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Effects of multimodal balance training supported by rhythmical auditory stimuli in people with advanced stages of Parkinson's disease: a pilot randomized clinical trial

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ABSTRACT

Non-pharmacological interventions such as physiotherapy are recognized as important elements in the overall clinical management of motor impairments in PD, but evidence of physiotherapy in advanced disease stages is sparse. A recent trial found positive effects of multimodal balance training in people with mild to moderate PD, with greater and more sustained effects when rhythmical auditory stimuli were added. It is unclear whether such multimodal balance training is also effective in people with advanced PD (Hoehn & Yahr stage 4).

Methods: We performed a pilot prospective single-blind, randomized clinical trial to study the effectiveness of multimodal training with and without rhythmical auditory stimuli. We screened 76 people with Parkinson's disease and Hoehn & Yahr stage 4 by telephone; 35 patients were assigned randomly into two groups: (1) multimodal balance training with rhythmical auditory stimuli (RAS-supported intervention, $n = 17$) and (2) multimodal balance training without rhythmical auditory cues ($n = 18$). Training was performed for 5 weeks, two times/week. Primary outcome was the Mini-BESTest (MBEST) score immediately after the training period. Assessments were performed by the same two blinded assessors at baseline, immediately post intervention, and after one and 6-months follow-up.

Results: Immediately post-intervention, both intervention groups improved significantly on Mini-Best scores, without differences between both intervention modalities. In both groups, results were retained at one-month follow-up. At 6-months follow-up, the effects were retained only in the RAS-supported intervention group. For both intervention groups, no improvements were found on secondary outcome measures for gait.

Conclusion: Both RAS-supported multimodal balance training and regular multimodal balance training improve balance in PD patients in advanced disease stages. Effects appear to sustain longer in the RAS-supported training group.

1. Introduction

People in late stages of Parkinson's disease (PD) have severe balance and gait impairments which dramatically impact on their quality of life [1–3]. Gait and balance impairments frequently result in falls and fall-related injuries [4]. Unfortunately, dopaminergic medication has only limited effect on these balance and gait impairments [5,6]. Complementary non-pharmacological interventions, such as physiotherapy, are therefore essential [7]. There is growing evidence to support the role of such non-pharmacological interventions (in particular physiotherapy) in mild and moderate stages of PD [8,9]. Compensation strategies such as rhythmic auditory cueing have an immediate and short effect on walking speed, stride length and cadence [10–16]. However, the evidence of non-pharmacological interventions

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for PD in late stages is sparse [11,17–21] and there is a lack of methodological strength.

A recent prospective randomized clinical trial evaluated the efficacy of adding rhythmical auditory stimuli to standard physiotherapy (RAS-supported multimodal balance training) by comparing RAS-supported multimodal balance training to multimodal balance training without auditory stimuli and a control group receiving an educational program [22]. Both RAS-supported multimodal training and regular multimodal balance training (without auditory stimuli) improved balance and gait performance after 5 weeks of training, compared to controls. However, the effects were larger for the RAS-supported training group than regular training group. Moreover, only the RAS-supported training group retained the effects at long-term follow-up (6 months). As this trial only included people with mild to moderate PD, the effect of RAS-supported multimodal balance training in patients with more advanced disease stages remains unknown. Here, we therefore investigated the effects of RAS-supported multimodal balance training compared to multimodal balance training without auditory stimuli in people with Hoehn & Yahr stage 4 PD.

2. Methods

2.1. Study design and participant

We performed a pilot prospective single-blind, randomized clinical trial between May 2017 and October 2019 at the Movement Disorders Center of the University of São Paulo Faculty Medicine Clinics Hospital. The current study was approved by the local ethical committee (3.986.215), and participants signed an informed consent form before participation. Patients were recruited via the outpatient clinic (either via the treating neurologist, physiotherapist and via a noticeboard in the waiting room) and via posts on social media (Facebook and Instagram). Inclusion criteria were: (1) diagnosis of PD according to the UK Brain Bank criteria [23]; (2) Hoehn and Yahr (H&Y) stage 4 [1]; (3) history of falls (at least once in the previous 12 months); (4) Mini Mental Status Examination (MMSE) ≥ 15 [24]; (5) able to walk indoors (either independently, or with supervision, or walking aid); (6) no hearing or visual problems interfering with the tests or training. Exclusion criteria were: (1) unstable medication over the past 3 months; and (2) unstable deep brain stimulator settings during the past year. After the inclusion, no other physiotherapy interventions or complementary exercises were allowed during the study.

2.2. Study procedure

After screening for eligibility, subjects were assigned randomly (1:1) into one of the two arms of the intervention (RAS-supported multimodal balance training (experimental group), regular multimodal balance training (control intervention group)). A computerized block randomization procedure (block size 4) was performed by an independent study collaborator before the baseline assessment. Group allocation was performed by the same study collaborator, who was not involved in either of the interventions and assessments. This collaborator delivered a sealed envelope to the physiotherapist to ensure concealment.

All measurements were performed by the same two blinded assessors (physiotherapists) at four time points: baseline, i.e. 14 days prior to training; one day after the last 5th week training; at one-month follow-up; and 6-months follow-up. Both assessors and patients were instructed not to talk about the allocation. We did not formally test for the success of blinding. All participants were tested while they were on their usual Parkinson medication (ON-medication state), which was defined as maximally 1 h after ingestion of their regular dose of dopaminergic medication (as self-reported by the patients) and when patients experienced a subjectively good ON state.

2.3. Intervention

Interventions were delivered at the University of São Paulo Clinics Hospital, Movement Disorders Center, Department of Neurology. The two interventions occurred on the same day and at the same location, but during different timeslots during the afternoon. Both experimental groups received balance training; one intervention group received all exercises combined with rhythmical auditory stimuli, provided by a metronome (RAS-supported multimodal balance intervention, see Supplementary Video S1), whereas the other intervention group received balance training without rhythmical auditory stimuli (regular multimodal balance training (control intervention)). Both intervention groups also received gait training with visual cues (as this is part of routine physiotherapy care based on the European guideline for physiotherapy in PD [25,26]), but rhythmical auditory stimuli to augment the balance exercises were only added in the RAS-supported group on top of the training. The physiotherapist gave instructions to the patients to perform the movements by following the beat of the metronome. The training program was performed in groups of four participants, supervised by two physiotherapists to ensure safety. Training in both intervention groups involved 20 balance and gait exercises, provided during 10 sessions of 45 min (2 sessions/week over a 5-week period). The exercises, training progression and intensity are described in Supplementary Table 1 and 2. The rhythmical auditory stimuli were delivered in an open-loop by a metronome and in a personalized manner when the patient was not able to perform the movement safely or with good quality. We used a MA-1 KOR metronome, with amplifier model JBL GO Portable Wireless Speaker. Progression over time was facilitated by dividing the training period into two 5-week sessions. Each exercise component was introduced separately to the participants in week 1, with emphasis on the quality of performance rather than on difficulty level. In week 2, the level of difficulty for each exercise component was increased, whereas movement complexity was further increased in week 3, 4 and 5 by combining the exercise components and increasing the demands. To further promote training progression, the aim was to increase or decrease the speed throughout the parts of the training.

2.4. Outcome measures

The primary outcome was Mini-BESTest (MBEST) [27]. Secondary outcomes included measures of balance and gait: Berg Balance Scale (BBS) [42], Timed Up and Go Test (TUG) [45], TUG-dual task condition (14 domain in MBEST) [41] and Rapid Turns Test [37] and New Freezing of Gait Questionnaire (N-FOGQ) [36]. Activities of daily living and motor performance were assessed using the MDS-UPDRS part 2 and part 3 [28]. Fear of falling was evaluated using the Falls Efficacy Scale-International (FES−I) [46]. To optimally reflect common daily practice, treating physicians were allowed to make medication adjustments during the course of the physiotherapy intervention if this was deemed clinically necessary. To control for the possible effect of this, the levodopa equivalent daily dose (LEDD) was reported by interview (patients and caregivers) and was checked using patient's medical reports. Falls and serious adverse events were assessed and monitored through standardized weekly interviews.

2.5. Statistical analysis

Statistical analysis was performed according the intention-to-treat (ITT) principle which was defined as all patients who were allocated to the intervention, had a full baseline assessment, and from whom at least one measurement after baseline was obtained. Linear mixed models were used for all outcomes. The primary endpoint was the MBEST score immediately post-intervention. We used treatment (RAS-supported multimodal balance training vs. regular multimodal balance training), visit (immediately post-intervention, one-month follow-up, and

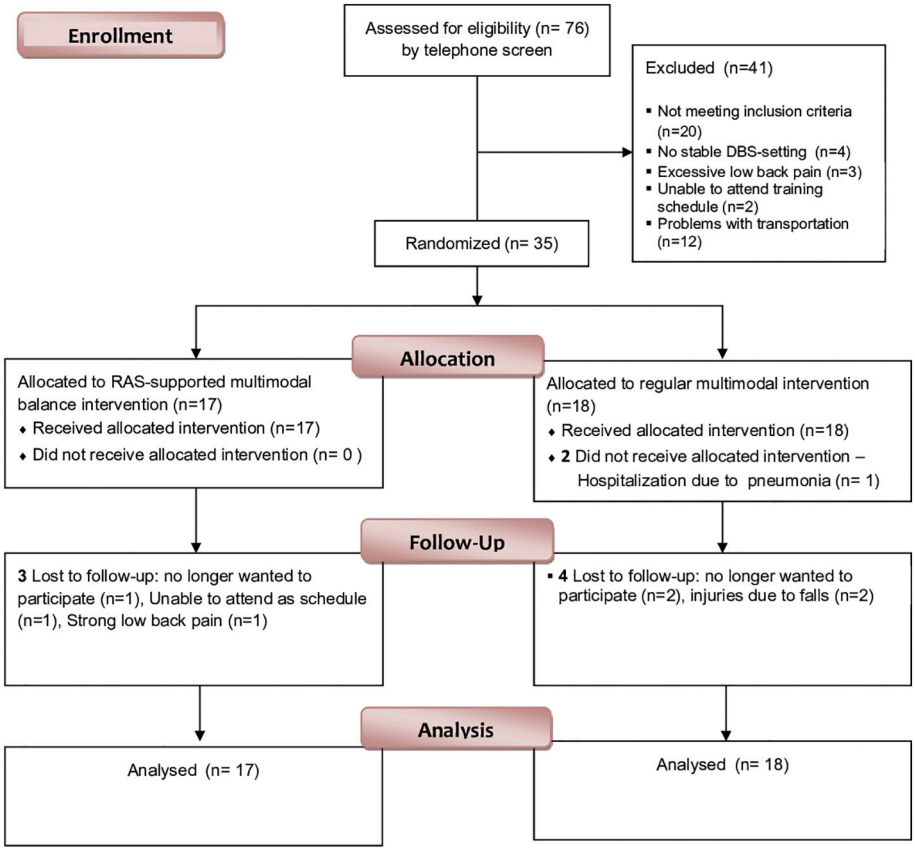

Fig. 1. Flow diagram of participants through the trial,number of participants.

6 months follow-up) and the interaction between visit and treatment group as fixed factors. The model was adjusted for baseline MBEST, MDS-UPDRS part 2 and 3 and levodopa equivalent daily dose (LEDD), and for the baseline value of the dependent variable. Patient was included as a random factor. A Bonferroni adjustment for multiple testing (three pairwise comparisons at 5 weeks follow-up) was applied, resulting in a significance threshold of 0.017 that was used for all tests. No interim analyses were performed.

3. Results

We screened 76 potential candidates, and 35 were randomized (of which 23 were recruited from outside the outpatient clinic) (Fig. 1). Reasons for others subjects not being included were not meeting inclusion criteria, no stable DBS-setting, excessive low back pain, unable to attend training schedule and problems with transportation. Both intervention groups were similar on baseline characteristics (Table 1). A total of 7 patients dropped out of the study (Fig. 1). Reasons for not being compliant (20%) were lack of time, problems with transport, injuries not related to the intervention, or illness and fatigue not related to the intervention. No adverse events related to the intervention occurred during the study period.

3.1. Primary outcome

Fig. 2 shows the results on our primary outcome, the MBEST. Immediately post-intervention, both intervention groups improved significantly on Mini-Best scores, without significant differences between both groups. In both groups, results were retained at one-month follow-up. At 6-months follow-up, however, the effects were retained only in the RAS-supported intervention group (Table 2).

Table 1
A. Participants' characteristics at the baseline visit, Hoehn & Yahr stage 4.

	Multimodal $N = 17$	Standard $N = 18$
Age, years (mean (SD))	77 (7)	78 (10)
Gender, men (N (%))	9 (53%)	12 (66%)
Disease duration (mean (SD))	17 (9)	11 (4)
LEDD, mg/day (mean (SD))	749 (381)	869 (327)
MMSE, score (mean (SD))	21 (3)	18 (6)
MoCA, score (mean (SD))	19 (5)	18 (5)
MDS-UPDRS 2, ADL score (mean (SD)) (ON)	22 (6)	20 (7)
MDS-UPDRS 3, motor score (mean (SD)) (ON)	38 (8)	35 (9)

Group: Multimodal Training Group (MT), Standard training Group (ST), N, number of participants; SD, *Standard Deviation*; ON (ON-medication); LEDD, levodopa equivalent daily dose; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MDS-UPDRS 2, ADL, Activities of daily living score; MDS-UPDRS 3, motor score.

3.2. Secondary outcomes

3.2.1. Balance

Only the RAS-supported intervention group improved immediately post-intervention on the Berg Balance Scale. Improvements were retained at one-month and 6-month follow-up (Table 2). In both intervention groups, no improvements were found on FES-I. Fewer falls and severe injuries (outside the intervention) were reported after the intervention by all groups.

3.2.2. Gait

No significant improvements or differences were found on TUG in both intervention groups at all time points. Also, no improvements or differences were observed in the TUG Dual Task and N-FOGQ (Table 2).

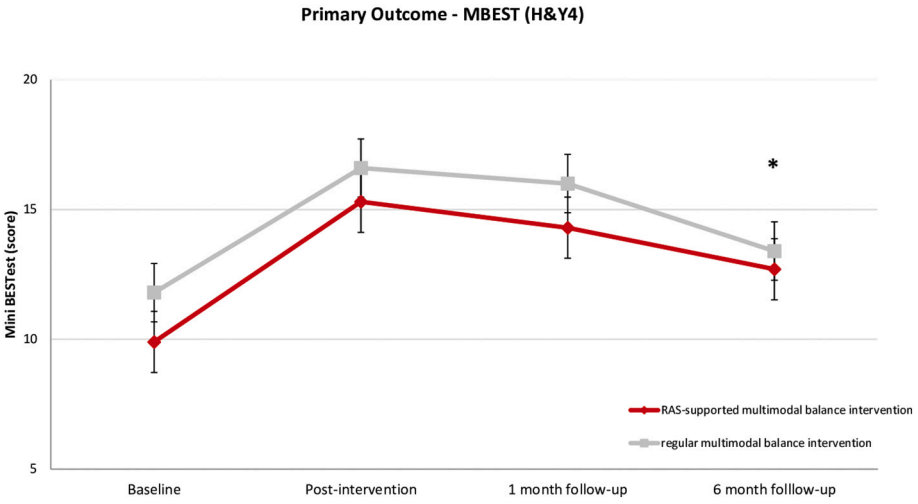

Fig. 2. Mni-BESTest (MBEST) at each test visit.

Table 2
Observed mean values and estimated differences and 95% confidence intervals for primary and secondary outcome measures.

		Total Group	Total Group	Total Group
		RAS-supported 1	Regular 2	RAS-supported vs Regular 1–2
Mini BESTest	Baseline	9.6 (7.7; 11.5)	12.8 (9.9; 15.7)	
	Post Intervention	15.2 (13.4; 17.1)	16.6 (12.8; 16.2)	1.4 (−0.1; 3.0), $P = 0.070$
	1-month Follow-up	14.2 (14.3; 16.5)	16.0 (13.0; 15.4)	1.2 (−0.4; 2.8), $P = 0.133$
	6-months Follow-up	12.4 (12.7; 14.8)	13.5 (10.2; 12.5)	2.3 (0.7; 3.9), $P = 0.005$
Berg Balance Scale	Baseline	29.0 (24.6; 33.0)	37.5 (32.8; 42.3)	
	Post Intervention	37.7 (33.2; 42.2)	39.0 (33.9; 44.0)	3.9 (0.0; 7.9), $P = 0.049$
	1-month Follow-up	36.8 (31.9; 41.7)	37.4 (32.1; 42.8)	3.9 (0.0; 7.9), $P = 0.051$
	6-months Follow-up	33.1 (28.3; 37.9)	35.3 (29.9; 40.6)	2.6 (−1.3; 6.6), $P = 0.183$
Falls Efficacy Scale - International	Baseline	37.1 (28.0; 46.2)	48.3 (39.0; 57.5)	
	Post Intervention	35.8 (25.5; 46.1)	42.5 (35.7; 49.8)	0.8 (8.1; 9.8), $P = 0.853$
	1-month Follow-up	36.4 (26.1; 46.7)	42.8 (35.7; 49.9)	1 (−7.9; 10.4), $P = 0.812$
	6-months Follow-up	39.6 (29.8; 49.4)	48.0 (40.6; 55.3)	−4.2 (−13.0; 4.7), $P = 0.336$
Timed Up and Go	Baseline	29.8 (22.1; 37.4)	26.2 (17.9; 34.6)	
	Post Intervention	23.6 (16.5; 29.4)	26.8 (14.7; 37.7)	−3.8 (−8.2; 0.5), $P = 0.065$
	1-month Follow-up	25.8 (17.8; 33.8)	26.7 (15.2; 38.2)	−2.1 (−6.4; 2.2), $P = 0.324$
	6-months Follow-up	27.5 (19.5; 35.5)	29.6 (19.0; 40.1)	−3.3 (−7.5; 0.9), $P = 0.124$
Timed up and Go Dual Task	Baseline	43.2 (29.0; 57.3)	34.5 (20.5; 48.6)	
	Post Intervention	35.2 (23.1; 47.4)	36.4 (17.5; 55.2)	−2.6 (−11.9 6.6), $P = 0.567$
	1-month Follow-up	40.3 (23.2; 57.3)	37.0 (18.3; 55.7)	0.3 (−9.0; 9.7), $P = 0.942$
	6-months Follow-up	45.7 (26.5; 64.8)	42.2 (22.0; 62.4)	−0.3 (−9.4; 9.3), P = 0. 994
New Freezing of Gait Questionnaire	Baseline	14.3 (6.7; 21.8)	8.9 (3.9; 13.9)	
	Post Intervention	11.2 (4.7; 17.6)	8.3 (3.3; 13.22)	−0.8 (−3.3; 1.7), $P = 0.518$
	1-month Follow-up	11.8 (4.7; 18.9)	8.7 (3.4; 14.0)	0.4 (−2.0; 3.0), $P = 0.697$
	6-months Follow-up	13.7 (5.8; 21.6)	10.0 (4.6 15.3)	0.8 (−1.6; 3.4), $P = 0.476$
LEDD	Baseline	794 (668; 919)	869 (693; 1046)	
	Post Intervention	803 (668; 938)	941(686; 1197)	−49.9 (−119.5; 19.6), $P = 0.156$
	1-month Follow-up	803 (668; 938)	918 (720; 1117)	−33.1 (−102; 36.4), $P = 0.343$
	6-months Follow-up	830 (688; 972)	931 (704; 1158)	−29.9 (−99.1; 40.0), $P = 0.398$
MDS-UPDRS 2	Baseline	22.4 (19.43; 25.5)	20.1 (16.3; 24.0)	
	Post Intervention	21.4 (18.8; 24.7)	20.8 (16.7; 24.8)	−1.5 (−2.6; −3.7), $P = 0.010$
	1-months Follow-up	22.6 (18.8; 26.3)	21.6 (17.5; 25.7)	−1.1 (−2.3; −0.4), $P = 0.042$
	6-months Follow-up	23.7 (19.8; 27.5)	22.1 (18.0; 26.2)	−0.5 (−1.6; 0.6), P = 0.398
MDS-UPDRS 3	Baseline	38.6 (34.4; 42.7)	35.8 (29.8; 39.9)	
	Post Intervention	33.9 (29.8; 38.6)	34.9 (30.4; 39.3)	−1.4 (−2.4; −0.3), $P = 0.011$
	1-month Follow-up	34.3 (29.4; 39.2)	35.7 (31.0; 40.4)	−1.3 (−2.4; −0.2), $P = 0.018$
	6-months Follow-up	36.0 (31.4; 40.5)	36.7 (32.2; 41.3)	−0.7 (−0.3; 1.8), $P = 0.157$

Group: Multimodal balance training supported by rhythmical auditory stimuli (RAS-supported), Multimodal balance training without rhythmical auditory stimuli (Regular). Confidence Intervals (CI) –Adjusted Mean Difference (95% CI) Between Baseline and 35-week. Primary analysis: Adjusted for baseline MBEST score; Secondary analyses: also adjusted for baseline LEDD, baseline MDS-UPDRS 2 and 3. Mini BESTest – 14 items, total 28 of points, scored 0–2 (higher score better balance). Berg Balance Scale - 14 items total 56 of points, scored 0–4 points (higher score better balance). Falls Efficacy Scale International – 16 items, total 64 of points scored 1-), higher scores greater fear of fallen. TUG and TUGDT were measured in time in seconds (time in seconds is the unit) with a range from 5 to 60 s (which is the range). A lower score means better mobility. N-FOGQ - 10 items, total 29 of points, scored 0–3 or 4. A lower score, less freezing problems.

3.2.3. Levodopa equivalent daily dose (LEDD)

The LEDD was not significantly different between RAS-supported and regular intervention groups for either of the follow-up moments post-intervention (Table 2).

3.2.4. MDS-UPDRS

For both intervention groups, no improvements were observed when looking at MDS-UPDRS part 2 scores (Table 2). Only the RAS-supported intervention group improved on the MDS-UPDRS part 3 immediately post-intervention, which was maintained at one month follow-up, but not at 6-months follow-up (Table 2).

4. Discussion

Here, we investigated the effects of RAS-supported multimodal balance training compared to multimodal balance training without auditory stimuli in people with PD and in H&Y stage 4. Our study shows for the first time that specialized physiotherapy with a specific protocol of exercises with RAS can improve balance performance in PD patients in advanced disease stages and mild cognitive decline. Only a few rehabilitation studies have included a subgroup of H&Y4 patients [20,29–31], but no studies have focused specifically on balance training with RAS on advanced disease stages (H&Y4).

Our study highlights that multimodal balance training (both with and without rhythmical auditory stimuli) is feasible in patients with advanced disease stages, as it did not result in falls and serious adverse events. The minimally clinically relevant difference for the MBEST test in PD is 3.4 points [32], and the minimal detectable change is 3 to 3.5 [32–34], which means that the average improvement (both immediately post-intervention and at one-month follow-up) exceeded these values in both intervention groups. Our secondary analyses suggest that retention at six-month follow-up is larger in the RAS-supported multimodal balance training group compared to the multimodal balance training without auditory stimuli, but these findings should be replicated in future trials.

Using rhythmic auditory cues may improve training effects by making it more explicit than training without auditory cues (regular training or conventional therapy) [13,22,35]. By doing so, PD patients may shift their habitual motor control (predominantly relying on the posterior putamen) to more goal-directed motor control (involving the anterior putamen), thereby improving motor learning [36]. Additionally, cueing may improve attention and task prioritization (better executive control) [37–39], thereby helping to prioritize balance control over other tasks. External cues may also serve as an external reward, thereby further facilitating the learning processes [40].

In compare to our previous study with patients in early and moderate disease stages [22], no significant improvements on secondary gait-related outcomes was found. The lack of effects on gait speed outcomes in both groups may indicate that patients in advanced disease stages experience difficulties to transfer balance improvements to gait tasks. Moreover, gait not only depends on balance control [41,42], but also on several other factors such as motor control and executive function [41–44], which are frequently impaired in advanced disease stages [3]. Alternatively, our study may have been underpowered to detect differences (this was a pilot exploratory study), as a trend towards improvement was observed in the RAS-supported intervention group.

Our study is not without limitations. First, our study lacks a control group receiving no intervention. Second, as indicated above, our sample size was relatively small, and our study may have been underpowered to detect differences on secondary outcomes. Studies with large samples are therefore needed, using the present outcomes as input for the power analysis. Larger future studies may also perform a correlation or regression analysis to evaluate which patient characteristics influence the results. Finally, we did not investigate the RAS-supported multimodal balance training effect on quality of life, which could be an important determinant of the efficacy of physiotherapy. This aspect deserves further investigation in future studies.

Taken together, our findings further support the importance of non-pharmacological intervention in the management of axial problems as gait and balance in PD patients in advanced stages (H&Y4). Current physiotherapy guidelines [26,45] provide no recommendations on specific approach for the H&Y4 subgroup. The present results, indicating that multimodal balance intervention (combined with rhythmical auditory cues) is effective, can help to fill this gap and contribute to an increasing evidence base for physiotherapy, eventually leading to optimized care for PD patients in advanced stages. The field of physiotherapy and rehabilitation generally needs more studies to determine the long-term effects, and to identify how any initially achieved clinical improvements can be maintained in the long term. Concerns about a possible tapering of improvements over time may apply in particular to the more vulnerable group of patients with advanced disease. The RAS-supported intervention that we tested here is no exception. Future studies should therefore also evaluate how often a RAS-therapy should be repeated in patients with advanced disease stages (e.g. continuous training sessions twice a week, or '10 boost-sessions' every 6 months).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.117086.

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