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Study Protocol Article

Study protocol: Acute effects of lower limb strength exercises on gait asymmetry in people with Parkinson's disease - AsymmGait-Parkinson study

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ABBREVIATIONS

EMG	Electromyographic
fNIRS	Functional Near-Infrared Spectroscopy
MDS-UPDRS III	Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III
MoCA	Montreal Cognitive Assessment
MOVI-LAB	Human Movement Research Laboratory
PD	Parkinson's disease
PFC	prefrontal cortex
PwPD	People with Parkinson's disease
RMS	Root Mean Square
RPE	rating of perceived exertion
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials checklist
UNESP	São Paulo State University
UTN	Universal Trial Number

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BACKGROUND: Gait asymmetry in individuals with Parkinson's disease (PD) refers to an imbalance in the movement between the left and right sides of the body during walking, which is often associated with disease progression. This asymmetry is associated with more severe gait deficits, such as freezing of gait, falls, and stumbling. Because PD progression is associated with motor asymmetry, it is crucial to address this issue when developing targeted rehabilitation strategies. Physical exercise focused on lower limb strengthening shows promise in reducing gait asymmetry.
AIM: The proposed randomized clinical trial will compare the immediate effects of physical exercise focused on the most affected lower limb, the least affected lower limb, and both lower limbs on gait asymmetry in people with PD.
METHOD: The study will involve 36 participants with idiopathic PD (Trial registration: Brazilian Clinical Trials Registry RBR-5s234bn). Participants will attend seven laboratory visits, which will include clinical evaluations, strength exercise sessions, and gait assessments conducted at three specific time points: baseline (before the intervention), immediately after the intervention, and 24 hours post-intervention. Each intervention will involve strength exercises specifically targeting the lower limbs, focusing on improving muscle function and addressing gait asymmetry in people with PD. Three acute interventions will be tailored to i) the most affected limb, ii) the least affected limb, and iii) both. Gait assessments using inertial sensors will acquire the spatial-temporal parameters. Surface-electromyography signals from lower-limb muscles as well as prefrontal cortex activity recorded from a portable functional near-infrared spectroscopy will be analyzed.
RESULTS AND CONCLUSION: This paper provides a thorough description of a randomized, controlled, cross-over, and single-blind clinical trial. Results can bolster understanding of the immediate impact of targeted strength exercise on gait asymmetry in PD, which can help in developing rehabilitation strategies to improve gait deficits in people with PD.

KEYWORDS: Parkinson's disease | Gait asymmetry | Strength training | Neurorehabilitation | Motor control

INTRODUCTION

Marked asymmetry is a significant and distinct gait impairment in people with Parkinson's disease (PwPD). Clinical and experimental evidence supports the pathogenic role of pronounced asymmetry during walking in Parkinson's disease (PD) [1]. For instance, PwPD exhibit greater asymmetry in step length and duration compared to neurologically healthy individuals, both during unobstructed [2] and with obstacles [3] walking. While a stable gait pattern is crucial for safe and effective mobility, providing a stable foundation for navigating daily challenges [4], asymmetric gait patterns can disrupt intersegmental coordination and compromise whole-body angular momentum control during perturbations, thereby increasing the risk of instability [5].

Gait asymmetry is associated with reduced walking velocity [6,7] and increased energy expenditure [8], largely due to the metabolically demanding step-to-step transitions required for locomotion [9]. Notably, asymmetry in swing time and its variability, which are

prominent in PwPD, have been associated with freezing episodes, falls, and reduced executive function [10], further exacerbating the already high costs associated with PD for both individuals and society [11]. Additionally, PwPD show a significant reduction in the activation of key gait-related muscles [12] and increased prefrontal cortex activation [13] during walking, suggesting increased reliance on attentional resources, which may increase the risk of falls and mobility difficulties [13]. Studies indicate that hemispheric asymmetry in prefrontal cortex (PFC) activity plays a crucial role in motor control, with the left hemisphere being more prone to early degeneration in PD, particularly in frontal regions [14]. Moreover, the prefrontal cortex is involved in the cognitive control of gait, and reductions in PFC asymmetry could contribute to improved locomotion [15]. As a result, restoring walking symmetry has been proposed as a means to decrease the energetic demands of walking and enhance overall safety [16].

Dopaminergic medication has been demonstrated to enhance gait aspects such as walking speed and step-timing coordination, particularly in the early stages of Parkinson's disease, by enhancing cortico-muscular connectivity during the stance and swing phases [17]. However, its effects on gait asymmetry and motor control aspects such as cadence and postural adaptations are limited [18], as highlighted by Son et al. [19], who demonstrated that while levodopa improves phase coordination index in PwPD, it does not significantly alter gait asymmetry. Over time, the effectiveness of dopaminergic treatment diminishes, and side effects, such as dyskinesias, further complicate its use [20]. These limitations highlight the necessity for complementary interventions, such as targeted physical exercise, to address gait asymmetry.

Systematic reviews have demonstrated that strength exercise protocols—both acute effects, referring to immediate outcomes observed within 24 hours after a single session, and long-term effects, involving interventions over several weeks to months—have a significant positive impact on gait parameters in PwPD. These protocols enhance walking speed and balance [21,22], with some significant improvements in gait observed as early as 24 hours after exercise [23]. Additionally, bodyweight exercises have been shown to improve various aspects of physical fitness, including cognitive function, cardiovascular fitness, flexibility, and functional capacity, especially in older adults [24,25]. Furthermore, these exercises are associated with neuromuscular adaptations that help address gait asymmetry, improve balance, and enhance motor control, as observed in individuals with chronic neurological conditions [26].

Ricciardi et al. [27] conducted a double-blind pilot feasibility study to evaluate the efficacy of an asymmetric training protocol in PwPD, assigning participants to one of three groups: (1) targeting the most affected limb, (2) targeting the least affected limb, or (3) standard therapy targeting both limbs, with the target limb performing twice the number of repetitions compared to the non-target limb. The protocol focusing on the least affected limb yielded greater improvements in motor performance, balance, and gait compared to standard therapy, highlighting the potential of asymmetry-focused physiotherapy to enhance mobility and stability in PwPD. However, the study lacked specific gait parameter measurements and follow-up, emphasizing the need for further research. Additionally, a preclinical animal study [28] suggests that training the most affected limb while immobilizing the least affected limb has a neuroprotective effect on contralateral brain structures and may enhance neuroplasticity. While these findings are promising, further research is needed to validate the long-term effectiveness of asymmetric protocols and strengthen their theoretical basis for clinical application.

Considering the promising positive effects of lower limb strengthening on gait asymmetry, this randomized clinical trial protocol aims to compare the acute effects of physical exercise focused exclusively on the most affected lower limb, the least affected lower limb, and both lower limbs on spatial-temporal gait variables, as well as on muscle and cortical activation parameters in PwPD.

METHODS

Study protocol and setting

A randomized, controlled, cross-over, single-blind clinical trial will be conducted at the Human Movement Research Laboratory (MOVI-LAB) of the Department of Physical Education at São Paulo State University (UNESP), Bauru, Brazil. This study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [29]. The project was approved by the research ethics committee of the Faculty of Sciences at São Paulo State University, Bauru (CAAE: 73001023.5.0000.5398), and registered on the Brazilian Clinical Trials Registry platform (RBR-5s234bn), with the Universal Trial Number (UTN) code U1111-1302-5321. Table 1 shows a SPIRIT diagram for the timeline of procedures.

Study population, recruitment, and inclusion

The sample size was determined using G*Power software (version 3.1). A total of 36 individuals with idiopathic PD will participate in the study, accounting for a potential 30% sample loss. The calculation was based on a target of 27 participants, assuming a statistical power of 90% ($\alpha = 0.05$) and an effect size of 0.91 for detecting changes in step length asymmetry, the primary outcome of the study [30]. If participants consent to participate in the study, they will be asked to sign an informed consent form.

Participants will be recruited from rehabilitation programs in the Bauru, São Paulo, Brazil region. These programs focus on general exercise and do not target gait asymmetry or lower limb strengthening, ensuring that the effects observed in this study are due to the specific interventions outlined in the protocol. PwPD who meet the following criteria will be eligible: (1) a diagnosis of idiopathic PD by a neurologist [31], (2) independent mobility without assistive devices, (3) no advanced cognitive decline (Montreal Cognitive Assessment (MoCA) score >19) [32], (4) no history of musculoskeletal, orthopedic, vestibular, or uncorrected visual problems that prevent participation, and (5) stable levodopa treatment for at least 3 weeks [33]. Additional criteria include no uncontrolled cardiovascular, metabolic, or

inflammatory conditions, a medical certificate authorizing physical exercise, and no previous brain surgery or deep brain stimulation for PD.

Table 1. SPIRIT diagram of enrollment, interventions, and assessments.

	STUDY PERIOD									
	Enrolment	Allocation	Post-allocation							Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_x
ENROLMENT:										
Eligibility screen	X									
Informed consent	X									
Allocation		X								
INTERVENTIONS:										
EMALB				X		X		X		
ELALB				X		X		X		
EBLB				X		X		X		
ASSESSMENTS:										
Clinical and cognition			X							
Gait, muscle and cortical activity				X	X	X	X	X	X	
Exercise outcomes				X	X	X	X	X	X	

Note: EMALB: Exercise for the most affected lower limb; ELALB: Exercise for the least affected lower limb; EBLB: Exercise for both lower limbs.

Study intervention

Each participant will attend seven laboratory visits, including three evaluations 24 hours after the intervention protocol. On the first visit, clinical assessments and interviews will be conducted. The order of the exercise conditions (most affected, least affected, or both limbs) will be counterbalanced and randomized for each participant to minimize potential biases and ensure the reliability of the results. Before, immediately after, and 24 hours after each intervention, gait assessments (as described in the "Gait Assessment" section) will be conducted alongside items from the Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III - items 3.3, 3.8, 3.17) [34]. The researcher analyzing the data will be blinded to the intervention, using anonymized, coded data to ensure unbiased and objective analysis. Assessments and interventions will occur during the ON state of the medication [35], with participants instructed to avoid physical activity 48 hours prior. Figure 1 shows the study design describing all the steps of the study.

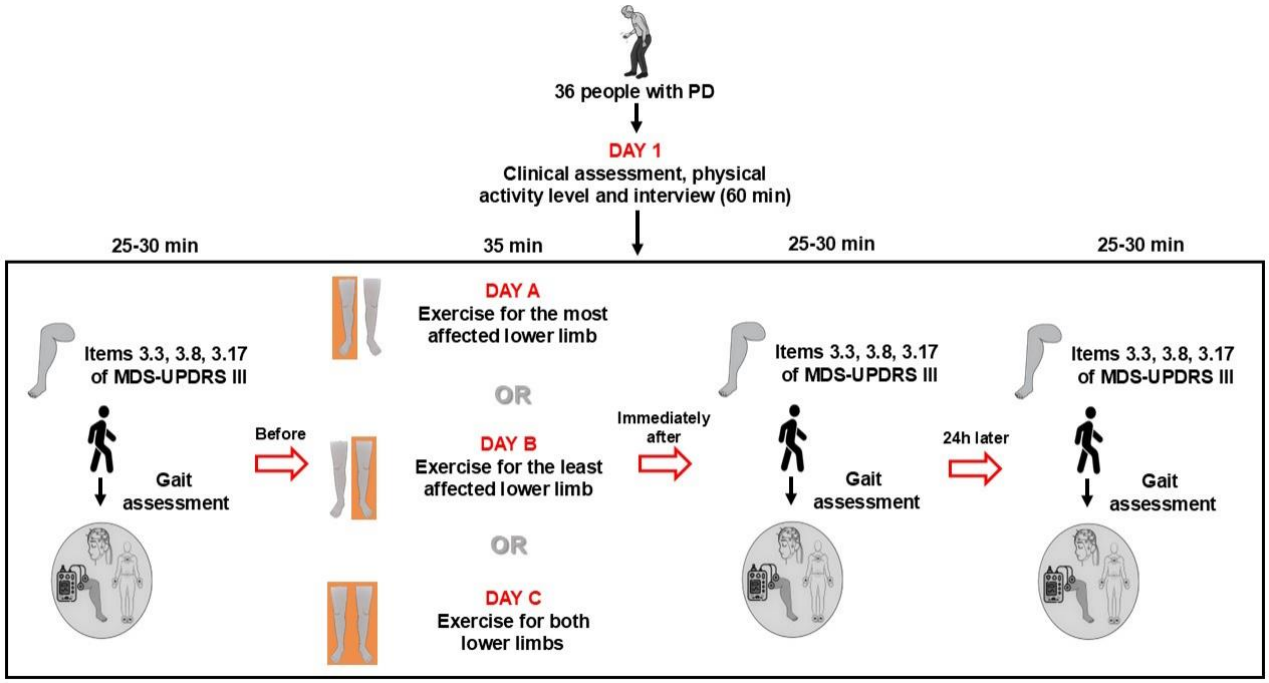

Figure 1. Proposed design for evaluating acute adaptations in gait asymmetry induced by the strength exercise protocol.

Clinical and physical activity level assessment

The disease stage and severity will be evaluated using the MDS-UPDRS III [34] and the Modified Hoehn and Yahr Scale [36]. Cognitive capacity will be assessed using the MoCA [32]. Physical activity level will be evaluated with the Physical Activity Scale for Individuals with Disabilities [37].

Gait assessment

Gait data collection will follow a block design, in line with recommendations for Functional Near-Infrared Spectroscopy (fNIRS) data collection [38]. A 20-second baseline measurement will be taken before each block of every walking condition. During the baseline, participants will be instructed to stand still to minimize movement-related artifacts. After the baseline, participants will complete five 17-meter walking blocks, each separated by a 20-second interval, under three different conditions: (a) unobstructed walking at preferred speed, (b) obstacle crossing (15 cm high, 80 cm wide, and 2 cm thick) placed midway, performed at preferred speed, and (c) unobstructed walking at maximum speed. In the obstacle condition, participants will be instructed to avoid contact with the obstacle. Gait data will be collected using three inertial sensors (Opals, APDM Inc., USA), with the data transmitted to a computer for storage and analysis. Electromyographic (EMG) activity will be measured using a Wireless Ultium EMG system (Noraxon, USA), with electrodes placed on the lateral gastrocnemius, tibialis anterior, rectus femoris and biceps femoris muscles of both legs. Cortical activity will be recorded via fNIRS using the NIRSport system (NIRx Medical Technologies), focusing on cortical oxygenation [39].

Strength exercise protocol

The strength exercise protocol will last 35 minutes, including a 5-minute warm-up and 30 minutes of bodyweight exercises targeting lower limb strength and muscular endurance. The protocol will follow a crossover design, allowing each participant to serve as their own control for more robust comparisons. This approach reduces inter-individual variability, improves statistical power, and allows for a direct comparison of the effects of the interventions: 1) only the most affected lower limb, 2) only the least affected lower limb, and 3) both lower limbs. To ensure the independence of each session, a washout period of at least seven days will be implemented between exercise days. The instructions, order, duration, and intensity of the exercises (controlled through the rating of perceived exertion (RPE) – between 3 to 4 according to the modified CR-10 BORG scale [40]) will be the same on all three days and for all participants (a checklist will be used to ensure consistency). All exercises will be supervised by trained professionals to ensure safety, proper execution, and high-quality movement throughout the sessions (Figure 2).

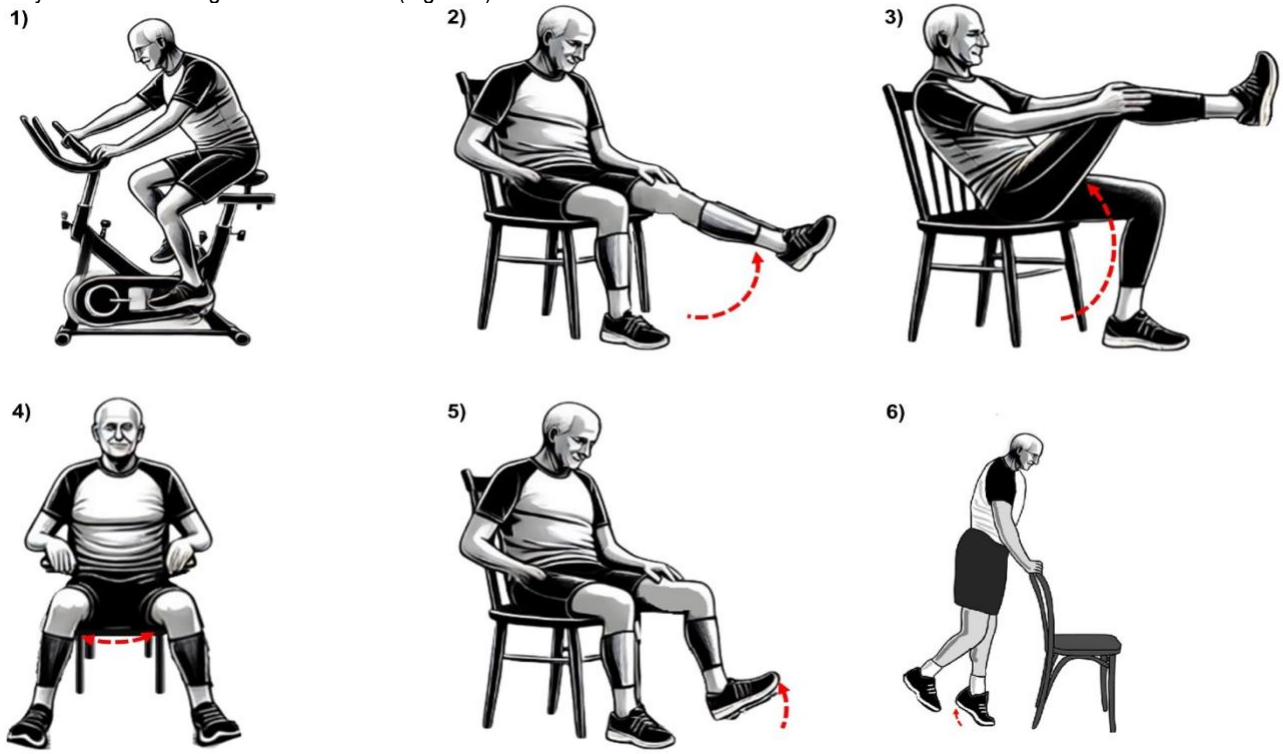

Figure 2. Illustration of the physical exercises that will be performed by participants in this protocol. Note: 1) Warm-up on an ergometric bike; 2) Seated knee extension; 3) Seated hip flexion; 4) Seated hip abduction; 5) Seated ankle dorsiflexion; 6) Standing plantar flexion.

The exercises performed during the intervention are illustrated in Figure 2 and described as follows:
1) 5-minute warm-up on an ergometric bike (RPE of 1 to 2).

2) Seated knee extension: This exercise is performed in a chair or on a bench with the back straight and feet positioned on the floor. The movement involves fully extending the knees, raising the lower legs relative to the torso.
3) Seated hip flexion: Performed with the back straight and feet on the floor, this exercise involves raising the thighs toward the torso and bending the hips.
4) Seated hip abduction: In this exercise, participants, seated with their backs straight and legs extended forward, move their legs laterally apart.
5) Seated ankle dorsiflexion: Performed by lifting the front part of the foot (toes) towards the leg while keeping the heel in contact with the ground.
6) Standing plantar flexion: Performed standing on an elevated surface with feet shoulder-width apart, the movement consists of raising the heels and standing on the balls of the feet.

Data analysis

The most affected side will be determined using the bilateral lower limb items of the MDS-UPDRS III, excluding participants with subtraction values of zero. Primary outcomes include spatiotemporal gait asymmetry indices such as step duration and the percentage of time spent in the double support and swing phases. These variables will be measured using Mobility Lab software. Secondary outcomes include muscle activation (EMG) and prefrontal cortex activity (fNIRS). EMG data will undergo visual inspection, high-pass filtering, rectification, and will be analyzed to determine the Root Mean Square (RMS), coactivation index, and median signal frequency of each muscle [41]. fNIRS data processing will follow the procedures outlined by Santinelli et al. [42], utilizing a custom MATLAB script (Homer3 toolbox). This will include conversion to optical density, motion artifact correction, hemoglobin concentration calculation, visual inspection, filtering, channel grouping, and analysis of relative oxy-hemoglobin and deoxy-hemoglobin concentrations during baseline and task periods. The symmetry index [43] will be applied to all spatiotemporal, EMG, and cortical activity parameters to quantify asymmetry.

$$\text{symmetric index} = \left[\frac{(\text{value of less affected limb} - \text{value of more affected limb})}{(\text{value of less affected limb} + \text{value of more affected limb})}\right] \times 100\%$$

Statistical analysis

Statistical analysis will be conducted using SPSS 26.0, with a significance level set at 0.05. Shapiro-Wilk and Levene tests will assess normality and homogeneity. MDS-UPDRS III items will be compared across interventions (most affected limb, least affected limb, and both limbs) and analysis periods (before, immediately after, and 24 hours after) using two-way repeated measures ANOVAs to assess interactions between the intervention conditions and time points. Symmetry index values for spatiotemporal, EMG, and cortical activity parameters will also be compared using two-way repeated measures ANOVAs, with Tukey's post hoc tests applied in the event of significant interactions. If assumptions are violated, non-parametric tests will be used.

Data access will be limited to principal investigators and will require email registration. The data will be anonymized, compiled into an Excel sheet, and imported into SPSS. Missing data will be addressed using the multiple imputation method. Once the findings are published and shared, the data will be made freely available upon formal request. In accordance with journal policies, data may also be included as supplementary materials when feasible.

DISCUSSION

This paper outlines a single-blind, placebo-controlled crossover clinical trial designed to compare the acute effects of targeted physical exercise on gait asymmetry in PwPD. The study focuses on exercises applied to the most affected lower limb, the least affected, or both, assessing gait in various contexts, such as unobstructed walking, walking with obstacles, and maximum speed walking. This design aims to enhance understanding of how limb-specific exercises impact gait asymmetry in PwPD.

The innovation of this intervention lies in its exploration of the differential effects of asymmetrical exercise training, an area with limited prior research, particularly in humans [27]. This approach is informed by neuroplasticity, with animal studies [28] suggesting that training the most affected limb can offer neuroprotective benefits to contralateral brain structures, potentially improving overall motor function. A key aspect of the intervention is the use of bodyweight exercises, chosen for their functional relevance, accessibility, and ability to engage multiple muscle groups [44]. Focusing on the duration of the sets can help control fatigue, maintain consistent effort, continuously engage neuromotor function, and better adapt to the disease's limitations [45]. The study's results could inform future long-term rehabilitation strategies by providing novel perspectives on optimizing treatment for gait asymmetry in PwPD.

Conducting the study presents practical challenges, particularly in maintaining consistency in the strength exercise protocol across participants. The crossover design demands strict control over exercise variables, standardized using checklists and the Borg Scale for perceived exertion [46]. Additionally, timing assessments related to medication states and ensuring participants avoid physical activity 48 hours prior to interventions add complexity to scheduling and compliance.

This study emphasizes the importance of measurement quality and consistency. Precise sensor placement, calibration, and specialized software for analyzing spatial-temporal gait variables, EMG activity, and cortical activation data are essential to ensuring reliable outcomes. The use of the Borg Scale, combined with rigorous data pre-processing, strengthens the robustness of the findings, ensuring they accurately reflect the intervention's impact on gait asymmetry.

Data management presents significant challenges, particularly in collecting and analyzing spatiotemporal gait variables, EMG activity, and cortical activation data. Ensuring accuracy requires precise sensor placement, careful calibration, and rigorous data processing using specialized software. For fNIRS data, pre-processing to remove motion artifacts is crucial for obtaining reliable cortical activation measures [39]. Additionally, the 17-meter walking distance is sufficient for capturing hemodynamic responses, particularly during fast walking, as PwPD are expected to take more than 4-7 seconds to complete the distance. This provides enough time to record the average hemodynamic activity [38] during movement tasks, such as gait, enabling a more comprehensive analysis of cortical activity. This approach aligns with Santinelli et al. [42], ensuring robust statistical analysis and enhancing the reliability of our findings.

While this study aims to offer meaningful perspectives, the short-term nature of the intervention may limit its applicability to long-term rehabilitation. Future research should investigate the lasting effects of asymmetrical training on gait asymmetry in PwPD. A key strength of this study is its integration of kinematic, EMG, and neural data, allowing for a comprehensive analysis of the relationship between motor and neural aspects. This multidisciplinary approach enhances our understanding of how targeted exercises influence gait dynamics and reveals the neurophysiological mechanisms involved. By analyzing gait patterns alongside EMG and fNIRS data, we aim to identify neuromuscular aspects relevant to intervention effectiveness, contributing to a more comprehensive understanding of motor control in PwPD. These advancements pave the way for future studies focused on optimizing individualized rehabilitation strategies.

The findings will be shared in open-access journals and presented at national and international conferences, leveraging our connections with participants and their families to broaden dissemination efforts.

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