018) and registered on ClinicalTrial.gov (number: NCT05842577). Each participant signed an informed consent form before any study-related procedures. Each record in the database was identified by a unique alphanumeric code to protect participants' privacy. The study was in accordance with the Declaration of Helsinki.

Sample size

The sample size estimation was based on an effect size of treatment measured with the Mini-BESTest of 0.44 points for people with PD.[30] The analysis was based on a one-sided paired *t*-test at 80% power with a significance level at 0.025: 43 participants per group are needed. Considering a 10% dropout rate the sample size of 47 participants per group was estimated. The sample size was estimated using GPower 3.1.

Statistical analysis

Demographic and clinical data were reported with frequencies and percentages if they were categorical variables, while continuous variables were expressed with mean and standard deviation, median, and interquartile range. Baseline differences between groups were studied with paired *t*-test or Chi-square test. The normal distribution of continuous variables was checked with the Kolmogorov-Smirnov test with the Lilliefors correction. Data for all normally distributed variables were analyzed by two-way repeated measures analysis of variance (ANOVA). Clinical changes associated with the therapy were assessed by the absolute differences between study time points (factor TIME: T1 *vs*. T2) and compared between groups (factor GROUP: TG *vs*. CG); the time x group interaction was assessed as well. The effect size was calculated by using Cohen's *d*. Statistical significance was set at $P<0.05$. All statistical analyses were performed on SPSS v. 27.0 (SPSS Inc., Chicago, IL, USA, 2020).

Results

Among the 156 screened participants, 105 were eligible for the study and were randomly allocated to TG (N.=54) or CG (N.=51). Eight participants dropped out because of drug changes (TG, N.=2; CG, N.=2), medical complications (TG, N.=1), or discontinued treatment (TG, N.=2; CG, N.=1). Figure 1 shows patients' dispositions. Eventually, the data from 97 participants (TG: N.=49; CG: N.=48) were analyzed for the outcome measures. The demographic and clinical characteristics at baseline are illustrated in Table I. The two groups did not differ in terms of demographic features or clinical data: the primary (mini-BESTest total score) and secondary (mini-BESTest subcompo-

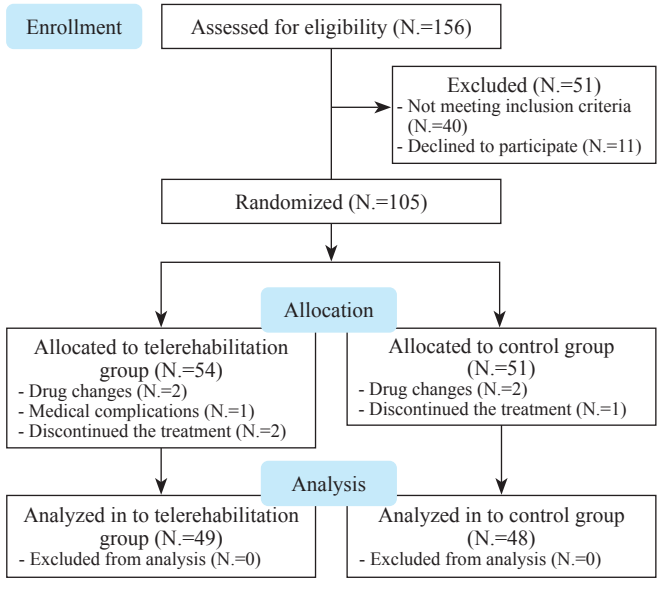

Figure 1.—CONSORT flow diagram of the study.

TABLE I.—*Demographic and clinical characteristics of the telerehabilitation group (TG) and control group (CG) at baseline (T1).*

Variable	TG (N.=49)	CG (N.=48)	P value
Sex (M/F)	27/22 (55.1/44.9)	24/24 (50.0/50.0)	0.686
Age (year)	67.8±6.6	68.2±5.8	0.744
Education level			0.394
Low (≤8 years)	18 (36.7%)	24 (50.0%)	
Medium (9-13 years)	14 (28.6%)	12 (25.0%)	
High (15-20 years)	17 (34.7%)	12 (25.0%)	
Disease duration (year)	4.0 [2.0-8.0]	5.0 [1.75-9.0]	0.858
H&Y [1;5]	2.0 [1.5-2.0]	2.0 [1.5-2.5]	0.982
MoCA [0;30]	25.0 [23.0-27.0]	24.0 [23.0-27.0]	0.331
Mini-BESTest – primary outcome [0;28]	20.8±4.9	20.5±5.1	0.867
Mini-BESTest anticipatory postural control [0;6]	4.3±1.5	4.0±1.3	0.400
Mini-BESTest reactive postural control [0;6]	4.3±1.3	4.1±1.8	0.532
Mini-BESTest somatosensory orientation [0;6]	4.9±1.3	4.9±1.2	0.993
Mini-BESTest dynamic walking [0;10]	7.2±2.0	7.4±1.9	0.556
TUG (s)	10.5±3.0	11.0±3.3	0.443
6mWT (m)	347.0±123.6	339.7±119.2	0.768
MDS-UPDRS Part III [0;132]	35.5±15.7	40.2±19.5	0.251

Data are depicted as number (percentage), mean±SD or median [IQR].
SD: standard deviation; IQR: interquartile range; H&Y: Hoehn & Yahr Score; MoCA: Montreal Cognitive Assessment total score (no correction); mini-BESTest: mini-Balance Evaluation Systems Test; TUG: Timed Up and Go Test; 6mWT: 6-Minute Walking Test; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale.

TABLE II.—*Pre-post treatment changes in primary and secondary outcomes in the telerehabilitation group (TG) and control group (CG).*

Outcome measures	Group	T1	T2	T2-T1	Effect size (Cohen's *d*)	Time effect (η^2)	Group effect (η^2)	Time x group effect (η^2)
mini-BESTest – primary outcome [0;28]	TG CG	20.8±4.9 20.5±5.1	22.4±4.0 21.2±4.3	1.7±0.33*** 0.70±0.34*	0.29 [0.003-0.57] 0.29 [0.003-0.58]	F=17.630, P<0.001 (0.273)	F=1.013, P=0.319 (0.021)	F=5.050, P=0.029 (0.097)
mini-BESTest anticipatory postural control [0;6]	TG CG	4.3±1.5 4.0±1.3	4.8±1.3 4.5±1.1	0.46±0.16** 0.45±0.15**	0.40 [0.11-0.69] 0.43 [0.13-0.72]	F=14.397, P<0.001 (0.234)	F=1.397, P=0.243 (0.029)	F=0.0, P=1.000 (0.00)
mini-BESTest reactive postural control [0;6]	TG CG	4.3±1.3 4.1±1.8	4.5±1.2 4.1±1.6	0.18±0.13 0.0±0.15	0.2 [-0.08-0.48] 0.0 [-0.28-0.28]	F=0.378, P=0.542 (0.234)	F=1.710, P=0.197 (0.035)	F=0.434, P=0.513 (0.009)
mini-BESTest somatosensory orientation [0;6]	TG CG	4.9±1.3 4.9±1.2	5.1±1.0 4.9±1.2	0.2±0.7 0.04±0.1	0.27 [-0.009-0.56] 0.06 [-0.22-0.34]	F=2765, P=0.103 (0.056)	F=0.416, P=0.522 (0.009)	F=1.403, P=0.242 (0.029)
mini-BESTest dynamic walking [0;10]	TG CG	7.2±2.0 7.4±1.9	8.0±1.6 7.6±1.7	0.79±0.17*** 0.25±0.17	0.67 [0.35-0.97] 0.21 [-0.08-0.49]	F=13.436, P<0.001 (0.222)	F=0.106, P=0.746 (0.002)	F=6.653, P=0.013 (0.124)
TUG (s)	TG CG	10.5±3.0 11.0±3.3	9.8±2.8 10.2±3.0	-0.70±0.19*** -0.78±0.23*	-0.52 [-0.81-0.22] -0.48 [-0.8-0.17]	F=26.048, P<0.001 (0.357)	F=0.527, P=0.471 (0.011)	F=0.073, P=0.789 (0.002)
6mWT (m)	TG CG	347.0±123.6 339.7±119.2	376±139.7 350.3±122.5	29.7±8.5*** 10.6±6.3	0.50 [0.20-0.79] 0.24 [-0.04-0.52]	F=25.672, P<0.001 (0.353)	F=2.078, P=0.156 (0.042)	F=2.413, P=0.127 (0.049)
MDS-UPDRS Part III [0;132]	TG CG	35.5±15.7 40.2±19.5	32.9±16.3 40.5±19.9	-2.5±0.8** 0.35±0.8	-0.43 [-0.72-0.14] 0.07 [-0.22-0.35]	F=3.394, P=0.072 (0.067)	F=5.759, P=0.020 (0.109)	F=7.077, P=0.011 (0.131)

Data are depicted as mean±SD or median [IQR].
SD: standard deviation; IQR: interquartile range; mini-BESTest: mini-Balance Evaluation Systems Test; TUG: Timed Up and Go test; 6mWT: 6-Minute Walking Test; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale.
***P value <0.001; **P value <0.01; *P value <0.05. The significant results were highlighted with bold characters. The standardized difference between T2-T1 changes in the two groups was computed to provide the effect size (Cohen's d). Effect sizes > 0.50 are highlighted as clinically relevant.

nents, TUG, 6mWT, and MDS-UPDRS Part III) outcome measures were also equally distributed at baseline and did not differ between groups (P>0.05).

Both TG and CG showed improvement in all outcome measures after treatment. The results of the comparative statistics are reported in Table II. The mini-BESTest total score (primary outcome) significantly increased by 1.7±0.33 and 0.70±0.34 in the TG and CG, respectively with a significant TIME effect (P<0.001) and "TIMExGROUP" effect (P=0.029). The 10.3% of participants in

the TG showed an improvement beyond the MCID[30] *versus* the 5.15% in the CG group.

When analyzing individually the subcomponent of the mini-BESTest, the anticipatory postural control subcomponent showed significant within-group differences (TIME effect with P<0.001) without between-group differences. Conversely, the mini-BESTest dynamic walking subcomponent and the 6MWT significantly improved in the TG only, with a significant within-group (TIME effect with P<0.001) and between-group differences (time x group effect with P=0.013) in favor of TG, with a fair medium effect size (Cohen's d: 0.653). The reactive postural control and somatosensory orientation subcomponents did not register any significant variation between T1 and T2 in both groups.

As regards TUG, we detected significant within-group differences (TIME effect with P<0.001) without between-group differences.

In the case of the motor section of MDS-UPDRS (part III) we observed a significant variation in the TG only, with a score decrease of -2.5±0.8 points *vs.* 0.35±0.8 points in the CG group (P<0.05).

Discussion

The findings from this multicenter RCT conducted on 97 subjects support the efficacy of non-immersive VR-based TR in the motor rehabilitation of persons with PD and show that this approach seems more effective than at-home conventional rehabilitation. The low dropout rate in the TG (3.7%) suggests that the TR approach was feasible and well accepted, in accordance with the literature on TR in PD.[14, 16]

Considering the importance of regular balance rehabilitation for preventing falls and maintaining a good level of QoL in PD,[6] this study contributes an important addition to the armamentarium of rehabilitative options for the rehabilitative approach to these patients showing that non-immersive VR-based TR is a well-accepted and useful solution for improving the static and dynamic postural control. These outcomes are in accordance with studies that employed the same TR system with subjects with stroke,[36-39] brain injury,[40, 41] and mild cognitive impairment.[42] We assume that the outcomes of our study were related more to the TR modality than to the VR-based intervention, especially considering that the employed VR technology was a non-immersive one.[33] Although the TR treatments were asynchronous, the periodically synchronous session to set the exercise parameters allowed the physiotherapist to easily monitor adherence to the program. Moreover, the VR task-oriented exercises were indeed more engaging and motivating than at-home self-administered conventional exercises.

The primary outcome of the study, postural balance assessed with the mini-BESTest total score, significantly improved in both intervention groups. However, the significant between-group difference, in favour of TR, confirmed the study hypothesis and is in agreement with most of the published literature.[19, 20, 43] Our results partially agree with Chen *et al.*,[21] Lei *et al.*,[22] and Truijen *et al.*[23] who reported a similar effect in the TG and the CG. On the other hand, our findings are similar to the ones from Gandolfi *et al.*,[20] where at-home rehabilitation (based on a commercial exergaming system) induced in people with PD an improvement at the Berg Scale significantly more marked than the patients who were treated with in-clinic sensory integration balance training. Considering the limited number of published studies on the effects of TR on gait and balance in PD,[19] to our best knowledge, this is the first multicentric RCT investigating the effect of non-immersive VR-based TR using a system specifically developed for the rehabilitation of neurological patients.[19]

Dynamic balance abilities and gait improved significantly at T2 in both groups, but dynamic walking improved more in the TG than the CG. Thus, the increased ability in controlling posture in people of the TG allows them to excel in the following motor tasks: change in gait speed; walk with head turns; walk with pivot turns; step over obstacles; and timed up & go with a dual task. This outcome is in accordance with the literature on the ability of TR of increasing dynamic balance and gait abilities.[19, 20, 22, 44]

We believe that the more marked improvements observed in the TG group may be related to the greater involvement and enjoyment of the subjects using the non-immersive VR. Indeed, thanks to the acoustic and visual feedback while playing different exercises, the subject received feedback on the results and the performance, which is fundamental for learning reinforcement. We can therefore speculate that VR-based training may boost neural plasticity and, consequently, functional recovery.[45] Furthermore, the regular remote follow-ups performed by the physiotherapist and the sensor-guided exercises may have contributed to improve the outcomes, by ensuring that the exercises were performed correctly.[20]

Limitations of the study

Some study limitations are worth mentioning: 1) the study included only subjects with mild disability (H&Y score

between 2.5 and 3), which may limit the transferability of our findings, although this subgroup of patients evidences the least postural problems and the most significant benefit from any rehabilitation intervention; the effects of TR on freezing of gait were not assessed as the TR system used in this study does not include exercises to train gait and endurance; 2) no follow-up evaluation was planned. Therefore, future trials targeting more severely impaired patients, including a wider range of motor exercises delivered and assessing the potential long-term effects of the treatments are required to evaluate the full spectrum of efficacy of the non-immersive VR-based TR tested in this study.

Nevertheless, our findings provide an effective and well-tolerated modality of rehabilitation of a highly disabling motor symptom of people with PD that can be delivered at home and for prolonged periods of time. In this context, the TR modality tested in the present study is perfectly in line with the World Health Organization's Rehabilitation 2030 agenda suggestions to improve access and scale up rehabilitation services.[46]

Conclusions

A chronic and progressive disease like PD requires effective and long-lasting rehabilitative approaches to maintain as long as possible a satisfactory QoL and social participation. The recent COVID-19 pandemic has highlighted the need to introduce new modalities to ensure the continuum of care. Our results showed that non-immersive VR-based TR is feasible, improves static and dynamic balance, and is a reasonably valuable alternative for reducing postural instability in people with PD.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Michela Goffredo, Marco Franceschini, and Rocco S. Calabrò conceived the design of the work. Andrea Turolla, Sara Federico, Giorgio Maggioni, Federica Zeni, Sanaz Pournajaf, Matteo Cioeta, Cristina Tassorelli, Roberto De Icco, Francesca Baglio, Johanna Jonsdottir acquired the data. Stefania Proietti and Michela Goffredo analyzed the data. Michela Goffredo, Rocco S. Calabrò drafted the manuscript. Giorgio Maggioni, Federica Zeni, Cristina Tassorelli, Roberto De Icco, Francesca Baglio, Johanna Jonsdottir revised it critically for important intellectual content. All authors contributed to interpreting data for the work. All authors read and approved the final version of the manuscript.

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History
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Supplementary data
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