

## Peer-review Comments and Author Responses

### Reviewer 1

#### 1. Title

*The title of the article highlights the challenges and advances in the application of physical training in PD, but it is worth specifically mentioning that a protocol and reporting standard are proposed.*

Author response: We think this is an excellent point. Then, we have made adjustments to the title: Advances of research in exercise Training for Parkinson's disease: a standard reporting of an exercise protocol according to the Consensus on Exercise Reporting Template (CERT).

#### 2. Introduction

*In the second paragraph, data from the study by Belvisi et al. (2020) are provided. It is mentioned that there are 5 prospective cohorts indicating the protective effect of physical activity in PD. For accuracy, it is important to indicate that there is a sixth study that did not demonstrate this effect. Also, review the wording, as two consecutive sentences begin with "These studies..."*

Author response: Thank you for pointing this out. We have made the corrections as follows:

- 3. Investigating modifiable protective/risk factors for PD, Belvisi et al. (2020) reviewed longitudinal studies and found six prospective cohorts, five of which indicated the protective effect of physical activity against PD. These studies were based on 43,368 to 143,325 participants followed up for 9 to 12 years and identified between 286 and 767 PD individuals and reported a range of PD risk reduction between 50 to 30% (RR=0.50 to 0.70). One prospective study did not find the same result and according to the authors, it was probably because of the lower number of participants and lower PD diagnosis rate.*

*In the fourth paragraph, it is important to explain to the reader what "de novo stage" of PD means. It is necessary to elaborate more on how to define this "de novo" stage or which classification is used to determine if the proposed intervention occurs in the early stages of PD. Since the protocol includes Hoehn and Yahr stages up to 4, there may be ambiguity in the definition of the de novo stage. It is also important to clarify here that in the reference by Amara et al. (2019), although there were self-reports of a reduction in the progression of motor symptoms, there was no significant difference in physical activity levels between PD patients and healthy controls.*

Author response: The reviewer mentioned a good point, then we rewrote the paragraph and also inserted that there is no difference between PD and controls in self-reported physical activity. In this context, Amara et al. (2019) conducted a case-control study for four years to investigate the relationship between levels of physical activity and the progression of motor and non-motor symptoms in individuals in the early stage who are not yet taking prescribed PD-specific medications. The authors observed no differences in the self-reported physical activity of the cases and controls, but activity levels decreased significantly throughout the study in the PD participants.

- 4. Regarding the "de novo" definition, this term was changed to "early stage who are not yet taking prescribed PD-specific medication". Moreover, this early stage was mentioned*

*only to emphasize the importance of starting the exercise as early as possible, immediately after the diagnosis. However, it was not the criteria used in the protocol reported.*

Before ending the introduction, the description of the knowledge gap can be expanded, emphasizing that although it is known that physical exercise seems to be a protective factor in PD, the ideal time to initiate the intervention, the dose, duration, or specific regimen are not well understood. Additional literature that may help expand this point. Here, I suggest some valuable papers on the topic:

- Ellis et al. (2021). Evidence for Early and Regular Physical Therapy and Exercise in Parkinson's Disease. *Seminars in neurology*, 41(2), 189–205. <https://doi.org/10.1055/s-0041-1725133>.
- Mantri et al. (2018). Physical Activity in Early Parkinson Disease. *Journal of Parkinson's disease*, 8(1), 107–111. <https://doi.org/10.3233/JPD-171218>.
- Tambosco, et al. (2014). Effort training in Parkinson's disease: a systematic review. *Annals of physical and rehabilitation medicine*, 57(2), 79–104. <https://doi.org/10.1016/j.rehab.2014.01.003>.
- Mak, M. K. Y., & Wong-Yu, I. S. K. (2019). Exercise for Parkinson's disease. *International review of neurobiology*, 147, 1–44. <https://doi.org/10.1016/bs.irn.2019.06.001>
- Konerth, M., & Childers, J. (2013). Exercise: a possible adjunct therapy to alleviate early Parkinson disease. *JAAPA: official journal of the American Academy of Physician Assistants*, 26(4), 30–33. <https://doi.org/10.1097/01720610-201304000-00007>

Response author: We agree with the reviewer that the description of the knowledge gap can be expanded, however as it is a short communication with a word and reference limit, we rewrite the paragraph to improve the gap description, as follows below. Moreover, another reviewer suggests that the introduction will be more concise.

Additionally, crafting a suitable exercise prescription is not only essential for maximizing improvements in motor and non-motor symptoms but also for enhancing adherence to the exercise. However, the programs described in the literature vary depending on frequency, intensity, duration and type of exercise, which makes it difficult to determine and design the best exercise program for PD patients. Despite the known protective and modifier effects of the exercise, a consensus on the optimal dosage has yet to be reached (Cui et al., 2023).

## 5. Results

*It is worthwhile to elaborate on how the physical therapist can modify the progression of the protocol based on the patient's progress to avoid variability in results among patients or intervention duration.*

Author response: We completely agree with the reviewer, and what we mean is that there is the individualization possibility despite being a protocol. Then, we improved the description of the criteria to increase the difficulty of the protocol. The progression of each exercise was provided on table 1.

## 6. Discussion

*Consider the impact that the availability of human resources and the protocol can have on the feasibility of its application in different facilities. For example, the availability of 2 physical*

*therapists with experience in neurological diseases for each patient or the possibility for patients to attend a rehabilitation center 3 times a week. Especially if the protocol is considered for application outside major US cities.*

*It is important to elaborate on the expected duration of the intervention's effect (2 weeks) in PD, considering that this is a chronic disease. Is a clinically significant effect expected to be measurable in a clinical study? In everyday clinical practice? Support it with existing evidence. Since the protocol is designed to standardize the reporting or description of physical exercise interventions in PD, you could eventually suggest feasible outcome measures for the protocol.*

Author response: Thank you for pointing this out. The main objective of this communication is to present how an exercise protocol could be described in future clinical trials, taking as an example a physical therapy protocol focused on gait and balance, which is going to be performed combined with transcranial direct current stimulation (tDCS) in individuals with PD at Spaulding Neuromodulation Center in an ongoing clinical trial. Therefore, this protocol lasts two weeks (5 times/week) because of the combination with tDCS (not reported here). The tDCS protocol usually has a minimum of 10 sessions lasting 2 weeks. However, we agree that it is important to highlight that the exercise practice should be regular in this population, as PD is a progressive and neurodegenerative disease. Regarding the human resources, if this protocol will be performed at home or even in a rehabilitation center, the caregiver can be trained to assist the physical therapist. Finally, as suggested by the reviewer, we included some outcome measures in the discussion that are recommended by Movement Disorders Society in the European Physiotherapy Guideline for Parkinson's disease.

Domingos JMM, Capato TTC, Almeida LRS, Godinho C, van Nimwegen M, Nijkrake M, de Vries NM, Bloem BR. The European Physiotherapy Guideline for Parkinson's Disease: translation for non-English speaking countries. *J Neurol.* 2021 Jan;268(1):214-218.

#### *7. Table 1*

*Explain the abbreviation TIFF at the bottom of the table.*

Author response: The explanation has been inserted on table, as the reviewer's recommendation. I hope that these recommendations may help you to increase the structure and impact of your manuscript.

#### **Reviewer 2**

- 8. While the detailed background information in the second paragraph aids in constructing the research gap, I suggest considering a rearrangement in the discussion section for a clearer and more concise introduction.*

Author response: Thank you for this suggestion. We have revised the introduction and the paragraph below has been removed to the discussion.

- 9. The considerable variability in exercise dosage for PD could stem from influences within health systems, such as funding models and available resources, or from provider preferences, including variations in facility-based, regional, or national practices.*

*Additionally, disparities within the evidence base may arise from differences in study design, participant demographics, access to facilities, and the level of supervision provided. The absence of a consensus on the optimal exercise dosage may, in part, be attributed to insufficient reporting of interventions in PD research studies. Frequently, rehabilitation studies on exercise interventions lack the necessary level of detail to determine the exercise dosage and its impact on health outcomes (Burgess et al., 2021). The reproducibility of effective interventions relies on accurate and comprehensive descriptions of the intervention content and delivery (Cotterill et al., 2018). Moreover, the absence of a complete published description impedes other researchers from building upon the findings, leaving clinicians uncertain about how to effectively implement such interventions (Hoffmann et al., 2014).*

*Additionally, I would like to acknowledge the authors for the graceful flow of sentences that take the readers from preclinical data regarding potential mechanisms of neuroplasticity to research with clinically relevant outcomes.*

*The methods section is clear. The broad inclusion criteria based on Hoehn and Yahr stages makes recruitment easier, but results can be highly variable among participants. Moreover, UPDRS scale is notably described and the most commonly used scale for Parkinson's disease. Although the major focus of the exercise protocol is motor performance, the assessment of non-motor symptoms is relevant, because it may affect adherence and compromise the results.*

Author response: Thank you for this suggestion. We agree that UPDRS is one of the most important scales for this population. However, despite Hoehn and Yahr only considering motor symptoms, we thought that it is adequate to stratify the sample and to divide for protocol A or B, as the protocol focuses on gait and postural stability, which are criteria used on Hoehn and Yahr Scale.

I appreciate the authors' commitment to advancing clinical research and look forward to seeing the revised version of this manuscript.

### **Reviewer 3**

10. *Recommendation: Accept Submission*

### **Reviewer 4**

#### *Minor Comments*

11. *In the sentence: "The authors included forty-nine trials and suggested that exercise had a neuroplastic effect, by improving activation and network connectivity or by improving the efficiency of compensatory networks (Li et al., 2023).", it is not understood what is improving activation. What neuronal networks show larger activation after exercise? "Improving activation" seems a bit vague.*

Previous studies that evaluated the functional connectivity by the MRI in this population related to reduced connectivity in the supplementary motor area (Agosta et al., 2014), posterior putamen (Tessitore et al. 2019), and within the basal ganglia network (Rolinski et al. 2015; Szewczyk-Krolkowski et al. 2014). Moreover, other studies reported increased connectivity in the primary motor cortex and cerebellum and disrupted connectivity between the cerebellum and sensory-

motor network (Wu et al., 2011), which has been interpreted as a compensatory mechanism aimed at maintaining preserved motor function. In this regard, the exercise has been proposed as a modifying disease therapy. A recent systematic conducted by Li et al. (2023) included forty-nine trials and the authors suggested that exercise promotes neuroplasticity, by improving activation and network connectivity or by improving the efficiency of compensatory networks, effects indicative of attenuating PD progression.

12. *In sentence: “Moreover, other studies have shown that exercise increases serum brain-derived neurotrophic factor level and decreases inflammation in PD patients (Zoladz et al., 2014).”: you only*

*cite one study but you mention other studies. Should be another, right?*

Author response: Thank you for pointing this out. Yes, other studies observed increased BDNF serum levels after an exercise program. Below are two more studies which have been added to the manuscript.

Frazzitta G, Maestri R, Ghilardi MF, Riboldazzi G, Perini M, Bertotti G, Boveri N, Buttini S, Lombino FL, Uccellini D, Turla M, Pezzoli G, Comi C. Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. *Neurorehabil Neural Repair*. 2014 Feb;28(2):163-8.

Marusiak J, Żeligowska E, Mencil J, Kisiel-Sajewicz K, Majerczak J, Zoladz JA, Jaskólski A, Jaskólska A. Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. *J Rehabil Med*. 2015 Apr;47(4):372-5.

13. *In Results you mention: “The physical therapist could modify the progression based on the patient’s performance.”. However, one of the main criticisms raised by the authors is the lack of objective guidelines in the exercise protocols. Can this be modified following an objective structure that could be replicated by other authors?*

Author response: We completely agree with the reviewer, and what we mean is that there is an individualization possibility despite being a protocol. Then, we improved the description of the criteria to increase the difficulty of the protocol. The progression of each exercise is provided in Table 1.

14. *Typo in Results: “programme”.*

Author response: Thank you for pointing this out. The word has been corrected.

15. *I found this sentence in the Discussion confusing: “It is frequent in PD research that exercises comparators and interventions cannot be pooled in the meta-analysis because the treatment parameters are unclear.” This means that it is difficult to pool in a meta-analysis because we do not know the parameters of the exercise intervention and the*

*control group (like the sham condition in non-invasive brain stimulation studies). Or do interventions here also refer to drugs?*

Author response: Thank you for the feedback. In this sentence what we mean is that the studies do not sufficiently detail the parameters of the exercise in both the intervention and control groups. Therefore, this makes it difficult to compare interventions in terms of dose and volume of exercise performed.

#### References

- Domingos JM (2021, Jan 1). The European Physiotherapy Guideline for Parkinson's Disease: translation for non-English speaking countries. *J Neurol*, p.268(1):214-218.
- Agosta F (2014, Nov 1). Cortico-striatal-thalamic network functional connectivity in hemiparkinsonism. *Neurobiol. Aging*, p.35(11):2592–2602.
- Tessitore A (2019). Functional connectivity signatures of Parkinson's disease. *J. Park. Dis*, p.9(4): 637–652.
- Rolinski, M (2015, Apr 9). Aberrant functional connectivity within the basal ganglia of patients with Parkinson's disease. *Neuroimage Clin*, p.8:126–132.
- Szewczyk-Krolikowski K (2014, Jul 5). Functional connectivity in the basal ganglia network differentiates PD patients from controls. *Neurology* 83: 208–214.
- Wu T (2011, Sep 1). Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. *Hum. Brain Mapp.* 32(9):1443–1457.
- Frazzitta G (2014, Feb 1). Intensive rehabilitation increases BDNF serum levels in parkinsonian patients: a randomized study. *Neurorehabil Neural Repair*, p.28(2):163-8.
- Marusiak J (2015, Apr 1). Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. *J Rehabil Med*, p.47(4):372-5.