Parkinsonism and Related Disorders 64 (2019) 280–285

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Improvements in temporal and postural aspects of gait vary following single- and multi-modal training in individuals with Parkinson's disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Dual task
Single task
Gait
Cognition

ABSTRACT

Introduction: Gait deteriorates under dual task conditions in individuals with Parkinson's disease (PD). Therapeutic interventions have the potential to improve dual task performance, although it remains unclear how training affects gait performance under varying cognitive domains. The primary aim of this trial was to determine the effect of an 8-week single- or multi-modal gait and cognitive training intervention on dual task performance across cognitive domains in individuals with PD.

Methods: Twenty individuals with PD completed a 24-session single-modal training (SMT, n = 10) or multi-modal training (MMT, n = 10). The SMT group performed gait and cognitive training sequentially; the MMT group performed gait and cognitive training simultaneously. Gait was analyzed using motion capture analysis during simultaneous performance of six untrained cognitive tasks.

Results: Both SMT and MMT resulted in significant improvements in MDS-UPDRS III scores and gait performance. Improvements in arm swing were more prevalent in the less affected extremity, while improvements in the more affected upper extremity favored the MMT group. Temporal aspects of gait (velocity, step length) improved under all dual task conditions, while postural aspects of gait (step width, arm swing) varied by cognitive task.

Conclusions: Both SMT and MMT were effective in improving motor and dual task performance in PD. Improvements in upper extremity gait variables in the MMT group may indicate that the complexity of the training is be beneficial in PD. The different responses in temporal and postural aspects of gait highlights the need for clinicians to train multiple cognitive domains during behavioral therapy.

1. Introduction

Gait dysfunction is a hallmark of Parkinson's disease (PD), affecting approximately 87% of individuals within three years of diagnosis [1]. In PD, the neurodegeneration of the basal ganglia results in decreased motor automaticity (i.e. the ability to perform movements with minimal cognitive resources directed to the task), making it difficult for patients to achieve and sustain the consistent rhythmic movements necessary for normal gait [2]. Gait further deteriorates under dual task conditions, or the simultaneous performance of two attention-demanding tasks, as decreased automaticity is exacerbated when attentional resources are divided between two tasks [3]. Spatiotemporal gait deficits have been well-characterized in PD under dual task conditions and include decreased gait velocity, step length, and arm swing [4,5].

Behavioral interventions utilizing dual task training have demonstrated the potential to improve step length and gait velocity [6,7]. The DUALITY study reported that integrated and consecutive cognitive and gait training improved spatiotemporal gait variables and cognitive performance under single and dual task test conditions [8,9]. It is unknown if improvements in gait and cognition following training are ubiquitous across cognitive domains or if improvements vary depending on the cognitive domain that is paired with the motor task. Recent data indicate that the type and difficulty of the cognitive task may impact specific aspects of motor performance as arm swing was reduced and less smooth under more challenging dual task conditions [4].

The primary aim of this trial was to determine the effect of an 8-week single-modal training (SMT) or multi-modal training (MMT) intervention on dual task gait performance over a range of cognitive domains (i.e. attention, memory, language, and executive function) in

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https://doi.org/10.1016/j.parkreldis.2019.05.021
Received 1 February 2019; Received in revised form 30 April 2019; Accepted 12 May 2019

individuals with PD. Temporal and postural gait variables under various cognitive domains were collected prior to and following the 8-week training program. It was hypothesized that the MMT intervention would produce greater improvements in temporal measures of gait variables across multiple cognitive domains compared to SMT due to the simultaneous motor and cognitive training associated with MMT.

2. Method

2.1. Study design & participants

This study was approved by the Cleveland Clinic Institutional Review Board, and participants completed the informed consent process prior to participation. A sample of convenience was recruited from the Center for Neurological Restoration at the Cleveland Clinic. Inclusion criteria were: diagnosis of idiopathic PD, Hoehn & Yahr II-IV, two or more falls in the previous 12 months, and ability to ambulate 300 feet with or without an assistive device. Exclusion criteria were: deep brain stimulation, musculoskeletal injury that restricted ambulation, uncontrolled cardiovascular risk factors per the American College of Sports Medicine screening questionnaire [10], inability to follow 2 step commands, and three or more errors on the Short Portable Mental Status Questionnaire.

Assessments were completed at: baseline, end of treatment (EOT), and four weeks post-intervention (EOT + 4) (Fig. 1). The following were acquired at each assessment: 1) Movement Disorder Society-Unified Parkinson's disease Rating Scale motor subscale (MDS-UPDRS III) [11], 2) seated cognitive assessment, and 3) single and dual task biomechanical gait analysis. Participants were asked to take their anti-parkinsonian medication one hour prior to the assessment to ensure they were in the "on medication" state with the exception of one de novo individual. All assessments were completed by an experienced rater blinded to group assignment.

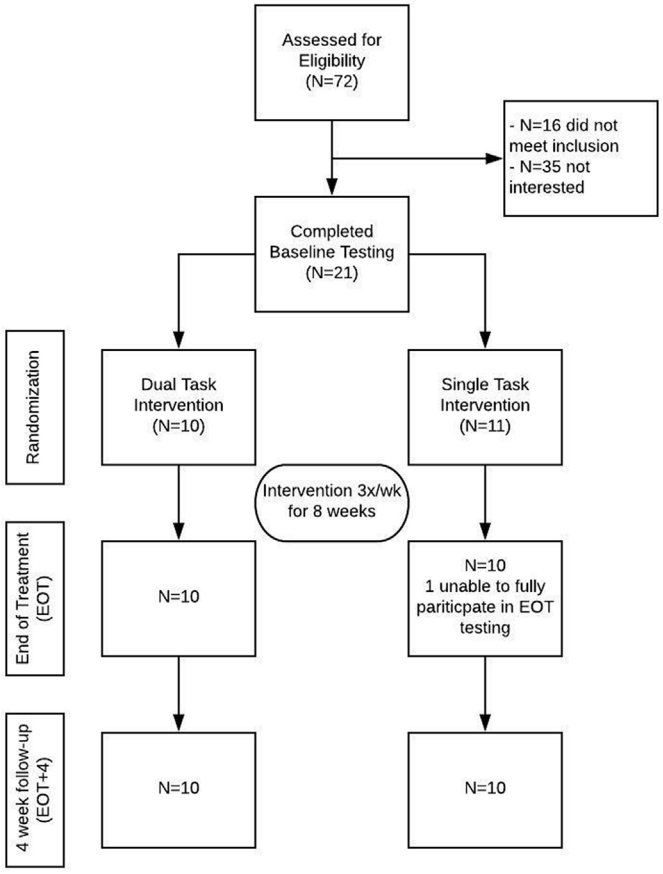

Fig. 1. Consort diagram.

2.2. Cognitive assessment

To assess baseline cognitive function over a range of cognitive domains, a series of cognitive tests were administered in a seated position in random order: N-back (working memory), Serial 7 subtraction (attention), Digit Recall (working memory), Controlled Oral Word Association (COWA, verbal fluency), and visual Stroop test (executive function).

During the N-back, specifically the 1-back and 2-back, a letter was displayed every 2 seconds for a 60 second trial. The participant was asked to recall the letter presented one or two letters previously. For Serial 7 subtraction, the participant was given a randomly generated number between 300 and 400 and asked to count backward by seven over a two minute trial. Digit Recall evaluated working memory by asking the participant to repeat an increasingly complex string of numbers until memory failure. The COWA test of verbal fluency required the participant to list words begin with the letter "L, C, or F" (randomized) over a 60 second trial [12]. The visual Stroop test is a test of inhibition and executive function where there is incongruity between a written word and the color of which it is printed. For example, the word BLUE written in an orange script. The subject was asked to state the color of the word [13]. The visual Stroop was presented on a projection screen with a new word presented every 1.5 seconds for 60 seconds.

2.3. Gait analysis

The Computer Assisted Rehabilitation Environment (CAREN, Motekforce Link, Amsterdam, Netherlands) system is a virtual reality system with a 3-D motion capture system, treadmill, a safety harness, and programmable software that can be used to create interactive modules on a projection screen. The treadmill was used in self-pace mode, and participants controlled the speed by anterior-posterior pelvis position relative to the center of the treadmill [14]. The Human Body Model [15] was used for analysis using 32 retro-reflective markers placed on anatomic landmarks; the 10-camera Vicon system in combination with D-Flow software captured the 3D position at 100 Hz. Marker data were filtered using a 2nd order low-pass Butterworth filter with a 6 Hz cut-off frequency.

Gait cycles were defined as heel strike to heel strike of the same foot by using the anterior-posterior heel marker position data [16]. Step length and step width were calculated for each gait cycle and the average for each trial was used for analysis. Cadence and velocity were averaged over the course of the trial. Arm swing path length was determined by subtracting the positional data from wrist markers from the pelvis center to calculate relative displacement [4].

For the testing protocol, participants were given a minimum of five minutes to acclimate to the self-paced treadmill and demonstrate understanding of how to control the speed. Following the warm-up, a trial of single task walking (two minutes) was performed. Participants then performed the same cognitive tasks listed above while ambulating on the self-paced treadmill. A final bout of single task walking was performed at the end to account for a learning effect. The greater distance of the two single task walking trials was included for analysis.

2.4. Randomization

Following baseline testing, participants were randomized via a non-replenished envelope pull into the SMT or MMT group. Both groups trained 3x/week for eight weeks (24 sessions).

3. Intervention

3.1. Single-modal training (SMT)

The SMT consisted of gait training followed by cognitive training, each performed separately. Treatment time duration totaled 45 minutes, evenly divided between gait training and cognitive training. Gait interventions were administered by a neurologically-trained physical therapist and individually tailored to meet the physical needs of each participant. To be consistent with the intervention across participants, the therapist used high velocity, high amplitude training principles with an external focus of attention [17]. Example of interventions included high-knee marching with coordinating upper extremity arm swing, large amplitude stepping to targets with coordinated arm movements, and walking with increased gait speed while emphasizing heel strike.

The cognitive training program targeted four cognitive domains: attention, memory, language, and executive function, as these are domains that individuals with mild to moderate PD often display cognitive decline [18]. The program was created in consultation with a speech therapist and neuropsychologist. All participants trained the tasks, with each task graded based on individual's cognitive function. For example, participants were asked to spell a word forward and backward. The therapist graded task difficulty (i.e. using the word 'cat' verses 'television') depending on the participant's level of education and cognitive abilities. The therapist increased the difficulty of the cognitive task when the individual was able to correctly respond approximately 80–85% of the time. Cognitive tasks included in the training program differed from those in the pre- and post-testing protocol.

Time spent in gait and cognitive training, number of cognitive domains covered, and number of steps measured using a wrist worn activity monitor (Movband 3, DHS Group, Houston, TX) were recorded during each session in REDCap® [19], a secure electronic database.

3.2. Multi-modal training (MMT)

Individuals in the MMT group received 45 minutes of simultaneous gait and cognitive training administered by the same neurologically-trained physical therapist. The gait and cognitive training were identical to the SMT group; however they were performed concomitantly. No instructions were provided for task prioritization. Data were recorded in an identical manner as the SMT group.

3.3. Statistical analysis

One subject was unable to fully participate in EOT testing and was excluded from the analysis. For the remaining 20 participants, baseline participant demographics and outcome variables were summarized by group using mean ± standard deviation for normally distributed variables, median [25th percentile, 75th percentile] for data that is not normally distributed, or N (%) (categorical data). One subject in the SMT group used a walker during ambulation, and thus held on to the arm rails of the CAREN system during testing. Her data was not included in the arm swing analysis. Each participant was asked to designate a more and less affected upper extremity, which was confirmed by laterality scores on the MDS-UPDRS III.

The intervention effects on outcomes were assessed using separate linear mixed effects models, each including a random intercept, main effects for group, time, and a group-by-time interaction term. Given a significant group-by-time interaction, post hoc pairwise comparisons were performed between groups to assess how groups change differently over time. In the absence of a group-by-time interaction, the overall change across collapsed groups between each evaluation was estimated (i.e., change from Baseline to EOT and Baseline to EOT + 4).

All comparisons were performed at the 0.05 significance level. Within each outcome, pairwise comparisons were Bonferroni corrected to maintain a 5% type I error rate per outcome. Analyses were conducted using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) and the "nlme" package [20].

Table 1
Participant demographics.

	SMT (N = 10)	MMT (N = 10)
Age (years)	65 ± 8	59 ± 9
Sex (male)	9 (90%)	5 (50%)
Disease duration (years)	4 [3,6]	8 [4,12]
Baseline MDS-UPDRS III Score (points)	38 ± 13	35 ± 10
H&Y Stage:		
2	8 (80%)	6 (60%)
3 (Moderate)	2 (20%)	4 (40%)
Number of falls in the previous 12 months	5 [2,10]	5 [2,10]
Levodopa Equivalent Daily Dose (LEDD), mg/100 mg L-dopa	550 [412.5, 756.5]	437.5 [405, 916.3]

4. Results

Participant demographics are summarized in Table 1. There were no significant between groups differences.

All subjects completed all of the 24 intervention sessions. The SMT group evenly divided their session between gait, 22.4 ± 3.1 minutes/session, and cognitive training, 22.1 (0.1) minutes/session; the MMT group spend the entire 45 minute session performing gait and cognitive training simultaneously. The SMT group took fewer steps/session compared to the MMT group with 1509.2 ± 346.8 and 2700.3 ± 576.8 steps/session, respectively, $p < 0.001$. The SMT group also completed a fewer number of cognitive domains/session than the MMT group with 3.0 ± 0.8 and 3.6 ± 0.9 cognitive domains/session, respectively, $p < 0.001$.

One participant experienced a fall without injury during training. He typically fell several times per week at home. No other study-related adverse events occurred over the course of the trial.

4.1. Arm swing path length– more affected upper extremity

Table 2 provides data for all spatiotemporal gait variables. There was a significant group-by-time interaction for Serial 7 ($p = 0.02$) and digit recall ($p = 0.03$) favoring the MMT group for the more affected arm swing path length. Path length significantly increased in the MMT group from baseline to EOT ($p = 0.002$ and 0.008, respectively) and baseline to EOT + 4 ($p = 0.007$ and 0.003, respectively), but not in the SMT group. For single task walking, more affected arm swing significantly increased in both groups from baseline to EOT ($p = 0.002$) and baseline to EOT + 4 ($p < 0.001$).

4.2. Arm swing path length – less affected upper extremity

There was no significant group-by-time interaction for less affected arm swing path length. During single task walking ($p = 0.001$), Serial 7 ($p = 0.048$), Stroop ($p = 0.02$), digit recall ($p = 0.01$), and 2-back ($p = 0.04$) the less affected arm swing increased from baseline to EOT in both interventional groups. Improvement persisted at EOT + 4 for the single task walking ($p < 0.001$), Serial 7 ($p = 0.02$), and digit recall ($p = 0.005$).

4.3. Lower extremity gait variables

There was no significant group-by-time interaction for any lower extremity gait variable. For gait velocity, there was a significant main effect of time from baseline to EOT ($p < 0.001$) and from baseline to EOT + 4 ($p < 0.001$) across all cognitive conditions with gait velocity significantly increasing after both SMT and MMT.

For step length, there was a significant main effect of time under all

Table 2
Summary of gait variables during single and dual task condition.

Outcome	Baseline		EOT		EOT + 4	
	SMT	MMT	SMT	MMT	SMT	MMT
Velocity, m/s						
Single Task Walking	1.20 ± 0.27	1.31 ± 0.33	**1.32 ± 0.37**‡	**1.49 ± 0.26**‡	**1.36 ± 0.39**‡	**1.49 ± 0.24**‡
Serial 7	0.91 ± 0.26	1.22 ± 0.28	**1.15 ± 0.41**‡	**1.38 ± 0.27**‡	**1.20 ± 0.36**‡	**1.37 ± 0.24**‡
Digit Recall	0.94 ± 0.25	1.27 ± 0.29	**1.17 ± 0.38**‡	**1.40 ± 0.29**‡	**1.22 ± 0.38**‡	**1.35 ± 0.27**‡
Controlled Oral Word Association	1.08 ± 0.29	1.28 ± 0.31	**1.25 ± 0.38**‡	**1.41 ± 0.29**‡	**1.24 ± 0.39**‡	**1.37 ± 0.28**‡
Stroop	1.10 ± 0.37	1.40 ± 0.33	**1.30 ± 0.42**‡	**1.53 ± 0.26**‡	**1.34 ± 0.40**‡	**1.48 ± 0.23**‡
1-Back	1.13 ± 0.30	1.37 ± 0.35	**1.28 ± 0.39**‡	**1.51 ± 0.26**‡	**1.30 ± 0.38**‡	**1.46 ± 0.24**‡
2-Back	1.15 ± 0.32	1.33 ± 0.32	**1.29 ± 0.44**‡	**1.51 ± 0.27**‡	**1.32 ± 0.39**‡	**1.42 ± 0.26**‡
Cadence, steps/min						
Single Task Walking	110 ± 16	113 ± 12	111 ± 21	118 ± 9	**113 ± 20**‡	**118 ± 9**‡
Serial 7	106 ± 23	110 ± 13	106 ± 25	114 ± 9	111 ± 19	114 ± 11
Digit Recall	105 ± 21	113 ± 13	106 ± 26	115 ± 10	110 ± 22	114 ± 12
Controlled Oral Word Association	108 ± 19	111 ± 12	110 ± 20	114 ± 10	110 ± 23	115 ± 13
Stroop	111 ± 21	116 ± 12	112 ± 23	120 ± 10	115 ± 21	120 ± 12
1-Back	112 ± 21	116 ± 13	111 ± 20	119 ± 10	113 ± 24	119 ± 11
2-Back	112 ± 21	114 ± 14	111 ± 23	119 ± 10	114 ± 23	118 ± 11
Step Length, m						
Single Task Walking	0.64 ± 0.11	0.69 ± 0.13	**0.69 ± 0.16**‡	**0.74 ± 0.10**‡	**0.70 ± 0.15**‡	**0.75 ± 0.09**‡
Serial 7	0.51 ± 0.11	0.66 ± 0.10	**0.62 ± 0.17**‡	**0.72 ± 0.11**‡	**0.63 ± 0.15**‡	**0.71 ± 0.08**‡
Digit Recall	0.53 ± 0.10	0.66 ± 0.10	**0.63 ± 0.15**‡	**0.72 ± 0.10**‡	**0.64 ± 0.16**‡	**0.70 ± 0.10**‡
Controlled Oral Word Association	0.58 ± 0.11	0.68 ± 0.12	**0.65 ± 0.16**‡	**0.72 ± 0.10**‡	**0.65 ± 0.15**‡	**0.70 ± 0.10**‡
Stroop	0.57 ± 0.15	0.70 ± 0.12	**0.67 ± 0.17**‡	**0.75 ± 0.09**‡	**0.67 ± 0.17**‡	**0.73 ± 0.08**‡
1-Back	0.59 ± 0.12	0.69 ± 0.13	**0.66 ± 0.17**‡	**0.75 ± 0.10**‡	**0.66 ± 0.15**‡	**0.72 ± 0.09**‡
2-Back	0.59 ± 0.14	0.68 ± 0.11	**0.66 ± 0.18**‡	**0.74 ± 0.10**‡	**0.67 ± 0.16**‡	**0.71 ± 0.10**‡
Step Width, m						
Single Task Walking	0.10 ± 0.05	0.11 ± 0.04	0.09 ± 0.03	0.11 ± 0.03	0.09 ± 0.04	0.11 ± 0.04
Serial 7	0.12 ± 0.07	0.12 ± 0.04	**0.08 ± 0.04**‡	**0.11 ± 0.04**‡	**0.09 ± 0.05**‡	**0.11 ± 0.04**‡
Digit Recall	0.11 ± 0.06	0.11 ± 0.04	0.09 ± 0.04	0.11 ± 0.04	0.09 ± 0.05	0.11 ± 0.04
Controlled Oral Word Association	0.11 ± 0.06	0.12 ± 0.04	0.09 ± 0.04	0.11 ± 0.05	0.09 ± 0.04	0.11 ± 0.04
Stroop	0.11 ± 0.07	0.11 ± 0.04	0.09 ± 0.03	0.11 ± 0.04	0.09 ± 0.04	0.11 ± 0.04
1-Back	0.11 ± 0.06	0.12 ± 0.04	**0.08 ± 0.04**‡	**0.11 ± 0.04**‡	**0.09 ± 0.04**‡	**0.11 ± 0.04**‡
2-Back	0.11 ± 0.06	0.11 ± 0.04	**0.08 ± 0.04**‡	**0.11 ± 0.04**‡	0.09 ± 0.04	0.11 ± 0.04
More Affected Arm Swing, m						
Single Task Walking	0.30 ± 0.16	0.75 ± 0.58	**0.45 ± 0.28**‡	**0.97 ± 0.41**‡	**0.46 ± 0.24**‡	**1.10 ± 0.57**‡
Serial 7	0.20 ± 0.08	0.76 ± 0.41	0.23 ± 0.12	**1.07 ± 0.71**‡	0.28 ± 0.16	**1.04 ± 0.52**‡
Digit Recall	0.22 ± 0.09	0.58 ± 0.26	0.27 ± 0.17	**1.00 ± 0.62**‡	0.30 ± 0.20	**1.03 ± 0.61**‡
Controlled Oral Word Association	0.19 ± 0.07	0.83 ± 0.69	0.25 ± 0.17	1.03 ± 0.68	0.31 ± 0.20	0.82 ± 0.43
Stroop	0.20 ± 0.09	0.80 ± 0.57	0.28 ± 0.17	1.05 ± 0.66	0.28 ± 0.17	0.86 ± 0.45
1-Back	0.23 ± 0.09	0.80 ± 0.62	0.28 ± 0.17	1.01 ± 0.57	0.30 ± 0.19	0.84 ± 0.44
2-Back	0.20 ± 0.08	0.76 ± 0.47	0.27 ± 0.18	0.99 ± 0.64	0.28 ± 0.18	0.84 ± 0.46
Less Affected arm swing, m						
Single Task Walking	0.54 ± 0.39	0.86 ± 0.30	**0.78 ± 0.53**‡	**1.06 ± 0.28**‡	**0.78 ± 0.47**‡	**1.07 ± 0.30**‡
Serial 7	0.42 ± 0.31	0.82 ± 0.25	**0.52 ± 0.42**‡	**1.01 ± 0.39**‡	**0.56 ± 0.43**‡	**1.04 ± 0.31**‡
Digit Recall	0.40 ± 0.23	0.80 ± 0.27	**0.52 ± 0.41**‡	**1.00 ± 0.37**‡	**0.57 ± 0.41**‡	**0.99 ± 0.34**‡
Controlled Oral Word Association	0.42 ± 0.28	0.90 ± 0.35	0.53 ± 0.41	1.05 ± 0.38	0.59 ± 0.43	0.96 ± 0.28
Stroop	0.43 ± 0.24	0.86 ± 0.34	**0.60 ± 0.39**‡	**1.05 ± 0.40**‡	0.58 ± 0.44	0.99 ± 0.30
1-Back	0.48 ± 0.34	0.83 ± 0.32	0.55 ± 0.43	1.00 ± 0.37	0.56 ± 0.41	0.96 ± 0.30
2-Back	0.50 ± 0.41	0.76 ± 0.24	**0.58 ± 0.44**‡	**1.01 ± 0.38**‡	0.56 ± 0.45	0.88 ± 0.30

‡ $p < 0.05$.

EOT, end of treatment; EOT + 4, 4 week follow-up after EOT; MMT, multi-modal training; SMT, single-modal training.

cognitive conditions from baseline to EOT and baseline to EOT + 4 ($p < 0.05$), with step length increasing following SMT and MMT.

Step width demonstrated a significant main effect of time under Serial 7, 1-back, and 2-back conditions with step width decreasing from baseline to EOT ($p = 0.009, 0.02, 0.02$, respectively). At EOT + 4, the reduction in step width remained significant for Serial 7 and 1-back ($p = 0.02, 0.04$), but not for 2-back.

4.4. MDS-UPDRS III

There was no group-by-time interaction in MDS-UPDRS III score ($p = 0.66$). The SMT group improved their MDS-UPDRS III score from 38.2 ± 12.9 points at baseline to 35.6 ± 14.4 and 34.5 ± 12.1 points at EOT, and EOT + 4, respectively. The MMT group also improved their MDS-UPDRS III scores from 34.9 ± 9.7 points at baseline to 29.9 ± 7.8 and 29.3 ± 8.4 points at EOT, and EOT + 4, respectively. Motor scores significantly decreased over time for the combined patient population, with an estimated mean difference (95% CI) of −3.8 (−7.2, −0.4) points from baseline to EOT ($p = 0.02$) and −4.7 (−8.0, −1.3) points from baseline to EOT + 4 ($p = 0.005$).

4.5. Cognitive outcomes

Cognitive outcomes are provided in Table 3. Under single tasks conditions (i.e. the cognitive condition was performed in a seated position) for Serial 7 responses, there was a significant group-by-time interaction favoring the MMT group ($p = 0.04$). At EOT, the MMT group increased the number of Serial 7 responses ($p = 0.01$), and that improvement was maintained at EOT + 4 ($p = 0.005$).

Under dual task conditions (i.e. providing cognitive responses while ambulating on the treadmill), there was no significant group-by-time interactions in cognitive response. There was a significant main effect of time for Serial 7s and Stroop.

Table 3
Cognitive performance during single and dual task conditions.

	Baseline		EOT		EOT + 4	
Outcome	SMT	MMT	SMT	MMT	SMT	MMT
Seated (single task)						
Serial 7's - # of responses	26.2 ± 16.9	28.4 ± 16.3	26.3 ± 16.9	**33.6 ± 18.2**‡	28.2 ± 17.8	**34.2 ± 18.7**‡
Serial 7's - # correct	24.2 ± 17.4	26.2 ± 17.5	24.8 ± 16.6	30.8 ± 21.0	**26.2 ± 18.5**‡	**30.9 ± 21.9**‡
Digit recall	5.6 ± 0.8	6.3 ± 2.0	6.2 ± 1.3	6.3 ± 1.4	**6.4 ± 1.3**‡	**6.7 ± 1.7**‡
Verbal fluency	16.5 ± 4.6	13.2 ± 4.6	16.3 ± 5.2	14.9 ± 5.0	16.4 ± 5.0	17.3 ± 5.6
Stroop total score (max score 40)	39.5 [37.0,40.0]	39.0 [38.2,40.0]	37.5 [36.0,39.0]	40.0 [36.0,40.0]	39.0 [38.2,40.0]	39.0 [38.0,40.0]
1-back total score (max score 29)	29.0 [29.0,29.0]	29.0 [29.0,29.0]	29.0 [28.2,29.0]	29.0 [29.0,29.0]	29.0 [29.0,29.0]	29.0 [29.0,29.0]
2-back total score (max score 28)	25.5 [22.2,26.8]	26.5 [23.2,27.0]	26.5 [25.2,27.0]	25.5 [24.2,27.0]	27.0 [24.5,27.0]	27.5 [25.2,28.0]
Gait (dual task)						
Serial 7's - # of responses	28.3 ± 17.4	30.9 ± 17.8	**30.8 ± 17.8**‡	**38.7 ± 21.8**‡	27.6 ± 16.3	34.2 ± 19.9
Serial 7's - # correct	25.1 ± 18.4	28.2 ± 19.5	**29.0 ± 18.8**‡	**36.2 ± 24.1**‡	25.3 ± 17.0	31.4 ± 22.3
Digit recall	6.1 ± 1.7	6.2 ± 1.5	6.0 ± 0.9	6.3 ± 1.7	6.1 ± 1.3	6.2 ± 1.5
Verbal fluency	15.6 ± 4.2	14.5 ± 3.8	16.3 ± 4.7	15.7 ± 3.6	17.4 ± 5.4	16.2 ± 3.9
Stroop total score (max score 40)	37.5 [30.0,38.0]	39.5 [38.0,40.0]	**39.0 [37.5,39.0]**‡	**40.0 [39.0,40.0]**‡	**39.0 [37.2,40.0]**‡	**40.0 [39.2,40.0]**‡
1-back total score (max score 29)	29.0 [29.0,29.0]	29.0 [28.2,29.0]	29.0 [29.0,29.0]	29.0 [29.0,29.0]	29.0 [29.0,29.0]	29.0 [29.0,29.0]
2-back total score (max score 28)	24.0 [18.8,27.8]	26.5 [24.2,27.0]	27.0 [25.5,27.8]	26.0 [24.2,26.8]	**27.0 [26.2,27.8]**‡	**27.0 [25.2,27.0]**‡

‡ **$p < 0.05$.**
EOT, end of treatment; EOT + 4, 4 week follow-up after EOT; MMT, multi-modal training; SMT, single-modal training.

5. Discussion

This study was the first to report improvements in dual task performance over a range of cognitive domains and provide support for the concept that behavioral interventions stressing cognitive and motor processing may enhance the automaticity of gait and cognition resulting in improvements in dual task performance. An intervention simultaneously presenting cognitive and motor challenges, such as the MMT, was superior to single-task training alone in improving arm swing, indicating that the complexity of the training may be beneficial in PD. Arm swing asymmetry is associated with dopaminergic depletion [21] and has been proposed as a prodromal marker for PD [22], indicating that a reduction in arm swing may be a biomechanical marker reflecting disease progression. Consequently, improvements in arm swing provide insight into potential compensatory CNS changes following MMT. While mechanistic research needs to be investigated, it is possible that the use of MMT may facilitate neuroplasticity within the cerebello-thalamic-cortical pathway [23] and nigrostriatal pathway [24] and may contribute to preservation of motor function despite basal ganglia dysfunction [25]. Notably, changes in arm swing followed a different pattern of improvement than the lower extremity (Table 2). The differences in upper and lower extremity impairment under dual task conditions have been reported previously from our laboratory and others [4,5,22]. Together, these findings suggest that upper and lower limb oscillatory movements are at least partially controlled by independent pathways [26] and may be modifiable with a SMT or MMT intervention.

Temporal and postural aspects of gait followed different patterns of improvement. Temporal aspects of gait (velocity, step length, and cadence) showed consistent improvement across all dual task conditions. While velocity and step length improved, cadence remained unchanged. Notably, unchanged cadence with increased step length and velocity indicate that the individual moved away from a festinating gait pattern by taking longer, faster steps; thus stable cadence in this scenario likely indicates an improved gait pattern. In contrast, postural components of gait (step width and arm swing) [27,28] displayed a varied response following training depending on secondary task. Previous studies suggest that temporal and postural aspects of gait have different control mechanisms, with temporal aspects showing greater responsiveness to antidopaminergic medication compared to postural components of gait [29]. Taken together, differing patterns of improvement in temporal and postural gait variables support the hypothesis that gait is controlled by both dopaminergic and non-dopaminergic pathways, including cholinergic pathways and input from cortical and cerebellar regions [30]. The differences in temporal and postural aspects of gait highlight the importance of examining both sets of gait variables to provide insight into PD pathology and to better gauge interventional effectiveness.

Both the SMT and MMT groups improved their motor performance as measured by the MDS-UPDRS III and gait velocity under all dual task conditions, exceeding the minimal clinical important difference (MCID) of 3.25 points [31] and 0.06 m/s [32], respectively. Improvements in global motor functioning and walking speed indicate that SMT or MMT intervention stressing both cognitive and motor aspects of function may provide another adjunct method of managing PD symptomlogy. Namely the improvements in gait speed were encouraging as following the intervention all participants ambulated at speeds exceeding 1.1 m/s under all cognitive conditions. The functional and practical implication of increasing gait velocity is important as previous data indicate a gait velocity of less than 1.1 m/s is associated with falling in individuals with PD [33]. Further long-term studies are necessary to systematically test the effectiveness of MMT in prolonging independence in PD.

While not our primary outcome, modest improvements in cognitive function following the intervention in Stroop (executive function) and Serial 7 (attention) were observed in the MMT group. Clearly, larger and more systematic study is necessary to determine the impact of this behavioral intervention on enhanced cognition in PD, which has historically been challenging to treat with behavioral, pharmacologic, and surgical interventions.

The initial data from this trial expands our previous knowledge of dual task deficits in PD and how MMT may alter function. Nevertheless, there were limitations to this trial. While our inclusion criteria was for Hoehn & Yahr II-IV, no patients were enrolled in the later phase (IV) of PD. It is difficult to know if those in the later stage of PD could have successfully completed MMT or SMT as delivered. A lack of understanding the impact of MMT on more advanced PD patients underscores the need for a long-term intervention in a diverse patient group. Overall, gait and cognitive improvements were sustained at the 4-week follow-up; the DUALITY trial also demonstrated sustained improvements following SMT and MMT training at a 12-week follow up [8]. While prolonged effects are encouraging in terms of long-term change, it is unknown whether the effects of SMT and MMT are sustained over a longer period of time or if they can be maintained via a less frequent intervention schedule (i.e. a single MMT session per week). Lastly, some individuals did exhibit a ceiling effect on tasks such as the Stroop and N-back. Despite the cognitive ceiling, gait deficits were exaggerated

under each condition.

6. Conclusion

In conclusion, both the MMT and SMT interventional groups resulted in significant improvements in PD motor symptoms, gait performance, and cognitive function under single and dual task conditions. Improvements in arm swing, particularly on the more affected side, may be more amenable to change with MMT. Temporal aspects of gait responded uniformly to training, while postural aspect of gait varied by the secondary cognitive task, highlighting the need for rehabilitation professionals to employ a variety of cognitive tasks during training. Upper and lower extremity improvements following training appear to be relatively independent of each other, indicating that each likely utilize different supraspinal pathways.

Conflicts of interest

The authors report no conflicts of interest.

7. Contributors

ABR: study design and implementation, manuscript preparation. ALP: data collection, manuscript editing. MCS: data collection, manuscript editing. NMZ and MMK: statistical analysis. JLA: study design, manuscript editing.

Role of funding source

This trial was supported by the Davis Phinney Foundation, Boulder, CO [DPF1507JA] and the Edward and Barbara Bell Endowed Chair. The funding sources had no role in study design, data analysis and interpretation, and manuscript publication. This trial is listed at ClinicalTrials.gov, registration number NCT02538029.

Acknowledgements

The authors would like to thank Christina Makowski, SLP for her assistance developing the cognitive intervention and Sara Davidson, PTA and Susan Linder, DPT for their assistance with the intervention delivery.

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