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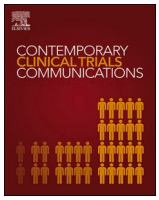

Quantitative assessment of training effects using EksoGT® exoskeleton in Parkinson's disease patients: A randomized single blind clinical trial

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ABSTRACT

Background: Gait alterations are among the most disabling motor-symptoms associated with Parkinson's Disease (PD): reduced stride length, stride velocity and lower limb joint range of motion are hallmarks of parkinsonian gait. Research focusing on optimal functional rehabilitation methods has been directed towards powered lower-limb exoskeletons which combines the advantages delivered from the grounded robotic devices with the ability to train the patient in a real-world environment. As gait involves both central (CNS) and peripheral nervous systems (PNS), targeted rehabilitation must restore not only mechanics but also neurophysiological gait patterns. *Methods:* Two cohorts of subjects will be enrolled and equally distributed between one group (n = 25) who will undergo a functional kinematic therapy, and one group (n = 25) who will undergo an overground wearable-exoskeleton training. Participants are evaluated at three time points: before the therapy (T0), after the therapy (T1), 4-weeks after T1 (T2). Comprehensive gait analysis and surface electromyography will be combined into neuromusculoskeletal modelling to determine modifications at the PNS level. Functional magnetic resonance imaging coupled with electroencephalography will be used to determine modifications at the CNS level. *Conclusion:* The findings of the proposed trial will likely give substantial solutions for the management of gait and postural disorders in PD where valid interventions are lacking. The coupling of movement evaluation, which assesses neuromuscular and biomechanical features, with neurological data, will better define the impact of the therapy on the relationship between PD motor alterations and brain activity. This will provide an active treatment that is personalized and shared to large populations.

1. Introduction

The ability to walk independently is a primary goal when rehabilitating an individual with Parkinson's disease (PD). Indeed, people with PD frequently display a flexed posture that coupled with an excessive joint stiffness leads to poor walking mechanics which increases their risk of falls. Literature reported that locomotor functions are positively recovered by functional gait training. Studies involving post-stroke participants, who underwent such a rehabilitation program, have shown to be more likely to achieve independent walking than people who did not receive the treatment. Although studies have already shown the many benefits of robotic-assisted gait training in people with PD on spatiotemporal parameters [1–3], this walking environment showed less control over the gait initiation by the patient and lacked in variability of visuospatial flow [4]. Therefore, research focusing on optimal rehabilitation methods has been directed towards powered lower-limb exoskeleton. In post-stroke rehabilitation the effect of this treatment enhanced potential for patient-specific rehabilitation [4,5], showing improvement in spatiotemporal parameters and kinematics [1]. As gait involves both central (CNS) and peripheral nervous systems (PNS), targeted rehabilitation must restore not only mechanics but also neurophysiological gait patterns. This requires improvements at the level of both balance and lower limb joint motion [1]. In this direction, wearable lower-limb powered exoskeletons promote functional training in a realistic walking environment, combined with a greater patient's engagement than in grounded devices.

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Gait in people with PD has been thoroughly studied with 3-dimensional gait analysis systems in recent years, documenting a typical hypokinetic gait with an increment of cadence, stance and double support phases, which compensates for the reduced stride length, step length and velocity [6]. Recently it has been shown that combining gait analysis and neuromusculoskeletal modeling (NMSM) enables to track disease progression with enhanced precision [7,8]. For each individual, a neuromusculoskeletal model is created, driven by the individual's own surface electromyography (sEMG) signals, and tracking their biomechanics [9,10]. This allows to link in vivo neuromuscular functions to the individual, providing new biomarkers to assess and track PD motor impairment. On the other hand, a stalwart of PD research has been electroencephalography (EEG) [11], which is widely used to evaluate executive dysfunction. Functional magnetic resonance imaging (fMRI) can detect cortical changes in motor activations during motor tasks [12]. The protocol to combine it with gait analysis has already been successfully adopted by the investigators to display the impacts of the rehabilitation process on the neural network reorganization, quantifying the neural activity after treatment [13]. Therefore, a framework is proposed to quantitatively assess the individual's gait and neuromuscular functions recovery of the sensorimotor alterations at the PNS and CNS after an over-ground wearable exoskeleton training (OWET). Comprehensive gait analysis and sEMG will be combined into NMSM to determine modifications at the PNS level, fMRI coupled with EEG will be used to determine modifications at the CNS level. As health care professionals and researchers need objective, reliable, and valid tools to plan subject-specific interventions, quantify therapeutic outcomes, and monitor changes over time, the proposed investigation includes coupling of neuromechanical variables with clinical scales.

2. Material and methods

2.1. Participants

Patients with clinically established diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic criteria will be recruited. The diagnosis will be reviewed by a neurologist specialized in movement disorders. This study is currently recruiting patients (study start date: May 2020 – due to pandemic COVID-19 enrolment start date: January 2021). Local Ethic Committee approval has been obtained (Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza – CE/PROG. 55/20). Participants eligible for enrollments must adhere to the following inclusion/exclusion criteria:

Inclusion Criteria:

- Aged between 20 and 90 years old
- Patient with rigid-akinetic bilateral PD form
- Hoehn-Yahr between 3 and 4
- At least 4 years of disease history
- Stable drug therapy response without any change performed in the 3 months before the study
- Presence of freezing of gait and of postural instability not responding to parkinsonian therapy
- Mini Mental State Evaluation >24/30

Exclusion Criteria:

- Systemic illness
- Presence of cardiac pacemaker
- Postural abnormalities, orthopedic comorbidities that do not match the active physiotherapy treatment and the use of the proposed robotic device
- Presence of deep brain stimulation
- Presence of severe disautonomia with marked hypotension
- Obsessive-Compulsive disorder
- Major depression
- Dementia and psychosis
- History or active neoplasia
- Pregnancy
- Other criteria that do not respect the device counterindications

Additionally, this trial is registered in ClinicalTrials.gov (a service of U.S. National Institutes of Health) Identifier NCT04778852 (March 3, 2021) named "Quantitative Assessment of training Effects Using a Wearable Exoskeleton in Parkinson Disease Patients". All participants will be asked for written informed consent according to the standard forms.

2.2. Device description

The overground wearable gait trainer adopted for the study is EksoGT® (EksoBionics, Richmond, CA, USA), a class IIa medical device (approval certificate: Annex II (excluding section 4) of Council Directive 93/42/EEC concerning medical devices; Product code: G/UMDN 58943; CE 852.170,501, 2017/05/01). The device is a wearable, battery-operated exoskeleton that enables individuals with lower extremities weakness or paralysis to stand and walk and be used for rehabilitation (Height range: 158–188 cm. Maximum permitted weight: 100 kg. Maximum hips width: 41 cm) [14,15].

The device is worn by the patient over his clothes and adjusted to his anatomy (Fig. 1). The embedded software enables the patient to walk during the first therapy session where he learns to manage both the stance phase and the different walking modes.

2.3. Study design

The study will be carried out over a 36-months period. Fifty patients with mild-to-moderate disease severity will be enrolled according to the inclusion\exclusion criteria described in Section 2.1. The activities will

Fig. 1. Subject wearing the overground wearable exoskeleton during the robotic gait training.

be organized into 4 work packages (WP), each with measurable outputs verified by scheduled deliverables/milestones.

- WP1: Clinical Trial. Being the present study, a pilot study investigating for the first time the effect of an OWET in PD individuals, and being some of the outcomes still explorative, a specific statistical power analysis to determine the adequate sample size for the study is so far not applicable. Thus, the sample size has been obtained considering a study in which the aim was to evaluate the potential benefits of a hydrokinetic treatment on an analogous PD population [16]. The contemplated study considered changes in gait speed assessed via instrumented gait analysis as parameter to evaluate the treatment effect (primary motor outcome). The sample size has been defined through Altman Diagram [17] based on the results on gait velocity changes obtained in Ref. [16], and a target of 25 PD patents per each group has been identified to reach a statistical power of 80% to detect statistically significant differences in the same parameter ($p < 0.05$). The selected variable has been chosen as both the studies are characterized by the same gait analysis acquisition protocol and data analysis.

  Two cohorts of subjects will be enrolled equally distributed between one (n = 25) who will undergo a functional kinematic therapy (FKT), and the other (n = 25) who will be treated with OWET (see Section 2.4). Participants are evaluated at three time points: time point 1 (T0) that is before the therapy, time point 2 (T1), that is after the therapy, and time point 3 (T2), that is 4 weeks after the therapy to evaluate the maintenance of the treatment. Evaluations at T0 are made within three days before the treatment begins; evaluations at T1 are made within three days after the treatment stops. Evaluation sessions averaged 2 hours in duration, and, to avoid fatigue, frequent breaks will be provided to keep participants alert and motivated during testing. At baseline (T0) subjects will undergo neurophysiological evaluation (EEG-fMRI) and gait analysis (see Section 2.6). Participants will then undergo a 4-weeks OWET\FKT. After the therapy (T1), the subjects will be evaluated, with the same protocol as at T0. After another 1 month, a follow-up (T2) will be conducted assessing only clinical scales and gait analysis (Fig. 2).
- WP2: Motion analysis. State-of-the-art posture and gait analysis will be performed pre- and post-rehabilitation and after a 4-weeks follow up (see Section 2.6).
- WP3: NMSM. Using the data collected in WP1 and WP2, NMSM will be performed to obtain muscular force and joint stiffness. This NMSM will be used to assess PD neuromuscular function pre- and post-rehabilitation and after a 4-weeks follow up (see Section 2.6).
- WP4: Neurophysiological assessment. A High-Density EEG (HD-EEG) recordings and analysis will be used to assess brain oscillation activity changes before and after the treatment. Multimodal brain imaging will be performed by simultaneous acquisition and analysis of neurophysiological signals (EEG/sEMG) and fMRI data to assess the resting state connectivity and activation differences between pre- and post-treatment and to identify their changes (see Section 2.6). EEG-fMRI is needed to overcome their complementary weaknesses, and to achieve an investigation of brain behavior of the subjects with both high spatial and high temporal resolution.

2.4. Treatment arms

The robotic gait training will be delivered in 12 sessions, spanned in 4 weeks by trained physical therapists, in possession of the patent to deliver the robotic training and under the supervision of medical mentors. Each session dosage will be of 45 minutes duration.

The active comparator group will undergo a traditional functional kinematic training which will be carried out for 3 days a week for 4 weeks, in the same amount of the OWET. No robotic devices will be included in the treatment.

2.5. Randomization, allocation and blinding

The randomization procedure to allocate the participants in one of the two intervention arms will be carried out through sequences generated using a designated software by an independent researcher who will not be aware of the numeric code for the intervention groups. The physical therapists involved in the intervention will not be able to maintain the blindness of the study. Thus, they will be omitted from other aspects of the patient care and/or evaluation. Both clinical and instrumental evaluations will be performed by clinicians, physical therapists and bioengineers who are blind to the patients' allocation. In order to maintain the single blindness of the study, personnel who have been contaminated by the information on subjects' allocation will be excluded by participants' experimental assessment. The researcher in charge of the statistical analysis will also be blind to treatment allocation until the main treatment analysis has been completed.

2.6. Clinical and instrumental evaluation

Clinical and instrumental evaluations will be assessed in three domains: clinical scales, gait and posture, and neurophysiological assessment. All tests will be administered in the Villa Margherita clinics

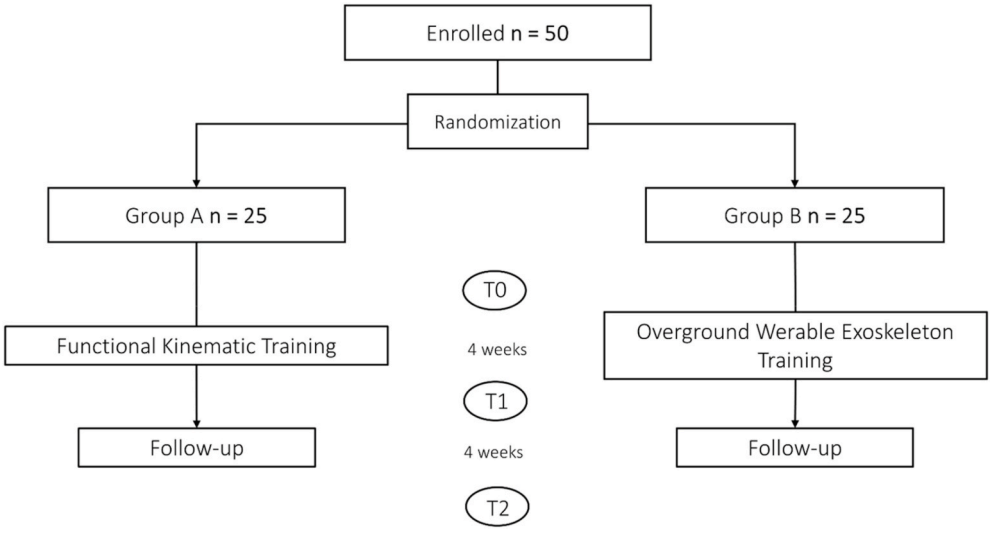

Fig. 2. Study workflow.

facilities laboratory setting by trained assessors who are blind to group assignment. Each participant will complete the tests while "ON" medication.

2.6.1. Clinical scales

For the clinical assessment, the following scales will be delivered by trained physical therapists at each time frame.

- *Unified Parkinson's Disease Rating Scale (UPDRS)* – Consists of four parts: Part I investigates non-motor experiences of daily living, Part II follow motor experiences of daily living up. Part III includes instructions that the researcher can either provide or show to the patient for the motor assessment. Part IV is completed by the researcher investigating motor complications. Higher scores show increased severity [18].
- *Activity-specific Balance Confidence Scale (ABC Scale)* – Is a structured questionnaire that measures an individual's confidence in performing activities without losing balance. Consists of 16 questions that require the patient to rate his confidence that he will not lose balance or becoming unsteady while performing tasks required. Each item has a value that varies from 0 to 100, where 0 is no security at all, 100 represents the total security [19].
- *Parkinson's Disease Questionnaire – 39 (PDQ-39)* – Assesses how often people affected by Parkinson's experience difficulties across eight dimensions of daily living including mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily pain. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure) [20].

2.6.2. Gait and posture

Gait and posture will be measured at the Motion Analysis Laboratory (10 m walkway) of the Fresco Parkinson Center of Villa Margherita (Arcugnano, Vicenza, Italy). Several gait cycles will be collected with an 8-cameras optoelectronic system (120Hz, Vicon, USA), synchronized with two force plates (1000Hz, AMTI, USA) and an 8-channel electromyographic system (1000Hz, Cometa, Italy). A modified version of the IOR-Gait protocol will be adopted both for anatomical landmarks identification and joint angles calculation. The following anatomical landmarks will be tracked in space by applying spherical retroreflective markers onto: the 5th lumbar and the 7th cervical vertebrae, the most anterior border of the two acromia, the two most anterior and the two most posterior margins of the iliac spines, the most lateral prominence of the great trochanters, the lateral and medial epicondyles, the proximal tip of the head of the fibulae, the most anterior border of the tibial tuberosities, the lateral prominence of the lateral malleoli, the lower ridge of the calcanei posterior surface, the dorsal margins of the first, the second and the fifth metatarsal heads [21]. As regards the sEMG analysis, the protocol described in Ref. [22] will be adopted and the activity of 4 muscles is acquired bilaterally (Biceps Femoris, Rectus Femoris, Gastrocnemius Lateralis, Tibialis Anterior). Gait analysis data will be processed in Matlab (MathWorks) and spatiotemporal parameters of gait will be extracted for each gait cycle. Concerning the knee joint, the unique motion over the sagittal plane will be considered, due to the large impact of skin artefact on knee rotations on the coronal and mediolateral planes [23]. After applying intra-class correlation, trials with a coefficient greater than 75%, will be included in the statistical analysis [24].

In order to extract the neuromuscular parameters, the following pipeline for NMSM will be applied [25]. MOtoNMS [26] will be adopted to export the motion data used in OpenSim framework and to normalize EMG signals with the respect of the value of the envelope peak obtained during each walking trial per each subject [27]. A generic musculoskeletal model (gait2392 [28]) will be used to linearly scale each subjects' geometry in OpenSim, matching the virtual markers of the model with the experimental ones of the subjects acquired during the static pose trial. Then a muscle optimizer tool will be used to adjust musculotendon parameters [29]. Inverse kinematics, inverse dynamics and muscle analysis tools will be used to obtain joint angles and moments and musculotendon lengths and moment arms during the recorded trials. CEINMS [30] will be adopted as a toolbox to estimate the muscle forces that best match the experimental sEMG and joint moments. Experimental sEMG will be used to directly drive their associated muscles in CEINMS [31].

Postural assessment will be carried out exploiting the instrumented Romberg Test which consists of two static acquisitions (one in eyes close (EC) condition and one in eyes open (EO)) standing still on the force plate, both of 60 s. The extracted variables are descriptive either of the center of pressure (COP) displacement over the force platform (e.g., ellipse area, sway area, path, and velocity) either of the frequency of COP oscillation in a spectrum between 0.01Hz and 5Hz, both in eyes open and close conditions [32].

A summary of the extracted variables is proposed in Table 1.

2.6.3. Neurophysiological domain

Neurophysiological functions will be evaluated in two different setups.

Firstly, EEG will be acquired simultaneously to gait cycles data collection (see Section 2.6.2) with a 64-channel cap (Ag/AgCl, waveguard™, ANT Neuro, Netherlands) and a 64-channel EEG amplifier (2048 Hz, ANT Neuro, Netherlands). Synchronization among the different acquisition systems will be achieved with a self-developed synchronization box. One minute of resting-state data acquisition both at eye-open and eye-closed conditions will be performed before and after gait cycles data collection.

Data analysis will be performed both in Matlab (Mathworks, MA, USA) and EEGLab Toolbox [33]. Brain dynamics will be evaluated by investigating event-related spectral perturbations (ERSPs) time-locked to the gait cycle. Moreover, corticomuscular coherence (CMC) and inter-trial coherence (ITC) are computed for EEG and sEMG during the different gait phases [34]. These measures will be correlated with kinetic and kinematic data and temporal gait parameters derived from the gait analysis to assess the neuro-control of gait in PD subjects.

Secondly (only for a small sample of five subjects), multimodal brain imaging acquisitions will be performed collecting fMRI, EEG and sEMG data simultaneously. MR-compatible systems will be used for both EEG and sEMG data acquisition. The latter will be acquired by placing the electrodes in the Tibialis anterior and Gastrocnemius lateralis muscles bilaterally. Regarding MR acquisition, anatomical imaging includes T1-weighted (T1w) 3D magnetization-prepared rapid acquisition gradient echo (TR = 2400 ms, TE = 3.24 ms, TI = 1000 ms, FA = 8°, FOV = 256 × 256mm, voxel size = 1x1x1mm^3) images, a 3D T2-weighted (T2w) image (TR = 3200 ms, TE = 535 ms, FOV = 256 × 256mm, voxel size = 1x1x1mm^3), a 3D fluid attenuation inversion recovery (TR = 5000 ms, TE = 284 ms, TI = 1800 ms, FOV = 256 × 256mm, voxel size = 1x1x1mm^3) image. In addition, functional imaging fMRI EPI scans will be acquired (TR = 2000 ms, FA = 68°, FOV = 204 × 204mm, voxel size = 3x3x3mm^3, phase encoding direction antero-posterior) and two spin echo-EPI acquisitions with reverse phase encoding (TR = 4200 ms, FOV = 204 × 204mm, voxel size = 3x3x3mm^3) for EPI distortion correction purposes.

fMRI data will be collected with a 3T MRI scanner. Subjects will be asked to stay quite with eye open within the scanner in order to acquire 15 min of resting state. After, subjects will perform a task-rest blocked design during the fMRI scan. Two tasks will be performed: passive and imaginary ankle dorsal-plantar flexion (ADPF). ADPF, indeed, is considered a proxy of gait since there is an overlap of the activation of a cortical network with the one activated during gait [[13,35]]. The motor paradigm consists of six 30 s periods of passive ADPF, each one followed by 30 s of rest first for the left leg and afterwards for the right one, and then six periods of imaginary ADPF (again followed by rest blocks) for both sides. Data analysis will be performed using the

Table 1
Outcomes measures for the gait and posture assessment.

Variable	Instrumentation	Measurement unit	Notes
Joint kinematics	3D markers trajectories	degrees	trunk, pelvis, hip, knee, ankle (flexion-extension, ab-adduction, internal - external rotation)
Gait velocity	3D markers trajectories, force plates	m/s	
Spatial parameters	3D markers trajectories, force plates	m	Step width, step length
Temporal parameters	3D markers trajectories, force plates	s	Step duration, gait period, stance period, swing period, double support
Cadence	3D markers trajectories, force plates	steps/minute	
Center of pressure (COP) spatial parameters	Force plate	m	Mean distance from center of COP trajectory, root mean square of COP time series, sway path, total COP trajectory length, range of COP displacement
COP velocity	Force plate	mm/s	
COP frequency	Force plate	Hz	Mean frequency, (number, per second, of loops that must be run by COP to cover total trajectory equal to sway path); median frequency (frequency below which 50% of total power is present); 95% power frequency (frequency below which 95% of total power is present), centroidal frequency (frequency at which spectral mass is concentrated)
COP ellipse parameters	Force plate	mm^2	area of 95% confidence circumference, area of 95% confidence ellipse
COP sway area	Force plate	mm^2/s	computed as area included in COP displacement per unit of time
Musculotendon forces	3D markers trajectories, force plates, surface electromyography	% body weight	Forces estimated via musculoskeletal modeling for semimembranosus, semitendinosus, biceps femoris, rectus femoris, vastus lateralis, vastus medialis, vastus intermedius, tibialis anterior, gastrocnemius lateralis, gastrocnemius medialis, soleus

following software: FMRIB Software Library (FSL [36]) [37], MELODIC Toolbox (FSL, Multivariate Exploratory Linear-Optimised Decomposition into Independent Components) and ad-hoc routines implemented in Matlab (Mathworks, MA, USA). The same data analysis pipeline as [13] will be adopted: it exploits the percentage of active voxels in different anatomical ROIs. Preprocessed fMRI images based on the spatial/activation maps will be used for the computation of quantitative indexes in order to describe the neural activity during the different tasks.

2.7. Statistical analysis

The outcome measures will be compared at baseline, after 4 weeks, and after 8 weeks. Parametric and non-parametric tests will be applied, after appropriately checking for normality assumption (Shapiro-Wilk test), for comparing data across different time frames. Categorical variables will be compared with chi-squared test or exact Fisher test. Significance level will be set with $p < 0.05$.

3. Discussion

Although studies have already shown the many benefits of robotic-assisted gait training in PD patients, research focusing on optimal rehabilitation methods has been directed towards powered lower-limb exoskeletons. Combining the advantages delivered from the grounded robotic devices with the ability to train the patient in a real-world environment, these systems provide a greater level of subject participation for maintaining trunk and balance control, as well as navigating their path over different surfaces and increasing the subject's functional abilities while the wearable robotic system guarantees less support. Furthermore, the stability the exoskeleton addresses to the patient, allows a hands-free walking trial, which represents an integral part for a physiological locomotion restoration. Modern motion analysis methods enable us to objectively assess the required assistance providing a means to tailor the assistance to each individual and remove the risks of clinical guesswork. Robotic devices assist the physical therapist by providing task-specific repeatable mechanical action to support therapies and enable higher intensity of training [38].

The purpose of the present work is to evaluate the effects of an OWET on gait impairments in comparison with an FKT in individuals affected by PD. As gait is a complex task that involves both CNS and PNS, targeted rehabilitation must restore not only gait mechanics (e.g., spatio-temporal parameters) but also neurophysiological gait patterns (e.g., joint kinematics and dynamics, muscle activity and brain connectivity). In order to link the brain activity and the motor behavior in a quantitative fashion, standard methods and innovative analysis will be applied for data acquisition, processing and analysis. Gait analysis provides a great amount of valuable information, while fMRI offers a powerful approach to define networks involved in motor control. The present study reports a methodology based on both fMRI and gait analysis outcomes to investigate the phases of motor learning before/after OWET.

Human movement analysis quantitatively assesses the neuromuscular and biomechanical features of movement [39]. Recent literature has highlighted the benefit of coupling gait analysis and NMSM for treatment planning and supplementing this approach with robotic rehabilitation [5,9], however there is no study investigating gait effects from an OWET in those with PD, and no assessment that uses comprehensive gait analysis and NMSM to reveal mechanistic changes as a result of the therapy.

Thus, the hypothesis of the proposed randomized clinical trial is that OWET could enhance quality of gait and balance in those affected by PD. Additionally, we are confident in the potential effects of OWET, which might impact the patients' quality of life as well. The results obtained by the analysis of muscle forces via NMSM will provide innovative information for rehabilitative programs, useful for clinicians to adapt interventions to the subject's specific needs. Moreover, both fMRI and EEG could reflect training-related neural reorganization and provide a neurophysiological insight into the optimal dose of additional gait training. From the interpretation of simultaneously acquired fMRI and EEG data, we can derive the EEG frequency bands more linked to the

functional activation of a specific network, i.e., the sensory motor network. Having learned how to link fMRI and EEG, and to evaluate potential relationships between activations in patients and their ability to walk, we will use neurophysiological data to evaluate the cerebral activity during active and passive ADPF; indeed, ankle dorsiflexion could be considered a proxy of gait. Given the activation of a cortical network overlapping with that activated by gait [40], EEG recorded during ankle flexion-extension task will be taken as a reference to identify purely sensorimotor EEG activity. The modulations of brain activity during gait initiation and walking will be investigated using well-established features, e.g., event-related desynchronization. The coupling of movement evaluation, which assesses neuromuscular and biomechanical features, with neurological data, will better define the impact of OWET on the relationship between PD motor alterations and brain activity. This project addresses the potential for OWET to restore normal gait in PD patients both at the level of improving the overall body motion and the lower joint stiffness, thereby improving function, quality of life, and reducing risk of injurious falls [1,41]. The proposed robotic device relies on functions by providing passive assistance to the ankle joint, which affects the rest of the body through mechanical coupling. Currently, the amount of device assistance is estimated based on a therapist's experience and expertise. It is worth mentioning that OWET is expected to reduce lower limb joint stiffness, which is a recognized biomarker of PD, thereby enhancing rehabilitation for PD patients. Findings linked with the proposed study will likely give substantial solutions to the management of gait and postural disorders (posture, balance, and gait) in PD where valid interventions (pharmacological, neurosurgery, traditional physiotherapy) are lacking. Moreover, a NMSM that identifies patient-specific variables for therapy could be used to assess treatment outcomes but also to conduct on-line rehabilitation therapy by means of remote control of the assistive device. This will provide several advantages over conventional approaches, proposing an active treatment that is personalized and scalable to a larger population and including a standardized training environment and an adaptable support that has the ability to increase the treatment intensity and dose, without being a burden on therapists. Lastly, the neurophysiological assessment will provide insights on brain oscillation activity changes in the pre-/post-treatment investigation.

3.1. Strength and limitations

We cannot rule out selection bias: people with PD will be all evaluated in "ON" stage, and patients are subjected to variable response to Levodopa which cannot be considered. In order to counteract the consequent motor fluctuations either patients will be evaluated, or treatment administered, at the same daytime. Nonetheless, this study provides important information about the outcomes that are most likely to improve with OWET intervention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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