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Original article

Effect of different types of exercises on psychological and cognitive features in people with Parkinson's disease: A randomized controlled trial

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ABSTRACT

Background: Parkinson's disease (PD) is a neurodegenerative and progressive disease marked by the presence of motor and non-motor symptoms, as psychological and cognitive impairment. Physical exercises have been prescribed as complementary therapy for PD, and the type of intervention and duration of the intervention should be taken into account.
Objective: We aimed to compare the effect of different exercise modalities (functional mobility, multimodal and cognitive) and length (4 and 8 months) on psychological and cognition in people with PD. This study followed the CONSORT extension for non-pharmacological trials.
Methods: In this randomized controlled trial, we assessed 107 participants between 2011 and 2013. At the end of 3 years, participants with PD (mild to moderate stages) who achieved the criteria were assessed considering 3 different groups of exercise: Multimodal ($n = 38$), Functional Mobility ($n = 33$) and Mental/Leisure ($n = 36$). All 3 interventions were performed for 32 weeks, twice a week, with 60 min for each session (64 sessions in total). Psychological and cognitive function were assessed at baseline and after 4 and 8 months.
Results: The Functional Mobility and Mental/Leisure training had a potential effect on maintaining cognitive function (executive function, attention and work memory). The Multimodal training did not show a benefit for cognitive features and was not even able to delay the progressive decline in cognitive functions; however, this modality had a positive effect on physical stress after 8 months of exercise.
Conclusions: An intervention that requires high complexity and specific activities, such as locomotor and cognitive exercise, provides a maintenance effect against the degeneration in cognition associated with the progression of PD and thus can delay the progressive decline in cognitive function in PD.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative and progressive disease marked by the presence of motor and non-motor symptoms [1]. Non-motor symptoms, in particular, include psychological (i.e., anxiety, depression and stress), cognitive impairment (i.e., executive dysfunction, attentional deficits, memory loss and impaired language), autonomic dysfunctions, apathy, fatigue and sleep disorders [1,2]. For instance, cohort and epidemiologic data identified that the prevalence of non-motor symptoms affects approximately 45% of people with PD [3]. Discussion regarding non-motor symptoms has recently gained prominence because they affect quality of life (QoL), even more so than motor symptoms [4], and are also intrinsically related to the progression and severity of PD [2] and movement control

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[5]. Antiparkinsonian medication, the standard therapy for PD, has limited effects on reducing non-motor symptoms, chiefly cognitive features [6]. Hence, non-pharmacological interventions, such as cognitive and physical exercises, can be alternative therapies to attenuate these symptoms [7–9].

Physical and cognitive exercises seem to indicate neural and brain function benefits, which attenuate the progressive course of non-motor symptoms in PD [10–12]. Specifically concerning physical exercise, the effects on brain functions and cognition are well established. For instance, in humans, aerobic exercise increases serum levels of brain-derived neurotrophic factor [13] and the brain connectivity and volume of areas [14], including those associated with cognitive functioning [15]. In contrast, although 3 months of exercise can benefit memory and executive function in community-dwelling older adults [16], the mechanism regarding cognitive exercise and brain functions in PD is not completely clear. Thus, both forms of exercise should improve or at least delay the progressive course of non-motor symptoms in people with PD. However, the advantages of physical versus cognitive interventions on non-motor symptoms are unclear.

Physical and cognitive exercises seem to be alternative interventions to maintain and even decrease the presence of non-motor PD symptoms, in particular, cognitive symptoms [7,17]. Additionally, multimodal and gait-specific exercises are beneficial for not only reducing PD motor impairments [18] but also improving executive function [19,20] and scores for non-motor symptoms, such as depression [21]. Cognitive exercises can improve a range of non-motor symptoms such as executive dysfunction [22–24], attentional deficits [24], deficits in working memory [22], processing speed [22], logic memory and verbal fluency [25]. Thus, different models of exercise might improve non-motor symptoms depending on the type of activity and the duration of the protocol.

Preliminarily, we observed that 3 different 16-week exercise programs (multimodal, gait-specific, and cognitive) were equally beneficial to improve episodic declarative memory and stress [9]. However, when exercises are performed for a longer duration, the likelihood of changes in cognition would be larger [26,27]. Regardless, we must understand the effect of different long-term physical and cognitive exercises on non-motor symptoms [17].

Previous findings in the literature had limitations, such as global cognition as the primary outcome [7,17], assessing only cognitive or psychological outcomes [17,23] and not considering psychological impairment. Also, the heterogenous characteristics of non-motor symptoms in PD justify the need for specific exercises for each symptom [17]. Finally, different exercise modalities (motor and cognitive) and different duration (short and long duration) allow for identifying the best modality to improve specific symptoms for tailoring specific interventions for each case.

Thus, we aimed to compare the effect of different exercise modalities (functional mobility, multimodal and cognitive) and length (4 and 8 months) on psychological and cognition in people with PD. We hypothesized that:

- physical and cognitive modalities would maintain and/or improve cognition and psychological features of these individuals;
- exercises performed for a longer duration would be more beneficial than short-term exercises.

This study followed the CONSORT extension for non-pharmacological trials (Supplementary checklist) [28].

2. Methods

2.1. Design

A randomized controlled trial was undertaken from 2011 to 2013. One assessor included 152 participants with PD. Those participants were further assigned by another assessor (using sequentially numbered containers) to 3 groups: Multimodal ($n = 57$), Functional Mobility ($n = 48$) and Mental/Leisure ($n = 47$) exercise. Individuals who took part in the Multimodal exercise group in the first year were allocated (switched) to the Functional Mobility or Mental/Leisure group in the second year and Mental/leisure or Functional Mobility for the third year. Individuals who started in the second or third year were allocated randomly into one of the 3 groups. Fig. 1 shows the details of the number of participants in each group per year. Between each year, there were 20 weeks ($\sim$4 months) without exercise (detraining period), to decrease cross-over effects.

2.2. Participants

Initially, participants from a support group [Program of Physical Activity for People with Parkinson's disease (PROPARKI)] volunteered to participate in the study. People with idiopathic PD according to the United Kingdom PD Brain Bank criteria [29], who walked unassisted and without ambulation aids during the intervention, did not have any other neurological (self-reported) or cognitive impairment [assessed by the Mini-Mental State Examination (MMSE)] [30,31] and were >40 years old were eligible for the study. The protocol was approved by the Human Studies Ethics Committee at São Paulo State University (n. 1058), and all participants gave their signed informed consent. Fig. 1 shows the flow of participants who completed all the assessments in this study. Participants who attended at least 70% of the sessions without 5 consecutive absences were included in the final analysis.

2.3. Interventions

All 3 intervention programs were performed for 32 weeks, twice a week, and all sessions lasted 60 min (10 min warm-up, 40 min main stage, and 10 min cool-down). The participants were encouraged to take their antiparkinsonian medication 1 hr before starting and, if necessary, regularly during the sessions. The intervention programs are described below:

The Mental/Leisure program: participants performed activities focused on cognitive and leisure. This program included 2 periods (32 sessions per period), including 3 sub-periods each. The sub-periods, based on different leisure dimensions (social, manual, and artistic), were always combined with intellectual and social aspects, such as social activities, math problem-solving, card and memory games, drawing, debates, and lectures.

The Multimodal program focused on improving/maintaining all components of functional capacity:

- aerobic resistance;
- general flexibility;
- lower/upper limbs and trunk strength;
- motor coordination;
- balance.

This program was based on the American College of Sports Medicine Guidelines for Physical Activity in Adults over age 65 [32] and previous findings [9]. The Multimodal program involved 2 main parts of 4 months. Each part consisted of 2 phases, with

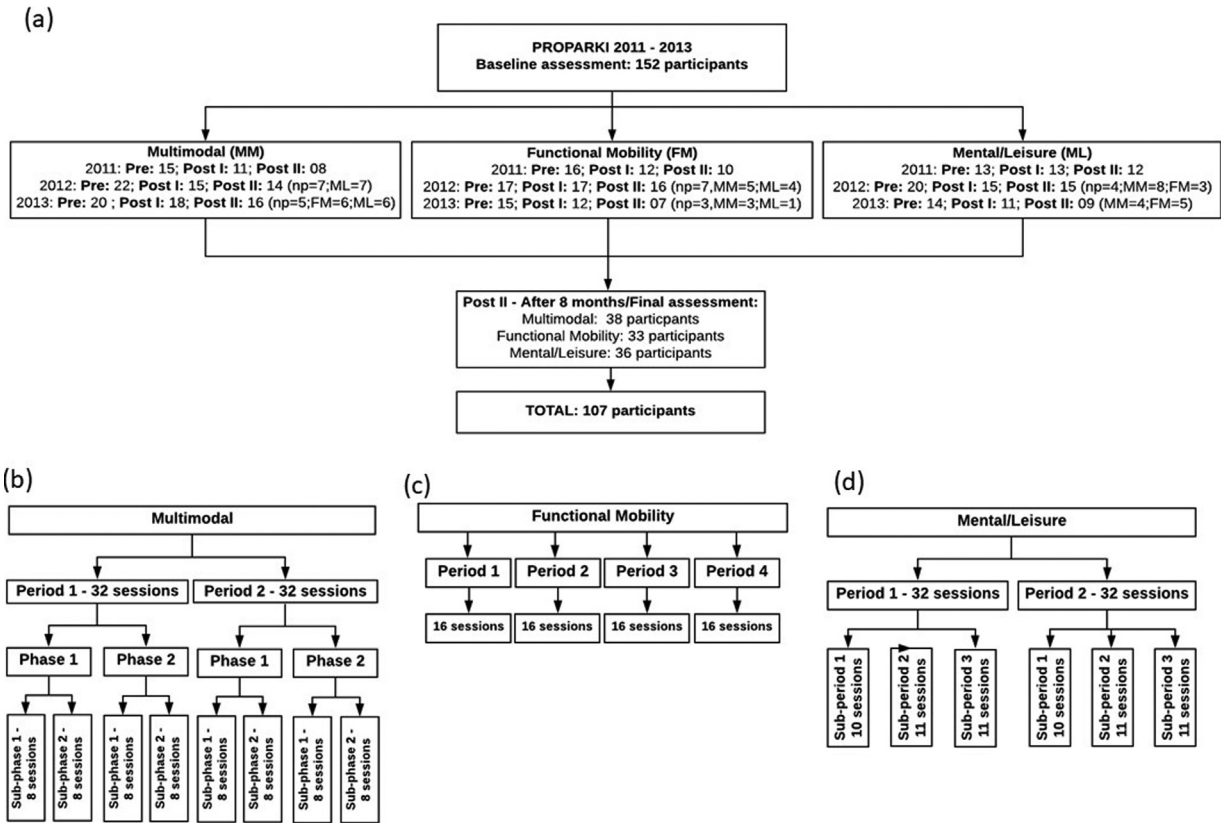

Fig. 1. (a) Flowchart of participants over time (2011 to 2013), considering Pre (baseline), Post I (after 4 months), and Post II (after 8 months). Post II indicates the number of new participants (np) and participants reallocated from Multimodal (MM), Functional Mobility (FM) and Mental/Leisure (LM) groups. (b–d) Structure of exercise interventions, considering Multimodal, Functional Mobility and Mental/Leisure groups, respectively.

2 sub-phases of 8 sessions, for a total of 64 sessions. The main stage of this program was split into 2:

- one functional capacity component was developed alone (i.e., force);
- two others were combined (i.e., motor coordination and aerobic resistance).

In the end, each component of functional capacity was trained solely for a total of 256 min, plus an extra 128 min when combined with a second component. In total, 2560 min of exercise was used to improve the 5 components of functional capacity mentioned above. At the end of each phase, the volume was implemented for each subject.

The Functional Mobility program aimed to improve/maintain balance and locomotion parameters as well as functional capacity and participants' QoL. This program was designed in 4 periods, containing 16 sessions each. All sessions were split into 2 and the main difference of the Multimodal program was in the first half of each class, which included 20 min of specific and challenging gait and balance activities. The volume of exercises focused on balance and mobility was larger in this program than in the other programs: 1280 min. In the second half of all sessions, the exercises were executed the same as in the second part of the Multimodal program. Therefore, functional capacity components were trained in a lower volume in the Functional Mobility than Multimodal program, only 5% of the time (128 min), for each functional capacity component. The first period was designed to improve general strength of muscles necessary for walking and balance maintenance and educational exercises. Periods 2 to 4 focused on posture control and walking improvement. The progression of the exercises was based on complexity increments concerning individual aspects. Participants were always encouraged to challenge their balance as much and long as possible, performing the highest number of repetitions. The task complexity was always increased from one period to the next.

2.4. Protocols and outcomes

Participants attended the Posture and Gait Studies Laboratory (LEPLO) at São Paulo State University at 3 different times (baseline, and after 4 and 8 months) and completed the clinical, cognitive, and psychological tests on the same day. The assessors were trained and consistent in conducting all the cognitive tests during the 3 periods. Participants reported their medical history and medications. Medication reports were used to calculate levodopa equivalency of dose (LED) [33]. All assessments were held in the "on" phase of the antiparkinsonian medication (self-reported by participants). The Unified Parkinson's Disease Rating Scale (UPDRS) [34] was used to assess:

- mentation, behavior and mood (part I);
- activities of daily living (part II);
- motor impairment (part III).

Also, the stage of the disease was analyzed by using the Hoehn and Yahr stage (1–5), modified version [35].

The following cognition tests were applied:

- MMSE for global cognition [30,31];
- Clock-Drawing Test (CDT), which indicates cognitive deficits in measuring components, such as memory and executive function [36]. This test involves the participant drawing a clock showing a specific time (i.e., a time on the clock at 2 hr and 45 min);
- Wechsler Memory Scale-Revised (WMS-R) [37], considering the subtests logical memory I and II (immediate memory, episodic declarative memory, and recall ability) and verbal paired associates (VPA easy combinations I, II, III and recall late immediately, and difficult combinations I, II, III and recall late after 30 min), which analyze immediate memory, learning, episodic declarative memory and recall ability;
- Wechsler Adult Intelligence Scale (WAIS version III) specifically considering the Digital span and Search symbol [37];
- Digital span is a complimentary evaluation of working memory in which the participants should listen to a sequence of numbers and repeat them in ascent and reverse order [37]. The Search Symbol test evaluates the processing speed because participants should mark whether or not the target symbols match those that appear in the equivalent rows [37];
- Wisconsin Card Sorting Test (WCST) [38] with "categories completed," "perseverative errors" and "failure to maintain set" to analyze the executive function specifically for abstractions, mental flexibility and attention;
- the Verbal Fluency test entails generating names of animals from a pre-selected letter within a pre-set time of 60 sec [39];
- the Corsi block-tapping test assesses visuospatial short-term working memory. Participants mimic an assessor who taps a sequence of up to 9 identical spatially separated blocks.

The test was evaluated in direct and inverse orders [40].

Psychological characteristics of participants were tested with:

- the Hospital Anxiety and Depression Scale (HAD) used to evaluate anxiety and depression, with 7 questions each [41];
- Lipp's Stress Symptoms Inventory (LSSI) [42] for assessing stress, physical, psychological and overall, according to the phase in which it is found: alert, resistance and exhaustion.

We assessed overall QoL by using the Parkinson's Disease Questionnaire (PDQ-39), which assesses how often participants experience difficulties in activities across 8 dimensions (mobility, activities of daily living, emotions, stigma, social, cognition, communication and bodily pain) [43].

The level of physical activity (LPA) was monitored by using the Modified Baecke Questionnaire for Older Adults [44], which quantifies physical activity level considering household, sports, and leisure time activities.

2.5. Statistical analyses

Power calculation (G*Power software) considered the total sample size (107 participants). We detected statistical power of 99.9% with an α risk of 0.05 to find differences in outcomes. Data were checked for skewed distributions and log-transformed if required. Demographic, clinical, psychological and cognitive measures assessed at baseline were compared between groups (Multimodal $\times$ Functional Mobility $\times$ Mental/Leisure) by ANOVA (normally distributed variables), Kruskal-Wallis tests (non-parametric variables) or chi-square test for cross-tabulation (binary categorical variables). Regarding LED, LPA and UPDRS, we used ANOVA between factors to Group and within factors to Time (Baseline X Post I X Post II) and Bonferroni post-hoc analysis to identify differences. Kruskal-Wallis tests were used to compare changes between groups in the effect of the intervention on psychological and cognitive features after 4 months (Δ1) and 8 months (Δ2). When significant interactions were found, Dunn's adjusted post-hoc tests were used. For post-hoc analysis, Cohen's d was calculated; values of 0.21 to 0.50, 0.51 to 0.79 and $>$ 0.79 were interpreted as small, medium and large effect size (ES) [45]. For each program, we calculated the delta between baseline and 4 months and baseline and 8 months, as follows:

Δ = (Mean value of the variable after $\times$ months–Mean value of value at baseline)

Significance level was set at 0.05. Data were analyzed with SPSS v24 (SPSS, Inc., Chicago, IL).

3. Results

As opposed to an "intent-to-treat" analysis, we included individuals who reached the minimum attendance of 70% and those who remained in the study until the last assessment (after 8 months of intervention). With that, we analyzed 107 participants (Multimodal = 38; Functional Mobility = 33; Mental/Leisure = 36). Specifically considering each year and group, in 2011, among 44 participants initially randomized in each study group, 30 met the criteria post-intervention (Multimodal, n = 8; Functional Mobility, n = 10; Mental/Leisure n = 12). In 2012, 45 of 59 participants completed the interventions (Multimodal, n = 14 [7 new participants, and 7 participants reallocated from Mental/Leisure]; Functional Mobility, n = 16 [7 new participants, 5 participants reallocated from Multimodal and 4 participants from Mental/Leisure]; and Mental/Leisure, n = 15 [4 new participants, 3 reallocated from Multimodal and 8 from Functional Mobility]). In 2013, among 49 participants initially included, 39 met the criteria post-intervention (Multimodal, n = 16 [5 new participants, 5 reallocated from Functional Mobility and 6 from Mental/Leisure]; Functional Mobility, n = 7 [3 new participants, 3 participants reallocated from Multimodal and 1 from Mental/Leisure]; and Mental/Leisure, n = 9 (4 reallocated from Multimodal, and 5 from Functional Mobility]) (Fig. 1). The groups did not differ in demographic and clinical (Table 1), psychological (Table 2), or cognitive measures (Table 3) at baseline.

Concerning LED (Table 1), the Time main effect ($F_{2.103}$: 5.29, P = 0.006) indicated that regardless of group, participants subtly increased the LED from baseline to 4 months (P = 0.01, ES: 0.12).

For LPA (Table 1), ANOVA revealed a Group by Time interaction ($F_{4.206}$: 10.69, $P > 0.05$). Post-hoc analysis indicated similar LPA values between groups at baseline ($P > 0.05$). Multimodal and Functional Mobility groups increased the LPA after 4 and 8 months as compared with baseline (all $P < 0.03$, ES: 0.24 to 0.61).

For UPDRS (Table 1), a Time main effect ($F_{2.103}$: 6.64, $P > 0.01$) indicated that after 8 months, participants showed slightly increased total UPDRS as compared with baseline and 4 months ($P > 0.04$, ES: 0.11 to 0.17).

3.1. Exercise effects on psychological measures

Table 2 shows comparisons of the effect of different interventions between groups on psychological measures after 4 and 8 months. After 4 months, the interaction (P = 0.036) showed differences between Multimodal and Functional Mobility groups (P = 0.032): scores for mobility were greater for the Functional Mobility than Multimodal group (ES: 0.71) (Fig. 2a). The groups did not differ in other measures after 4 months of intervention. After 8 months, statistical interactions were observed for Social Support and Physical Stress III (P = 0.035 and P = 0.028, respectively). Scores for social support were greater for the Functional Mobility than Multimodal group (P = 0.029, ES: 0.52) (Fig. 2b). Physical stress

Table 1
Demographic and clinical measures of groups at baseline and 4 and 8 months.

	Baseline			After 4 months			After 8 months		
	Multimodal $n=57$	Functional Mobility $n=48$	Mental/Leisure $n=47$	Multimodal $n=44$	Functional Mobility $n=41$	Mental/Leisure $n=39$	Multimodal $n=42$	Functional Mobility $n=33$	Mental/Leisure $n=36$
Male (%)	31 (54)	28 (58)	19 (40)	26 (59)	22 (53)-	15 (38)	23 (60)	17 (51)	15 (43)
Age, years	69.6 (8.2)	67.8 (9.1)	69.5 (7.6)	69.0 (9.0)	68.2 (8.9)	69.1 (7.1)	68.8 (9.5)	69.8 (7.5)	68.9 (7.6)
Disease duration, years	8.0 (5.7)	5.0 (3.0)	5.9 (3.2)	7.2 (4.8)	5.0 (2.7)	5.6 (3.2)	6.3 (4.5)	5.5 (2.7)	6.0 (3.5)
Hoehn and Yahr, stage (1–5)	1.9 (0.6)	1.8 (0.6)	1.7 (0.5)	1.8 (0.5)	1.8 (0.4)	1.8 (0.5)	1.7 (0.4)	1.7 (0.5)	1.7 (0.5)
UPDRS									
Part I score[a]	3.5 (2)	2.9 (1.6)	3.3 (2.1)	3.5 (2.4)	3.0 (1.8)	3.1 (1.7)	3.7 (2.4)	3.2 (1.7)	3.6 (2.1)
Part II score	11.1 (4.6)	11.8 (6.1)	11.8 (5.4)	11.0 (5.2)	11.9 (5.7)	11.9 (5.9)	11.9 (4.4)	11.78 (6.0)	12.7 (5.9)
Part III score[a]	23.7 (8.5)	22.8 (9.1)	22.6 (10.1)	24.5 (10.4)	23.2 (9.9)	23.3 (9.3)	25.4 (8.8)	23.7 (9.9)	24.5 (8.9)
Total score[a]	38.3 (12.5)	37.5 (14.2)	37.7 (13.7)	39.0 (15.3)	38.4 (14.9)	38.3 (15.1)	41.0 (13.6)	38.4 (15.8)	40.8 (14.3)
Levodopa equivalent dose, mg[a]	557.9 (413.3)	552.3 (385.2)	605.8 (376.1)	584.1 (394.4)	633.4 (433.2)	659.7 (438)	623.2 (432.1)	608.1 (388.1)	623.6 (414.6)
Modified Baecke Questionnaire, score[b]	3.8 (3.1)	4.9 (3.2)	5.4 (3.1)	4.9 (2.3)	5.6 (2.5)	5.0 (3.1)	5.4 (2.2)	6.2 (2.3)	4.8 (3.5)

Data are mean (SD) unless otherwise stated. UPDRS, Unified Parkinson's Disease Rating Scale
[a] Time main effect.
[b] Group by time interaction.

scores were lower for the Multimodal than Mental/Leisure group (p = 0.038, ES: 0.70) (Fig. 2c).

3.2. Exercise effects on cognitive measures

Table 3 shows comparisons of different interventions on cognitive features after 4 and 8 months. After 4 months, interactions were observed in MMSE ($P = 0.018$), WMS–R Logic Memory I ($P = 0.037$) and II ($P = 0.038$), WMS–VPA Easy I ($P = 0.008$), Easy late ($P = 0.01$), Difficult II ($P = 0.028$), and WCST Categories achieved ($P = 0.019$) and Perseverative response ($P = 0.002$). As compared with the Functional Mobility group, the Multimodal group exhibited better performance in Easy late ($P = 0.008$, ES: 0.67) and Difficult II ($P = 0.037$, ES:0.54) (Fig. 3b and

Table 2
Neuropsychological measures at baseline and changes between baseline and 4 and 8 months (Δ1 and Δ2).

	Baseline				Δ1 Values				Δ2 Values			
	Multimodal	Functional Mobility	Mental/ Leisure	*P*	Multimodal	Functional Mobility	Mental/ Leisure	*P*	Multimodal	Functional Mobility	Mental/ Leisure	*P*
HAD (score)												
Anxiety	6.4 (3.3)	6.6 (4.1)	6.7 (4.2)	0.975	−0.29 (2.47)	−0.18 (3)	−0.76 (3.08)	0.546	−0.05 (2.26)	−0.25 (3.58)	−0.21 (4.02)	0.975
Depression	7.2 (3.9)	6.3 (3.6)	7.7 (4.2)	0.345	−0.55 (3.01)	0.12 (2.95)	−0.82 (2.52)	0.249	−0.08 (3.51)	0.56 (2.35)	−0.61 (2.71)	0.235
PDQ-39 (%)												
Mobility	24.5 (18.6)	32.3 (23.6)	32.5 (27.9)	0.46	2.83 (13.72)	−7.5 (15.42)	−3.43 (18.52)	*0.036*	5.79 (13.5)	−2.58 (14.7)	−0.07 (19.47)	0.157
ADL	24.7 (22.6)	23.4 (21.3)	24.6 (23)	0.968	0.11 (12.76)	−1.42 (17.16)	0.91 (19.25)	0.667	1.53 (16.25)	0.89 (19.23)	1.9 (23.51)	0.813
Emotional well-being	28.8 (21)	29.79 (19)	35.4 (27.3)	0.625	−0.11 (18.08)	−0.88 (18.42)	−6.9 (23.55)	0.127	0.76 (13.63)	−1.89 (16.31)	−6.08 (23.49)	0.294
Stigma	17.4 (24.1)	16.3 (19.6)	16.4 (27.1)	0.86	0.82 (12.6)	−1.14 (14.27)	−1.61 (22.86)	0.814	2.47 (17.04)	−1.89 (12.84)	−3.39 (16.07)	0.304
Social support	15.3 (24.2)	15.1 (16.3)	19.5 (21.2)	0.263	0.66 (19.22)	3.54 (17.92)	3.57 (23.51)	0.772	5.6 (23.38)	−5.06 (13.96)	0.58 (22.66)	*0.035*
Cognition	29.1 (17.7)	25.9 (16.2)	30.2 (17.7)	0.658	0.3 (17.66)	1.14 (15.35)	−2.68 (18.83)	0.404	2.47 (18.81)	4.42 (15.78)	0.36 (18.69)	0.4
Communication	19.1 (21.3)	22 (19)	21.9 (22.6)	0.677	3.07 (14.16)	−2.78 (19.39)	−0.71 (22.72)	0.269	4.82 (12.94)	2.02 (18.04)	4.28 (23.51)	0.149
Bodily discomfort	47.6 (28)	42.4 (29.7)	49.4 (23)	0.522	−3.07 (20.08)	−0.76 (30.93)	1.55 (28.41)	0.87	−0.44 (23)	6.57 (24.45)	−5.36 (25.83)	0.097
LSSI (score)												
Physical stress I	2.76 (2.11)	2.85 (1.7)	3.11 (2.07)	0.664	0.29 (2.3)	−0.36 (1.97)	−0.26 (1.87)	0.444	−0.08 (1.96)	−0.15 (1.6)	−0.11 (2.01)	0.875
Psychological stress I	0.92 (1.1)	0.91 (0.98)	0.89 (1.08)	0.946	−0.11 (1.16)	0.45 (1.94)	−0.17 (1.22)	0.495	−0.42 (1.22)	−0.18 (1.01)	−0.2 (1.21)	0.709
Overall I	3.68 (2.49)	3.76 (1.84)	4 (2.69)	0.894	0.18 (2.66)	−0.3 (2.42)	−0.43 (2.34)	0.603	−0.5 (2.47)	−0.33 (1.83)	−0.31 (3.02)	0.883
Physical stress II	3.53 (1.93)	3.09 (1.77)	3.37 (2.34)	0.611	−0.71 (1.59)	−0.88 (1.49)	−0.4 (2.21)	0.7	−0.71 (1.63)	0.24 (1.54)	−0.17 (2.06)	0.073
Psychological stress II	1.55 (1.2)	1.39 (1.3)	1.6 (1.44)	0.764	−0.03 (1.17)	0.48 (1.91)	−0.11 (1.23)	0.342	0.11 (1.23)	−0.09 (1.4)	−0.06 (1.51)	0.637
Overall II	5.08 (2.52)	4.48 (2.73)	4.97 (3.45)	0.582	−0.74 (1.84)	−0.76 (2.4)	−0.51 (2.88)	0.703	−0.61 (1.91)	0.15 (2.5)	−0.23 (2.89)	0.583
Physical stress III	2.63 (2.07)	2.3 (1.7)	2.46 (1.56)	0.902	−0.26 (1.65)	0 (1.77)	−0.03 (1.62)	0.64	−0.79 (1.95)	0.12 (1.62)	0.4 (1.4)	*0.028*
Psychological stress III	3.37 (2.77)	2.91 (2.25)	3.49 (2.99)	0.788	−0.13 (2.13)	0.52 (2.93)	−0.46 (2.27)	0.843	0.21 (2.46)	0.27 (2.37)	−0.34 (2.5)	0.636
Overall III	6 (3.86)	5.21 (3.21)	5.94 (4.04)	0.763	−0.39 (2.55)	−0.64 (3.43)	−0.49 (2.89)	0.578	−0.58 (3.35)	0.42 (3.23)	0.06 (2.98)	0.405

Data are mean (SD). HAD: Hospital Anxiety and Depression scale; PDQ–39: Parkinson's Disease Quality of life questionnaire; ADL: Activities of daily living; LSSI: Lipp's Inventory Scale of Stress for Adults.

Table 3
Cognitive measures at the baseline and changes between baseline and 4 and 8 months (Δ1 and Δ2).

	Baseline				Δ1 Values				Δ2 Values			
	Multimodal	Functional Mobility	Mental/ Leisure	*P*	Multimodal	Functional Mobility	Mental/ Leisure	*P*	Multimodal	Functional Mobility	Mental/ Leisure	*P*
MMSE (score)	28.2 (1.54)	28 (2.14)	27.7 (2.04)	0.645	−0.53 (2.06)	0.21 (1.43)	0.5 (1.54)	0.018	−0.11 (1.54)	0.31 (1.8)	0.91 (1.7)	0.026
CDT (score)	9 (1)	8.8 (1)	8.9 (0.8)	0.246	−0.29 (1.2)	0.06 (0.88)	0.09 (0.79)	0.288	−0.59 (1.23)	0.06 (0.5)	0.28 (0.96)	0.003
Verbal fluency (score)	15.6 (4.8)	14.2 (3.8)	15.3 (4.7)	0.569	−0.08 (2.7)	−0.59 (3)	0.56 (4.05)	0.499	0.27 (2.87)	0 (2.82)	0.24 (4.02)	0.913
WMS-R (score)												
Logic Memory I	21.2 (9)	22 (8.3)	22.9 (9.6)	0.758	1.61 (6.2)	−0.48 (4.48)	2.06 (4.36)	0.037	3.68 (5.66)	1.45 (4.52)	2.29 (4.48)	0.167
Logic Memory II	19.1 (9.9)	18.4 (10.4)	19.7 (9.4)	0.855	0.45 (5.21)	−2.67 (9.32)	1.26 (4)	0.038	3.53 (5.96)	2.88 (5.8)	2.34 (4.28)	0.798
WMS-VPA II (score)												
Easy I	3 (1.1)	3 (1)	3.5 (0.7)	0.105	0.34 (0.88)	0.03 (0.73)	−0.23 (0.65)	0.008	0.47 (0.86)	0.33 (0.96)	−0.11 (0.72)	0.018
Easy II	3.5 (0.6)	3.4 (0.8)	3.7 (0.5)	0.73	−0.13 (0.84)	0.09 (0.68)	0.03 (0.51)	0.695	0 (0.8)	0.09 (0.84)	−0.14 (0.73)	0.452
Easy III	3.7 (0.5)	3.6 (0.7)	3.8 (0.5)	0.371	−0.05 (0.61)	−0.06 (0.66)	−0.17 (0.51)	0.486	0 (0.73)	0.09 (0.63)	−0.11 (0.47)	0.353
Easy late	3.5 (0.9)	3.5 (0.7)	3.8 (0.5)	0.358	0.11 (0.92)	−0.64 (1.27)	−0.14 (0.43)	0.01	0.18 (0.9)	0.06 (0.7)	−0.11 (0.4)	0.234
Difficult I	0.9 (1)	0.8 (1)	1 (1.1)	0.838	0.32 (1.02)	0.15 (1.12)	0.23 (1.19)	0.597	0.39 (0.85)	0.3 (0.92)	0.14 (1.29)	0.461
Difficult II	1.3 (1.4)	1.5 (1.1)	1.5 (1.1)	0.619	0.29 (1.25)	−0.33 (1.05)	0.4 (1.31)	0.028	0.66 (1.1)	−0.18 (1.07)	0.09 (1.31)	0.009
Difficult III	1.5 (1.3)	1.6 (1.1)	1.9 (1.1)	0.218	0.47 (0.89)	0.3 (0.95)	0.31 (1.02)	0.574	0.71 (1.04)	0.09 (1.33)	0 (1)	0.016
Difficult late	1.4 (1.4)	1.4 (1.1)	1.6 (1.2)	0.573	0.29 (1.04)	0.24 (1.46)	0.23 (0.97)	0.835	0.68 (0.99)	0.09 (1.04)	0.23 (1.03)	0.056
WMS–CBTT (score)												
Direct order	4 (0.7)	3.9 (0.9)	3.9 (0.9)	0.6	−0.08 (1.02)	0.12 (1.02)	0.17 (0.82)	0.586	−0.08 (0.85)	0.18 (1.1)	−0.03 (0.747)	0.417
Inverse order	3.8 (1.2)	3.6 (1.1)	3.6 (1)	0.576	−0.24 (1.17)	0.24 (1.03)	0.03 (1.01)	0.264	0 (1.04)	0 (0.97)	0.03 (0.98)	0.974
WAIS-III-Digit span (score)												
Direct order	4.9 (1)	4.9 (1.1)	4.9 (1.4)	0.703	−0.21 (1.28)	−0.27 (0.84)	−0.03 (0.98)	0.419	0.21 (1.32)	0.39 (0.86)	0.46 (1.44)	0.62
Inverse order	3.5 (0.8)	3.4 (1.1)	3.4 (0.8)	0.598	0.05 (0.84)	0.09 (0.91)	−0.03 (0.82)	0.686	0.11 (0.76)	0.12 (1.08)	0.14 (0.84)	0.992
WAIS−III–Symbol search (score)												
Number correct	20.4 (8.8)	20.1 (6.7)	20.7 (8.2)	0.879	0.29 (4.72)	−1.76 (5.98)	−1 (4.31)	0.267	1.89 (5.04)	−0.91 (6.99)	0.31 (5.89)	0.286
Number of errors	3.6 (3.2)	2.8 (3.4)	3.7 (2.7)	0.164	−0.37 (3.31)	0.42 (3.65)	−0.94 (2.83)	0.086	−0.63 (2.54)	0.79 (2.7)	−0.51 (3.78)	0.093
WCST (score)												
Categories achieved	2.4 (1.4)	2.2 (1)	2.3 (1.3)	0.986	−0.58 (1.06)	0.06 (1)	0.11 (1.1)	0.019	0.21 (1.21)	−0.03 (1.59)	0.4 (1.35)	0.388
Number correct	24.7 (7.2)	20.6 (6.1)	23 (7.7)	0.102	−0.74 (7.31)	1.12 (5.47)	1.6 (7.13)	0.321	1.58 (6.39)	2.82 (6.82)	3 (7.29)	0.608
Total errors	23.3 (7.2)	27.6 (6)	25 (7.7)	0.075	0.29 (7.39)	−0.52 (7.4)	−1.6 (7.13)	0.533	−1.87 (6.41)	−2.27 (8.61)	−3.2 (7.36)	0.715
Non-perseverative errors	10.42 (4.4)	11.1 (4.78)	11.2 (4)	0.722	1.63 (5.15)	2.21 (5.1)	0.14 (6.61)	0.538	−0.39 (4.72)	−0.03 (6.3)	−1.09 (4.57)	0.706
Perseverative errors	10.8 (7)	14.1 (7.9)	11.3 (7.5)	0.12	−0.79 (7.33)	−2.55 (6.67)	−0.94 (5.42)	0.71	−1.95 (5.78)	−2.94 (8.21)	−2.06 (6.59)	0.887
Failure to maintain set	0.8 (1.2)	0.3 (0.5)	0.9 (1.3)	0.052	0.13 (1.38)	−0.03 (0.85)	−0.03 (1.48)	0.473	−0.13 (1.42)	0.45 (1.15)	−0.37 (1.42)	0.079
Failure to maintain rule	1.5 (1.6)	1.2 (1.6)	1.6 (1.8)	0.365	0.71 (2.58)	0.45 (1.62)	−0.29 (2.16)	0.067	−0.08 (2.12)	0.52 (1.68)	0.26 (2.17)	0.611
Others errors	0.03 (0.16)	0.09 (0.29)	0.29 (0.79)	0.099	0.39 (1.13)	0.06 (0.5)	−0.11 (1.1)	0.052	0.37 (1.02)	0.18 (0.68)	0.14 (1.03)	0.686
Perseverative response	2.3 (1.4)	2 (1.1)	2.1 (1.2)	0.898	−0.68 (0.96)	0.03 (1.1)	0.14 (1.11)	0.002	−0.16 (1.22)	0.03 (1.59)	0.4 (1.44)	0.25
% perseverative errors	42.9 (17.8)	49.4 (17.4)	41.1 (18.2)	0.118	−3.73 (18.56)	−6.3 (16.03)	−0.8 (15.39)	0.428	−5.49 (16.32)	−7.07 (21.3)	−2.52 (16.19)	0.775

Data are mean (SD). MMSE: Mini−Mental State Examination; CDT: Clock Drawing Test; WMS, Weschler Memory Scale; VPA: Verbal Paired Associates; CBTT: Corsi Block-tapping test; WAIS-III: Weschler Adult Intelligence Scale; Wisconsin Card Sort Test.

c) but worse performance in Perseverative response ($P = 0.011$, ES: 0.69) (Fig. 3e). As compared with the Mental/Leisure group, the Multimodal group exhibited better performance in Easy 1 ($P = 0.006$, ES: 0.74) (Fig. 3a) but worse performance in MMSE score ($P = 0.014$, ES: 0.57), Perseverative response ($P = 0.006$, ES: 0.64) and Categories achieved ($P = 0.041$, ES: 0.64) (Fig. 3e and 3f).

After 8 months of intervention, interactions were observed in MMSE (p = 0.026), CDT ($P = 0.03$), Easy I ($P = 0.018$) and Difficult II ($P = 0.009$) and III (0.016). As compared with the Functional Mobility group, the Multimodal group exhibited worse performance in CDT ($P = 0.042$, ES: 0.74) but better performance in Difficult II ($P = 0.01$, ES: 0.77) (Fig. 3c). As compared with the Mental/Leisure group, the Multimodal group exhibited better performance in Easy I ($P = 0.016$, ES: 0.73) and Difficult III ($P = 0.022$, ES: 0.70) (Fig. 3a and 3d) but worse performance in MMSE ($P = 0.022$, ES: 0.63) and CDT ($P = 0.003$, ES: 0.79).

As additional analyses, for each intervention, we compared the baseline values for neuropsychological and cognitive measures across the years. We observed similar baseline values between years for all interventions (Supplementary material 1 and 2).

4. Discussion

Our hypotheses that physical and cognitive modalities of exercise would be able to maintain and/or improve cognition and psychological features of people with PD and that longer duration would be more beneficial were partially confirmed. In fact, our findings revealed that the locomotor and cognitive training had a potential effect on maintaining executive function, attention, and work memory. Unexpectedly, the multimodal training did not have any substantial benefits on executive functions, despite subtle positive effects on logic memory and "physical stress" after 8 months of exercise. In agreement with the preliminary published data for 4 months, similar results were evidenced in terms of locomotor and cognitive exercises on the maintenance of the

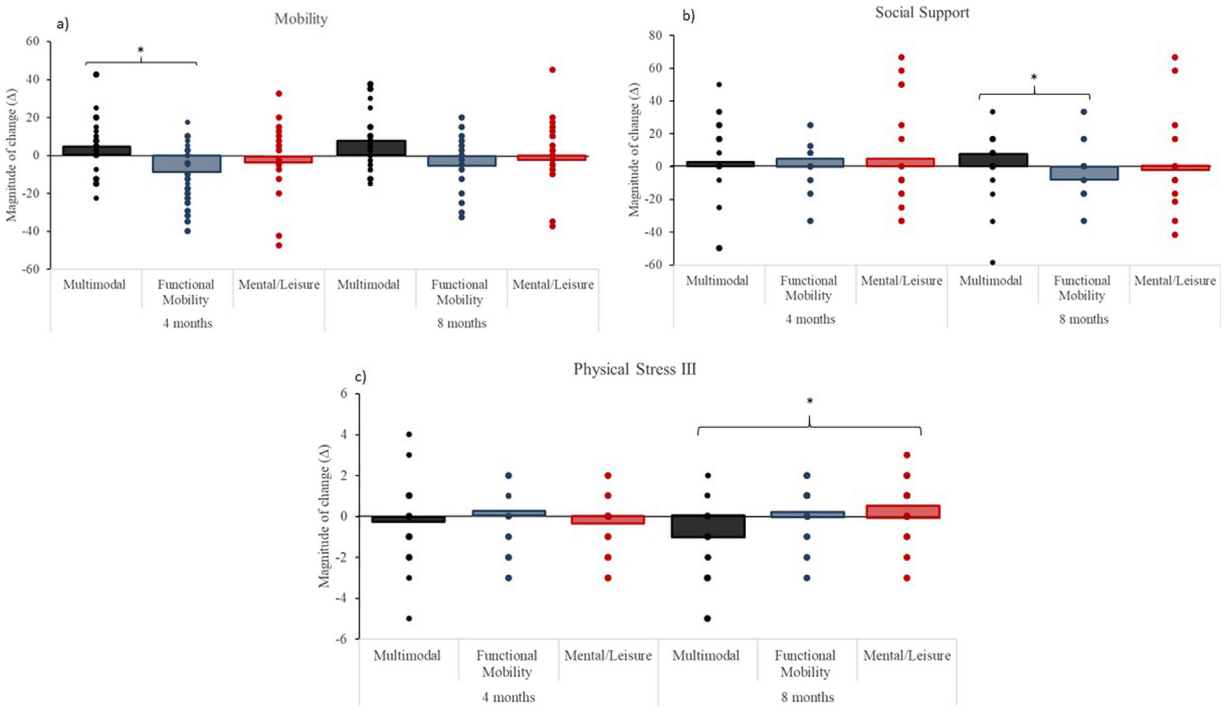

Fig. 2. Mean (bars) and individual distribution (circles) of the magnitude of change (Δ) for (a) mobility, (b) social support and (c) physical stress considering 4 (Post I–Pre) and 8 (Post II–Pre) months for Multimodal (black), Functional Mobility (blue) and Mental/Leisure (red) groups.

cognitive features [9]. These findings support the importance of continuous exercises, considering the mid- and long-term positive/maintenance effects on non-motor symptoms in PD [17]. We discuss the results comparing neuro-mechanisms involved in each type of training in people with PD and neurological healthy individuals.

Our findings revealed that the locomotor and cognitive exercises reduced, to some extent, the PD-related decline in cognitive function. Neurophysiological effects of exercise would explain our findings in part, because motor interventions (i.e., aerobic and strength exercises) involves:

- an increase in levels of brain-derived neurotrophic factor and insulin-like growth factor [12,13];
- enhanced cerebral blood flow (up to 18%) [46];
- increased neurotransmitter release [14];
- increased dopamine receptor expression and, consequently, neuroplasticity [12].

Such neurophysiological benefits caused by exercise may extend to motor and non-motor improvements in PD [7,17,22]. Systematic reviews confirmed the extension of the physical exercise effects on global cognition, attention, executive function, depressive symptoms, and anxiety traits in healthy older adults and people with PD [7,17,22]. Such aspects might explain the maintenance effect of the Functional Mobility intervention on these cognitive features in people with PD.

Recent findings showed that mobility and cognitive impairments are regulated by shared brain resources [5]. Indeed, neural control of mobility involves activation and connectivity of brain areas, such as the pre-frontal cortex and subcortical structures [5], which are closely related to cognitive function [14]. This argument of shared brain resources in both mobility and cognitive function presumably supports that activities targeting improvements in gait lead to improvements in cognitive function. The opposite is likely to occur, whereby possible benefits of cognitive function generate improvements in gait [5]. Functional mobility exercises involving activities with several stimuli from the environment are also related to benefits extending to cognitive function [47]. Furthermore, the greater complexity of locomotor exercise would represent more stimuli in the pre-frontal cortex. This observation could explain possible mechanisms that involve the neurophysiologic benefit after exercise practice, such as:

- an increase in the level and sensitivity of neurotransmitter and receptors;
- an increase in neuronal firing;
- an association between exercise benefits and neuroplasticity, decreasing the rate of neurodegeneration, characteristic of PD [14,26].

The effect of exercise types on cognitive features fluctuated between individuals and tasks. Such fluctuations were high for all exercise types but were more visible in the Multimodal training (Figs. 2 and 3). High fluctuations (variability) in the Multimodal group could be another reason for the lack, or even decline, of effects on cognitive outcomes. Particularities of participants, such as PD subtype, disease severity, and fitness level, might explain the high variability, also observed in other studies [19,20]. It could raise the need for individualization and/or longer-term approaches to PD, which is indeed relevant. However, activities in groups may increase adherence and adhesion and enhance the benefits of group exercises. Therefore, combining regular long-term individual and group exercises may be important to observe consistent and effective results on the non-motor symptoms in PD. Additional reasons for such elevated high variability on the outcomes may be attributed to the reallocation of individuals with a short period of detraining. Some reallocated participants might have carried over some effects of previous interventions, resulting in cross-over effects and more variation among participants across the years,

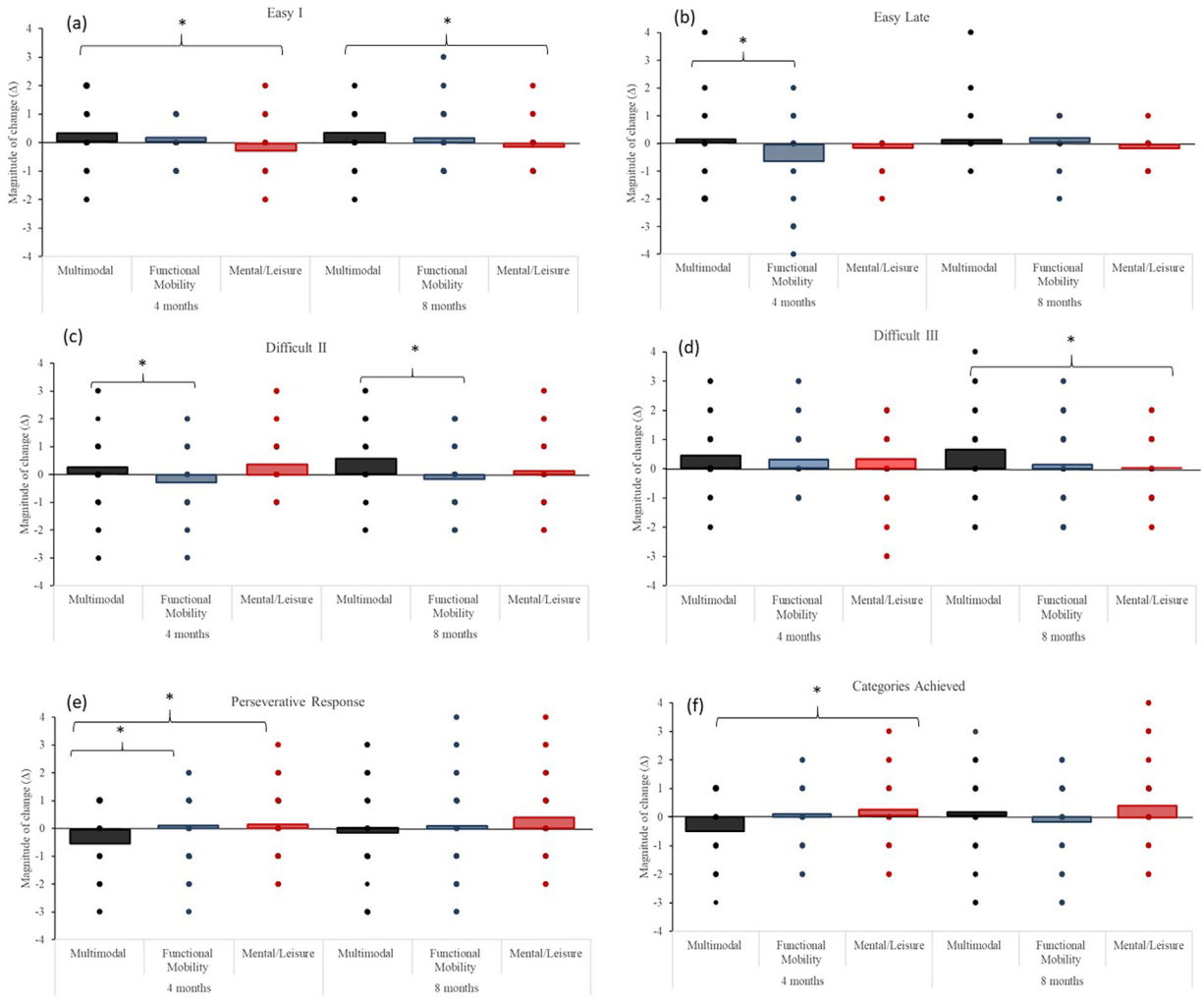

Fig. 3. Mean (bars) and individual distribution (circles) of the magnitude of change (Δ) for (a to d) verbal paired associates (Easy I, Easy late, Difficult II and Difficult III, respectively), (e) perseverative response, and (f) categories achieved considering 4 (Post I–Pre) and 8 (Post II–Pre) months for Multimodal (black), Functional Mobility (blue) and Mental/Leisure (red) groups.

although a period of 3 months with no practice of physical activity can lead to a decline in balance and quality of life [48], which would have accounted for a detraining in the individuals in the current study. Furthermore, the cognitive condition at baseline across the years was similar in each group, which minimizes possible issues related to the reallocation of participants.

The multimodal activities were performed with a focus on the interaction between tasks and individuals with less involvement of the environmental constraint, which could indicate differences between locomotion and multimodal exercises. Also, the locomotion exercise involved more complex tasks that required attention as well as predictive and reactive control mechanisms. Complex walking tasks and/or less automatic movements require high prefrontal cortical involvement, normally tested in dual-task paradigms [5], which might also explain the differences between modalities. This argument is supported by our findings indicating better performance in executive functions for the locomotion exercise. Lack of a Multimodal training effect in maintaining/improving executive function features (i.e., WCST) might be due to combinations of aerobic characteristics not reaching the target zone with lower-complexity activities. It may explain in part the difference between our findings and those of Tanaka et al. [19], indicating improvements of executive function (i.e., ∼60% of improvement in mental flexibility) after 8 months of exercise. Nonetheless, the lower-complexity activities could allow participants of the multimodal group greater social interaction, which may explain the benefits in physical stress after 8 months in multimodal exercise versus no differences for the other intervention programs. This reasoning can also be extended to the subtle benefits of this modality on VPA, because social interaction combined with aerobic exercise indicated improvements in working memory [10].

Our results suggest that task specificity is an intervening factor in the progression of cognitive dysfunction. Similar to what was observed with functional mobility exercises, cognitive training was able to maintain cognitive function in people with PD. The benefits on executive function were observed after cognitive training [8,23]. For instance, 10 sessions of cognitive exercises improved executive function in people with PD (∼ 4 times greater), which suggests that cognitive training promotes neuroplasticity related to mental flexibility [11]. Thus, cognitive training represents a crucial aspect to improve, or to maintain, the cognitive function in people with PD. A remarkable aspect is that the participants of this study presented relatively good performance on cognitive tasks, which reinforces the importance of maintaining cognitive features achieved by the locomotion and cognitive training, even considering the slow progression of cognitive decline [49]. Furthermore, the maintenance of cognition became more relevant because of its

association with functional activity [19], postural, gait control [5], and QoL in people with PD [1,4] and also is associated with maintenance of the progression of PD [2]. Physical exercise positively improved the LPA, but the intervention could not prevent the slight progression of motor symptoms (i.e., subtle increase in UPDRS part III score and increase in LED). This lack of protective effect on disease progression also supports the potential pronounced effects of the intervention on cognitive features.

4.1. Study limitation and conclusion

Our study has some limitations. We partially randomly distributed the participants in terms of disease stage to avoid the influence of the severity of PD during the development of the exercises and on results. Because of the number of participants (> 100) and the number of sessions (> 550), all evaluators and members of LEPLO supported the sessions to guarantee the safety of the participants and the quality of the interventions, so blinded evaluation of participants was not possible, although all evaluators were trained to assess with consistent criteria and in accordance with ethical standards. We did not include a group that did not receive any kind of intervention so that we would not deprive the participants of the benefits of doing exercises. We tried to diminish the lack of a control group by assessing participants at baseline without regular exercise practices in the last 4 months. However, the same participants assessed with the same tools across the 3 years could lead to test–retest familiarization effect and a cross-over effect. Although Lipp's stress symptoms inventory is often used to screen stress symptoms, this tool is not validated in PD. We chose this tool instead of a specific one for PD (e.g., Parkinson Anxiety Scale) because PROPARKI also involves the comparison of PD and healthy subjects, which was not the focus of this study.

Despite the limitations, we emphasize the social and clinical relevance of non-pharmacological therapy, which has been extensively proposed, in this study. These sorts of interventions are promising in terms of reducing cognitive decline in PD. A recent multidisciplinary symposium report stated the importance and need for cognitive and physical exercises as a potential therapy to maintain cognitive health [50]. In agreement, we strictly recommend novel studies with physical, cognitive and combined exercises as additional therapy to PD, considering that these interventions can attenuate the expected rate of cognitive decline in PD [11]. We recommend long-term exercise studies targeting non-motor symptoms in PD. Such studies would probe whether and which exercise interventions are beneficial for non-motor symptoms to PD.

We conclude that the effect of interventions on non-motor symptoms was training-specific. Interventions that required specific aspects of cognitive function maintained cognitive functions, but aerobic exercise was important to maintain the psychological aspect. Overall, exercise can delay the decline of cognitive function in PD.

Data availability

The data used in this study are available from the corresponding author on reasonable request.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2020.05.011.

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