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ABSTRACT

Objectives: To analyze the feasibility and efficacy of a novel system (Gamepad) for biofeedback rehabilitation in Parkinson's Disease (PD). It is hypothesized that Gamepad-based training is feasible and provides larger improvements of balance and gait, compared to physiotherapy without biofeedback.

Design: Randomized controlled trial.

Settings: Clinical rehabilitation gym.

Participants: Forty-two PD subjects randomized into Experimental (EG) and Control Group (CG).

Interventions: Both groups underwent a 20-session training for balance and gait. EG performed tailored functional tasks using Gamepad. The system, based on wearable inertial sensors, provided users with real-time visual and acoustic feedback about their movement during the exercises. CG underwent individually structured physiotherapy without feedback.

Main Outcome Measures: Assessments were performed by a blinded examiner pre-, post-intervention and at 1-month follow-up. Primary outcomes were Berg Balance Scale (BBS) and 10-meter Walk Test (10MWT). Secondary outcomes included instrumental stabilometric indexes and the Tele-healthcare Satisfaction Questionnaire.

Results: Gamepad was well-accepted by participants. Statistically significant between-group differences in BBS suggested better balance performances of EG compared to CG both post-training [EG-CG mean (SD): 2.3 (3.4) points, p=0.047] and at follow-up [EG-CG: 2.7 (3.3) points, p=0.018]. Post-training stabilometric indexes showed that medio-lateral body sway during upright stance was significantly reduced in EG compared to CG [EG-CG: -1.6 (1.5) mm, p=0.003). No significant between-group differences were found in the other outcomes.

Conclusions: Gamepad-based training was feasible and superior to physiotherapy without feedback in improving BBS performance and retaining it for one month. Following training, 10MWT data were comparable between groups. Further development of the system is warranted to allow the autonomous use of Gamepad outside clinical settings, enhance gait improvements, and increase transfer of training effects to real-life contexts.

Keywords: Parkinson Disease; Physical Therapy Techniques; Biofeedback; Postural Balance; Gait.

List of abbreviations

PD: Parkinson's Disease;

EG: Experimental Group

CG: Control Group

RCT: Randomized Controlled Trial

H-Y: Hoehn-Yahr stage

AP: Antero-Posterior

ML: Medio-Lateral

CoM: Center of Mass

CoP: Center of Pressure

BBS: Berg Balance Scale

10MWT: 10-Meter Walk Test

UPDRS-III: Unified Parkinson Disease Rating Scale – Motor Examination III

TUG: Timed Up and Go test

ABC: Activities-specific Balance Confidence scale

FOGQ: Freezing Of Gait Questionnaire

PDQ-39: Parkinson’s Disease Questionnaire-39

TSQ-WT: Tele-healthcare Satisfaction Questionnaire – Wearable Technology.

INTRODUCTION

Balance and gait impairments are among the most disabling features of Parkinson's disease (PD) and play a key role in the progressive deterioration of patients' autonomy.[1] For this reason, motor rehabilitation is now considered essential in the treatment of PD, as a complement to pharmacological therapy and neurosurgery.[1,2]

It has been shown that physiotherapy has small and short-term effects in PD[3] and that such effects can be improved by providing patients with real-time additional sensory information on their own motion during training (i.e. biofeedback).[4,5] Biofeedback is thus used by subjects to correct their movements, with increasing attentional engagement and motivation.[4] The working principles of biofeedback are: extracting the appropriate variable from specific body signals, coding this information into appropriate sensory signals, and feed the sensory information back to the user in real-time.[6] Several devices, providing visual[7-10], auditory[6,11-13] and vibrotactile[14,15] biofeedback, have been already applied on PD subjects with encouraging results, but some aspects still need to be investigated to demonstrate its real added value.

Firstly, most of the existing devices are devoted to a specific aspect of motor rehabilitation, e.g. balance[7,8,12,14,15] or gait.[6,10,11,13] Since biofeedback and cueing rehabilitation in PD has shown to induce improvements specific to the trained task and poorly transferred to other functional movements,[1,5,11] new devices integrating a wide set of personalized balance and gait tasks, similar to activities of daily living (ADL), should be developed.[2,5] Secondly, as discussed in a recent review,[3] more randomized controlled trials (RCT) are needed to support the effectiveness of one physiotherapy intervention over another in PD and justify the inclusion of biofeedback as a training option.

Following these considerations, we developed a new biofeedback system (Gamepad: GAMing Experience in PArkinson's Disease) for balance and gait rehabilitation in PD. The system, based on wearable sensors, provided subjects with real-time visual and auditory feedback and included different motor exercises similar to ADL and tailored to subject's specific deficits. The aims of this study were to test the feasibility of using the system in a typical rehabilitation gym, and analyze balance and gait outcome measures comparing Gamepad-based training versus physiotherapy without biofeedback. We hypothesized that biofeedback provision through Gamepad can enhance the effects of balance and gait rehabilitation, by complementing the impaired sensory inputs typical of PD,[16] and by increasing attentional engagement toward the motor processes, thus enhancing motor learning[5] and bypassing defective basal ganglia.[2,16]

METHODS

Participants

A consecutive sample of fifty-four PD subjects from the Neurorehabilitation Department in –*masked*– was assessed for eligibility from January 2013 to April 2015. Inclusion criteria were: Hoehn-Yahr stage (H-Y) 2 to 4, ability to stand up more than 10 seconds and inability to stand on one foot more than 10 seconds, ability to walk for at least 6 meters, stable drug usage. Exclusion criteria were: implanted deep brain stimulator and Mini-Mental State Examination[17]<24. Recruited sample consisted in forty-two subjects (Figure 1). After baseline assessment, participants were randomly allocated to Experimental group (EG: balance and gait biofeedback training with Gamepad) or Control group (CG: structured physiotherapy without biofeedback). A randomization procedure based on computer-generated coin flip was used.[18] All participants gave written informed consent approved by the local ethical committee and conformed to the declaration of Helsinki.

Gamepad system

Gamepad system (Figure 2A) consisted of six wearable inertial sensors (TMA)[a], and a PC with a LCD screen (16'') and a customized software, developed using .NET technology[b] and Matlab/Simulink environment[c], for real-time data acquisition/processing and feedback generation.

Each inertial unit contained 3D accelerometer, 3D gyroscope, 3D magnetometer and a microcontroller computing sensor's orientation in space (Euler angles). The sensors, fixed on upper trunk, lower trunk and lower limbs through elastic belts (Figure 2A), transmitted signals to the PC via Bluetooth (sampling frequency: 50 Hz).

Gamepad software allowed the following actions:

- Selecting the exercise from a menu containing a set of tasks, defined by the clinical staff according to previous studies[8,19,20] and practical guidelines for physiotherapy in PD.[2,21] The exercises, following a functional task-oriented approach, focused on controlling weight-shifting and body posture in antero-posterior (AP) and medio-lateral (ML) directions during static (e.g. upright sitting and standing), quasi-dynamic (e.g. sit-to-stand and gait initiation) and dynamic tasks (e.g. getting on a step, straight-line walking at different speeds, walking with turns and over obstacles).

- Selecting the kinematic variable to be controlled during the exercise. Gamepad allowed the control of AP/ML trunk angular displacements, AP/ML movements of body center-of-mass (CoM), knee flexion angle, and combination of two variables (e.g. trunk ML inclination and CoM displacement). Trunk inclination and knee flexion angles were estimated with the Euler angles directly provided by the sensors, while a specific algorithm was implemented for real-time computation of CoM displacements, that were estimated following a 3-link model[22] based on the orientation of sensors positioned on lower trunk, thighs and shanks and scaled on each subject's anthropometry.

- Calibrating the exercise. Gamepad allowed clinicians to perform a subject-specific calibration of the exercise by setting the reference values for the correct task execution and feedback provision. During the calibration, the patient was asked to execute the chosen task following the instruction of the therapist. Once he was satisfied with the performance of the patient, kinematic data were stored and used to compute the reference values for subsequent training.

- Starting the exercise. The therapist started the session and the patient executed the exercises by receiving online visual feedback (moving avatar displayed on the monitor) and/or auditory feedback (sounds) about his/her motion. During walking exercises, only auditory feedback was provided about upper trunk inclination and ML angular displacement of lower trunk, the latter used as an estimate of ML body weight-shifting during gait.[15] Biofeedback was positive or negative depending on the task. After each exercise, a score from 0 to 10, rating patient’s performance, was automatically provided. Some examples of Gamepad tasks and feedback are described in Supplementary Material. A typical scenario is shown in Figure 2B.

Intervention

Both groups underwent a training consisting in 20 sessions of 45 minutes each, 3 times a week in a typical rehabilitation gym.

Experimental Group (EG)

A set of balance and gait tailored exercises included within Gamepad was defined by clinical staff for each patient. The setup of the system took about 5 minutes, after which participants executed the selected tasks using Gamepad with the supervision of the physiotherapist. Throughout the training, the therapist monitored individual performances by analyzing the scores assigned by Gamepad after each task. Based on this inspection, the physiotherapist progressively adjusted training complexity by changing the reference values of the exercise, including more difficult tasks, changing the perceptive context (e.g. altering proprioception through foam pads under feet), and/or including a dual-task (e.g. walking holding a tray with a ball above). Moreover, a fading schedule of feedback (frequent feedback during early sessions that gradually reduces toward the end of treatment) was used to enhance learning.[23]

Control Group (CG)

Personalized exercises were defined by clinical staff following guidelines for physiotherapy in PD.[2,21] Each session included 5 minutes of muscle stretching (hamstrings, quadriceps and calves) and mobilization exercises (e.g. trunk rotation, hip abduction and flexion), followed by 40 minutes of balance and gait exercises similar to those performed by EG, but without any instrumentation producing biofeedback or external cues. Subjects executed the tasks following verbal instructions and qualitative feedback from the physiotherapist.

Outcome measures

Assessments were taken by a trained examiner, unaware of group assignment, at baseline (T0), post-training (T1) and at 1-month follow-up (T2). Assessments and treatments were conducted when participants were in the ON-phase of medication.

Primary outcomes were balance and self-selected gait speed, assessed, respectively, with Berg Balance Scale (BBS)[24-26] and 10-meter walk test (10MWT).[26] Both tests are recommended tools for clinical assessment of PD.[27] BBS was chosen as it evaluates balance in static and transfer tasks, according to the proposed intervention. 10MWT was selected as it represents a quick test (~5 minutes) to assess gait speed, that we expected to increase following training for gait and balance, the latter being an important factor affecting walking velocity in PD.[28]

Secondary outcomes included: disease-specific impairments (UPDRS-III: Unified Parkinson Disease Rating Scale–Motor examination)[26,29], basic mobility function (TUG: Timed Up and Go test)[26], perceived confidence during ADL (ABC: Activities-specific Balance Confidence scale)[26], freezing severity (FOGQ: Freezing Of Gait Questionnaire)[30], perceived quality of life (PDQ-39: Parkinson's Disease Questionnaire-39)[31], and stabilometric assessment using a force platform (Prokin-PK252)[a]. In the latter assessment subjects were tested for 30 seconds during upright standing in four sensory conditions, according to Cattaneo et al.[32]: eyes open, eyes closed, eyes open with foam pads under feet, and eyes closed with foam pads under feet. Center of Pressure (CoP) sway in AP and ML directions was computed as the standard deviation of the AP and ML CoP displacements recorded by the platform (sampling frequency: 20 Hz). CoP AP (ML) Sway values, averaged among the four sensory conditions, were used for the analysis. Finally, at T1, the Tele-healthcare Satisfaction Questionnaire–Wearable Technology (TSQ-WT)[33] was administered to EG patients to assess user satisfaction about Gamepad. Further details about clinical tests are provided in Supplementary Material.

Statistical analysis

Between-group comparisons of baseline characteristics were performed using independent samples t-test. Differential effects of the two treatments were assessed using ANCOVA with one between-group factor (Group: EG, CG) and one within-group factor (Time: T1, T2). For each outcome measure, corresponding baseline score (T0) was used as covariate. In this model, between-group differences (EG vs CG) at post and follow-up were used to assess treatment effect since baseline score was used as covariate, as reported by Norman and Streiner.[34] Following ANCOVA, separate pre-planned between-group comparisons at T1 and T2 were performed using independent samples t-test, also correcting for T0 score (contrasts analysis). Given the exploratory nature of this pilot study, the significance level was set to 0.05 and no corrections for multiple comparisons were applied. Between-group differences and effect size (Cohen's *d*)[35] at T1 and T2 were also computed. Cohen's *d* of 0.2, 0.5 and 0.8 represents small, moderate or large effect size, respectively.[35] Some variables did not meet the assumptions of data normality and/or homogeneity of variances (Shapiro-Wilks test and/or Levene's test $p<0.05$). In these cases, statistical tests were applied on transformed data (Box-Cox transformation).[36] Where explicitly indicated, results were presented as estimated from back-transformed data[37] to facilitate interpretation. Statistical analysis was performed using STATISTICA[d].

RESULTS

Twenty-two participants were allocated to EG and twenty to CG (Figure 1). Five patients discontinued the training and five were lost at follow-up. Dropout reasons (Figure 1) were unrelated to the study. All patients who received allocated treatment and underwent post-training assessment were analyzed (EG: n=17, CG: n=20). Missing follow-up values (5 subjects X 9 variables) were estimated using multiple regression.[38] For each outcome measure, the predictors were: the corresponding pre and post-treatment scores, age, disease duration, H-Y stage, and UPDRS-III baseline score. Table 1 shows the baseline characteristics of analyzed participants. Control group showed statistically significant worse scores on 10MWT, UPDRS-III, TUG and ABC. The five subjects who discontinued the training were excluded as they underwent less than 10 sessions. Baseline characteristics of these patients were comparable to those of analyzed EG participants (p>=0.150).

Primary outcomes

Table 2 reports between-group comparisons at T1 and T2. ANCOVA revealed a significant effect of group in BBS [F(1,34)=6.29, p=0.017], showing better balance performances of EG compared to CG both post-treatment [EG-CG mean (SD) = 2.3 (3.4) points, p= 0.047, Cohen's *d*=0.68] and at follow-up [EC-CG = 2.7 (3.3) points, p=0.018, *d*=0.82]. No significant Group or Time X Group effects were found in 10MWT, although a small effect size favoring EG was present (T1: *d*=0.32; T2: *d*=0.28).

Secondary outcomes

ANCOVA (Table 2) revealed a significant effect of group [F(1,34)=6.12, p=0.018] in CoP ML sway, that was significantly smaller in EG compared to CG at T1 [EG-CG = -1.6 (1.5) mm, p=0.003, *d*=-1.06], but not at T2 [EG-CG = -0.7 (2.1) mm, p=0.306, *d*=-0.34]. No significant Group or Time X Group effects were found in UPDRS-III, TUG, ABC, FOGQ, PDQ-39 and AP sway.

TSQ-WT (Table 3) showed that all patients but one (Statement-1 score: 1) found the device beneficial (Statement-1 score: 3-4). Gamepad was considered reliable, easy-to-use and safe by all patients (Statements-7-9 score: 2-4), and comfortable by 15/17 subjects (Statement-11 score: 2-4). The 65% of patients found that using Gamepad required effort (Statement-6 score: 3-4) and that such effort was worthwhile for them (Statement-2 score: 2-4).

Physiotherapists were positive about Gamepad training, but suggested to reduce the number of sensors and simplify the procedures for task calibration.

DISCUSSION

In the present study a new system for biofeedback motor rehabilitation in PD (Gamepad) was developed and clinically applied in a pilot RCT to test its feasibility and efficacy compared to physiotherapy without feedback. Compared to existing devices, to our knowledge this is the first wearable system integrating both balance and gait tailored exercises similar to ADL.

Between-group comparisons through ANCOVA showed statistically significant higher scores on BBS in EG compared to CG at T1 (+2.3 points) and T2 (+2.7 points). These differences were in the range of those emerged in other studies using BBS to compare physiotherapy methods [mean (95%CI): 2.79 (0.50-5.08)][39], highlighting the positive impact of the proposed intervention on balance performance in PD. Moreover, the mean post-training increase in BBS by 4.0 points in EG and 1.7 in CG suggested that only the mean improvement of EG was consistent with the minimal detectable change between 2.8 and 5 points found in previous studies on PD.[25,26] Noteworthy, no between-group differences were found in studies using biofeedback systems based on balance boards,[8,9] suggesting higher efficacy of wearable devices that allow the execution of more ecological tasks.

The above result is enforced by instrumental indexes describing static balance in different sensory conditions. In particular, the amplitude of CoP ML sway at post was lower in EG compared to CG, with a statistically significant large effect size favoring Gamepad group (d= -1.06). This finding is particularly notable since medio-lateral sway amplitude (significantly increased in PD)[32], was found to be the best stabilometric parameter predicting future falls.[40]

Although this improvement was not maintained at follow-up, this result corroborated previous studies,[7,14] and suggested beneficial effects of biofeedback in increasing balance control in altered sensory conditions, which strongly affect postural stability in PD.[32]

Taken together, the above findings about BBS and ML body sway seemed to support the hypothesis that Gamepad-based training is superior to physiotherapy without feedback in improving balance in PD and increasing retention of some beneficial effects in the short-term (1 month). As suggested by Nieuwboer et al,[5] the present findings can be ascribed to the contribution of biofeedback in enhancing motor learning, that is feasible in PD although impaired.[1] In particular, provision of additional sensory information could have helped patients not only during the first (cognitive) stage of learning, by focalizing their attention toward the task,[2,5] but also during the last (automatization) stage, as suggested by follow-up BBS scores showing higher retention in Gamepad group.[5] In this context, a second possible explanation about the greater benefits attained by EG could be related to the better baseline characteristics compared to CG, that can be potentially associated to higher learning abilities.[1] However, we think that this hypothesis can be excluded given the lack of correlation (see Supplementary Material) between change scores in BBS and age, disease duration and severity level (H-Y and UPDRS-III), suggesting that balance improvements were independent from these factors. Moreover, statistical analysis was conducted by adjusting for baseline scores.

Contrarily to balance, no significant between-group differences emerged in walking speed and freezing of gait questionnaire. Hence, our findings did not support the hypothesis that Gamepad-based training is superior to physiotherapy without biofeedback in improving gait in PD. This could be due not only to the need of a PC that restricted the use of Gamepad to rehabilitation gyms, but also to the training paradigms which included tasks for the control of trunk posture and body weight-shifting during locomotion, but not exercises specifically devoted to the biofeedback-based regulation of spatio-temporal gait parameters typically impaired in PD[2] (e.g. velocity, cadence, stride length), or to the reduction of freezing episodes.[11,13]

Finally, no significant between-group differences were found in PDQ-39 and ABC scale, suggesting that the beneficial effects of Gamepad training did not increase perceived quality of life and confidence in ADL, compared to physiotherapy without biofeedback. Although the rehabilitation paradigms implemented within Gamepad followed a functional approach,[2,4] these findings seemed to confirm previous results about limited transfer of training effects to ADL and quality of life.[5,11] This also suggested further developments of Gamepad to extend its use outside clinical settings, making the training environment as closely as possible to real-life contexts.[5,13]

Study limitations

The present study had some limitations. Firstly, the small sample size underpowered the study. A power analysis on post-treatment BBS scores revealed that 70 subjects (35 per group) are required to achieve a between-group effect size of 0.68, given α=0.05 and 1-β=0.8. Besides, the analysis of post-training 10MWT scores showed that 152 patients per group are necessary to achieve an effect size of 0.32 with the same values of α and β. A second limitation regards the randomization procedure used for patients' allocation, which resulted in unbalanced baseline characteristics between the two groups. Alternative methods (e.g. block or stratified randomization), more suitable for small trials, would have reduced the occurrence of such unbalancing.[18] A third limitation is that the placebo effect resulting from increased motivation during Gamepad training was not controlled for. Application of sensors, without biofeedback, also to control group would have acted as a sham-device, also providing objective measures of motor performances. Finally, some technical aspects of Gamepad should be further developed in future studies to improve system portability and gain more meaningful improvement in gait, e.g. reduction of sensors, replacement of PC with a wearable processing unit (e.g. Smartphone),[6,13] and implementation of algorithms allowing online computation of spatio-temporal gait parameters to be used as biofeedback variables and objective measures of locomotion.[10,13]

CONCLUSIONS

Gamepad was proven feasible for clinical use on PD subjects, was generally well-accepted by patients and physiotherapists and seemed more effective than physiotherapy without biofeedback in improving balance. Future studies should be performed to include more sophisticated rehabilitation paradigms for gait training,[10,13] and to realize a simplified, completely wearable system, potentially usable by patients in autonomy also outside hospital (e.g. at home), to enhance the improvements, prolong their retention and increase transfer of training effects to real-life contexts.

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CAPTIONS TO FIGURES

Fig. 1. Flowchart of the trial.

Fig.2. A) Schematic representation of Gamepad system. B) Example of a subject controlling the antero-posterior inclination of his trunk while placing a foot on a step (left panel). The patient performs the task by looking at an avatar replicating the motion of his trunk on the PC screen (right panel). If the avatar is not maintained within the black bar (tailored reference target area), its head becomes red and an “alarm” sound is provided.

Table 1. Demographic and baseline clinical characteristics of training groups.

	Experimental Group (EG)		**Control Group (CG)**
Number of patients	17		20
Gender (Male/Female)	14/3		9/11
Age (years)	73.0 (7.1)		75.6 (8.2)
Time since diagnosis (years)	7.5 (3.2)		10.3 (5.7)
H-Y (0-5) ↓	2.7 (0.7)		2.9 (0.5)
BBS (0-56) [a] ↑	46.0 (9.3)		42.1 (10.9)
10MWT - Gait speed (m/s) ↑	1.04 (0.25)	*	0.78 (0.29)
UPDRS-III (0-56) ↓	16.6 (6.8)	*	22.3 (7.3)
TUG (s) [a] ↓	14.7 (6.3)	*	23.9 (16.3)
ABC (0-100) ↑	59.3 (21.8)	*	44.3 (19.1)
FOGQ (0-24) ↓	11.3 (4.9)		13.1 (3.8)
PDQ-39 (0-100) ↓	46.4 (22.9)		61.5 (24.1)
CoP ML Sway (mm) [a] ↓	5.7 (2.9)		6.7 (3.5)
CoP AP Sway (mm) [a] ↓	7.7 (3.4)		8.4 (3.1)

Values are mean (standard deviation) or number.

↑: higher scores indicate better performance; ↓: lower scores indicate better performance.

*$p < 0.05$ (EG vs CG, t-test for independent samples).

[a] These variables did not meet assumptions of data normality and/or homogeneity of variances. In this cases, t-test was performed on transformed data (Box-Cox transformation).

Table 2. Outcomes characterizing Experimental (EG) and Control (CG) groups at post and follow-up.

Outcome measure	**Post treatment (T1)**					**Follow up - 1 month (T2)**				
	EG (n = 17) Mean (SD)	**CG (n = 20)** Mean (SD)	**Between-group difference (EG -CG)** [a] Mean (SE)	**p-value**	**Cohen's *d*** Mean (95%CI)	**EG (n = 17)** Mean (SD)	**CG (n = 20)** Mean (SD)	**Between-group difference (EG -CG)** [a] Mean (SE)	**p-value**	**Cohen's *d*** Mean (95%CI)
Primary										
BBS (0-56)[b] ↑	50.0 (6.2)	43.8 (10.9)	2.3 (1.1)	0.047 *	0.68 (0.02;1.34)	48.1 (10.7)	42.3 (11.5)	2.7 (1.1)	0.018 *	0.82 (0.15;1.49)
10MWT - Gait speed (m/s) ↑	1.17 (0.23)	0.87 (0.33)	0.06 (0.06)	0.335	0.32 (-0.33;0.97)	1.17 (0.29)	0.87 (0.33)	0.05 (0.06)	0.395	0.28 (-0.37;0.93)
Secondary										
UPDRS-III (0-56) ↓	13.6 (6.8)	19.1 (7.9)	-1.1 (1.8)	0.545	-0.20 (-0.85;0.45)	16.2 (7.1)	18.2 (6.9)	2.2 (1.7)	0.196	0.43 (-0.22;1.08)
TUG (seconds)[b] ↓	13.7 (5.6)	24.3 (18.0)	-1.8 (1.6)	0.269	-0.37 (-1.02;0.28)	13.4 (6.5)	20.2 (12.0)	-1.2 (1.4)	0.380	-0.29 (-0.94;0.36)
ABC (0-100) ↑	67.2 (22.3)	47.8 (22.2)	7.6 (5.6)	0.186	0.45 (-0.20;1.10)	60.6 (22.7)	45.3 (19.2)	2.3 (4.1)	0.580	0.18 (-0.47;0.83)

FOGQ (0-24) ↓	10.8 (5.1)	12.5 (3.9)	-0.4 (1.1)	0.695	-0.13 (-0.78;0.52)	11.1 (4.9)	12.6 (4.3)	0.06 (0.9)	0.947	0.02 (-0.63;0.67)
PDQ-39 (0-100) ↓	44.6 (24.7)	59.2 (23.3)	-0.7 (3.7)	0.844	-0.07 (-0.71;0.58)	48.4 (27.2)	56.8 (22.4)	5.0 (4.7)	0.285	0.36 (-0.29;1.01)
CoP ML sway (mm)[b] ↓	4.8 (2.7)	6.7 (2.1)	-1.6 (0.5)	0.003*	-1.06 (-1.75;-0.37)	6.3 (4.1)	7.8 (4.3)	-0.7 (0.7)	0.306	-0.34 (-0.99;0.31)
CoP AP sway (mm)[b] ↓	7.1 (3.2)	8.8 (3.2)	-1.2 (0.6)	0.075	-0.61 (-1.27;0.05)	7.6 (3.9)	8.5 (3.0)	-0.7 (0.8)	0.359	-0.31 (-0.96;0.34)

SD: standard deviation; SE: standard error; 95%CI: 95% confidence interval.

[a] Adjusted for pre-treatment score (T0) by ANCOVA.

[b] These variables did not meet assumptions of data normality and/or homogeneity of variances. In this cases, statistical tests and Cohen's d computation were performed on transformed data (Box-Cox transformation). Reported between-group differences were estimated from back-transformed results to facilitate interpretation.

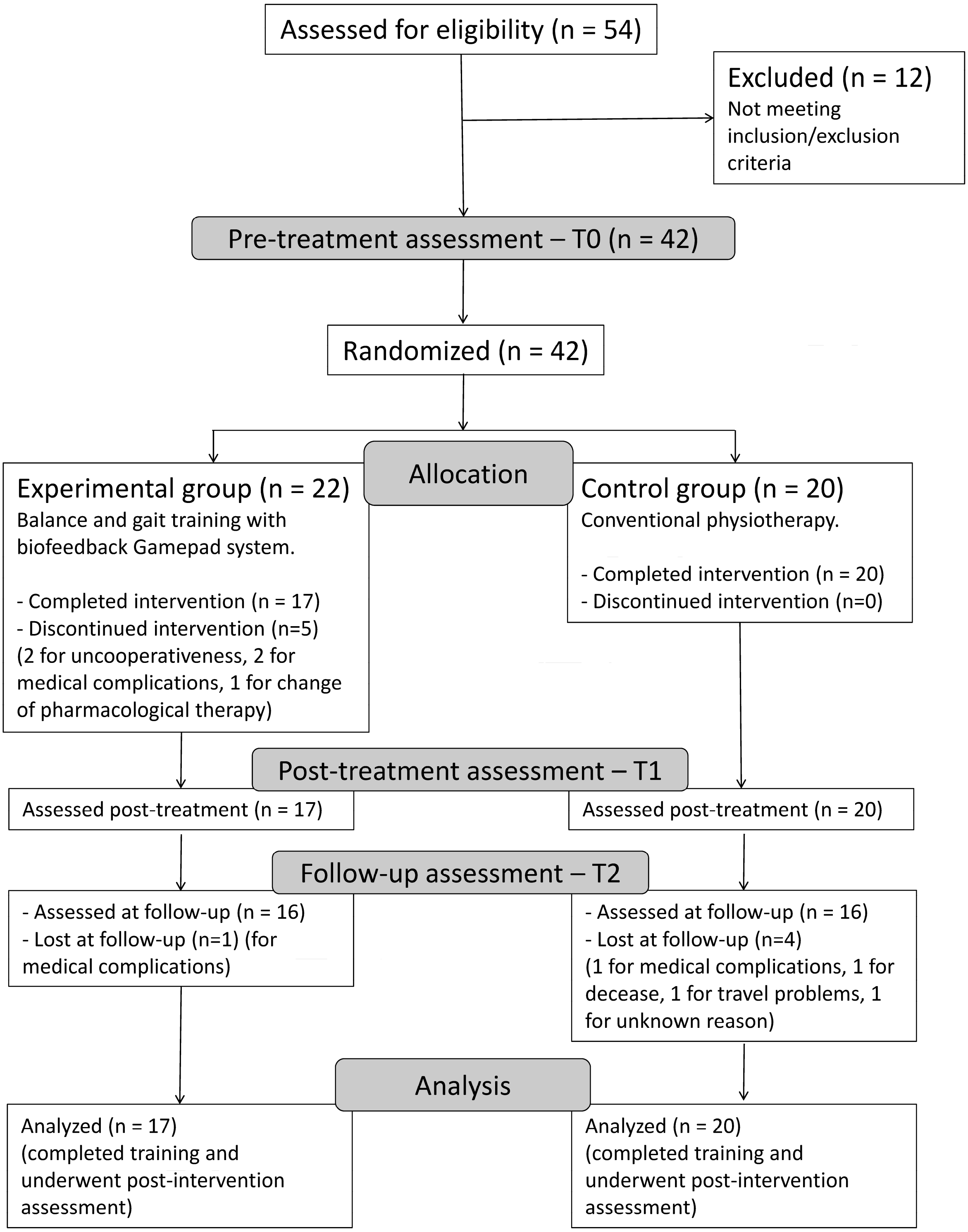
*p < 0.05 (EG vs CG, contrast analysis using independent sample t-test).

↑: higher scores indicate better performance; ↓: lower scores indicate better performance.

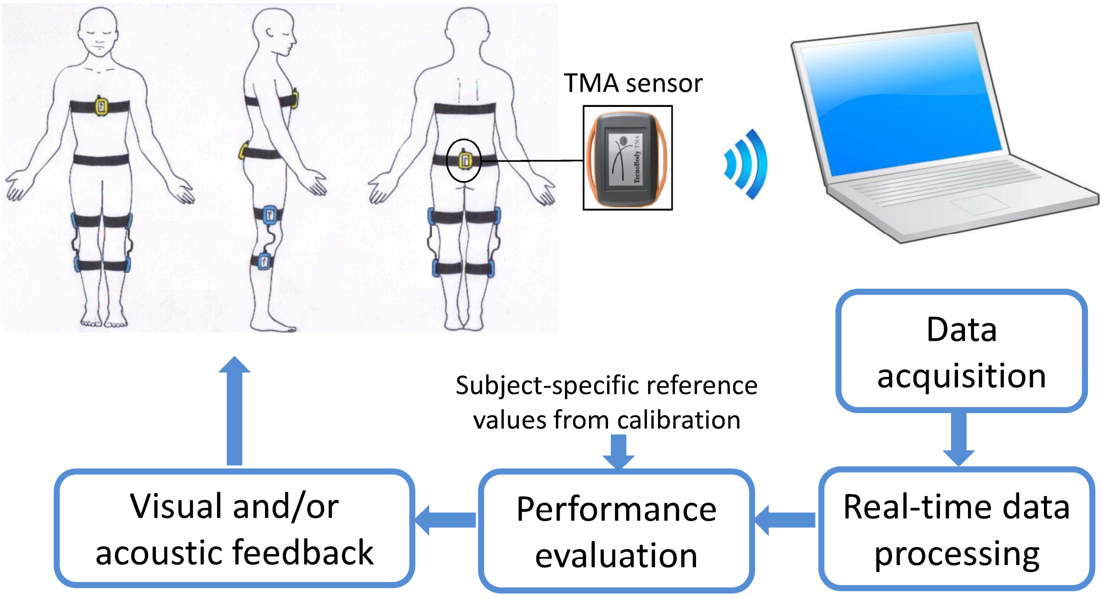
Table 3 - Descriptive statistics of TSQ-WT Satisfaction Questionnaire for Benefit, Usability and Wearing Comfort of Gamepad system.

Area and Statement	Score
BENEFIT	
1 I can benefit from this technology	3 (1-4)
2 The effort of using this technology/method is worthwhile for me	4 (2-4)
3 I am confident I'm getting the most out of this technology/method	4 (1-4)
4 This Technology/method is helping me to achieve my goals	3 (1-4)
5 I would recommend this technology/method to other people in my situation	4 (1-4)
USABILITY	
6 The use of this technology/method requires effort	3 (0-4)
7 The technology/method is reliable according to my estimation and experience so far	3 (2-4)
8 This technology/method is easy to use	4 (2-4)
9 I feel safe when using this technology/method	3 (2-4)
10 I feel good while using this technology/method	3 (1-4)
WEARING COMFORT	
11 Wearing this device (parts of the device) is comfortable	4 (1-4)
12 I am pleased with the size of the device (parts of the device)	4 (2-4)
13 I would wish another look and design of the device (parts of the device)	1 (0-2)
14 I am pleased with the weight of the device (parts of the device)	3 (2-4)
15 The body-worn parts of the device are difficult to adjust (fix, fasten)	1 (0-3)

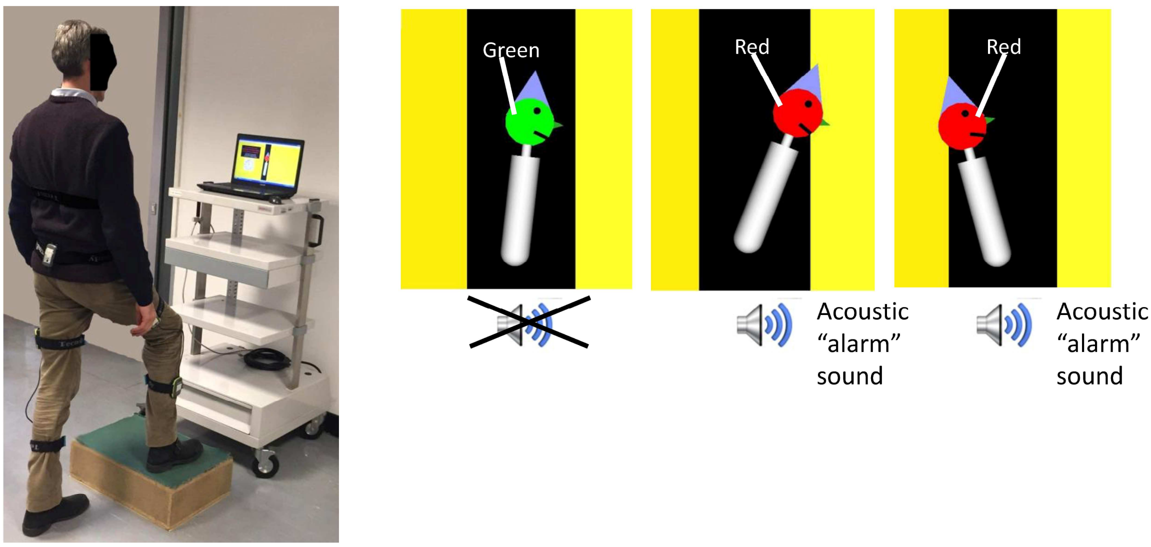
Values represent median (minimum-maximum) score given by patients to each statement on a 5-point Likert scale (0: strongly disagree, 1: mostly disagree, 2: neither agree nor disagree, 3: mostly agree, 4: strongly agree).


Assessed for eligibility (n = 54)
Excluded (n = 12)
Not meeting inclusion/exclusion criteria
Pre-treatment assessment – T0 (n = 42)
Randomized (n = 42)
Allocation
Experimental group (n = 22)
Balance and gait training with biofeedback Gamepad system.
- Completed intervention (n = 17)
- Discontinued intervention (n=5)
(2 for uncooperativeness, 2 for medical complications, 1 for change of pharmacological therapy)
Control group (n = 20)
Conventional physiotherapy.
- Completed intervention (n = 20)
- Discontinued intervention (n=0)
Post-treatment assessment – T1
Assessed post-treatment (n = 17)
Assessed post-treatment (n = 20)
Follow-up assessment – T2
- Assessed at follow-up (n = 16)
- Lost at follow-up (n=1) (for medical complications)
- Assessed at follow-up (n = 16)
- Lost at follow-up (n=4)
(1 for medical complications, 1 for decease, 1 for travel problems, 1 for unknown reason)
Analysis
Analyzed (n = 17)
(completed training and underwent post-intervention assessment)
Analyzed (n = 20)
(completed training and underwent post-intervention assessment)

A)


TMA sensor
Data acquisition
Subject-specific reference values from calibration
Real-time data processing
Performance evaluation
Visual and/or acoustic feedback

B)


Green
Red
Red
Acoustic “alarm” sound
Acoustic “alarm” sound

Electronic supplementary material

1. Examples of tasks included within Gamepad system

Static

Task: upright standing by controlling the knee flexion and the medio-lateral-ML (or antero–posterior-AP) inclination of the trunk.
Instruction and feedback: the patient is asked to maintain upright balance trying to keep the knee extended and to control the ML (or AP) inclination of upper trunk. A visual feedback is provided about knee flexion/extension angle, represented by a vertical bar on the monitor (Fig. S1). If knee extension is below a threshold defined by the physiotherapist, the bar is red, otherwise, if the patient maintains a correct extension, the bar turns green. Simultaneously, an auditory feedback is provided about ML (or AP) trunk inclination. If this variable is within a tailored reference band defined by the therapist, no sound is provided, otherwise Gamepad produces "alarm" sounds (negative feedback): high-pitch sound in case of excessive right (or forward) inclination, low-pitch sound in case of excessive left (or backward) inclination.
Note: the exercise can be performed on firm surface or with foam pad under feet.

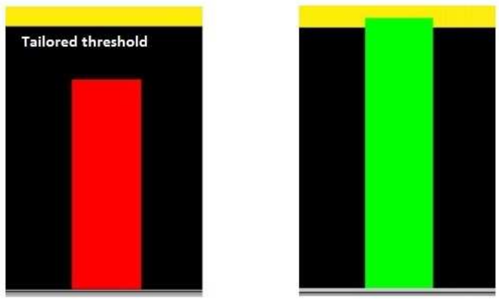


Figure S1. Example of visual feedback provided by Gamepad. The vertical bar represents the knee flexion/extension angle. The bar is red in case of excessive knee flexion (left panel), while it turns green in case of adequate knee extension (right panel).

Quasi-dynamic

Task: place a foot on a step after a correct shift of body weight toward the supporting limb.
Instruction and biofeedback: the subject is asked to transfer the body weight toward the supporting leg, keep this position for a time defined by the therapist, and then place the opposite foot on a step placed in front of him. The patient performs the task by looking at a circle replicating the motion of the Center of Mass (CoM) on the PC screen (Fig. S2). The circle has to be moved from a starting position (white rectangle) toward a yellow target area, whose position and dimensions are defined by the therapist based on subjects' ability. If the circle is kept within the target area, its color is green, otherwise it turns red and an "alarm" sound is provided (negative feedback). After a given time, the patient places the leading foot on the step.

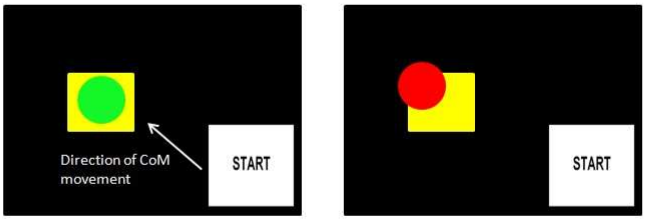


Figure S2. Example of visual feedback provided by Gamepad. The circle represents the CoM that has to be moved from a starting position (START rectangle) to a final target position (yellow rectangle) toward the left (supporting) leg. The circle is green if the CoM in maintained within the target area, otherwise it turns red.

<u>Dynamic</u>

1. *Task:* straight-line walking controlling the transfer of body weight between limbs.
   Instruction and feedback: the subject is asked to walk while controlling the ML shift of body weight, estimated with the ML angular displacement of lower trunk[15]. If this variable is above a tailored threshold indicating the correct transfer of body weight toward the stance limb, Gamepad provides a sound (positive feedback).

2. *Task:* walking over obstacles controlling the ML (or AP) inclination of upper trunk.
   Instruction and feedback: the subject is asked to walk over wooden sticks placed on the floor, maintaining the ML (or AP) inclination of the trunk within a reference band defined by the therapist. If trunk inclination is outside the target band, Gamepad provides “alarm” sounds (negative feedback): high-pitch sound in case of excessive right (or forward) inclination, low-pitch sound in case of excessive left (or backward) inclination.
   Note: the exercise can be executed at self-selected velocity or at fast speed, as indicated by the physiotherapist.

2. Brief description of the outcome measures

Primary outcomes

- *Berg Balance Scale (BBS)*[24-26] rates balance from 0 (cannot perform) to 4 (normal performance) on 14 items exploring the ability to sit, stand, lean, turn, and maintain the upright position on one leg. Maximum score (i.e. 56 points) indicates unimpaired balance.

- *10-meter Walk Test (10MWT)*[26] measures, with a stopwatch, the time (T) taken by the subject to walk between two lines at the distance of 10 meters. Walking speed is thus computed as 10/T (m/s). Both comfortable and fast gait speed can be measured. In the present study only comfortable gait speed was assessed.

Secondary outcomes

- *Unified Parkinson's Disease Rating Scale (UPDRS)*[29] is the gold standard instrument used to measure disease severity and disease-specific impairments in Parkinson's disease. It has 3 subscales: I—Mentation, Behavior, and Mood; II—Activities of Daily Living (ADL); III—Motor Examination. Each item is rated on a 5-point ordinal scale from 0 to 4, with 4 representing the greatest level of dysfunction. In the present study, only UPDRS III-Motor examination was administered.

- *Timed Up and Go test (TUG)*[26] is a mobility test evaluating the time taken by the subject to rise from a chair, walk 3 meters, turn around, walk back to the chair and sit down.

- *Activities-specific Balance Confidence scale (ABC)*[26] is a questionnaire through which the subject rates his/her perceived level of confidence while performing 16 daily living activities. Scores range from 0% (not confident) to 100 % (completely confident).

- *Freezing Of Gait Questionnaire (FOGQ)*[30] evaluates freezing severity with a 6-item interview. Each item is rated on a 5-point ordinal scale from 0 (absence of freezing) to 4 (severe freezing).

- *Parkinson's Disease Questionnaire-39 (PDQ-39)*[31] is a 39-item, self-report questionnaire, which assesses Parkinson's disease-specific health related quality of life over the last month. Scores are from 0 to 100, with 100 representing maximum level of problems.

- *Tele-healthcare Satisfaction Questionnaire – Wearable Technology (TSQ-WT)*[33], consists in six areas (Benefit, Usability, Self-concept, Privacy and loss of control, Quality of life, and Wearing comfort) that evaluate the satisfaction of the subject with the wearable part of a system. Each area includes 5 statements rated by the user on a 5-point Likert scale between 0 (strongly disagree with the statement) and 4 (strongly agree with the statement). TSQ-WT is described in Table T1. In the present study, only Benefit, Usability and Wearing Comfort areas were administered.

Table T1. The Tele-healthcare Satisfaction Questionnaire – Wearable Technology (TSQ-WT).

Area	Statement
BENEFIT	1 I can benefit from this technology
	2 The effort of using this technology/method is worthwhile for me
	3 I am confident I'm getting the most out of this technology/method
	4 This Technology/method is helping me to achieve my goals
	5 I would recommend this technology/method to other people in my situation
USABILITY	1 The use of this technology/method requires effort
	2 The technology/method is reliable according to my estimation and experience so far
	3 This technology/method is easy to use
	4 I feel safe when using this technology/method
	5 I feel good while using this technology/method
SELF CONCEPT	1 The use of this technology/method is an interesting challenge for me
	2 This technology/method reminds me of losing my independence
	3 The use of this technology/method is making me feel older than I am
	4 I (would) feel embarrassed using this technology/method visible around others
	5 I like to use technological products or systems like this technology/method
PRIVACY AND LOSS OF CONTROL	1 I feel there is too much supervision by this technology/method
	2 I use this technology/method by request of others (e.g. physician, therapist, relatives)
	3 I am sure that my personal data are stored or processed in an appropriate way
	4 The use of this technology/method may have unpredictable negative consequences for me
	5 This technology/method forces me to disclose personal facts that I prefer to keep to myself
QUALITY OF LIFE	1 Using this technology/method improves my physical wellbeing
	2 This technology/method evokes unpleasant feelings
	3 This technology/method enhances my social contacts
	4 This technology/method helps me to maintain or increase my independence (e.g. with regard to mobility, communication, medication)
	5 The use of this technology/method has a positive effect on me
WEARING COMFORT	1 Wearing this device (parts of the device) is comfortable
	2 I am pleased with the size of the device (parts of the device)
	3 I would wish another look and design of the device (parts of the device)
	4 I am pleased with the weight of the device (parts of the device)
	5 The body-worn parts of the device are difficult to adjust (fix, fasten)

3. Correlation analysis

Tables T2-3 showed the results of a correlation analysis performed on the entire sample of patients (n=37) between change-scores of primary outcome measures (Berg Balance Scale and gait speed) and age, time since diagnosis, Hoehn & Yahr stage and baseline score on the UPDRS-III scale. In particular Spearman correlation coefficients (Rho) and related p-values were computed.

Table T2. Coefficient of correlation (Spearman Rho) between change scores (T1-T0 and T2-T0) in Berg Balance Scale (BBS) and age, time since diagnosis, Hoehn & Yahr stage and UPDRS-III score for the entire sample (n = 37). p-values are reported.

	BBS Change score (T1-T0)		BBS Change score (T2-T0)	
	Rho	*p-value*	*Rho*	*p-value*
Age	-0.082	0.630	-0.039	0.818
Time since diagnosis	-0.152	0.369	-0.191	0.254
Hoehn & Yahr stage	0.141	0.406	-0.017	0.921
UPDRS-III baseline score	0.099	0.558	-0.061	0.721

Table T3. Coefficient of correlation (Spearman Rho) between change scores (T1-T0 and T2-T0) in gait speed and age, time since diagnosis, Hoehn & Yahr stage and UPDRS-III score for the entire sample (n = 37). p-values are reported.

	Gait speed Change score (T1-T0)		Gait speed Change score (T2-T0)	
	Rho	*p-value*	*Rho*	*p-value*
Age	0.074	0.664	-0.113	0.505
Time since diagnosis	0.140	0.407	0.089	0.600
Hoehn & Yahr stage	-0.005	0.977	-0.206	0.222
UPDRS-III baseline score	-0.031	0.857	-0.119	0.482

It can be noticed from the results that, for both outcome measures, change scores (T1-T0 and T2-T0) are not significantly correlated with the selected variables, suggesting that, independently from the received intervention, the improvements attained after rehabilitation are not related to age, disease duration and disease severity (Hoehn & Yahr stage and UPDRS-III score).