Remotely prescribed, monitored and tailored home-based gait-and-balance exergaming intervention using augmented-reality glasses: a clinical feasibility study in people with Parkinson's disease

Authors:

Lotte E.S. Hardeman[a] (corresponding author*), Daphne J. Geerse[a], Eva M. Hoogendoorn[a], Jorik Nonnekes[b,c] , Melvyn Roerdink[a]

a. Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences (sponsor)

b. Radboud University Medical Centre; Donders Institute for Brain, Cognition and Behaviour, Department of Rehabilitation, Centre of Expertise for Parkinson & Movement Disorders, Nijmegen, The Netherlands

c. Department of Rehabilitation, Sint Maartenskliniek, Nijmegen, The Netherlands

*Correspondence:

Lotte Hardeman

Van der Boechorststraat 9, 1081 BT Amsterdam, The Netherlands

Tel.: +31 20 598 1708

Email: l.e.s.hardeman@vu.nl

Word count: ±4000 (Introduction-Conclusion)

Abstract

BACKGROUND: Exergaming has the potential to increase adherence to exercise through play, individually-tailored training and (online) remote monitoring. Reality DTx® is a digital therapeutic software platform for augmented-reality glasses (AR) that enables a home-based gait-and-balance exergaming intervention specifically designed for people with Parkinson's disease (pwPD).

OBJECTIVE: The primary objective was to evaluate the feasibility and potential efficacy of Reality DTx® AR-exergaming intervention for improving gait, balance and walking-adaptability fall-risk indicators. Secondary objective was to evaluate potential AR-glasses superiority (Magic Leap 2 [ML2] vs. HoloLens 2 [HL2]).

METHODS: This waitlist-controlled clinical feasibility study comprised three laboratory visits (baseline; pre-intervention; post-intervention), a home visit and a 6-week AR-exergaming intervention. Five complementary gait-and-balance exergames were remotely prescribed (default five sessions/week of 30 active-minutes/session), monitored and tailored. Feasibility was assessed in terms of safety, adherence and user experience. During laboratory visits, gait-and-balance capacity was assessed using standard clinical gait-and-balance tests and advanced walking-adaptability fall-risk assessments.

RESULTS: 24 pwPD participated. No falls and four near falls were reported. Session adherence was 104%. User Experience Questionnaire scores for Reality DTx® ranged from above average to excellent, with superior scores for HL2 over ML2 for Perspicuity and Dependability. Intervention effects were observed for the Timed-Up-and-Go test (albeit small),

the Five-Times-Sit-to-Stand test and walking speed. Walking-adaptability fall-risk indicators all improved post-intervention.

CONCLUSIONS: Reality DTx® is a safe, adherable, usable, well-accepted and potentially effective intervention in pwPD. These promising results warrant future RCTs on the (cost-)effectiveness of home-based AR exergaming interventions for improving gait, balance and falls risk.

1. Introduction

People with Parkinson's disease (pwPD) experience a wide range of gait-and-balance impairments, significantly affecting functional mobility and quality of life [1-7]. Clinical (physiotherapy) guidelines stress the central role of exercise in disease management of motor and non-motor symptoms [8-12]. Exercise is defined as a planned, structured, repetitive and purposeful physical activity to maintain one or more components of physical fitness [7]. Despite increasing recognition of the importance of exercise in disease management, adherence to exercise remains challenging [13].

In this clinical feasibility study, we evaluated a 6-week remotely prescribed, monitored and tailored home-based augmented-reality (AR) exergaming (i.e., 'exercise' and 'gaming') intervention (Reality DTx®) designed for state-of-the-art AR glasses (Magic Leap 2 [ML2], Microsoft HoloLens 2 [HL2]). Our main therapeutic goal with this digital therapeutics program Reality DTx® was to improve gait and balance, including walking adaptability, in pwPD through gamified rehabilitation exercises. Moreover, Reality DTx® aims to increase dose and adherence to exercise by making exercise more accessible (at home, at any time) and enjoyable, thereby potentially increasing the number of (unsupervised) rehabilitation exercise hours.

Reality DTx® is designed to accommodate individually tailored exercise (following FITT principles; frequency, intensity, type and time [7]), to monitor exercise remotely (in terms of adherence and performance) and to motivate the user through gamification and feedback, all important aspects for delivering a progressive-but-achievable intervention. To date, research on home-based exergaming interventions for pwPD primarily focused on non-immersive

devices (e.g., Xbox Kinect or Nintendo Wii), showing promise in providing a safe and effective intervention for improving balance, mobility and gait [14].

The primary objective of this pre-registered waitlist-controlled clinical feasibility trial was to evaluate feasibility (in terms of safety, adherence and user experience) and potential efficacy for improving clinical gait-and-balance test scores and laboratory-based targeted walking-adaptability fall-risk indicators. The secondary objective was to evaluate potential superiority in state-of-the-art AR glasses (i.e., ML2 vs. HL2) for delivering Reality DTx®.

2. Methods

Here we summarize the methods. A detailed study protocol was pre-registered [15] while (minor) changes thereto are specified below.

2.1 Participants

Participants were eligible to participate if diagnosed with PD according to the UK PD Brain Bank criteria (Hoehn and Yahr scale [HY] stage 2-4) and experienced bothersome gait-and/or-balance impairments based on self-report. Participants were excluded if there was sign of inability to comply with protocol, additional neurological diseases and/or orthopedic problems seriously interfering with gait-and-balance function, insufficient physical capacity or cognitive and/or communicative inability to understand instructions and participate in the tests (as observed by the researchers), (severe) visual or hearing impairments (after corrective aids), (severe) visual hallucinations or illusions, inability to walk independently for 30 minutes, no stable dosages of dopaminergic medication. There were no restrictions to usual care. Eligibility

criteria were checked through telephone screening before enrolment and again during the baseline laboratory assessment.

-Figure 1-

2.2 Trial design, intervention and procedure

This waitlist-controlled feasibility trial (Figure 1) comprised:

i)   three laboratory assessments (baseline [t0], pre-intervention [t1], post-intervention [t2]),

ii)   a 6-week waitlist-period (between t0-t1),

iii)   a home visit to set up Reality DTx® for independent but remotely monitored use,

iv)   a 6-week home-based Reality DTx® intervention period with weekly telephone calls. Reality DTx® is an AR software application (registered as UKCA, FDA and CE-marked medical device) for delivering a home-based gait-and-balance exergaming rehabilitation program. Reality DTx® is remotely prescribed and monitored through a web portal and delivered through state-of-the-art ML2 or HL2 AR glasses, randomized over participants to evaluate potential AR-glasses superiority (Figure 1),

v)   The Reality DTx® intervention comprises five complementary gait-and-balance exergames, developed in collaboration with Strolll Limited (Figure 1; see Supplementary Material 1 for a video and Supplementary Table 1 for a detailed game description). Participants were initially instructed to use Reality DTx® for 30 active minutes/day (in one session or divided over the day in 'exercise snacks') for five

days/week but were allowed to train more. Reality DTx® was intended to be a progressive-and-achievable intervention. Hence, it was personalized (i.e., in terms of frequency, type, difficulty, duration or mode of the exergames) and updated on a weekly basis, with shared decision making among participant and trial managers using feedback from weekly telephone calls and remotely monitored adherence and performance data from the web portal as input [15].

2.3 Outcomes

Various complementary outcomes of potential efficacy for improving gait and balance were evaluated in the laboratory (t0, t1, t2), using clinical gait-and-balance tests and adaptive-walking tasks like obstacle avoidance with the Interactive Walkway [Figure 2] which allowed for a more in-depth targeted fall-risk assessment [16]). Complementary outcomes of feasibility were derived from the web portal (adherence and performance scores), telephone calls (safety and technical issues) and online (user experience) during (t1-t2) or after (>t2) the intervention, as specified in Table 1 and detailed in the pre-registration [15].

-Figure 2-

-Table 1-

2.4 Statistical analyses

2.4.1 Planned analyses

Independent-samples *t*-tests (or their non-parametric equivalents) were used to evaluate safety and user experience between groups (ML2 vs. HL2). Weekly adherence scores underwent 2 (between-subjects factor Group: ML2, HL2) × 6 (within-subject factor Week: 1 to 6) mixed ANOVAs, with polynomial contrasts for main effects of Weeks. Potential-efficacy outcomes were subjected to 2×3 mixed ANOVAs with between-subjects factor Group and within-subject factor Time (three levels: t0, t1, t2). For main effects of Time, the first and second reverse Helmert contrasts were used to evaluate waitlist and intervention effects, respectively. Data analysis was performed in JASP [17], with significance set at 0.05 and effect size reported as partial-eta squared. Missing data, due to for example technical issues and missed medication dose, was excluded analysis-by-analysis. Conditions for parametric testing were checked for all analyses. If violated, appropriate non-parametric tests were used. Bayesian hypothesis testing was performed to quantify the likelihood of support for the alternative hypothesis over the null (BF_{10}-values between 1 and 3, between 3 and 10 and above 10 reflect respectively anecdotal, moderate and strong evidence for the alternative hypothesis [18]).

2.4.2 Exploratory analyses (not specified in the pre-registration [15])

Reality DTx® was intended as a progressive-but-achievable rehabilitation intervention, where exergame-level settings can be tailored to the varying abilities and progression-rates of participants. To evaluate this progressive-but-achievable nature we compared for each game i) Reality DTx® exergame-level settings (5 levels) over the 6-week intervention using a Chi-square test for independence (an increase in game-play levels was expected over weeks) and

ii) the game-play performance scores over the 6-week intervention using a mixed ANOVA (high-but-submaximal scores were expected, without differences over weeks).

3. Results

3.1 Feasibility

3.1.1. Participant inclusion, characteristics, and dropouts

24 participants out of the 31 persons scheduled for a baseline assessment (t0) started the Reality DTx® intervention (Figure 3). There were three no-shows. Two persons were excluded for '*insufficient physical capacity as observed by the researchers*' (i.e., their fall-risk during unsupervised home-based exergaming was deemed too high; both had HY3, were freezers [New Freezing of Gait Questionnaire (NFOGQ)-scores of 13/28 and 24/28] and reported considerably higher fall rates [1-2 falls/week] than the other participants [max 10 falls/year; Table 2]). Two persons were excluded for '*comorbidities influencing gait*' (i.e., cerebral vascular accident, weakness in L5 musculature [dorsiflexors and hip abductors]). Baseline characteristics did not differ for the 24 participants randomized to ML2 (n=11) and HL2 (n=13) AR-glasses groups (Table 2). Four of these 24 participants dropped out of the study after t1, yielding a drop-out rate of 16.7% (Figure 3).

-Figure 3-

-Table 2-

3.1.2. Safety

There were no serious adverse events during the Reality DTx® intervention. Table 3 shows the number of reported adverse events per week. There were no falls and four near falls reported by three unique participants. Nine participants experienced 15 dizziness events, one participant experienced a headache twice, none reported eyestrain and 11 participants reported 27 experiences of other adverse events, like re-occurring prior injuries (e.g., low-back or shoulder pain, the latter due to fatigue, and pinched-nerve complaints), aggravated existing PD-related (e.g., dystonia, dyskinesia) or comorbid (e.g. COPD, fibromyalgia) symptoms, often reported by the same participant over multiple training weeks. There were no group effects (ML2 vs. HL2).

-Table 3-

3.1.3. Adherence

For the 20 participants completing the Reality DTx® intervention, a total of 606 Reality DTx® sessions were performed while 583 sessions were prescribed, amounting to an overall 104% session adherence. Session adherence varied significantly over weeks (F(5,90)=3.438, p=0.007, η_p^2=0.160, BF_{10}=6.789, with a significant quadratic contrast t(19)=3.441, p=0.003; Figure 4A), without main or interaction effects involving groups. One-sample t-tests against 100% only revealed a significant difference for week 1 *(Z*=102.500, *p*=0.014)*, wherein participants performed more sessions than prescribed (Figure 4A). Participants on average walked 9.989±892meters, performed 1.633±186 sit-to-stand/squat movements, performed 14.218±1.207 functional reaches and completed 790±55 active exercise minutes, amounting

to an 88% active-minutes/session adherence, which did not vary significantly over weeks (F(3.45,62.04)=0.765, p=0.535, η_p^2=0.041, BF_{10}=0.076). One-sample t-tests against 100% revealed that participants performed fewer-than-prescribed active-minutes/session in weeks 1, 2, 3 and 4 (t(19)=-4.332, p<0.001, t(19)=-4.808, p<0.001, t(19)=-2.888, p=0.009 and Z=28.000, p=0.007, respectively; Figure 4B).

-Figure 4-

3.1.4. Progressive-but-achievable intervention

Participants performed Reality DTx® with exergame-play levels tailored to their ability. There was a considerable variation in exergame-play level (Figure 5A, illustrated for Mole Patroll), suggesting a successful personalization to the varying abilities and progression profiles of our participants. Reality DTx® was a progressive-but-achievable intervention (Figure 5B-F), with exergame-play levels varying significantly over weeks for all exergames (χ^2(5)>64.155, p<0.001), with significant linear contrasts indicating that for all exergames the levels increased proportionally over weeks (all t(df)>5.840, p<0.001). Exergame-performance scores were overall high-but-submaximal and did not vary systematically over weeks, except for Basketballl (F(2.29,39.00)=10.417, p<0.001), showing a proportional improvement in performance over weeks (t(85)=7.128, p<0.001, Figure 5D).

-Figure 5-

3.1.5. User experience

Prescription lenses. All but one participant randomized to ML2 did not require insert prescription lenses to train with Reality DTx®, even though all ML2 participants used prescription (reading) glasses or lenses in daily life. For pragmatic reasons, this participant with a prescription of +2.25 was moved to the HL2 group so that his own spectacles could be worn during the intervention (i.e., to prevent delays and costs associated with ordering special lenses not part of the standard lens kit).

Technical issues. HL2-group participants reported predominantly issues related to shifts in, or loss of, the spatial map of the safe training area (with one dropout due to frustration with technical issues) and limited AR field of view. ML2-group participants reported predominantly issues related to hand tracking (affecting interaction with menus, Smash! and Hot Buttons) and Wi-Fi connection. Such technical issues experienced during the intervention were categorized into issues that did or did not prevent participants (Figure 3) to adhere to the prescribed intervention (Supplementary Material T2). In only 10 of the 131 prescribed training weeks more than two days per week were lost due to technical issues. These issues were solvable by participants themselves, by researchers visiting participants or remotely through a telephone call.

User Experience Questionnaire (UEQ). Reality DTx® reached above average scores for UEQ [19] subscales Efficiency and Dependability, good scores for Perspicuity and Novelty and excellent scores for Attractiveness and Stimulation (Figure 6A). User experience seemed

overall somewhat better for the HL2-group (Figure 6A), with significantly lower scores for the ML2-group on Perspicuity ($U=64$, $p<0.05$, $r_{rb}=0.580$, $BF_{10}=1.365$) and Dependability ($t(16)=2.473$, $p<0.05$, $d=1.166$, $BF_{10}=2.735$) and borderline-significant lower scores for Attractiveness ($U=63$, $p=0.051$, $r_{rb}=0.556$, $BF_{10}=1.615$).

-Figure 6-

Acceptability questions. Figure 6B depicts the score distribution on the acceptability evaluation Likert-scale questions, indicating that overall Reality DTx® was a well-accepted intervention. Participants scored the training as useful (8.4/10), motivating (8.2/10), challenging (8.1/10), fun (8.7/10), user-friendly (7.5/10) and suitable for improving gait and balance (7.5/10). On the question how participants would feel if we would stop developing Reality DTx®, 17/23 participants indicated that they would be very disappointed 5/23 indicated that they would be somewhat disappointed and 0/23 indicated not to feel disappointment.

3.2 Potential efficacy

We conducted a 2 (Group) × 3 (Time) mixed ANOVA on outcomes of gait, balance and walking-adaptability fall-risk indicators. We focus here on main effects of Time as effects with Group were generally not significant, except when explicitly mentioned here (full statistics in Supplementary Material T3).

3.2.1. Clinical gait-and-balance tests

For TUG, 10MWT and FTSTS a significant main effect of Time was observed (Table 4). For TUG, both inverse Helmert contrasts were significant, revealing that test-completion times decreased from t0 to t1 and then decreased further at t2. For 10MWT only the first and for FTSTS only the second inverse Helmert contrast was significant, indicating improvements in completion times during the waitlist and after the intervention, respectively. MiniBEST, UPDRS-III and LPAS did not vary significantly with Time.

3.2.2. Gait parameters

We quantified key gait characteristics during the instrumented 10MWT. For walking speed and step length, significant main effects of Time were observed (Table 4): speed and step lengths increased from t0 to t1 and walking speed improved further at t2 after the Reality DTx® intervention. Step width and cadence did not vary with Time.

3.2.3. Walking adaptability

Participants' walking adaptability, a targeted marker for falls risk [16], improved after the Reality DTx® intervention. That is, at t2 participants completed the obstacle-avoidance, goal-directed stepping, tandem-walking and time-pressured half-turn tasks significantly faster than before, as reflected by significantly faster (normalized) walking speeds and turning times after the Reality DTx® intervention (Table 4), without negatively affecting walking-adaptability performance indicators like obstacle-avoidance success rates and stepping accuracy (i.e., no effects of Time on walking-adaptability performance indicators; Table 4).

3.2.4. Patient-reported outcome measures

For the questionnaires only a significant main effect of Time ($F(2,36)=3.309$, $p=0.048$, $\eta_p^2=0.155$) was observed for FES-I, with a slightly but significantly 2.53±1.22 higher FES-I score at t1 than at t0 ($t(36)=2.076$, $p=0.045$). Furthermore, a significant main effect of Group ($F(1,18)=5.224$, $p=0.035$, $\eta_p^2=0.225$) was observed for NFOGQ, with a 6.88±3.01 higher score for ML2 (with 7/9 freezers) compared to HL2 (4/11 freezers).

4. Discussion

In this waitlist-controlled clinical feasibility study we evaluated a home-based gait-and-balance exergaming intervention (Reality DTx®), a digital therapeutics program that was specifically designed for pwPD and uniquely administered through state-of-the-art AR glasses. Below we discuss the findings in terms of its feasibility (safety, adherence, user experience) and potential efficacy for improving gait, balance and walking-adaptability fall-risk indicators.

4.1 Feasibility: Reality DTx® is a safe, adherable, well-accepted and usable intervention

A key feasibility aspect of new therapy interventions is safety, which seems especially relevant for Reality DTx® given its unsupervised remote delivery in an intrinsically high fall-risk population. We found that Reality DTx® was safe (no falls, only four near falls in >15.000 active minutes of gait-and-balance exergaming) with limited adverse events in relevant prespecified [15-17] domains (e.g., some reports of dizziness, no eyestrain, two headaches). We learned that exergame settings could be adjusted to prevent adverse events like dizziness, thereby further improving safety. For example, lower Smash! exergame-levels yielded high turning

rates, which may cause dizziness (i.e., 8/15 dizziness reports were attributed to turning) which can be remedied by lowering induced turning rates (e.g., demanding more punches, increasing inter-plinth distances). Exergame settings were also adjusted to tailor the physical load of the Reality DTx® intervention (according to FITT principles) to participant's physical capacity; still some adverse events in the 'other' class were reported (like re-occurring injuries).

A second important feasibility aspect is adherence. Our participants were able to exercise independently at home with Reality DTx®, with 104% session adherence, which is high compared to known adherence rates for home-based exercise interventions (e.g., 84% in [20]). This is an encouraging finding considering the high-dose default prescription of 30 active-minutes/session for five sessions/week for six weeks (i.e., note that total session duration was always longer than the prescribed active minutes due to e.g., switching or rests between exergames). Participants performed slightly fewer active minutes than prescribed (88% active-minute/session adherence). Still, this led to a high number of repetitions and high dose of sit-to-stands/squats, functional reaches and meters walked compared to other home-based interventions [21]. For some participants, the default 30 active-minutes/session was adjusted over weeks to tailor it, for example, to their physical capacity or time constraints. This again emphasizes how important remote monitoring and shared-decision making is for prescribing a progressive-but-achievable intervention, as will be discussed next.

Reality DTx® was not only remotely monitored for adherence, but also for exergame performance. Reality DTx® was intended as a progressive-but-achievable intervention, balancing task demands and capacity (not too easy to prevent boredom and not too difficult to prevent demotivation). We found that exergame-levels indeed progressed significantly over

16

weeks, with participant-specific exergame-levels and progression rates (i.e., tailored treatment), whereas the consistently high-but-submaximal exergame-performance scores over the weeks indicated that the intervention was achievable. Reality DTx® thus seemed to comply with the intended progressive-but-achievable principle, which is a prerequisite for reaching an intrinsically rewarding and highly engaged 'flow state', associated with exceptional performance and potentially increased long-term adherence [22, 23].

The third key feasibility aspect is acceptance and usability of interventions. Overall, Reality DTx® was a well-accepted intervention. User experience scores for Reality DTx® were excellent on UEQ domains Stimulation and Attractiveness, good on Novelty and Perspicuity and above average on Dependability and Efficiency compared to other established products (i.e., UEQ benchmark scores [19]). Note that we found superior Dependability ('*Does the user feel in control of the interaction? Is it secure and predictable?*') and Perspicuity ('*Is it easy to get familiar with the product and learn how to use it?*') scores for HL2 than for ML2 AR-glasses, most likely due to the -at that time- poorer hand tracking of ML2, as was also more often reported as a technical issue by ML2-group participants. We cannot conclude on a clear winner in terms of AR-glasses superiority (our secondary objective) as both AR-glasses had their distinct advantages and disadvantages for different feasibility aspects (e.g., use with own glasses better for HL2, AR field of view better for ML2, hand tracking superior for HL2, spatial mapping better for ML2). Furthermore, rapid progress in software developments for AR-glasses continue to improve usability and performance with each update (e.g., ML2 hand tracking has been improved considerably with a recent update), so future studies will likely not be hindered by the technical issues and limitations we experienced with specific AR-glasses.

The same holds true for issues related to the Reality DTx® digital therapeutics platform (e.g., connectivity, mapping, bugs), which were reported to Strolll Limited for further development and improvement.

All in all, Reality DTx® is a safe, adherable, well-accepted and usable intervention, and its feasibility is likely to improve even further based on the learnings of this study.

4.2 Potential efficacy: Reality DTx® is promising for improving targeted fall-risk indicators

Potential efficacy of Reality DTx® for improving gait, balance and falls risk was evaluated comprehensively, using outcomes covering standard clinical tests, gait characteristics and advanced walking-adaptability assessments as targeted fall-risk indicators.

With regard to standard clinical tests, significant intervention effects were observed for TUG and FTSTS, suggesting improvements in functional mobility, lower-limb strength and dynamic balance [7, 24-27] in a relatively high-functioning (i.e., HY2-2.5) group of pwPD recruited from the general public. The significant post-intervention TUG improvement of 0.85±0.31s against a ~11s baseline group TUG-time was smaller than the 1.63s minimal detectable change (MDC) [26], whereas the significant post-intervention FTSTS improvement of 2.97±1.16s against a ~16s baseline group FTSTS-time was substantially greater than the 1.66s MDC (i.e., derived from the standard error of measurement score of 0.6s in [28] and greater than the 2.5s minimal clinically importance difference in [29]). TUG and 10MWT were prone to small waitlist effects (i.e., significant improvements during the waitlist period), reminiscent of a Hawthorne effect [30, 31] as observed before (e.g., [32]) or due to

learning/familiarization with the tests or test setting. Other standard clinical tests did not vary systematically (Mini-BESTest and LPAS), probably hindered by ceiling effects (i.e., ≥20% of the sample received the maximum score on all Mini-BESTest subscales, expect for reactive postural control, and on the LPAS subscale scores; [33]). For the MDS-UPDRS III an absence of effect may be explained by the minor emphasis on gait and balance and the shorter-than-recommended 12-week training period for achieving clinically meaningful improvements in the severity of motor systems (as measured with MDS-UPDRS III [34]).

With regard to the assessments with the Interactive Walkway (Figure 2), we found an improved post-intervention walking speed for gait characteristics and profound intervention effects for adaptive walking, with faster test completion times without negatively affecting performance. These findings were robust (i.e., without any waitlist-period effects that hampered some of the standard clinical-tests and gait-characteristic outcomes), suggesting targeted effects of Reality DTx® for improving walking-adaptability fall-risk indicators [16]. This is encouraging as Reality DTx® exergames were designed to explicitly target this construct. Note that walking adaptability is not well captured with standard clinical tests [16]. The observed targeted improvements in walking adaptability are promising as they tentatively lower one's falls risk [16], as may be evaluated in future Reality DTx® effect studies.

All in all, Reality DTx® seems promising for improving aspects of gait and balance, in particular on lower-limb strength, dynamic balance (i.e., FTSTS) and walking-adaptability as fall-risk indicators [16, 24]

4.3 Recommendation for future research

Above-discussed results on the feasibility and potential efficacy of Reality DTx® warrant future controlled effect studies, for which we recommend to:

i) <u>change inclusion criteria</u>: we learned that Reality DTx® was a feasible unsupervised at-home intervention for participants with HY2 and HY2.5. Our inclusion criteria were HY2-4, but we excluded two participants with HY3 at t0 as their fall-risk was deemed too high to exergame unsupervised, while HY4 did not enter the study at all. We recommend to broaden inclusion to HY1. This is relevant as gait-and-balance impairments and falls risk is already present from an early stage [1] and people in this stage may benefit from targeted gait-and-balance interventions. People with PD with higher HY-stages with increased falls risk could use Reality DTx® first under supervision in the clinic (see ii) and/or tailored to their ability (e.g., see iii). These recommendations are implemented in the indications by Strolll Limited.

ii) <u>combine clinical and at-home exergaming settings</u>: with this study we were quite ambitious by starting home-based exergaming after limited familiarization and instruction time. By delivering Reality DTx® in a hybrid form, starting in the clinical pathway for some sessions before taking it home, more time for instructions, familiarization and evaluation of safety is available. This tentatively improves the confidence of inclusion/exclusion of people with HY3 and enables supervised in-clinic exergaming scenarios for people with HY4 (see iii);

iii) <u>extend the number of exergames</u>: to target other aspects of motor and/or cognitive impairments (e.g., dual-tasking; [14, 35, 36]), to include those at higher HY-stages with tailored game-play settings (e.g., playing when seated) and to increase longer-term

adherence (e.g., playing the same five exergames may become less engaging or

motivating over a longer period);

iv)   <u>consider changing outcome measures</u>: observed intervention effects of Reality DTx®

were convincing for improving targeted fall-risk indicators associated with walking

adaptability, fitting the nature of the exergames. Hence, future studies may consider

designing effect studies targeting falls risk or prospective falls as outcome measures,

which seems relevant given the high fall incidence in this population. Future studies

may also add health-economic outcomes as Reality DTx® may contribute to extending

the number of (unsupervised) rehabilitation exercise hours while lowering the burden

on healthcare professionals and increasing accessibility and adherence to treatment,

in the convenience of users' own home and time instead of supervised in the clinic;

v)   <u>extend intervention interval</u>: we used a 6-week intervention period, which may be on

the lower-end of the guideline recommendations [10, 12, 37]. Participants were positive

about continuing with Reality DTx® after the 6-weeks intervention (Figure 6).

5. Conclusion

We found that the remotely prescribed, monitored and tailored Reality DTx® intervention was

feasible: it is safe for use at home, adherable, progressive-but-achievable, well-accepted and

usable. Reality DTx® was potentially effective for improving gait and balance, in particular for

lower-limb strength, dynamic balance and walking adaptability as indicators of reduced falls

risk. Future controlled effect studies with this feasible and potentially effective Reality DTx®

digital therapeutics platform are thus warranted.

Conflict of Interest

Data availability statement

Anonymized study data will be made available on reasonable request.

Supplementary material

Supplementary material includes 1) a video of (the progression in) home-based exergaming with Reality DTx®, 2) an overview of the technical issues that did and did not prevent participants from adhering to the prescribed training program, 3) the full statistical results of the 2×3 mixed ANOVAs for all (adaptive) gait-and-balance outcomes.

References

[1]   Ellis TD, Colón-Semenza C, DeAngelis TR, Thomas CA, Hilaire MS, Earhart GM, Dibble LE (2021) Evidence for Early and Regular Physical Therapy and Exercise in Parkinson's Disease. *Semin Neurol* **41**, 189-205.

[2]   LeWitt PA, Chaudhuri KR (2020) Unmet needs in Parkinson disease: Motor and non-motor. *Parkinsonism Relat Disord* **80 Suppl 1**, S7-s12.

[3]   Nonnekes J, de Kam D, Oude Nijhuis LB, van Geel K, Bloem BR, Geurts A, Weerdesteyn V (2015) StartReact effects support different pathophysiological mechanisms underlying freezing of gait and postural instability in Parkinson's disease. *PLoS One* **10**, e0122064.

[4]   Gómez-Esteban JC, Zarranz JJ, Lezcano E, Tijero B, Luna A, Velasco F, Rouco I, Garamendi I (2007) Influence of Motor Symptoms upon the Quality of Life of Patients with Parkinson's Disease. *European Neurology* **57**, 161-165.

[5]   Allen NE, Sherrington C, Paul SS, Canning CG (2011) Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. *Mov Disord* **26**, 1605-1615.

[6]   Hess CW, Hallett M (2017) The Phenomenology of Parkinson's Disease. *Semin Neurol* **37**, 109-117.

[7]   Bouça-Machado R, Maetzler W, Ferreira JJ (2018) What is Functional Mobility Applied to Parkinson's Disease? *J Parkinsons Dis* **8**, 121-130.

[8]   Tomlinson CL, Patel S, Meek C, Herd CP, Clarke CE, Stowe R, Shah L, Sackley CM, Deane KHO, Wheatley K, et al. (2013) Physiotherapy versus placebo or no intervention in Parkinson's disease. *Cochrane Database of Systematic Reviews*.

[9]   Keus S, Munneke M, Graziano M, Paltamaa J, Pelosin E, Domingos J, Brühlmann S, Ramaswamy B, Prins J, Struiksma C (2014) European physiotherapy guideline for Parkinson's disease. *The Netherlands: KNGF/ParkinsonNet* **191**.

[10]   van Nimwegen M, Nijkrake M, Munneke M (2017) Ziekte van Parkinson. *KNGF-richtlijn. Koninklijk Nederlands Genootschap voor Fysiotherapie augustus*.

[11]   Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput J-P, Chastin S, Chou R (2020) World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British journal of sports medicine* **54**, 1451-1462.

[12]   Osborne JA, Botkin R, Colon-Semenza C, DeAngelis TR, Gallardo OG, Kosakowski H, Martello J, Pradhan S, Rafferty M, Readinger JL, Whitt AL, Ellis TD (2021) Physical Therapist Management of Parkinson Disease: A Clinical Practice Guideline from the American Physical Therapy Association. *Phys Ther*.

[13]   Lindop F, Skelly R (2021) Parkinson's Disease: An Interdisciplinary Guide to Management Elsevier Health Sciences.

[14]   Gallou-Guyot M, Nuic D, Mandigout S, Compagnat M, Welter ML, Daviet JC, Perrochon A (2022) Effectiveness of home-based rehabilitation using active video games on quality of life, cognitive and motor functions in people with Parkinson's disease: a systematic review. *Disabil Rehabil*, 1-12.

[15]   Hardeman L, Geerse, D., Hoogendoorn, E., Nonnekes, J., & Roerdink, M. (2023) Remotely prescribed and monitored home-based gait-and-balance therapeutic exergaming using augmented reality (AR) glasses: protocol for a clinical feasibility study in people with Parkinson's disease. *Research Square [preprint]*.

[16]   Geerse DJ, Roerdink M, Marinus J, van Hilten JJ (2019) Walking adaptability for targeted fall-risk assessments. *Gait Posture* **70**, 203-210.

[17]   JASP Team (2023). JASP (Version 0.18.1)[Computer software].

[18]   Jeffreys HS (1961) *Theory of probability / by Harold Jeffreys*, Clarendon Press, Oxford.

[19]   Laugwitz B, Held T, Schrepp M (2008) *Construction and Evaluation of a User Experience Questionnaire*.

[20]   Flynn A, Allen NE, Dennis S, Canning CG, Preston E (2019) Home-based prescribed exercise improves balance-related activities in people with Parkinson's disease and has benefits similar to centre-based exercise: a systematic review. *Journal of Physiotherapy* **65**, 189-199.

[21]   Pickering RM, Fitton C, Ballinger C, Fazakarley L, Ashburn A (2013) Self reported adherence to a home-based exercise programme among people with Parkinson's disease. *Parkinsonism Relat Disord* **19**, 66-71.

[22]   Nakamura J, Csikszentmihalyi M (2002) The concept of flow In *Handbook of positive psychology.* Oxford University Press, New York, NY, US, pp. 89-105.

[23]   Jackman PC, Hawkins RM, Crust L, Swann C (2019) Flow states in exercise: A systematic review. *Psychology of Sport and Exercise* **45**, 101546.

[24]   Duncan RP, Leddy AL, Earhart GM (2011) Five times sit-to-stand test performance in Parkinson's disease. *Arch Phys Med Rehabil* **92**, 1431-1436.

[25]   Mollinedo I, Ma Cancela J (2020) Evaluation of the psychometric properties and clinical applications of the Timed Up and Go test in Parkinson disease: a systematic review. *J Exerc Rehabil* **16**, 302-312.

[26]   Muñoz-Bermejo L, Adsuar JC, Mendoza-Muñoz M, Barrios-Fernández S, Garcia-Gordillo MA, Pérez-Gómez J, Carlos-Vivas J (2021) Test-Retest Reliability of Five Times Sit to Stand Test (FTSST) in Adults: A Systematic Review and Meta-Analysis. *Biology (Basel)* **10**.

[27]   Podsiadlo D, Richardson S (1991) The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* **39**, 142-148.

[28]   Paul SS, Canning CG, Sherrington C, Fung VS (2012) Reproducibility of measures of leg muscle power, leg muscle strength, postural sway and mobility in people with Parkinson's disease. *Gait Posture* **36**, 639-642.

[29]   Spagnuolo G, Faria C, da Silva BA, Ovando AC, Gomes-Osman J, Swarowsky A (2018) Are functional mobility tests responsive to group physical therapy intervention in individuals with Parkinson's disease? *NeuroRehabilitation* **42**, 465-472.

[30]   Robles-García V, Corral-Bergantiños Y, Espinosa N, Jácome MA, García-Sancho C, Cudeiro J, Arias P (2015) Spatiotemporal Gait Patterns During Overt and Covert Evaluation in Patients With Parkinson´s Disease and Healthy Subjects: Is There a Hawthorne Effect? *J Appl Biomech* **31**, 189-194.

[31]   Malchow C, Fiedler G (2016) Effect of observation on lower limb prosthesis gait biomechanics: Preliminary results. *Prosthet Orthot Int* **40**, 739-743.

[32]   van de Venis L, van de Warrenburg B, Weerdesteyn V, Geurts ACH, Nonnekes J (2023) Gait-Adaptability Training in People With Hereditary Spastic Paraplegia: A Randomized Clinical Trial. *Neurorehabil Neural Repair* **37**, 27-36.

[33]   Ban B, Sevšek F, Rugelj D (2017) A comparison of the ceiling effect between Berg Balance Scale and Mini-BESTest in a group of balance trained community-dwelling older adults. *Physiotherapy Quarterly* **25**, 3-9.

[34]   Ernst M, Folkerts AK, Gollan R, Lieker E, Caro-Valenzuela J, Adams A, Cryns N, Monsef I, Dresen A, Roheger M, Eggers C, Skoetz N, Kalbe E (2023) Physical exercise for people with Parkinson's disease: a systematic review and network meta-analysis. *Cochrane Database Syst Rev* **1**, Cd013856.

[35]   Alberts JL, Kaya RD, Scelina K, Scelina L, Zimmerman EM, Walter BL, Rosenfeldt AB (2022) Digitizing a Therapeutic: Development of an Augmented Reality Dual-Task Training Platform for Parkinson's Disease. *Sensors* **22**, 8756.

[36]   McNaney R, Balaam M, Holden A, Schofield G, Jackson D, Webster M, Galna B, Barry G, Rochester L, Olivier P (2015) in *Proceedings of the 33rd annual ACM conference on Human Factors in Computing Systems*, pp. 501-510.

[37]   Keus SHJ, Bloem BR, Hendriks EJM, Bredero-Cohen AB, Munneke M, Group obotPRD (2007) Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. *Movement Disorders* **22**, 451-460.

[38]   Kaufeld M, Mundt M, Forst S, Hecht H (2022) Optical see-through augmented reality can induce severe motion sickness. *Displays* **74**, 102283.

[39]   Vovk A, Wild F, Guest W, Kuula T (2018) in *Proceedings of the 2018 CHI Conference on Human Factors in Computing Systems* Association for Computing Machinery, Montreal QC, Canada, p. Paper 209.

[40]   Tunur T, DeBlois A, Yates-Horton E, Rickford K, Columna LA (2020) Augmented reality-based dance intervention for individuals with Parkinson's disease: A pilot study. *Disabil Health J* **13**, 100848.

[41]   Godi M, Arcolin I, Giardini M, Corna S, Schieppati M (2020) Responsiveness and minimal clinically important difference of the Mini-BESTest in patients with Parkinson's disease. *Gait Posture* **80**, 14-19.

[42]   Pearson M, Lindop F, Mockett S, Saunders L (2009) Validity and inter-rater reliability of the Lindop Parkinson's Disease Mobility Assessment: a preliminary study. *Physiotherapy* **95**, 126-133.

[43]   Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders* **23**, 2129-2170.

[44]   Washburn RA, Smith KW, Jette AM, Janney CA (1993) The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* **46**, 153-162.

[45]   Giladi N, Tal J, Azulay T, Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe WH, Stocchi F, Tolosa E (2009) Validation of the freezing of gait questionnaire in patients with Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society* **24**, 655-661.

[46]   Winser SJ, Kannan P, Bello UM, Whitney SL (2019) Measures of balance and falls risk prediction in people with Parkinson's disease: a systematic review of psychometric properties. *Clin Rehabil* **33**, 1949-1962.

[47]   Mehdizadeh M, Habibi S, Martinez-Martin P, Taghizadeh G, Fereshtehnejad S-M (2019) Reliability and Validity of Fall Efficacy Scale-International in People with Parkinson's Disease during On- and Off-Drug Phases. *Journal of Parkinson's Disease* **2019**.

[48]   Marinus J, Visser M, Jenkinson C, Stiggelbout AM (2008) Evaluation of the Dutch version of the Parkinson's Disease Questionnaire 39. *Parkinsonism & Related Disorders* **14**, 24-27.

Tables

Table 1. Data-collection methods, outcome measures and timepoints of data collection for aspects of feasibility (safety, adherence, user experience) and potential efficacy for improving gait and balance (including walking adaptability).

Data collection	Outcome measure	Timepoint of data collection
Feasibility		
Safety: Weekly telephone calls	Number of falls, near falls and adverse events (dizziness, headache, eyestrain, other [38-40])	t1 – t2
Adherence: - Reality DTx® web portal	Drop-out rate Session adherence (%) Active-minutes/session adherence (%)	t1 – t2 t1 – t2
Game performance: Reality DTx® web portal	Mole Patroll: Number of moles caught / Total number of moles spawned	t1 – t2
	Smash!: Number of vases smashed / Total number of vases spawned	
	Basketballl: Number of sit-to-stand movements / Target number of sit-to-stands movements per minute	
	Hot Buttons: Number of buttons pressed / Total number of buttons lit up	
	Puzzle walk: Number of pieces / Total pieces to be collected	
User experience: User Experience questionnaire (UEQ)	Contrasting attributes (1-7 Likert scale) related to Attractiveness, Perspicuity, Efficiency, Dependability, Stimulation and Novelty	t2
Acceptability evaluation questionnaire	Scores (between 0-10 and 0-100%) on various acceptability questions	t2
Weekly telephone calls	Number of reported technical issues	t1 – t2
Potential efficacy		
(adaptive) gait-and-balance tests:		t0, t1, t2
Mini Balance Evaluation Systems Test (Mini-BESTest) [41]	Total score (0-28)	

Timed Up-and-Go test (TUG) [25, 27]	Completion time (s)	
Five Times Sit-to-Stand Test (FTSTS) [24, 26]	Completion time (s)	
Lindop Parkinson's Physiotherapy Assessment Scale (LPAS) [42]	Total score of gait mobility subscale (0-18)	
Interactive Walkway* [16]	Obstacle avoidance: Outcome measures were walking speed (cm/s), success rate (%) and obstacle-avoidance margins (cm) Goal-directed stepping: Outcome measures were normalized walking speed (%) and stepping accuracy (cm) Tandem walking: Outcome measures were walking speed (cm/s) and mediolateral sway (cm) Half turns: Outcome measures were turning time (s) and success rate (%)	
10-meter walking task (as measured by the Interactive Walkway [16])	Walking speed (cm/s), step length (cm), step width (cm) and cadence (steps/min)	
Patient-reported outcome measures		t0, t1, t2
Movement Disorders Society Unified Parkinson Disease Rating Scale – motor score (MDS-UPDRS III) [43]	Total score (0 – 132); higher scores mean more lower motor functioning	
Physical Activity Scale for the Elderly (PASE) [44]	Total score (0-400); higher scores mean a higher level of physical activity	
New Freezing of Gait Questionnaire (NFOGQ) [45]	Total score (0-28); lower scores mean less freezing of gait	
Activities-Specific Balance Confidence Scale (ABC) [46]	Total score (0-100); higher scores mean more balance confidence	
Falls Efficacy Scale International (FES-i) [47]	Total score (16-64); higher scores mean more fear of falling	
Parkinson's Disease Questionnaire (PDQ-39) [48]	Total score (0-156); higher scores mean a lower experienced quality of life	

Note. Session adherence = Ratio of performed to prescribed number of exergaming sessions, Active-minutes/session adherence = ratio of performed number of sessions to performed active minutes during these sessions.
*Adaptive walking outcome measures were calculated as detailed in [16], with the addition of mediolateral sway

during tandem walking (standard deviation of mediolateral spine-shoulder positions).

Table 2. Baseline participant characteristics did not differ between HL2 and ML2 groups.

	ML2 (n=11)	HL2 (n=13)	Statistic
Age (years)	69.8 [53-82]	64 [51-74]	$t(22)=-1.639, p=0.116, BF_{10}=0.966$
Sex	8 M, 3 F	9 M, 4 F	$X^2(1)=0.035, p=0.851, BF_{10}=0.509$
Disease duration (years)	9 [1-15]	7 [1-20]	$t(22)=-0.949, p=0.353, BF_{10}=0.519$
Modified HY	2 (45.5%), 2.5 (54.5%)	2 (69.2%), 2.5 (30.8%)	$X^2(1)=1.386, p=0.239, BF_{10}=0.900$
MoCA score	27 [19-30]	26 [18-29]	$U(22)=41.000, p=0.078, BF_{10}=1.109$
LEDD (max. mg/day)	814 [150-1738]	866 [125-2400]	$t(22)=0.429, p=0.672, BF_{10}=0.411$
History of falls (per year)	2.5 [0-10]	2.6 [0-10]	$U(22)=70.500, p=0.976, BF_{10}=0.372$
Number of freezers	7	5	$X^2(1)=1.510, p=0.219, BF_{10}=0.942$
MDS-UPDRS (total score)	69 [50-79]	58 [34-78]	$t(22)=-1.904, p=0.070, BF_{10}=2.092$
PASE	117.7 [45.0-180.0]	128.0 [40.0-246.4]	$t(22)=0.404, p=0.690, BF_{10}=0.397$

Note. Data are mean [range]. Disease duration (years) = time since diagnosis, LEDD = Levodopa Equivalent Daily Dose, Modified HY = Modified Hoehn and Yahr scale, MoCA = Montreal Cognitive Assessment, MDS-UPDRS = MDS-Unified Parkinson's Disease Rating Scale, PASE = Physical Activity Scale for the Elderly.

Table 3. Adverse events.

|	Number of experienced adverse events per week						Total number of reported adverse events / total number of training weeks		Total number of unique participants reporting an adverse event / total number of participants	
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	HL2	ML2	HL2	ML2
Falls	0	0	0	0	0	0	0	0	0	0
Near falls	1/23	0/23	1/23	0/21	2/21	0/20	3/74	1/57	2/23	1/23
Dizziness	5/23	4/23	2/23	1/21	2/21	1/20	11/74	4/57	6/23	3/23
Headache	1/23	0/23	1/23	0/21	0/21	0/20	2/74	0/57	1/23	0/23
Eyestrain	0/23	0/23	0/23	0/21	0/21	0/20	0/74	0/57	0/23	0/23
Other	3/23	1/23	7/23	5/21	7/21	4/20	23/74	4/57	8/23	3/23

Table 4. Main effects of time and, when significant, their contrasts.

	t0	t1	t2	main effect of Time				1st inverse Helmert contrast (t1-t0)			2nd inverse Helmert contrast (t2 – t1,t0)		
	M±SD	M±SD	M±SD	$F(df)$*	p	η_p^2	BF_{10}	t	p	Δt1-t0	t	p	Δt2-t1,t0
Clinical gait-and-balance test													
TUG (s)	11.65±4.26	10.91±3.98	10.39±3.86	**F(1.496,25.434) =6.084**	**0.012**	**0.264**	**8.339**	$t(34)$=-2.206	**0.034**	-0.80±0.36	$t(34)$=-2.703	**0.011**	**-0.85±0.31**
FTSTS (s)	16.85±7.37	16.18±6.11	13.46±5.75	**F(2,34) =3.349**	**0.047**	**0.165**	**1.896**	$t(34)$=-0.347	0.731	-0.46±1.34	$t(34)$=-2.565	**0.015**	**-2.97±1.16**
10MWT (s)	9.13±1.97	8.51±1.20	8.40±1.33	**F(2,34) =5.216**	**0.011**	**0.235**	**6.788**	$t(34)$=-2.612	**0.013**	**-0.62±0.24**	$t(34)$=-1.900	0.066	-0.39±0.21
Mini-BESTest	22.00±3.71	22.16±2.97	22.58±3.95	F(2,34) =0.362	0.699	0.021	0.221	NA			NA		
MDS-UPDRS III	31.05±11.31	31.63±11.63	32.90±10.77	F(2,34) =0.957	0.394	0.053	0.302	NA			NA		
LPAS	17.21±1.55	17.42±1.12	17.53±1.22	F(2,34) =0.993	0.381	0.055	0.260	NA			NA		
Gait characteristics instrumented 10MWT													
Walking speed (cm/s)	113.86±20.48	119.61±16.50	121.71±16.95	**F(2,34) =5.425**	**0.009**	**0.242**	**8.467**	$t(34)$=2.400	**0.022**	**5.64±2.35**	$t(34)$=2.256	**0.031**	**4.59±2.03**
Step length (cm)	65.74±11.21	68.21±10.41	68.70±10.72	**F(2,34)=4.889**	**0.014**	**0.223**	**5.950**	$t(34)$=2.473	**0.019**	**2.43±0.98**	$t(34)$=1.914	0.064	1.63±0.85
Step width (cm)	11.13±3.89	10.83±3.43	10.76±3.88	F(2,34) =0.269	0.766	0.016	0.191	NA			NA		
Cadence (steps/min)	108.28±10.37	110.08±8.63	110.36±8.80	F(2,34) =1.479	0.242	0.080	0.521	NA			NA		
Walking adaptability: obstacle avoidance													
Walking speed (cm/s)	104.44±23.63	107.67±17.72	113.28±19.57	**F(2,32) = 3.347**	**0.048**	**0.173**	**1.800**	$t(32)$=0.985	0.332	3.13±3.18	$t(32)$=2.392	**0.023**	**6.58±2.75**
Success rate (%)	69.17±31.59	66.11±36.64	62.78±37.39	F(2,32) = 0.560	0.577	0.034	1.154	NA			NA		
Margins (cm)	11.61±6.10	12.07±6.10	13.78±5.18	F(2,32) = 2.410	0.106	0.131	0.957	NA			NA		
Walking adaptability: goal-directed stepping													
Normalized walking speed (%)	77.22±21.13	81.83±20.22	85.09±18.57	**F(2,32) = 3.671**	**0.037**	**0.187**	**2.321**	$t(32)$=1.609	0.117	4.48±2.78	$t(32)$=2.180	**0.037**	**5.25±2.41**
Stepping accuracy (cm)	4.48±1.39	4.13±0.99	4.61±1.37	F(2,32) = 2.024	0.149	0.112	0.570	NA			NA		
Walking adaptability: tandem walking													
Walking speed (cm/s)	82.89±29.00	90.02±22.53	98.22±22.64	**F(2,30) = 3.367**	**0.048**	**0.183**	**2.430**	$t(30)$=1.257	0.219	6.72±5.35	$t(30)$=2.270	**0.031**	**10.51±4.63**
Sway (cm)	4.24±1.47	3.83±1.19	3.63±1.36	F(2,30) = 2.244	0.124	0.130	0.883	NA			NA		
Walking adaptability: half turns													
Turning time (s)	1.95±0.82	1.78±0.82	1.51±0.47	**F(1.321,21.144) = 4.133**	**0.045**	**0.205**	**1.553**	$t(32)$=-1.276	0.211	-0.21±0.16	$t(32)$=-2.577	**0.015**	**-0.36±0.14**
Success rate (%)	27.78±30.79	27.78±35.24	27.78±30.79	F(2,32) = 0.023	0.977	0.001	0.143	NA			NA		

The assumption of sphericity was checked according to Girden (55). If Greenhouse–Geisser's epsilon exceeded 0.75, the Huynh-Feldt degrees of freedom (df) correction was applied; otherwise the Greenhouse–Geisser correction was used.

Figures
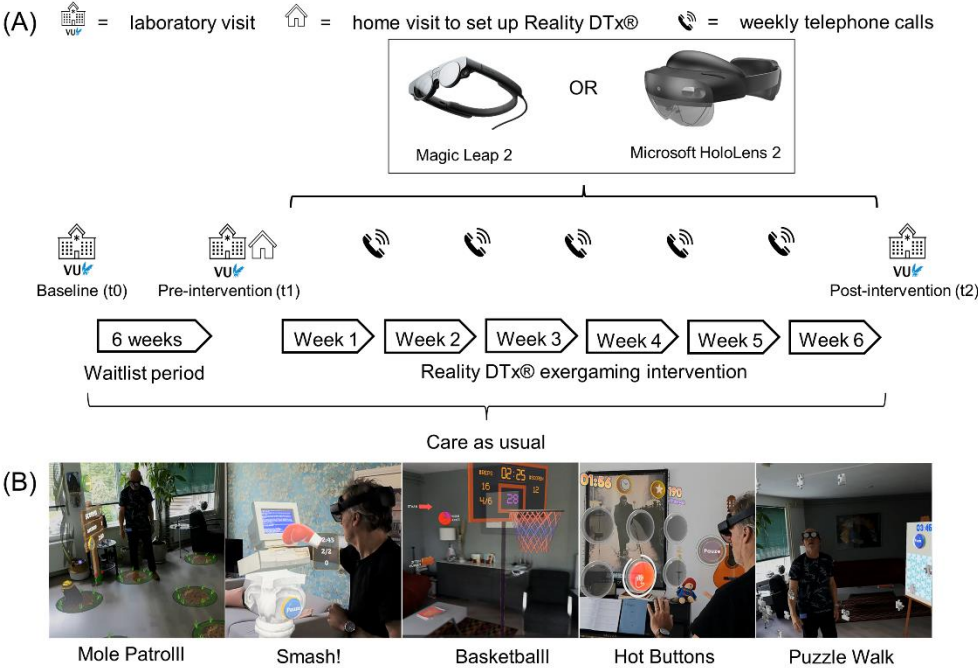
Figure 1. (A) Overview of the study design and procedure, with (B) images of the five

exergames of Reality DTx®. Participants have consented to the use of images and videos for

publication purposes.
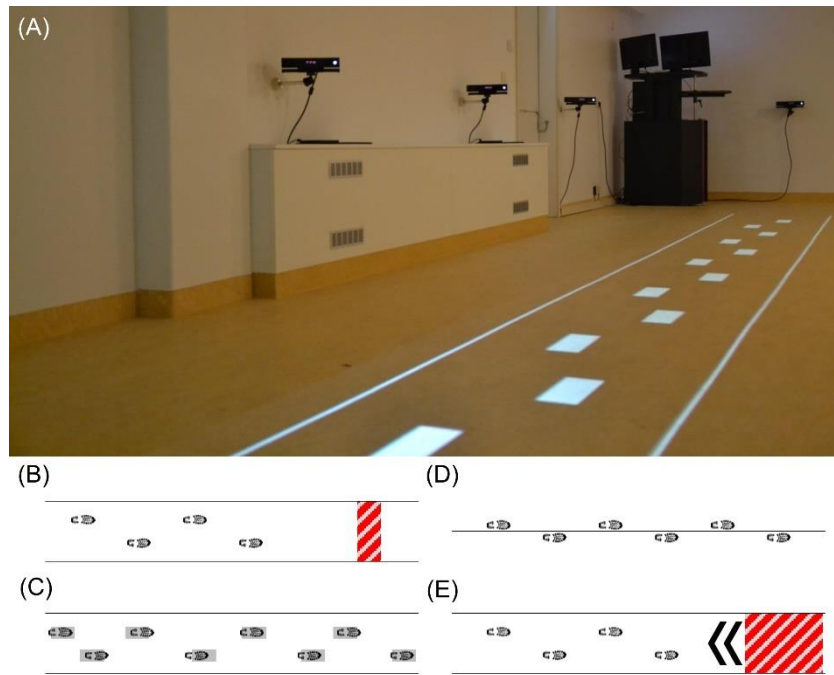
Figure 2. A visual representation of the Interactive Walkway (A) used for a targeted fall-risk assessment, including gait (instrumented 10m-walk test) and adaptive-gait (augmented obstacle-avoidance (B), goal-directed stepping (C), tandem-walking (D) and half-turn (E) tasks) assessments.

```
┌─────────────────────────┐
│  Assessed for eligibility│
│  (n = 64) by telephone   │
│       screening          │
└─────────────────────────┘
              │
              │      ┌──────────────────────────────────────────────────┐
              ├─────▶│ Excluded (n = 33)                                │
              │      │  •  Not meeting inclusion criteria (n = 19)      │
              │      │  •  Declined to participate (n = 7)              │
              │      │  •  Unable to attend to training schedule (n = 2)│
              │      │  •  Problems with transport (n = 5)              │
              │      └──────────────────────────────────────────────────┘
              ▼
┌─────────────────────────┐
│      Baseline (t0)       │
│        (n = 31)          │
└─────────────────────────┘
              │
              │      ┌──────────────────────────────────────────────────────────┐
              ├─────▶│ Excluded (n = 7)                                          │
              │      │  •  Insufficient physical capacity as observed by the     │
              │      │     researchers (i.e., risk of falls)(n = 2)              │
              │      │  •  Not earlier mentioned comorbidities influencing gait  │
              │      │     and therefore not meeting the inclusion criteria (n=2)│
              │      │  •  No show (n = 3)                                        │
              │      └──────────────────────────────────────────────────────────┘
              ▼
┌─────────────────────────┐
│   Allocation (n = 24)    │
└─────────────────────────┘
```

Excluded (n = 33)
- Not meeting inclusion criteria (n = 19)
- Declined to participate (n = 7)
- Unable to attend to training schedule (n = 2)
- Problems with transport (n = 5)

Excluded (n = 7)
- Insufficient physical capacity as observed by the researchers (i.e., risk of falls)(n = 2)
- Not earlier mentioned comorbidities influencing gait and therefore not meeting the inclusion criteria (n = 2)
- No show (n = 3)

Magic Leap (n = 11)

HoloLens (n = 13)

Dropped out (n = 2)
- Medical circumstances unrelated to the study, week 1 and 4 (n = 2)

Dropped out (n = 2)
- Medical circumstances unrelated to the study, week 6 (n = 1)
- Too many technological problems with the headset, week 4 (n = 1)

Included in analysis*
(n = 9)

Included in analysis*
(n = 11)

*Three of the four dropouts who trained for at least 3 weeks were included in the safety and user experience analyses. One participant changed medication dose (700 to 800 mg levodopa/carbidopa) in the waitlist-control period (three weeks before pre-intervention measures, t1) and was not excluded because we consider this small change in medication acceptable as part of this feasibility study.

Figure 3. Flow diagram of the 24 study participants.
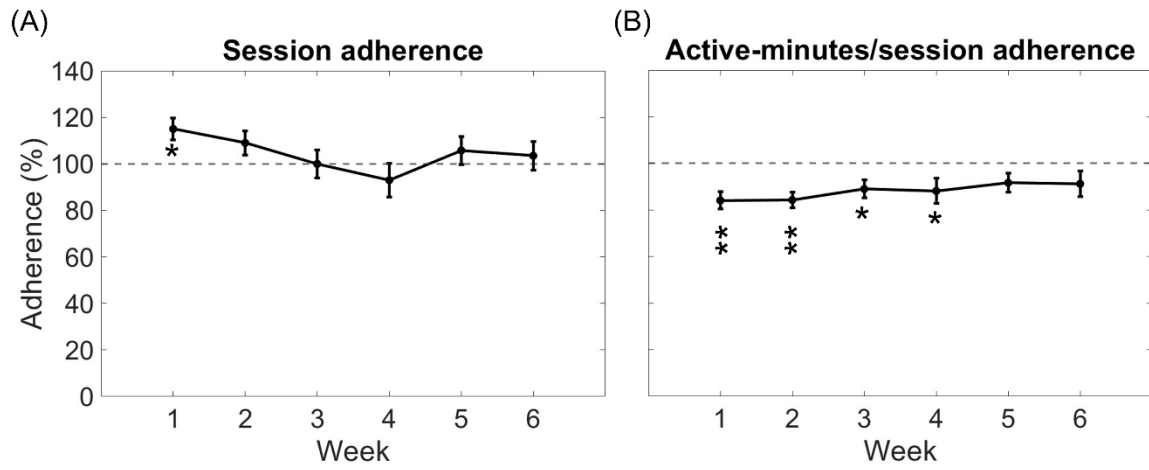
Figure 4. Reality DTx® adherence over weeks in terms of session adherence (A) and active-minutes/session adherence (B). Error bars represent standard error of the mean. *$p<0.01$, **$p<0.001$.
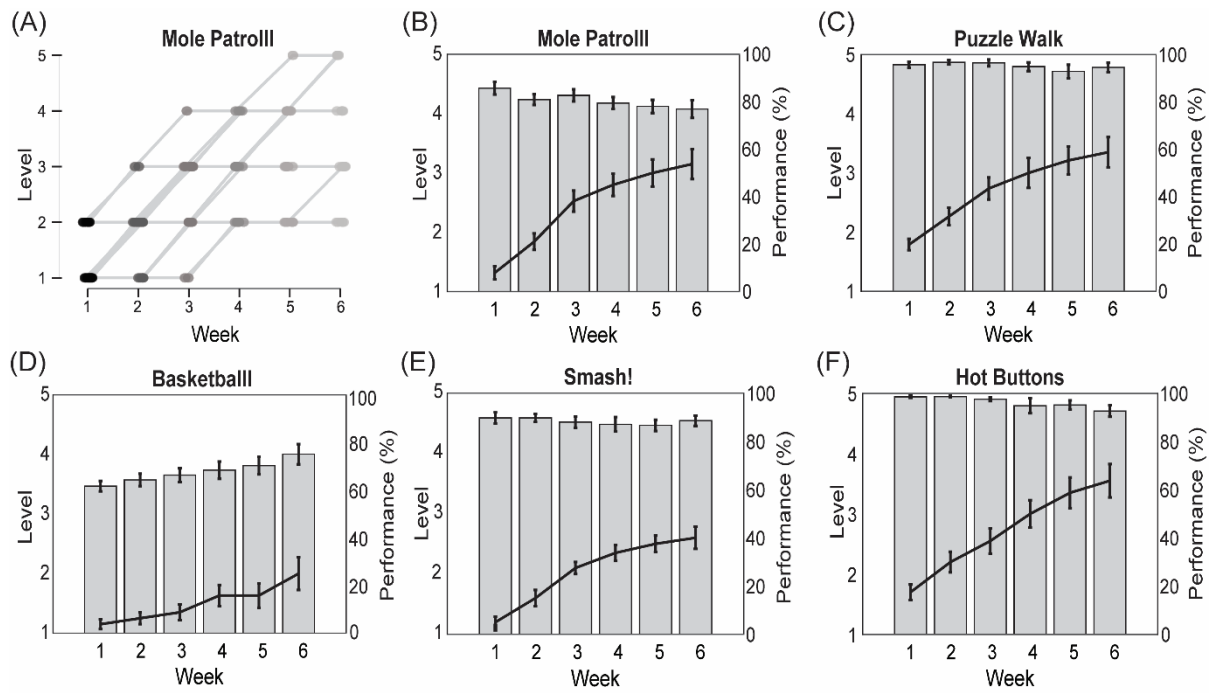
Figure 5. Reality DTx® exergame-play levels were personalized to participants' abilities and progression rates over the 6-week intervention (A) and prescribed in a progressive (i.e., significant increase in game-play levels over weeks; black lines) but achievable (high and non-varying game-play performance for all exergames but Basketballl; gray bars) manner (B-F).

(A)
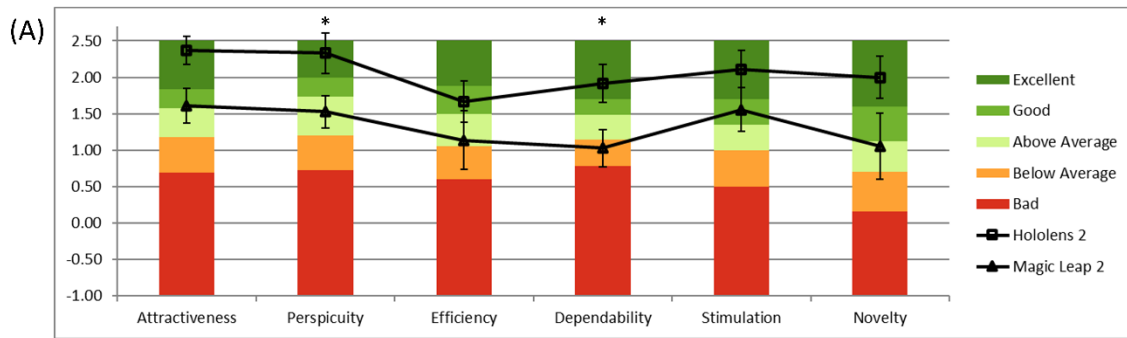
(B)

Score	0	1	2	3	4	5	6	7	8	9	10	
not useful	0	1	0	0	0	0	0	3	7	3	8	useful
not motivating	0	0	0	0	1	1	3	2	4	3	8	motivating
not challenging	0	0	1	0	0	2	2	1	4	4	8	challenging
not fun	0	0	0	0	0	0	0	5	6	2	9	fun
not user-friendly	0	1	0	0	0	3	0	6	5	2	5	user-friendly
not suitable	1	0	0	0	0	1	2	6	6	2	4	suitable

Score	<5	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85-94	≥95	
would not recommend it to peers	0	0	0	0	0	1	0	4	3	3	11	would recommend it to peers
would not continue training	0	0	0	0	0	0	2	4	1	2	13	would continue training

Figure 6. Reality DTx® user experience and acceptance. (A) HL2 and ML2 group mean scores on the six domains of the User Experience Questionnaire (UEQ) relative to the questionnaire's benchmark scores (*p<0.05; analyses was based on n=19 as four cases were excluded for inconsistencies following UEQ analysis guidelines [19]) and (B) distribution of the acceptability evaluation questionnaire scores.

Supplementary materials

Video S1. video showing the five Reality DTx® exergames, as well as progression therein in terms of exergame level and performance, as played by the same participant in his home in weeks 1 and 6 (detailed game descriptions can be found in Table S1). Participants have consented to the use of photos and videos for publication purposes.

Table S2. Description of the five AR gait-and-balance Reality DTx® exergames, including available game statistics.

Reality DTx® game	Description of the game	Game statistics
 Mole Patrolll	A goal-directed walking exergame to train gait initiation, dynamic balance, turning, stopping and strength (when performed in squat mode). The goal is to stomp as many moles as possible by scanning the room, spotting where they appear, and stomping on them either with both feet or squatting on them (a game-mode setting) before they disappear. Mole appearance duration reduces over difficulty levels to make the game more challenging.	**In-game feedback** Number of moles caught, distance walked **Post-game feedback** Number of moles caught **Web portal feedback** Prescribed and active minutes Meters walked
 Smash!	A boxing exergame to train gait, dynamic balance, weight shifting and turning. The goal is to smash as many items as possible from two plinths as they appear, demanding alternate left-right punches to promote weight shifting, with available items alternating between the plinths to promote walking and turning. The distance between the plinths is adjustable (ranging from 2 to 10 meters) and so is the number of required punches before the items drop from the plinth (ranging from 2-20 over difficulty levels) to make the game more challenging.	**In-game feedback** Number of items smashed, number of prescribed and performed punches **Post-game feedback** Number of items smashed **Web portal feedback** Prescribed and active minutes Meters walked Number of functional reaches
 Hot Buttons	A dynamic reaching exergame to train functional reaching, reaction time and dynamic balance. The goal is to press the button that lights up as quickly as possible before it disappears. Available buttons are presented in rows of three, stacked vertically totalling either 3, 6 or 9 buttons, dependent on the mode. The reach distance is adjustable	**In-game feedback** Number of buttons hit and streaks (i.e., hitting two or more buttons in a row with the prescribed hand) **Post-game feedback** Number of buttons hit. Bonus points for streaks which add up dependent on the number of buttons hit in a row. You

(40-90cm) and feet positioning is controlled to avoid cheating. Dependent on the mode, the participant presses the buttons either with the left, right or both hands at random. The appearance duration of the light-up buttons decreases over difficulty levels to make the game more challenging.

lose the streak when hitting a button with the wrong hand.

Web portal feedback
Prescribed and active minutes
Number of functional reaches

Basketballl

A sit-to-stand exergame to train dynamic balance and lower-limb muscle strength. The goal is to score as many points as possible by completing sit-to-stand or squat-to-stand movements (a game-mode setting) to spawn a set of three basketballs, and throw them into the hoop. The number of required sit-to-stand or squat-to-stand movements to earn basketballs increases over difficulty levels to make the game more challenging.

In-game feedback
Number of prescribed and performed sit- or squat-to-stands, number of basketballs scored

Post-game feedback
Number of sit- or squat-to-stands

Web portal feedback
Prescribed and active minutes
Number of sit-to-stands

Puzzle Walk

A goal-directed walking exergame to train gait, dynamic balance, turning, stopping and functional reaching. The goal is to find puzzle pieces in the room, pick them up by reaching the hand to them and place them on the easel to complete the puzzle before the time runs out. The required reaching height to collect the puzzle pieces is adjustable (selection from high, hip-level, knee-level or floor-level reaches). The number of puzzle pieces to complete the puzzle varies over difficulty levels to make the game more challenging.

In-game feedback
Number of prescribed and collected puzzle pieces, time left

Post-game feedback
Number of collected puzzles pieces within the set game duration (bonus points for every second left on the clock)

Web portal feedback
Prescribed and active minutes
Meters walked
Number of functional reaches

Table S2: Technical issues that did and did not prevent ML2 and HL2 participants from adhering to the prescribed training program (i.e., five sessions/week, 30 active-minutes/session).

Issues preventing participants to adhere to the training program:	Number of reported issues per group / total number of reported issues over 6 weeks		Categories of issues not preventing participants to adhere to the training program:	Number of reported issues per group / total number of reported issues over 6 weeks	
	ML2	HL2		ML2	HL2
1) The participant needs to make a new room scan but cannot do this independently	0/2	1/10	A) AR glasses suddenly switching off	24/162	26/146
2) Shifting of the digital spatial map of the training area. Guiding the participant to make a new room scan does not solve the issue	0/2	5/10	B) Limited field of view	6/162	18/146
3) Malfunctioning Wi-Fi connection preventing participants to log in with their personal pin number)	2/2	2/10	C) Hand tracking issues (e.g., participants experience difficulty punching items with Smash! or pressing buttons)	57/162	31/146
4) Games do not show in the game menu because of communication issues (i.e., communication with the web portal or through Wi-Fi)	0/2	2/10	D) Communicational issues related to the training program data from the web portal	4/162	18/146
			E) Connectivity issues related to Wi-Fi (i.e., participants cannot log in with their personal pin number)	15/162	2/146
			F) Issues with shifting or loss of digital spatial map of the training area (due to this issue, a new digital room scan was sometimes required)	29/162	41/146
			F) Issues with calibrating participant's length, sitting height and arm length resulting in misplacement of digital target in games (e.g., puzzle pieces)	17/162	10/146
			G) Other hardware-related issues (e.g., difficulty to train under certain lighting circumstances)	10/162	7/146

Note. Some issues that did and did not prevent participants from adhering to the training program are related. These are: 1, 2 – F; 3, 4 – D, E. HL2 = HoloLens 2, ML2 = Magic Leap 2.

Table S3: Group, time and interaction effects for (adaptive) gait-and-balance outcomes.

	Group (HL2, ML2)				Time (t0, t1, t2)				Group-by-Time Interaction			
	F^*	p	η_p^2	BF_{10}	F^*	p	η_p^2	BF_{10}	F^*	P	η_p^2	BF_{10}
Clinical gait and balance tests												
TUG	$F(1,17)=0.446$	0.513	0.026	0.706	**$F(1.496,25.434)=6.084$**	**0.012**	**0.264**	**8.339**	$F(1.496,25.434)=1.100$	0.331	0.061	0.421
5TSTS	$F(1,17)=2.781$	0.114	0.141	1.085	**$F(2,34)=3.349$**	**0.047**	**0.165**	**1.896**	$F(2,34)=0.570$	0.571	0.032	0.323
10MWT	$F(1,17)=0.004$	0.953	<0.001	0.568	**$F(2,34)=5.216$**	**0.011**	**0.235**	**6.788**	$F(2,34)=0.574$	0.568	0.033	0.331
Mini-BESTest	$F(1,17)=0.131$	0.722	0.008	0.595	$F(2,34)=0.362$	0.699	0.021	0.221	$F(2,34)=1.522$	0.233	0.082	0.607
MDS-UPDRS III	$F(1,17)=0.022$	0.883	0.001	0.667	$F(2,34)=0.957$	0.394	0.053	0.302	$F(2,34)=0.004$	0.996	<0.001	0.236
LPAS	$F(1,17)=0.001$	0.973	<0.001	0.504	$F(2,34)=0.993$	0.699	0.021	0.260	$F(2,34)=1.770$	0.186	0.094	0.694
Gait characteristics instrumented 10MWT												
Walking speed	$F(1,17)=0.019$	0.893	0.001	0.599	**$F(2,34)=5.425$**	**0.009**	**0.242**	**8.467**	$F(2,34)=0.777$	0.468	0.044	0.391
Step length	$F(1,17)=0.047$	0.832	0.003	0.715	**$F(2,34)=4.889$**	**0.014**	**0.223**	**5.950**	$F(2,34)=0.323$	0.726	0.019	0.286
Step width	$F(1,17)=0.111$	0.743	0.006	0.672	$F(2,34)=0.269$	0.766	0.016	0.191	$F(2,34)=0.832$	0.444	0.047	0.400
Cadence	$F(1,17)=0.842$	0.372	0.047	0.856	$F(2,34)=1.479$	0.242	0.080	0.521	$F(2,34)=1.172$	0.322	0.064	0.481
Walking adaptability: obstacle avoidance												
Walking speed	$F(1,16)=0.821$	0.378	0.049	0.697	**$F(2,32)=3.347$**	**0.048**	**0.173**	**1.800**	$F(2,32)=2.234$	0.124	0.123	0.928
Success rate	$F(1,16)=3.034$	0.101	0.159	1.154	$F(2,32)=0.560$	0.577	0.034	0.238	$F(2,32)=0.496$	0.614	0.030	0.315
Margins	$F(1,16)=0.332$	0.573	0.020	0.615	$F(2,32)=2.410$	0.106	0.131	0.971	$F(2,32)=0.476$	0.626	0.029	0.316
Walking adaptability: goal-directed stepping												
Normalized walking speed	$F(1,16)=0.225$	0.641	0.014	0.636	**$F(2,32)=3.671$**	**0.037**	**0.187**	**2.321**	$F(2,32)=0.764$	0.474	0.046	0.413
Accuracy	$F(1,16)=0.283$	0.602	0.017	0.550	$F(2,32)=2.024$	0.149	0.112	0.570	$F(2,32)=0.518$	0.601	0.031	0.333
Walking adaptability: tandem												
Walking speed	$F(1,15)=0.110$	0.745	0.007	0.500	**$F(2,30)=3.367$**	**0.048**	**0.183**	**2.430**	$F(2,30)=1.270$	0.296	0.078	0.561
Sway	$F(1,15)=0.838$	0.374	0.053	0.644	$F(2,30)=2.244$	0.124	0.130	0.883	$F(2,30)=1.025$	0.371	0.064	0.458
Walking adaptability: half turns												
Turning time	$F(1,16)=1.299$	0.271	0.075	0.671	**$F(1.321,21.144)=4.133$**	**0.045**	**0.205**	**1.553**	$F(1.321,21.144)=2.503$	0.121	0.135	0.982
Success rate	$F(1,16)=0.012$	0.915	<0.001	0.402	$F(2,32)=0.023$	0.977	0.001	0.143	$F(2,32)=1.877$	0.169	0.105	1.224

The assumption of sphericity was checked according to Girden (55). If Greenhouse–Geisser's epsilon exceeded 0.75, the Huynh-Feldt degrees of freedom (df) correction was applied; otherwise the Greenhouse–Geisser correction was used.