FATIGABILITY AND CARDIORESPIRATORY FITNESS
DURING SUSTAINED WALKING FOLLOWING
OVERGROUND LOCOMOTOR TRAINING IN
INDIVIDUALS WITH PARKINSON'S DISEASE

by

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DEDICATION

This work is dedicated to the research participants involved in the project, without whom none of this would have been possible.

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LIST OF ABBREVIATIONS AND SYMBOLS

Parkinson's disease…. PD

Pulmonary Oxygen Uptake Kinetics …. $\dot{V}O_2$ on-kinetics

Peak oxygen consumption…. $\dot{V}O_2$ peak

Ten Minute Walk Test…. 10MWT

Overground locomotor training …. OLT

Hoehn and Yahr…. H&Y

Phase-II time constant …. τ

Heart rate…. HR

Time delay …. TD

Oxidative response index …. ORI

ABSTRACT

FATIGABILITY AND CARDIORESPIRATORY FITNESS DURING SUSTAINED WALKING FOLLOWING OVERGROUND LOCOMOTOR TRAINING IN INDIVIDUALS WITH PARKINSON'S DISEASE

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George Mason University, 2021

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Purpose: Increased performance and perceived fatigability during sustained walking is often present in people with Parkinson's disease (PD). Cardiorespiratory fitness is also often diminished in people with PD, and this limitation may contribute to elevated fatigability during walking in members of this patient population. Pulmonary oxygen uptake kinetics during the rest-to-work transition ($\dot{V}O_2$ on-kinetics) is an objective measure of cardiorespiratory fitness that can be assessed during overground walking. Overground locomotor training (OLT) is a method that may be well suited to reduce fatigability during sustained overground walking and promote concomitant improvements in cardiorespiratory fitness in people with PD. The purpose of this study was to characterize changes in performance and perceived fatigability during overground walking and $\dot{V}O_2$ on-kinetics following a 12-week OLT program in people with mild-to-moderate PD. **Methods:** Twelve individuals with PD completed our OLT program.

Performance fatigability was measured using the performance fatigability index, which accounts for both speed fluctuations (indicated by a pacing index) and total distance walked during a 10-minute walk test (10MWT). Perceived fatigability was measured using the perceived fatigability index, which accounts for both changes in perceptions of tiredness following the 10MWT and the total distance walked. $\dot{V}O_2$ on-kinetics was determined by fitting a mono-exponential function to gas exchange data from the first 6 minutes of the 10MWT. The time constant (τ) of phase-II of the $\dot{V}O_2$ on-kinetics response and the oxidative response index (ORI) were used as indicators of cardiorespiratory fitness. **Results:** Following OLT, improvements in the performance fatigability index (mean difference = -0.1 (0.1) 1/m, 95% CI: [-0.2, 0], p = 0.0029, Cohen's $d_{(unbiased)}$ = 0.64), and total distance (mean difference = +83.6 (77.5) m, 95% CI: [34.3, 132.8], p = 0.0033, Cohen's $d_{(unbiased)}$ = 0.54) were observed. Small effects (mean difference = -0.3 (1.6) au, 95% CI: [-1.3, 0.7], p = 0.4921, Cohen's $d_{(unbiased)}$ = 0.24) were observed for the perceived fatigability index. Improvements in phase-II τ (mean difference = -7.8 (11.5) seconds, 95% CI: [-15.1, -0.5], p = 0.0393, Cohen's $d_{(unbiased)}$ = 0.54) and the ORI (mean difference = +12.8 (14.9) mL/min/s, 95% CI: [3.3, 22.3], p = 0.0126, Cohen's $d_{(unbiased)}$ = 0.83) were also observed. **Conclusion:** These data indicate preliminary success of OLT in people with PD for modifying performance fatigability during sustained overground walking in addition to cardiorespiratory fitness.

CHAPTER ONE

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the United States.[1] Fatigability is often elevated during sustained walking in people with PD, creating a barrier to physical and social participation.[2–4] As a function of the duration, intensity, and/or frequency of a specific activity, fatigability describes both the magnitude or rate of decline over time during the performance of an activity (i.e. performance fatigability) and the increases in perceptions of tiredness (i.e. perceived fatigability).[5] Cardiorespiratory fitness, defined as the integrated ability of the pulmonary, circulatory, respiratory, and muscular systems to deliver and utilize oxygen during sustained physical activity,[6] is often compromised in people with PD[7–10] and may be a key contributor to performance and perceived fatigability during walking in members of this patient population.[11]

Performance-based training emphasizes principles of task specificity, practice variation, and progressive overload in an attempt to promote active exploration of real-world movement solutions and physiological adaptation across multiple body systems supporting locomotor function.[12] Task-specificity in training applies to both the movements practiced and the environment in which training occurs, however, few gait-training studies in PD have applied both dimensions of this concept concurrently. Performance-based training also emphasizes that training should be metabolically

challenging, as to promote energy systems development, which, in the context of gait rehabilitation, may enable individuals to better meet the bioenergetic demands of sustained walking.[12,13] Energy demand is intrinsically tied to movement, thus, enhanced ambulatory ability resulting from training may involve adaptations that enable individuals to more appropriately meet the bioenergetic demands of whole-body activity.[12,13] This is a point of particular relevance to individuals with PD given that cardiorespiratory fitness is often diminished in members of this patient population.

Overall, the effects of performance-based interventions on walking performance have not been fully studied in individuals with PD, much less their effects on physiologic outcomes that may be related to improved sustained overground walking ability. Previous studies from our laboratory on the effects of performance-based gait training in people with incomplete spinal cord injury demonstrated improvements in pulmonary oxygen uptake kinetics during the rest-to-work transition ($\dot{V}O_2$ on-kinetics) and substantial reductions in both performance fatigability and perceived fatigability during walking.[12,14] Measures of $\dot{V}O_2$ on-kinetics are considered to be among the sentinel parameters of cardiorespiratory fitness, reflecting the integrated function of circulatory and skeletal muscle metabolic systems responsible for aerobic energy synthesis.[15,16] Additionally, $\dot{V}O_2$ on-kinetics have been proposed as a marker of fatigability, as it provides information regarding metabolic processes that influence contractile performance and perceptions of activity-induced discomfort.[17–20]

The $\dot{V}O_2$ on-kinetics response at the initiation of physical activity typically follows a tri-phasic pattern (Figure 1). In phase-I, often referred to as the cardio-dynamic phase, there is typically an initial rise in $\dot{V}O_2$ followed by a subtle change in slope, brief plateau of rise, or, in some cases, a plateau and a drop in values. The cardio-dynamic phase is believed to be less indicative of active skeletal muscle metabolism and therefore excluded during modeling of the $\dot{V}O_2$ on-kinetic profile.[21] Phase-II is characterized by an exponential rise in $\dot{V}O_2$ towards an asymptotic plateau that can be modeled using mathematical equations and is believed to be reflective of aerobic metabolic processes occurring at the level of active skeletal muscle.[16] The asymptotic plateau in $\dot{V}O_2$ is phase-III, which is generally interpreted to indicate a steady-state between energy demand and aerobic energy synthesis when the activity is of low to moderate intensity.

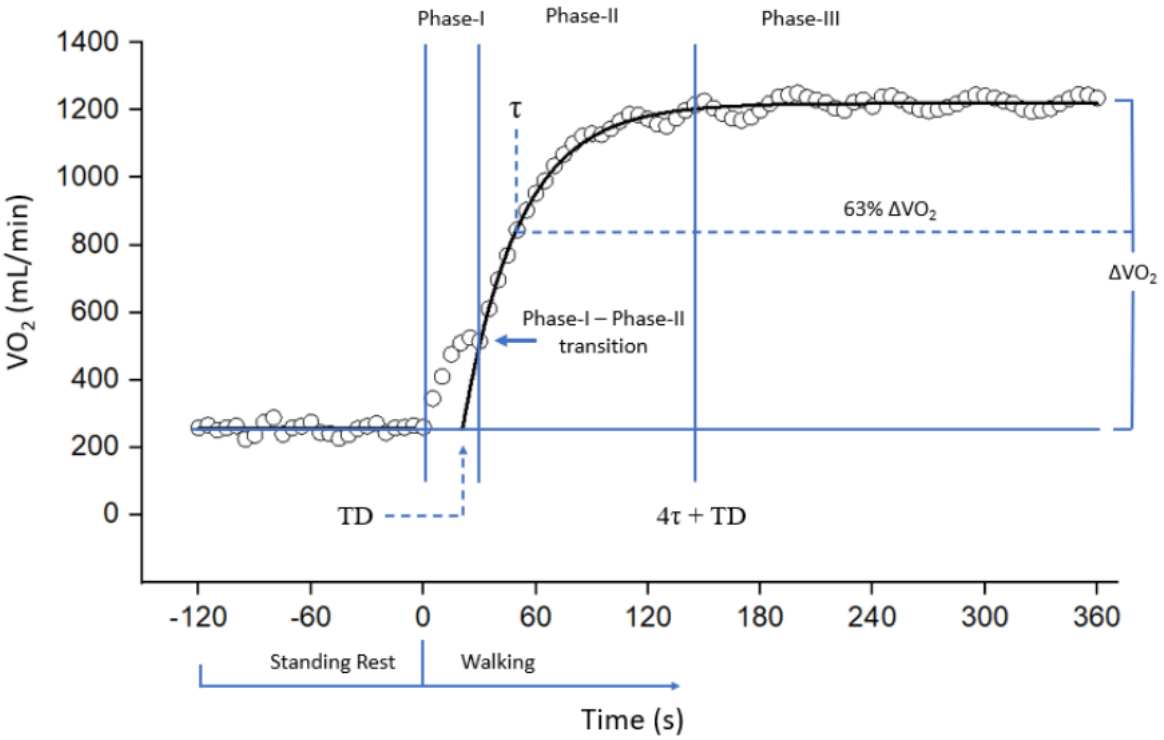


Figure 1: Schematic representation of $\dot{V}O_2$ on-kinetics during 10MWT.

Measures of $\dot{V}O_2$ on-kinetics may also be more sensitive to cardiorespiratory adaptations that relate to submaximal exercise performance than are measures of peak oxygen consumption ($\dot{V}O_2$ peak) during graded exercise testing, which instead are indicative of the maximum capacity of the cardiorespiratory system. Since $\dot{V}O_2$ peak has been the primary variable used to quantify cardiorespiratory fitness in the context of gait rehabilitation in PD, employing measures of $\dot{V}O_2$ on-kinetics to characterize potential cardiorespiratory adaptations in response to gait training may provide novel information that is more relevant to everyday activities performed sub-maximally over prolonged periods. Recent investigations in both healthy and patient populations have demonstrated

the feasibility of $\dot{V}O_2$ on-kinetics measurement during overground walking tests in an attempt to reduce subject burden and enable physiological assessment during testing that mirrors daily activity.[22–25]

While it appears that aerobic exercise training of sufficient intensity and volume may produce favorable improvements in physical work capacity and cardiorespiratory fitness in individuals with PD,[26,27] only one study has provided evidence that such adaptations occur alongside increases in sustained overground walking performance.[28] However, in the study mentioned, training was performed on a treadmill, rather than overground.[28] Thus, it remains an unanswered but important question whether overground gait training with a focus on skill acquisition is capable of producing meaningful effects on fatigability during sustained walking and concomitant improvements cardiorespiratory fitness in people with PD. To address these gaps in the literature, we adapted our previously developed overground locomotor training (OLT) program for people with incomplete spinal cord injury to people with PD. The broad objective of this study was to examine changes in performance fatigability and perceived fatigability during sustained overground walking and $\dot{V}O_2$ on-kinetics following a 12-week OLT program in ambulatory individuals with mild-to-moderate PD.

Specific Aims

Specific Aim 1: Characterize changes in fatigability following OLT as evidenced by measures of performance fatigability and perceived fatigability during a 10 Minute Walk Test (10MWT) in individuals with PD.

H1a) Performance fatigability will be reduced following OLT as evidenced by reductions in the performance fatigability index following OLT.

H1b) Perceived fatigability will be reduced following OLT as evidenced by reductions in the perceived fatigability index following OLT.

Specific Aim 2: Characterize changes in cardiorespiratory fitness following OLT as evidenced by measures of $\dot{V}O_2$ on-kinetics during a 10MWT in individuals with PD.

H2) VO_2 on-kinetics will be improved following OLT as evidenced by reductions in the phase-II time constant (τ) of the $\dot{V}O_2$ response during the initial portion of a 10MWT.

CHAPTER TWO

Methods

Study Design

This pre-experimental pilot study used a pre- and post-test design. Testing was performed at two time-points: before (pretest) and immediately following the OLT program (post-test). The OLT program was comprised of 24, one-hour training sessions performed twice weekly with at least 48 hours between training session. To be included in the analysis, subjects were permitted to miss no more than three consecutive sessions and were required to complete the training protocol within 15 weeks of their initial baseline assessment.

Ethical Approval

The protocol and procedures were approved by the Institutional Review Board of George Mason University (#1374615-3). The study was registered on clinicaltrials.gov (NCT03864393). Written and verbal explanations of the study protocol and risks related to testing and training procedures were presented to prospective subjects prior to enrollment. Written informed consent was obtained from all participants prior to initiation of testing or training activities.

Study Sample

Participants were recruited from the greater Washington, DC, metropolitan area using paper and electronic fliers, local support group networking, and online postings. Inclusion criteria consisted of the following: age between 18 and 85 years; diagnosis of mild-to-moderate PD (Hoehn and Yahr (H&Y) score ≤3); speaks English; and able to ambulate without requiring an assistive device. Exclusion criteria consisted of the following: neurological disease or diagnosis other than PD; uncontrolled cardiovascular, pulmonary, neurological, or metabolic disease which may impact the ability to exercise or in which exercise is contraindicated; medications that may alter heart rate or metabolic data; legal blindness; mini-Mental State Examination score <24; pregnancy; and concurrent participation in structured exercise similar to OLT.

Enrollment Procedure

The assessment of eligibility and enrollment procedures covered the following steps in the following order. First, participants reported their interest to the study coordinator via a phone call or an email. This was followed by a standardized telephone interview to screen eligibility. Lastly, eligible participants visited the laboratory where a study investigator provided a detailed explanation of the informed consent document. Once participants voluntarily signed the informed consent document, medical history and medication intake lists were reviewed to further screen eligibility. Next, the mini-Mental State Examination was administered and scored to screen for cognitive function according to the exclusion criteria. Finally, a study investigator administered the H&Y assessment to screen for PD severity according to the inclusion criteria.

Testing Day Procedure

Participants were asked to refrain from strenuous physical activity for 48 hours prior to testing sessions. All participants were asked to follow their normal dietary and PD medication schedules and were tested during the on-phase at the same time of day during the pretest and post-test. Each participant's height and weight were measured prior to the start of functional testing. Resting heart rate and blood pressure were recorded with the participant in a seated position prior to any functional tests to screen for excessive hypertension or excessive hypotension. Testing sessions featured two components separated by 20-30 minutes of seated rest. The primary component of testing was an overground 10MWT with continuous cardiopulmonary gas exchange monitoring using a portable metabolic system. The 10MWT also involved measurement of perceptual responses of tiredness/energy level prior to, and following, walking for the purposes of perceived fatigability measurement. We also assessed kinetics, kinematics, and muscle activity during short-performance walking tasks, the results of which are not the focus of the present study. Randomization of the sequence of the two components of testing procedure was performed for every other subject enrolled (i.e., 1^{st}, 3^{rd}, 5^{th}, etc.), with the subject in between (i.e., 2^{nd}, 4^{th}, 6^{th}, etc.) performing testing in the opposite order. This was done to ensure an equal balance of testing sequences across the study sample. The testing sequence was kept consistent within each subject from pretest to post-test.

10-Minute Walk Test Procedure

Subjects were fitted with a Cosmed K5 portable pulmonary gas exchange monitoring system consisting of a 900-gram computer worn like a backpack, and a facemask that covers the nose and mouth.[29] Previous reports in individuals with PD and healthy adults indicate that wearable gas exchange monitoring devices do not substantially disrupt sustained overground walking performance.[30,31] Testing was conducted in a 60-meter corridor with a flat concrete floor. Participants were instructed to "walk as far as you safely can" and to "walk as many laps as safely possible in 10 minutes". Prior to the 10MWT, participants sat quietly for 3 minutes and had their blood pressure recorded, then stood quietly for 4 minutes to obtain resting metabolic measurements. Blood pressure was measured again in a standing position to check for large orthostatic fluctuations upon standing. Immediately following the 4-minute standing period, subjects began the 10MWT. One test administrator continuously trailed the participant to mitigate the risk of falls, but was careful to remain behind the participant to avoid inadvertently pacing the subject. A separate test administrator recorded distances walked every minute to permit calculation of minute-by-minute walking velocity fluctuations. Verbal encouragement was not given to subjects while walking nor was indication of the remaining test time at any point. At the 10-minute mark, subjects were instructed to stop walking and to begin a 10-minute period of quiet standing recovery. Blood pressure was recorded in a standing position at multiple time points during

recovery. Subjects were permitted to sit in a chair during recovery if they indicated the desire to do so. Breath-by-breath gas exchange data were offloaded from the portable metabolic device to a separate computer and were analyzed using modeling software to compute $\dot{V}O_2$ on-kinetics parameters.

Fatigability Measurement and Calculation

Performance fatigability index and perceived fatigability index measurements and calculations were performed using the methods developed by Schnelle and colleagues.[32] The perceived fatigability index was determined as follows. During the standing rest period prior to initiation of the 10MWT, subjects were asked to rate their current level of tiredness on a seven-point scale from 7 (extremely tired) to 1 (extremely energetic). The subject's response to this question served as a benchmark measurement of fatigue against which post walk subjective ratings were compared. Immediately following the 10MWT, or earlier if subjects could not walk a full 10 minutes, subjects were asked, "Are you more tired, more energetic, or feeling the same as compared to before walking?" A score of 4 was assigned if the indicated that they felt the same as they did prior to walking. If subjects indicated that they felt more tired, they were then asked to rate their level of tiredness (i.e., a little tired, score of 5; somewhat tired, score of 6; extremely tired, score of 7). The same branching procedure was followed if they indicated feeling more energetic (i.e., a little energetic, score of 3, somewhat energetic, score of 2; extremely energetic, score of 1). To normalize changes in perceived fatigability to the level of activity performance, post walk perceptions scores were divided by total distance walked

then multiplied by 1000 for reporting purposes. Formula: perceived fatigability index = (post walk subjective rating / total distance walked) *1000.

Performance fatigability measures the change in an individual's performance normalized to the overall level of activity performance. To calculate the performance fatigability index, distance walked in the first 2.5 minutes was recorded to permit calculation of walking velocity in the first 2.5 minutes. Average velocity over the entire walk was divided by average velocity in the first 2.5 minutes to describe speed deterioration/increase throughout the 10MWT, which was then divided by total distance walked, and multiplied by 1000 for reporting purposes. Formula: performance fatigability index = ((entire walk average velocity / first 2.5 minutes average velocity) / total distance) *1000.

To examine the relative influence of changes in the degree of speed deterioration/increase during the 10MWT versus changes in total distance walked on the performance fatigability index, we also independently analyzed total distance walked and a "pacing index" statistic. The pacing index is part of the performance fatigability index calculation that describes subjects' overall speed trend during the 10MWT and was calculated as (entire walk average velocity / first 2.5 minutes average velocity) *100. A pacing index of 100 indicates that walking velocity in the first 2.5 minutes of the 10MWT was identical to the overall walking velocity throughout the test. A pacing index less than, or greater than, 100 indicates that walking velocity in the first 2.5 minutes of the 10MWT was faster, or slower, respectively, than the overall velocity throughout the test.

Intervention

A performance-based training paradigm was used to develop the OLT program implemented in this study. Specifically, the OLT protocol is grounded in dynamical systems theory of motor control and motor learning and incorporates programming principles from the fields of exercise physiology and neurorehabilitation. The central goal of our OLT program was to promote an expansion of subjects' motoric behavioral repertoire for real-world walking.

Primary emphasis was placed on providing subjects with a training experience that would theoretically promote motor learning specific to overground walking. More directly, subjects performed a sequence of challenging and repetitive locomotor-specific tasks in an exclusively overground environment without body-weight support or balance assistance. Secondary emphasis was placed on achieving a training stimulus that would theoretically promote cardiorespiratory adaptations. To achieve this goal, trainers modulated the characteristics of rest periods (i.e., interspersed half-squats, mini-multidirectional lunges, or high-knees when needed instead of passive rest) so that the bulk of each training session was performed above 60% age-predicted maximal heart rate (HR). These two overall training objectives were emphasized because a diverse body of literature suggests that recovery of ecologically valid walking capabilities may occur across multiple body systems and that such effects may be readily attained if training

concurrently targets motor skill acquisition and physiological adaptation in a task and environmentally specific manner.[12,33–36]

Subjects underwent 24, 60-minute bi-weekly OLT sessions over the course of 12-15 weeks. Every session incorporated practice of the actions involved in each sub-task of walking (e.g., weight shifting, stepping, propulsion). However, individual training sessions were "themed", meaning that the focus of the training session was to improve a specific characteristic of locomotor performance (i.e., power, stability, or stepping) in a specific direction of movement (i.e., forward, backward, lateral, rotational). Drills for each day were programmed and coached in a manner that emphasized the theme of the session. For example, a "lateral-power" session incorporated drills that challenged power development through the lower extremities during a variety of lateral walking tasks. In each session, following a brief circuit style warm up, sub-tasks of walking were isolated at the beginning of the session and drills progressed, in complexity throughout the session using pre-specified time blocks of specific drills (i.e., part-to-whole sequencing). Participants progressed from simple movements relevant to a specific walking action to dynamic walking exercises. Each session culminated with activity rehearsal consisting of dynamic walking at a variety of speeds and tempos and in various directions and patterns. Small hand weights and gait belts were frequently used during various exercises to provide external resistance and to increase the load, intensity, and balance demands of specific drills. Participants wore a heart rate monitor throughout training sessions for data recording and to aid trainers in adjusting the intensity of the session to meet the 60% HR minimum.

Gas Exchange Data

Raw $\dot{V}O_2$ breath-by-breath data from the 2 minutes prior to the onset of walking until the 6-minute mark of the 10MWT were analyzed using modeling software (Origin-Lab, 2019, Northampton, MA, USA). Raw data were initially filtered using a 3-step rolling average, were time-aligned to correspond to the start of walking, linearly interpolated on a second-by-second basis, and time-averaged into 5-second bins to reduce the noise of the signal and increase the confidence in parameter estimates.[21,37,38]

The phase-II $\dot{V}O_2$ on-kinetic response was modeled using a standard mono-exponential equation (Eq. 1), where $\dot{V}O_{2(t)}$ is the $\dot{V}O_2$ at any time point throughout the 6 minute portion of the walking bout, $\dot{V}O_{2(baseline)}$ is the average $\dot{V}O_2$ during the 2-minute standing rest period immediately prior to the walking bout, $\Delta\dot{V}O_2$ is the amplitude of the increase in $\dot{V}O_2$ above baseline, τ is the phase-II time constant (i.e., time taken to reach 63% of the steady-state response minus the phase delay, which is the cardio dynamic phase), and TD is the time-delay, which was allowed to vary freely to increase the accuracy of phase-II and phase-III parameter estimates.

$$Eq.1: \qquad \dot{V}O_{2(t)} = \dot{V}O_{2(baseline)} + \Delta\dot{V}O_2\left[1 - e^{-\left(\frac{t-TD}{\tau}\right)}\right]$$

The beginning of phase-II was determined by visual inspection of gas exchange data for each exercise bout, as reported previously.[39–41] The fitting window for the $\dot{V}O_2$

response during the walking bout began at the phase-I – phase-II transition and ended at the 6-minute mark of walking. This approach eliminated the data that is believed to describe the cardio-dynamic phase from the calculations of phase-II and phase-III parameters. To further increase the accuracy of phase-II and phase-III modeling, the TD was allowed to vary freely within the mono-exponential equation and was not forced to intersect the $\dot{V}O_{2(baseline)}$ values at the same time as the phase-I – phase-II transition (see Figure 1). Because of this modeling strategy, TD is considered a mathematical feature of the mono-exponential function that describes the metabolic transition to steady-state, but is not synonymous with time point that signifies the duration of phase-I and the beginning of phase-II, as described elsewhere.[39]

An additional measure was also derived to further characterize the $\dot{V}O_2$ on-kinetics response. The oxidative response index (ORI) describes responsiveness of the oxidative metabolic system and was calculated as the ratio of $\Delta\dot{V}O_2$ and phase-II τ. As proposed elsewhere,[42,43] ORI may provide information related to the physiologic capacity to consume oxygen per unit of time, as it accounts for both the speed and magnitude of $\dot{V}O_2$ increase above resting values in response to activity.

Descriptions of walking velocity fluctuations during the initial 6 minutes of the 10MWT were also included to verify the appropriateness of using a self-paced walking test for $\dot{V}O_2$ on-kinetics calculations.

Statistical Analysis

Statistical analyses were performed using Stata IC version 15.1 (Stata Corp., College Station, Texas, USA) and data are presented as mean ± standard deviation, with 95% confidence intervals (CI). Pre- and post-test changes in walking distance, performance and perceived fatigability, and $\dot{V}O_2$ on-kinetics outcomes were analyzed using paired *t* tests. The Shapiro-Wilk test was applied to all data to examine normality. If data were non-normally distributed, Wilcoxon signed-rank tests were used instead of paired *t* tests. Mean changes in outcomes and their 95% confidence intervals are presented for all outcomes. For normally distributed data, Cohen's $d_{(unbiased)}$ effect sizes are presented. Cohen's $d_{(unbiased)}$ effect sizes were calculated using an equation designed for single group, repeated measures analysis with paired samples that corrects for overestimation bias due to small samples (Eq. 2), where M_{pre} is the pretest mean, M_{post} is the post-test mean, S_{pre} is the standard deviation of pretest scores, S_{post} is the standard deviation of post-test scores, and n is the number of subjects being analyzed for a particular variable.[44] For non-normally distributed data, standardized effect sizes are presented as *r* (Eq. 3), where *Z* is the Z-score from a Wilcoxon signed-rank test and *N* is the total number of observations across pretest and post-test time points for a particular variable.[45] Statistical significance was accepted at $P \leq 0.05$ for 2-tailed hypotheses.

$$Eq.\,2: \quad Cohen's\ d_{(unbiased)} = \left(1 - \frac{3}{\left(4\left(2(n-1)\right)\right) - 1}\right) \times \left(\frac{M_{post} - M_{pre}}{\sqrt{\frac{S_{pre}^2 + S_{post}^2}{2}}}\right)$$

$$Eq.3: \quad r = \frac{Z}{\sqrt{N}}$$

CHAPTER THREE

Results

Of the 27 individuals screened for this study in response to advertisements, 17 individuals with PD were enrolled in the study. During the pretest functional assessment, one participant displayed uncontrolled hypertension and was thus excluded from further participation. Three participants ceased participation approximately half-way through the 24-session protocol, one citing excessive fatigue following training sessions, one citing dissatisfaction with the training protocol, and one due to exacerbation of a chronic knee condition. One participant reported mild chest discomfort during the first training session and was referred to a cardiologist for evaluation. This subject resumed the protocol after clearance from their cardiologist. Overall, thirteen individuals completed the 24-session intervention protocol. One subject who completed the protocol reported an increase in their dopaminergic medication during the training protocol, and was therefore excluded from the final analysis. Thus, twelve subjects are included in the final analysis. Participant characteristics for the final analysis are presented in Table 1. Characteristics of the five subjects not included in the final analysis can be found in the Appendix.

Table 1: Participant characteristics in final analysis.

Participant	Age (years)	Gender	Height (cm)	Weight (kg)	Hoehn and Yahr	More affected side
1	71	M	176.5	74.7	1	R
2	71	M	176.5	79.4	1.5	R
4	76	F	174.0	61.8	1	R
5	64	M	180.5	76.3	1	L
6	75	M	168.5	77.0	2	R
8	55	F	150.0	51.7	2	R
9	70	F	156.8	46.0	2	R
10	74	M	161.5	74.8	3	R
11	65	M	164.3	65.8	2	L
12	65	F	160.9	55.6	2	R
14	62	M	169.0	79.4	2	L
15	74	F	164.7	65.9	2	L
N=12	68.5(6.4)	7M	166.9(9)	67.4(11.5)	1-3	8R

Abbreviations: M, male; F, female; L, left; R, right. **Description:** Summary statistics is the bottom row for age, height, and weight are presented as mean (standard deviation), while gender and affected side are presented as totals. Summary H&Y scores in the bottom row are presented as a range.

Walking and Fatigability Outcomes

Total distance walked during the 10MWT was greater after OLT (mean difference = +83.6 (77.5) m, 95% CI: [34.3, 132.8], p = 0.0033, Cohen's $d_{(unbiased)}$ = 0.54) compared to baseline. Following OLT, performance fatigability index was lower (mean difference = -0.1 (0.1) 1/m, 95% CI: [-0.2, 0], p = 0.0029, Cohen's $d_{(unbiased)}$ = 0.64) compared to baseline. Additionally, pacing index was lower after OLT (mean difference = -0.7 (2.1), 95% CI: [-2, 0.7], p = 0.2941, Cohen's $d_{(unbiased)}$ = 0.25) compared to baseline. Small effects were observed following OLT for changes in perceived fatigability index (mean difference = -0.3 (1.6) au, 95% CI: [-1.3, 0.7], p = 0.4921, Cohen's $d_{(unbiased)}$ = 0.24) and raw scores of perceived tiredness/energy rating at the end of the 10MWT (mean difference = +0.2 (1.1) au, 95% CI: [-0.5, 0.9], p = 0.6147, Cohen's $d_{(unbiased)}$ = 0.11) (Table 5, Figure 2).

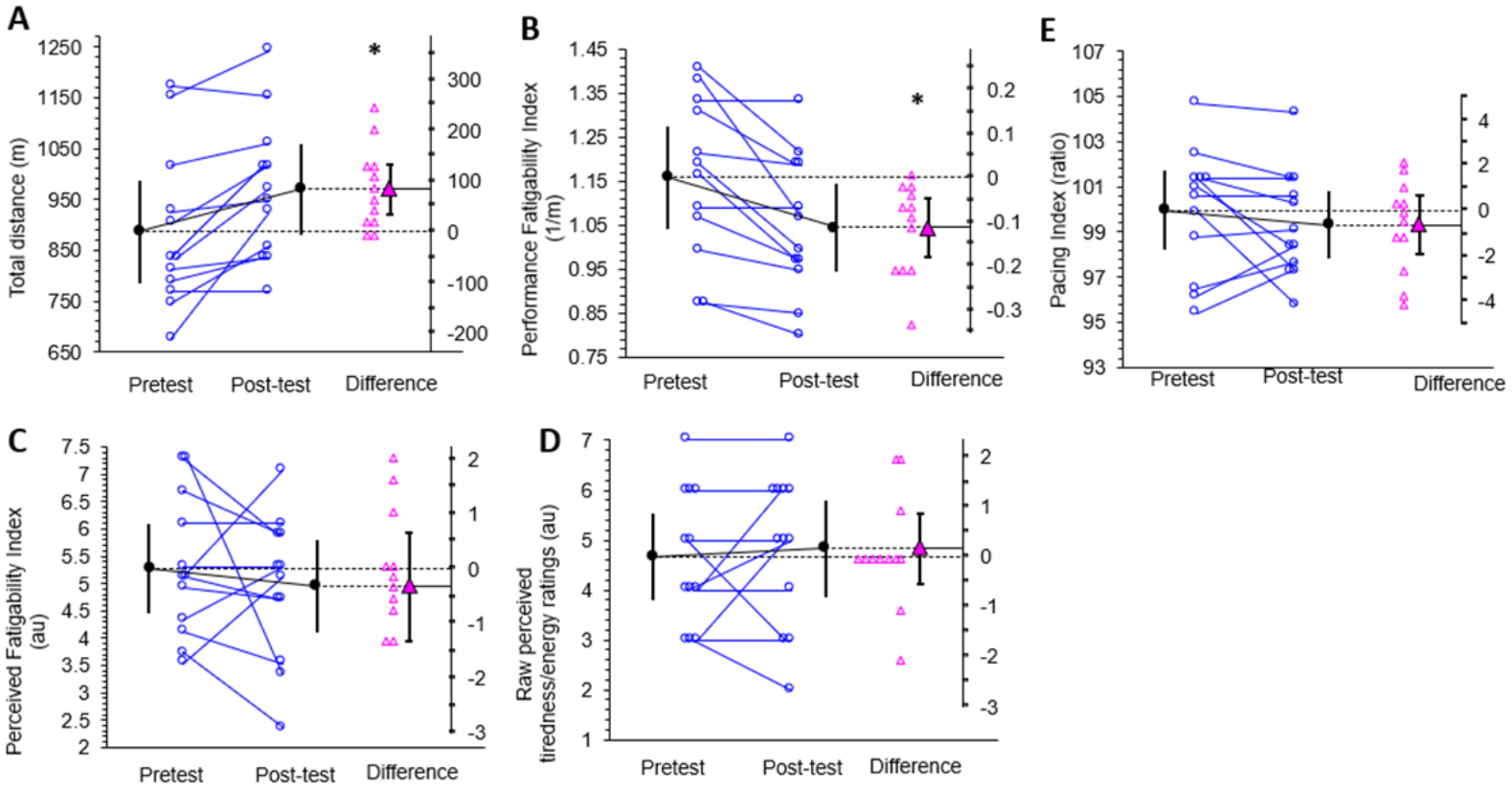


Figure 2: Results for changes in sustained overground walking performance. Individual and group changes in (A) total distance walked; (B) performance fatigability index; (C) perceived fatigability index; (D) raw perceived tiredness/energy ratings; (E) pacing index. Group means and their CI's are displayed with black circles and black lines. Individual changes are displayed with blue lines connecting hollow blue circles. Changes from baseline for each participant are depicted with hollow magenta triangles. Mean change from baseline and it's CI are depicted with a solid magenta triangle and black bars. Left axis depicts ranges for pretest and posttest scores. Right axis depicts effect sizes in the same units as left axis. "*" denotes $p \leq 0.05$.

$\dot{V}O_2$ Kinetics Outcomes

Small effects for $\dot{V}O_{2(baseline)}$ were observed following OLT (mean difference = +4.2 (57.7) mL/min, 95% CI: [-32.5, 40.9], p = 0.8051, Cohen's $d_{(unbiased)}$ = 0.05) compared to baseline (Table 3). Phase-II τ was faster following OLT (mean difference = -7.8 (11.5) seconds, 95% CI: [-15.1, -0.5], p = 0.0393, Cohen's $d_{(unbiased)}$ = 0.54) compared to baseline. Following OLT, small effects were observed for $\Delta\dot{V}O_2$ (mean difference = +15.8 (216.7) mL/min, 95% CI: [-121.9, 153.4], p = 0.8058, Cohen's $d_{(unbiased)}$ = 0.04) compared to baseline. Phase-I duration was faster following OLT (mean difference = -3.2 (8.1) seconds, 95% CI: [-8.3, -2], p = 0.0539, r = 0.39) compared to baseline. ORI also increased following OLT (mean difference = +12.8 (14.9) mL/min/s, 95% CI: [3.3, 22.3], p = 0.0126, Cohen's $d_{(unbiased)}$ = 0.83) compared to baseline. Furthermore, small effects for TD were observed following OLT (mean difference = +2.9 (11.5) seconds, 95% CI: [-4.5, 10.2], p = 0.4076, Cohen's $d_{(unbiased)}$ = 0.19) compared to baseline.

Table 2: $\dot{V}O_2$ On-Kinetics Outcomes.

Parameter	Pretest	95% CI	Posttest	95% CI	Pre-Post Change	95% CI	Standardized Effect Size	P value
$\dot{V}O_{2(baseline)}$ (mL/min)	261 (79.1)	[210.7, 311.3]	265.2 (75.5)	[217.2, 313.2]	+4.2 (57.7)	[-32.5, 40.9]	0.05*	0.8051
Phase-II τ (s)	33.7 (12.3)	[25.9, 41.5]	25.9 (15.3)	[16.2, 35.6]	-7.8 (11.5)	[-15.1, -0.5]	0.54*	0.0393
$\Delta\dot{V}O_2$ (mL/min)	954.7 (401.4)	[699.6, 1209.7]	970.4 (374.3)	[732.6, 1208.2]	+15.8 (216.7)	[-121.9, 153.4]	0.04*	0.8058
Phase-I duration (s)	33.1 (9.7)	[26.9, 39.2]	29.9 (11.5)	[22.6, 37.2]	-3.2 (8.1)	[-8.3, -2]	0.39⸸	0.0539ψ
ORI (mL/min/s)	29.7 (11.6)	[22.4, 37.1]	42.6 (17.7)	[31.3, 53.9]	+12.8 (14.9)	[3.3, 22.3]	0.83*	0.0126
TD (s)	15.9 (12)	[8.3, 23.5]	18.8 (16.5)	[8.3, 29.3]	+2.9 (11.5)	[-4.5, 10.2]	0.19*	0.4076

Description: $\dot{V}O_{2(baseline)}$ and $\Delta\dot{V}O_2$ are in units of mL/min. Phase-II τ and phase-I duration are in units of seconds (s). ORI is in units of mL/min/s. A superscript of "⸸" indicates calculation of r using Eq. 3. A superscript of "*" indicates calculation of Cohen's $d_{(unbiased)}$ using Eq. 2. A superscript of "ψ" indicates use of the Wilcoxon signed-rank test in lieu of a paired t-test.

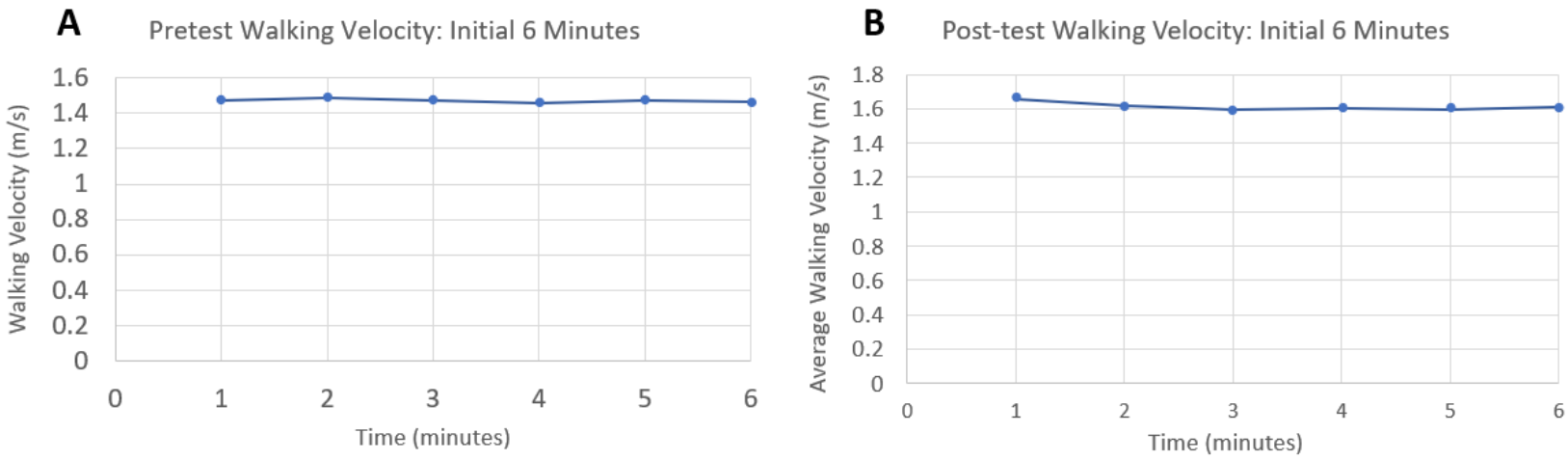


Figure 3: Walking velocity fluctuations. Pretest (A) and post-test (B) minute-by-minute walking velocity fluctuations during the first 6 minutes of the 10MWT. Graphs present mean data across all participants. Average pretest walking velocity during first 6 minutes of the 10MWT was 1.47 m/s and the fastest (1.48 m/s) and slowest (1.46 m/s) individual minute indicate a range of velocity fluctuation of 1.57% around the mean. Average post-test walking velocity during first 6 minutes of the 10MWT was 1.61 m/s and the fastest (1.66 m/s) and slowest (1.59 m/s) individual minute indicate a range of velocity fluctuation of 3.89% around the mean.

CHAPTER FOUR

Discussion

This study investigated the effects of a 24-session performance-based OLT program on performance and perceived fatigability and measures of $\dot{V}O_2$ on-kinetics during overground walking in a group of individuals with mild-to-moderate PD. The primary findings are as follows. First, our OLT program, which extends training concepts from the iSCI population to the PD population, induced reductions in performance fatigability during sustained overground walking. Second, following OLT, perceptual responses to sustained ambulation remained largely stable and only small effects for perceived fatigability index were observed. Third, faster $\dot{V}O_2$ on-kinetics were observed following OLT, suggesting potential improvements in cardiorespiratory fitness in response to gait training focused on skill acquisition in people with PD.

Our data demonstrate medium sized effects (Cohen's $d_{(unbiased)} = 0.64$) for the performance fatigability index following OLT in people with PD. We also observed small effects (Cohen's $d_{(unbiased)} = 0.25$) for pacing index following OLT, indicating that subjects displayed a minor change from baseline in the steadiness of their walking velocity during the 10MWT towards a pattern of slight speed deterioration in the posttest. However, pacing index scores of 100 at the pretest and 99.3 at the post-test indicate

relatively stable speed patterns throughout the 10MWT both before and after OLT. Thus, our analyses do not reveal any distinct or notable changes in the degree speed deterioration/increase throughout the 10MWT that would provide insight into how OLT may have impacted the regulators of walking pace in people with PD. We did, however, observe medium sized effects (Cohen's $d_{(unbiased)} = 0.54$) for total distance walked. It therefore appears as though the differences between subjects' pretest and post-test performance fatigability index scores were driven primarily by changes in total distance walked, rather than by drastic alterations in the degree of speed deterioration/increase throughout the 10MWT. Thus, total distance walked may be a more direct measure of performance fatigability in the context of sustained overground walking that does not require assumptions about the factors influencing speed regulation during the 10MWT.

Cross-sectional studies support the notion that perceived fatigability is often elevated during motor performance in people with PD.[2,4,10,46,47] Across our sample, we observed small effects for the perceived fatigability index (Cohen's $d_{(unbiased)} = 0.24$), which attempts to account for differences in activity demand by normalizing the raw perceptual scores to the total distance walked. However, when examining the individual components of the perceived fatigability index we observed relatively stable scores for raw perceptions of tiredness/energy (Cohen's $d_{(unbiased)} = 0.11$) alongside medium sized effects for increases in total distance walked. To our knowledge, there is only one previous study in PD to which we can compare the results of our analysis.[48] In the study mentioned by Burini et al., perceptions of breathlessness during a Six Minute Walk Test

(6MWT) decreased, and total distance walked increased, in people with PD following a bicycle ergometer training program. The results of our study differ from the results of Burini et al. in that they observed concurrent improvements in walking performance and walking-induced perceptual responses, while in our cohort, walking performance improved despite raw perceptions of energy/tiredness following the 10MWT remaining largely stable. The discrepancy between results may have been due to differences between intervention protocols with respect to the mode, intensity, or frequency of training. The discrepancy may have also been due to differences in subject recruitment (i.e., H&Y 1-3 in our study versus H&Y 2-3 in ours) or could be due to the fact that our self-report perceptual scale for measuring perceived fatigability differed from theirs. While our self-report scale queried participants on perceptions of energy/tiredness, theirs queried participants on perceptions of breathlessness, thus potentially leading to measurement of different aspects of the overall perceived fatigability construct. Moreover, both performance fatigability and perceived fatigability are believed influence endurance exercise performance through interactive mechanisms.[5,49,50] Despite our differing results from those of Burini et al., it has not escaped our attention that individuals in our cohort were able to walk, on average, 83.6 m further during the 10MWT following OLT while exhibiting relatively little change in their degree of self-reported tiredness/energy between pretest and post-test time points. This encouraging finding implicates underlying adaptations related to performance fatigability as potential modulators of overall improvements in walking endurance across our sample.

In the absence of previous reports on $\dot{V}O_2$ on-kinetics in people with PD, the closest comparison is a study by Murias and colleagues. The authors of that study observed an 11 second reduction in phase-II τ in a small group of older men following a 12-week aerobic training program.[51] Consistent with the findings of Murias et al., we observed medium sized effects (Cohen's $d_{(unbiased)}$ = 0.54) and mean reductions of 7.8 seconds in phase-II τ following OLT. Although the self-paced nature of the 10MWT differs from the more precise laboratory-based controlled perturbations typically used to measure $\dot{V}O_2$ on-kinetics we observed minimal walking velocity fluctuations during the initial 6 minutes of the 10MWT (Figure 3). Moreover, our measure provides a description of cardiorespiratory adjustments to increases in energetic demand that more closely reflect what occurs in everyday life, as reported previously.[22] Also, as indicated by large effects (Cohen's $d_{(unbiased)}$ = 0.83) and mean improvements of 12.8 mL/min/s for the ORI, which reflects both the magnitude of $\dot{V}O_2$ increase and the rapidity of adjustment, individuals in our sample displayed an increased capacity to adjust to a given change in energetic demand following OLT, suggesting an improved responsiveness of the oxidative metabolic system.

Currently, there is a paucity of research regarding the physiological factors most relevant to walking endurance in people with PD.[5,52] However, the findings of the current study provide preliminary evidence addressing this knowledge gap. Slower $\dot{V}O_2$ on-kinetics is associated with greater reliance on anaerobic metabolism during transient increases in energetic demand and are indicative of an upregulation of processes that are

associated with concomitant attenuation of skeletal muscle performance and increased perceived fatigability.[15–19] In contrast, faster $\dot{V}O_2$ on-kinetics following exercise training are associated with decreased reliance on anaerobic metabolism during activity and enhanced exercise tolerance.[17–19] While we cannot confirm the presence of these underlying relationships in our sample, our available data showing faster $\dot{V}O_2$ on-kinetics alongside improved walking distance and small changes in perceived fatigability index following OLT suggests that cardiorespiratory fitness could play an important role in determining walking endurance in people with PD. The concurrent improvements in overground walking endurance and $\dot{V}O_2$ on-kinetics reported in the present study lend support to the hypothesis that cardiorespiratory fitness may be a relevant target for interventions seeking to improve sustained ambulation in people with PD, however, future randomized and more mechanistic studies would be needed to definitively support this hypothesis.

The literature provides some clarity regarding the relative efficacy of different gait related interventions in people with PD, but offers no clear indication regarding the optimal methods to improve overground walking endurance in members of this patient population.[2,28,48,53–78] For example, evidence suggests that higher metabolic training intensity may bolster walking related outcomes[28,69,77,79] and that gait specific training may be more beneficial than multimodal approaches or training focused only on remediating impairments thought to constrain performance.[65,76,80] However, other key training parameters such as environmental specificity and practice variation have been less

rigorously studied in PD. The results of our study are notable because they indicate the initial success of a program derived from training concepts frequently used in healthy and other neurologically impaired populations.[12,33–36] Our low-tech and exclusively overground OLT protocol relies on established training principles such as task-specificity, practice variation, and progressive overload, rather than on specialized equipment or activities not closely related to walking, and therefore may provide a foundation and basis for further studies grounded in a similar approach. Our data also demonstrate the potential for submaximal measures of cardiorespiratory fitness to be improved by training focused on improving general aspects of multi-planar gait function performed in an exclusively overground environment. This is a potentially clinically important point, as maintenance or improvement of cardiorespiratory fitness is increasingly being recognized as a treatment priority in PD.[79,81–83]

CHAPTER FIVE

Limitations

A small sample size reduces the generalizability of our results. Second, the lack of a control group makes it difficult to determine if the changes in outcome measures observed were the result of natural changes over time rather than the result of our intervention. Third, for the purposes of increasing the precision of the measure, it is often recommended that $\dot{V}O_2$ on-kinetics parameters be calculated by averaging the data multiple bouts of exercise.[37] Since we analyzed $\dot{V}O_2$ on-kinetics parameters using only a single bout of exercise at each testing time point, one possible limitation to the present analysis is the contention that the changes observed are due to day-to-day variability inherent in our measure.[37,84] Lastly, the absence of a $\dot{V}O_2$ max test and a reliable determination of the $\dot{V}O_2$ at the first ventilatory threshold limits the comparability of our measures of $\dot{V}O_2$ on-kinetics to others reported in the literature.

CHAPTER SIX

Conclusion

These findings provide preliminary data supporting the potential for improved performance fatigability and $\dot{V}O_2$ on-kinetics during sustained overground walking following the OLT program described herein. Results for perceived fatigability during sustained ambulation were of smaller magnitude. Future studies are required to reinforce and clarify the present findings and to determine how training concepts intrinsic to our OLT protocol may be more successfully applied to improve walking performance and related variables in people with PD.

APPENDIX

DEPARTMENT OF REHABILITATION SCIENCE DISSERTATION COMMITTEE AND PROPOSAL APPROVAL FORM

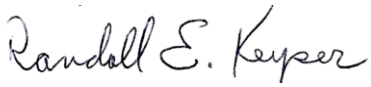
STUDENT: ANDREW E. PECHSTEIN

PROPOSAL TITLE:

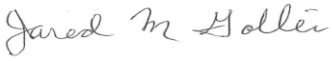
FATIGABILITY AND CARDIORESPIRATORY FITNESS DURING SUSTAINED WALKING FOLLOWING OVERGROUND LOCOMOTOR TRAINING IN INDIVIDUALS WITH PARKINSON'S DISEASE

Proposed Committee:

Andrew A. Guccione, PT, PhD, DPT, FAPTA,
Chair



Randall E. Keyser, PhD, FACSM
Committee Member



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Rosemary D. Higgins, MD
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Date: __June 16, 2020_____ Summer Semester 2020
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Dissertation Proposal

by
Andrew Pechstein, BA

Abstract and Proposal Summary

It has been demonstrated that multiple impairments are likely responsible for the full range of ambulatory disabilities in people with Parkinson's Disease (PD). Fatigability, a phenotype that describes the susceptibility to fatigue during activity performance, is a challenge for individuals with PD, especially when walking distances that require endurance. The traditional approach to addressing this problem in this population is to target each contributing impairment separately while assuming that piecewise remediation of constraints will fully translate to improved walking. However, this approach may fail to fully account for the emergent properties of human movement, specifically, the dynamic nature of constraint interactions that facilitate human performance, and therefore may fall short of intervention strategies that incorporate principles of task-specific training and motor learning.

Our department developed and piloted a 12-week 24-session performance-based overground locomotor training (OLT) program in people with PD based off of our previous departmental work with people with incomplete spinal cord injuries. The OLT program is grounded in the overall theory that improvements in human performance are most thoroughly attained when individuals are immersed in a therapeutic experience that challenges their ability to resolve multiple constraints concurrently within the context of an activity outcome of interest. Along this line, improvements may occur across multiple systems in a manner that is dictated by the unique constraints of each individual.

As part of a parent study that will characterize other domains of human performance improvement in response to OLT, this proposed project, using each subject as their own control, will examine how fatigability and cardiorespiratory fitness (CF) might improve concurrently following OLT in people with mild-to-moderate PD. The goal of this project is to demonstrate that fatigability and CF are mutable by OLT and to examine if improvements in fatigability may be associated with certain improvements in CF.

Specific Aims

Walking performance in individuals with Parkinson's Disease (PD) is often compromised and multiple impairments are likely responsible. Despite this complexity, poor cardiorespiratory fitness (CF), often present in people with PD, may stand out as a key contributor to reduced endurance walking performance (EWP). Ambulatory disability of this kind may predispose individuals with PD to increased fatigability (i.e., performance fatigability and perceived fatigability) and reduced volitional activity, which may hamper their ability to engage in life activities, limit their engagement in beneficial exercise participation, and degrade their overall health. Evidence to date suggests no consensus regarding the most optimal intervention(s) to improve endurance related walking outcomes in this population, despite the relevance of this type of outcome to real-life ambulatory activities.

Performance-based interventions, such as our recently developed overground locomotor training (OLT) program, have been shown to be well-suited for addressing complex mobility issues in other populations, however their effects in individuals with PD remain unknown. Given the multiplicity of constraints on movement in people with PD, and the potential for OLT to concurrently address many of these constraints as they relate to walking, improvements in EWP may be facilitated by adaptation across multiple systems in response to OLT.

One such adaptation to OLT, one that we consider to be critical for reducing fatigability, may be improvements in CF. However, in this population, it is unknown if fatigability and CF improve following OLT and it is unknown if any such changes are associated. Therefore, the purpose of this study is to characterize changes in fatigability and CF following a 12-week, 24 session OLT program in individuals with mild-to-moderate PD.

Specific Aim 1: Characterize changes in fatigability following OLT during a 10 Minute Walk Test (10MWT) in individuals with PD.

H1a) Performance fatigability will be reduced following OLT. This will be demonstrated by reductions in performance fatigability severity index.

H1b) Perceived fatigability will be reduced following OLT. This will be demonstrated by reductions in perceived fatigability severity index.

Specific Aim 2: Characterize changes in CF following OLT during a 10MWT in individuals with PD.

H2a) The pulmonary inspired oxygen on-kinetic response will be sped following OLT. This will be demonstrated by reductions in the phase-II time constant (τ) of the VO_2 response during the initial portion of a 10MWT.

Upon completion of this study we will have determined if our OLT program produces favorable effects on walking performance in individuals with PD. More specifically, we will have provided an initial characterization of what effects OLT may have on fatigability and certain aspects of CF in individuals with PD. If our hypotheses are supported, we will have demonstrated concomitant improvements in fatigability and CF in response to OLT.

Detailed Statement of Research Problem

Parkinson's Disease (PD) is now second to Alzheimer's Disease as the most prevalent neurodegenerative disease in the world and has overlapping etiologies with other synucleinopathies and Lewy body diseases.[85] An estimated 1.04 million individuals in the United States (US), and an estimated 6.1 persons worldwide live with the debilitating symptoms and functional limitations of PD.[86] In the US, the annual medical costs associated with PD were approximately $25.4 billion, $24,439 per patient/year above those not having PD.[86] 90% of this medical cost is borne by PD populations with Medicare coverage, placing a significant burden on the nations federal healthcare system.[86] In addition to the debilitating symptoms and comorbidities of PD, patients have more medical needs, frequently miss work, retire early, have reduced social participation, and require assistance from a caregiver.[86] When considered on a worldwide scale, the economic and social impact of PD becomes massive. The number of people age 65-and-over in the US is projected to nearly double from 48 million to 88 million by 2050 and the global population of people aged 80 and older is expected to triple between 2015 and 2050 from 126.5 million to 446.6 million.[87] These figures are sobering, given the critical fact that age is the greatest risk factor for PD.[86]

Reduced performance during sustained walking activities is common among people with PD,[2,3,88–92] and is an underappreciated phenotype of ambulatory disability in this population. Reduced endurance walking performance (EWP) has garnered much research interest in diseased and healthy populations because of its associations with fatigue,[93,94] fatigability,[93–95] frailty,[95,96] physical activity,[95,97] and mortality risk[96,98,99] in addition to its usefulness as a testing paradigm for identifying factors related to mobility limitation.[93–95,100–102] While not as rigorously studied as other aspects of gait in people with PD such as balance, spatiotemporal parameters, and short-distance ambulation, reduced EWP in people with PD may be associated with fatigue[103] and disease-specific symptom severity.[91] Taking a lesson from what has been demonstrated about the relationship between EWP and health in other populations, it seems logical that reduced EWP may pose a barrier to physical and social functioning in the lives of people with PD. Given these notions, preservation and improvement of capability and ability with respect to sustained ambulation is critical for people with PD. Additionally, reduced EWP in

people with PD may be indicative of underlying impairments which make continued engagement in structured exercise difficult. Recent evidence also shows that physical activity and structured exercise may have positive effects on primary and secondary PD symptoms,[104] potentially through neuroprotective mechanisms.[104,105] Thus, in addition to its role in facilitating physical and social participation, preservation or improvement of EWP may help individuals with PD garner the disease-specific benefits of regular physical activity.

Reduced EWP in people with PD is attributable to a complex interaction of numerous constraints that may arise from alterations in multiple physiological systems. In cross-sectional studies reduced EWP has been found to be associated with reduced economy of gait,[88,89] reduced balance performance,[89–91] freezing of gait,[91] and reduced quadriceps power.[106] Common symptoms such as bradykinesia, resting tremor, and rigidity are largely attributed to degeneration of nigrostriatal dopaminergic neurons.[107] Alterations in arm-leg coordination have been linked to changes in the function of the basal ganglia.[108–110] Non-dopaminergic dysfunction is implicated in motor problems including posture, balance, gait disturbances, and fatigue.[107] Reductions in skeletal muscle strength and power have been attributed to deficits in central activation, rate of force development, denervation-reinnervation processes, type-1 fiber type grouping, atrophy, and alterations in contractile morphology.[68,111–113] Reductions in physical work capacity have been linked to reduced exercise efficiency, reduced VO_2 peak, and blunted cardiovascular response during exercise.[8] The idea that variability in EWP may be attributable to variability in multiple constraints in people with PD is being increasingly recognized in the field.[107,114]

Recognition of this complexity has called for recommendations to perform training that specifically targets these deficits (e.g., cueing for coordination, balance drills for stability, stretching for rigidity, resistance exercises for reduced power, conditioning exercise for aerobic capacity, etc.) as part of comprehensive treatment for ambulatory disability.[80,115] Coordination, balance, rigidity, reduced power, and aerobic capacity all appear to be favorably mutable using training methods that target these deficits directly.[26,68,111,116–118] However, these favorable adaptations may not fully translate into improved EWP.

Even using training programs wherein improvement in walking performance was an explicit goal, changes in EWP are inconsistent. From the literature we identified 12 exercise rehabilitation studies that included 6MWT as an outcome measure.[28,54,55,58,61,62,64,67–70,119]Many modalities are efficacious for improving EWP, however evidence to date is insufficient to reach any consensus as to the optimal form of training to promote improvements in EWP in people with PD, a conclusion which is in agreement with the findings of Ni and colleagues in their 2018 review of exercise guidelines for gait function in PD.[80]

Theoretical Framework

Fatigability Describes Elements of Endurance Walking Performance

In this proposed project we will be operationalizing our primary measure of EWP within the framework of fatigability.[5,120,121] To understand the scope of the concept of fatigability, the construct of fatigue must first be defined. Fatigue is defined as a disabling symptom in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability[5]. Fatigue is believed to ensue during the performance of activities. Therefore fatigue is expressed in terms of fatigability; a broad concept operationalized as a composite measure. Fatigability measures and ranks activity performance at the level of organism-to-environment interaction (i.e., power output, walking speed) and captures any phenomena that may contribute to fatigue during such performance (Figure 1). Performance fatigability broadly denotes physical elements of such fatigue while perceived fatigability broadly denotes perceptual elements of such fatigue. By expressing the provocation of physical and perceptual elements of fatigue relative to the demands of activity performance (i.e., speed, power output, intensity, distance), fatigability, as a concept, is broad in scope and encompasses mechanistic contributors to performance through to the outcome of performance itself. This framework integrates well into our dynamic-systems constraints-based model for the emergence of human activity performance (see Figure 2). Reductions in fatigability may be a favorable by-product of gait interventions that intervene on movement performance using a dynamic-systems constraints-based approach (see OLT Training, in Methods section). In this study, performance fatigability and perceived fatigability will be operationalized using the index measurements developed by Schnelle and colleagues 2012, which characterize phenotypes of physical and perceptual elements, rather than mechanistic factors.[95]

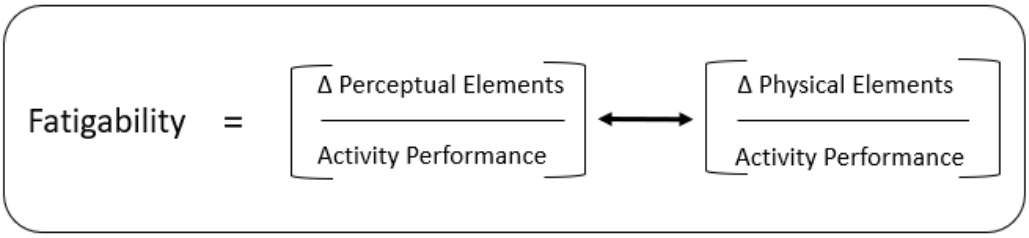

Figure 4: *Schematic of fatigability and its constituent domains. In this framework activity performance is used to rate the demands of the activity. Changes in perceptual and*

physical elements are understood within the context of the activity that provokes such changes. In our opinion, ratings of activity performance must be made using the same criteria that was communicated to the subject prior to testing (a measure of human performance), as the movement solution used to complete the task successfully is influenced by the intentions of the performer. In accord with this assertion, total distance walked on a 10-minute walk test will be the measure of "activity performance" and changes in specific phenotypes of perceptual and physical elements will be expressed as respective numerators in each domain (see Methods section).

Dynamic-Systems Constraints-Based Model of Human Performance

To date, interventions to improve EWP in people with PD have incompletely applied the treatment implications embedded in the frameworks of Sparrow and Newell 1998, Holt 2010, Glazier 2017, and Guccione et al 2019.[13,122–124] In these frameworks, movement, the phenomenon to be treated during rehabilitation, is considered as an emergent behavioral phenotype that arises from the interactions of task, environment, and organismic constraints (Figure 2, footnote A). The underlying theory of performance-based treatments, for any patient population, asserts, that within the context of an activity outcome of interest (EWP for example), improvements in human movement expression, and thus improvements in human performance, are facilitated by a more successful optimization of existing organismic constraints (constraints which may emanate from the structure and/or function of single, or multiple, body systems which influence the expression of movement in relative isolation or in dynamic concert), a remediation of such organismic constraints, or a combination of both processes (Figure 2, footnote B). For individuals with PD, performance-based treatment is theoretically well suited to improve the activity level outcome of EWP, thereby potentially reducing fatigability. Multiple adaptations may occur in tandem with these theorized improvements, thus potentially further reducing fatigability.

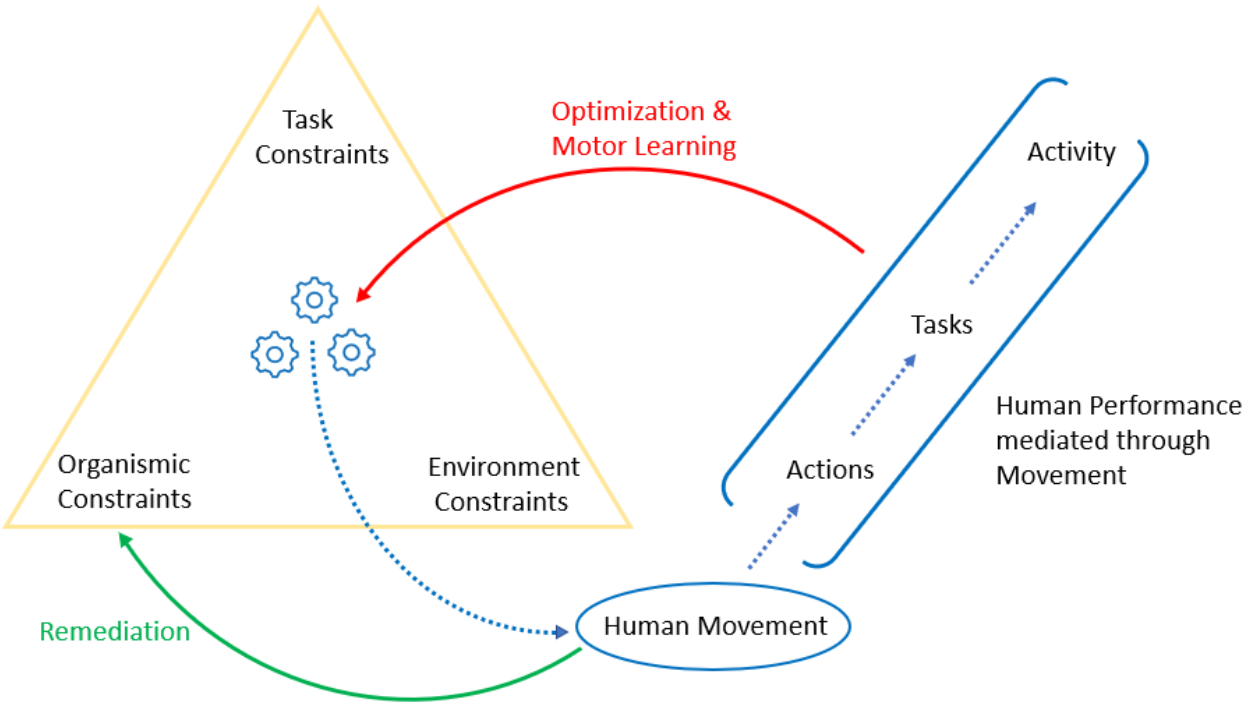

Figure 5: *A) Application of dynamical systems theory to a constraints-based framework that describes human performance.*[13,122–124] *Human movement, the primary mediator of human performance emerges from the interaction of organismic, environmental, and task constraints to produce the building blocks (actions and tasks) of activity performance: entire phenomenon depicted in blue. For people with PD, this model can be used to broadly conceptualize how various organismic constraints, at multiple levels of biological organization, are integrated with respect to environmental and task constraints to produce an activity performance phenotype. Because of the may organismic constraints common to people with PD, fatigability may be elevated during activity performance. B) To improve EWP during training, individuals practice movement drills that reflect the actions, tasks, and activities relevant to EWP. These drills are performed repetitively using sufficient practice variation. Drills also progress in difficulty and intensity. This training experience facilitates a more successful optimization of existing constraints through a process akin to motor learning (red arrow). The motoric and metabolic demands of the practiced drills also impose stress directly upon organismic constraints (green arrow). Theoretically, as optimization/motor learning occurs in tandem with organismic constraint remediation, future attempts at activity performance may occur using more optimal patterns of coordination and control alongside relaxation or removal of organismic constraints, via physiological adaptation of systems that previously posed limitations to activity performance.*[13] *Such adaptations may be favorable for reducing perceived and performance fatigability.*

Cardiorespiratory Fitness and its Relationship with Fatigability

Cardiorespiratory fitness (CF), defined here as the ability of an individuals' circulatory, respiratory, and muscular systems to deliver and utilize oxygen over prolonged periods of physical activity,[42] is often diminished in tandem with increased fatigability. In healthy and patient populations low levels of CF have been shown to be associated with increased physical[125–128] and perceptual[127] components of fatigability. CF may be compromised in individuals with PD because of impairments in oxygen delivery,[7,8,47,129–135] and/or intramuscular factors.[68,136–140] These impairments may restrict the ability of people with PD to sustain high levels of muscular activity,[8,133,137,141,142] which may contribute to increased performance fatigability. Concomitantly, reduced CF in people with PD may contribute to elevated feelings of exertion and higher perceptions of fatigue in response to activity.[4] A theoretical framework has been put forth and supported in which improvements in CF occur in association with improvements in fatigability,[143] however this framework has been incompletely characterized in people with PD. We believe that performance-based gait training may improve fatigability and CF concurrently in people with PD (Figure 3).

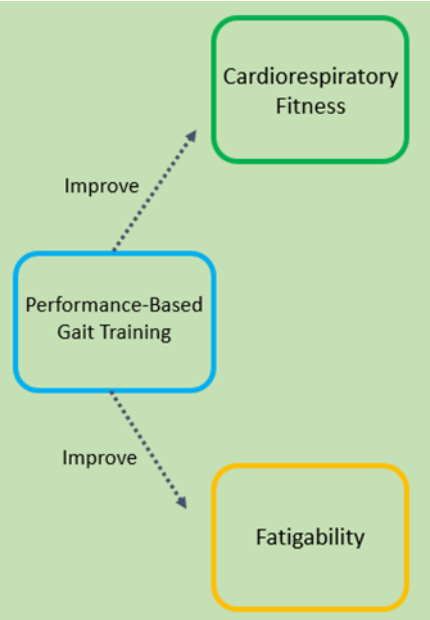

Figure 6: *Hypothesized impact of performance-based gait training on cardiorespiratory fitness and fatigability.*

Cardiorespiratory Fitness Operationalized by VO_2 On-Kinetics

VO_2 on-kinetics is an objective phenotype of aerobic function that is unaffected by subject motivation. Upon initiation of physical activity, muscular contraction creates an energy demand. The output of the oxidative metabolic pathway increases gradually to meet this energy demand while anaerobic metabolism compensates for what would otherwise be an energy deficit.[19,20,42] The degree of anaerobic contribution, indirectly determined by the rate of increase in aerobic metabolism, has been shown to be deleterious to muscle function and activity continuance. VO_2 on-kinetics reflect the ability of the oxidative metabolic system to increase ATP production in response to abrupt increases in muscular activity.[144] VO_2 on-kinetics are influenced by function of the circulatory, respiratory, and muscular systems, thus directly reflecting aerobic function.[16] VO_2 on-kinetics are often associated with other objective phenotypes of CF such as peak VO_2 and anaerobic threshold (AT).[42,145]

Study Design

As part of a parent study (ClinicalTrials.gov Identifier: NCT03864393) that will be assessing neuromuscular, kinetic, kinematic, and spatiotemporal, adaptations in response to OLT in people with PD, this proposed analysis will examine changes in two domains of fatigability during EWP (performance / perceived) and changes in CF according to one of its major phenotypes, VO_2 on-kinetics (see appendix for parent study details). A prospective longitudinal pre-experimental design will be used to determine the changes in outcomes following OLT in unblinded non-randomized subjects with mild-to-moderate PD. Monetary compensation will not be given to participants for participation in this study. There will be no incentives offered to prospective participants. All subjects will be diagnosed with mild-to-moderate PD. Subjects will undergo verbal phone screening to ensure meeting inclusion criteria and absence of any exclusion criteria. For the purposes of our study, mild-to-moderate PD will be defined as classification within stages 1-3 on the Hoehn and Yahr (H&Y) scale. During their first visit to the laboratory and prior to any data collection or experimental protocol implementation, the risks, benefits, procedures, and confidentiality agreements associated with participation in the study will be explained to the subjects. This proposed project is an analysis of subsets of data from the overall parent study. A complete copy of the informed consent used for the parent study is included in the Appendix section. Upon voluntary decision by the subject, the informed consent will be signed. After the informed consent is signed, height, weight, and anthropometric measurements will then be recorded (see data collection sheet in appendix section). Subjects will then be administered the Standardized Mini-Mental State Examination (SMMSE) (a copy of the SMMSE can be found in the Appendix). Subjects scoring <24 on the SMMSE will be excluded from the study. Subjects will then fill out a medical history form and will supply the research team with a list of all currently taken medications and supplements (see medical history form in appendix section), after which H&Y evaluation will be performed by a licensed Physical Therapist. Subjects will then undergo an over-ground 10-minute walk test (10MWT). Time intervals and distance iterations will be recorded throughout the 10MWT for performance fatigability test scoring (see data collection sheet in Appendix section). Self-reported changes in energy levels will be assessed following the 10-minute walk test to determine perceived fatigability (see Fatigue and Fatigability Scales image under Perceived Fatigability Severity Test Scoring section). A portable metabolic system will be used to measure gas exchange variables for VO_2 on-kinetics determination. Following pre-intervention testing subjects will complete the 12-week, 24-session OLT regimen. Following OLT, subjects will repeat the tests performed prior to the intervention. Intra-subject pre-post differences will then be determined and the changes in these outcome measures, and their associations, will be analyzed for clinical and biological relevance.

Study Management: Adverse events and serious adverse events will be managed according to the guidelines outlined in the parent study IRB application (see appendix for copy of parent study IRB application). Data privacy and data security procedures will be followed according to the guidelines outlines in the parent study IRB application (see appendix for copy of parent study IRB application). Based on our previous experience in implementing a similar training protocol in individuals with incomplete spinal cord injury

we know that for various reasons subjects infrequently miss training sessions. In the event that a subject misses a scheduled training session, the session will be rescheduled. Only subjects who complete the entire 24-session protocol will be included in the analysis.

Study Population: Participation of human subjects will be approved by an institutional review board prior to initiation of the study. Exercise and physical therapy are often recommended to individuals with PD, therefore, careful consideration of the nature of such activities will be evaluated prior to enrollment. Routine walking, light-to-moderate aerobic activity, stretching, yoga, and other physical activities primarily undertaken by the individuals to maintain physical functioning will not be considered an exclusion criterion. However, if individuals express the intention to progressively overload the intensity of these otherwise permissible activities with the goal of acutely expanding their functional capacity within the same timeframe as the study, such activities may confound the results of our study and will warrant delayed entry into the study until such time that said activities have ceased. Activities in which the primary nature and mode are similar to OLT will be considered criteria for exclusion. The inclusion and exclusion criteria for enrollment into the study are as follows.

Inclusion Criteria

- Participants must be between the ages of 18 and 85.
- Diagnosis of mild to moderate Parkinson's Disease (H&Y 1-3).
- Able to understand basic commands and communicate needs in English.
- Able to ambulate without the use of assistive or orthotic device in an indoor community environment for at least 150'.
- Desire and ability to complete the protocol.

Exclusion Criteria

- Participants must not have any neurological disease diagnosed other than PD.
- Participants must not have any cardiovascular, pulmonary, neurological, metabolic, or other condition whose severity or treatment limits the ability to engage in sustained exercise, or for which exercise is contraindicated.
- Participants must not be taking any medications, such as beta-blockers, calcium channel blocking agents, or antiretrovirals, or medications that may alter heart rate or gas-exchange metabolic data.
- Participants must not have a mini-Mental State Examination score of <24.
- Pregnancy
- Current participation in other clinical trials.

10 Minute Walk Test: The purpose of this test is to provide a measurement of EWP in a manner that has ecological validity and to provide a testing paradigm wherein performance fatigability, perceived fatigability, and VO_2 on-kinetics may be assessed. During testing subjects will be fitted with a portable metabolic unit (COSMED K5) so that breath-by-breath pulmonary gas exchange and other cardiorespiratory variables can

be recorded throughout the entire testing period. This metabolic unit is lightweight, and does not restrict natural movements of the body during walking. Previous investigations have confirmed that walking distances are unaffected by wearing of the unit.[31,146] and that overground walking tests with gas exchange monitoring yield a reliable testing paradigm within which measures of VO_2 on-kinetics can be accurately assessed.[22,147] Upon initiation of the test, subjects will rest in a seated position for 3 minutes, with blood pressure recorded after 2 minutes in the sitting position. After 3 minutes seated rest, subjects will stand and rest for 4 minutes in a standing position, with blood pressure taken 1 and 3 minutes after the transition from sitting to standing. After 4 minutes of standing rest, subjects will walk continuous laps for 10 minutes in a 60-meter flat indoor corridor. The instructions given prior to testing will be to, "walk as far as you can in 10 minutes" or "walk as many laps as possible in 10 minutes". Motivational support or encouragement will not be given during the test. Following the 10-minute walk period (or total time if ended early) subjects will rest in a standing position to obtain measurements of blood pressure. A chair will be provided to the subject during recovery if needed.

Performance Fatigability Severity Test Scoring: During the 10-minute walk test distance covered will be recorded at the 2.5-minute interval of the test and for the total test. Velocities for the entire test (total distance walked / total minutes of test) and the first 2.5 minutes of the test (distance covered in the first 2.5 minutes / 2.5 minutes) will be calculated. The fractional change in velocity will then be computed as the quotient of (total test velocity / velocity in first 2.5 minutes). Fractional change in velocity will then be divided by the total distance walked (m). Scores are multiplied by 1000 to facilitate reporting. The full equation is as follows: performance fatigability severity = {[(average velocity overall / average velocity first 2.5 mins) / (total distance)] * 1000}. A small score indicates lower fatigability.[95]

Fatigue and Fatigability Scales

Fatigue Scale Items (*Before Walking Test*)		Fatigability Scale Items (*After Walking Test*)
• Extremely Tired	7	• Extremely Tired
• Somewhat Tired	6	• Somewhat Tired
• A Little Tired	5	• A Little Tired
• Neither Tired nor Energetic	4	• Neither Tired nor Energetic
• A Little Energetic	3	• A Little Energetic
• Somewhat Energetic	2	• Somewhat Energetic
• Extremely Energetic	1	• Extremely Energetic

Figure 7: Fatigue and Fatigability

Perceived Fatigability Severity Test Scoring: After the initial 7-minute resting period, subjects will rate their perception of fatigue or vigor using the left side of the Fatigue and Fatigability Scale. The left side of this scale is considered a measure of fatigue because it measures subjective energy level prior to engaging in the 10-minute walk test. The subject's response to this side of the scale serves to provide a benchmark score of subjective rating of energy level. Following the 10-minute walk test, subjects will be asked "compared to when you started, how would you rate your energy level or tiredness

now?" using the right side of the scale, which provides a subjective metric of change in energy level following the 10-minute walk. By comparing responses prior to, and after the 10-minute walk, the research team will capture a subjective report of perceptual symptoms of fatigability following the 10-minute walk. Scores on the perceived scale (changes in energy level) are then divided by the total distance walked to capture perceptions of fatigue in the context of total test performance. Formal calculations of the perceived fatigability score are ((perceived fatigability severity = change in tiredness after walking / total distance walked) x 1000). Scores are multiplied by 1000 for reporting purposes. A smaller score indicates a lower severity of perceived fatigability.[95]

VO_2 On-Kinetics Modeling: Our primary variable of interest for this measurement is the phase-II time constant (τ). Breath-by-breath VO_2 data collected during the 10MWT from the COSMED K5 will first be exported. Data points from the first 6 minutes of the 10MWT will be analyzed. Data points deemed physiologically improbable due to coughing, sneezing, or talking be removed. VO_2 data will be filtered to remove data points that lay outside a 99% prediction band, interpolated into 1-second intervals, time-averaged into 5 second bins, and time aligned to correspond to the start of the 10MWT. Using computerized software (Origin Lab, 2019, Northampton, MA, USA), a mono-exponential model (Eq. 1) will be fit to data between the start of phase-II and 6 minutes of exercise.[42,127,148]

$$Eq.\,1: \qquad VO_2 = VO_{2(baseline)} + \Delta VO_2\left[1 - e^{-(\frac{t-TD}{\tau})}\right]$$

OLT training: In accordance with previous walking interventions for people with PD and with respect to departmental resources subjects will undergo 60-min bi-weekly training sessions for 12 weeks. Sessions focus on the actions involved in each sub-task of walking e.g., weight shifting and stepping. Power development through the lower extremities is coached relevant to its contribution to walking. Each component is isolated at the beginning of the session and drills progress in complexity and intensity throughout the session. Participants progress from isolated movements to dynamic agility exercises with specific foci. Each session culminates with activity rehearsal consisting of dynamic walking at a variety of speeds and tempos and in various directions and patterns. Small hand weights and gait belts are frequently used during various exercises to provide external resistance and to increase the load and intensity of drills. The American College of Sports Medicine defines aerobic training to be exercise of enough intensity to evoke a heart rate response of 55-90% age predicted maximum heart rate (220-age), therefore exercise programs with an aerobic component typically call for intensity that falls within that range.[149] Participants will wear a heart rate monitor throughout training sessions for data recording and to aid trainers in adjusting the intensity of the session to meet the 60% HR minimum. As previously outlined in detail, multiple constraints are likely responsible for increased fatigability during walking in people with PD. This training protocol is designed to coach individuals towards more successful movement solutions using repetitious and task-specific part-to-whole practice with sufficient variability. This approach is consistent with current motor learning paradigms.[12,126] Previously our department demonstrated improvements in walking economy using this approach to

training in a group of individuals with incomplete spinal cord injury.[150] Given the recent findings that performance fatigability and perceived fatigability is increased as a function of increased activity energy expenditure[151] it seems logical that an improvement in walking economy following OLT might reduce fatigability during sustained ambulation[122]. Furthermore, CF might be improved following training as a by-product of the aerobic intensity of training sessions, thus further reducing fatigability (see Theoretical Framework section for more details).

Power and Sample Size: Our primary outcome measure is changes in fatigability, which is comprised of index measurements of two sub-domains, performance fatigability severity and perceived fatigability severity (see Figure 1). A commonality to both sub-domains is the total distance walked during the 10MWT. We were unable to find any intervention study in the PD literature that assessed changes in a 10MWT, therefore we proceeded with power calculations based off of changes in 6MWT reported previously in the literature. In a study conducted by Shulman et al 2013 6MWT distance was assessed before and after participation in a 12-week thrice-weekly high intensity treadmill training program in 23 individuals with PD. In this group, 6MWT distances (measured in feet) were 1374.2±57.4 prior to training and were 1451.2±62.5 following training.[28] Using the formula for Cohen's d, we calculated this change to have an effect size of 1.29. Although the study by Shulman has some similarities to the study proposed here, we have decided to proceed conservatively with our power and sample size estimation using an effect size of 0.6. A Cohen's d effect size of 0.6 is considered to be moderate-to-large. In the context of a rehabilitation intervention study, a moderate-to-large effect size is considered to be clinically meaningful. We computed power to detect a change in 10MWT distance between pre- and post-measurements using a one-tailed paired t-test with a significance level of 0.05 at 80% power. Based on our calculations, our anticipated required sample size is 19 individuals with PD.

Descriptive Statistics: Means and standard deviations will be used to summarize continuous data, while frequency counts and proportions will be used to summarize categorical data.

Tests of Normality: A Shapiro-Wilk test will be used to determine the normality of data.

Analysis of Primary Outcome: Pre- to post-test intrasubject changes in performance fatigability severity scores and perceived fatigability severity scores will be characterized using one-tailed paired Student's t-tests. Statistical significance will be accepted at $p \leq 0.05$. Statistical tests of homogeneity of variance will be performed. In the event of heterogeneity of variance, non-parametric analyses will be substituted. Effect sizes will be calculated using the formula for Cohen's d in addition to 95% confidence intervals for the difference in means.

Analysis of Secondary Outcome: Pre- to post-test intrasubject changes in phase-II time constant and other derived measures of VO_2 on-kinetics will be characterized using a

one-way analysis of covariance model (ANCOVA). Statistical significance will be accepted at $p \leq 0.05$. The average velocity during the first 6 minutes of the 10MWT will be used as a covariate in the ANCOVA model. Statistical tests of homogeneity of variance will be performed. In the event of heterogeneity of variance, non-parametric analyses will be substituted. Effect sizes will be calculated using the formula for Cohen's d in addition to 95% confidence intervals for the difference in means.

Correlation Analyses: Relationships between pre-training and post-training measures of fatigability and CF will be assessed using Pearson product-moment correlation coefficients with a significance level of 0.05. Relationships between demographic and baseline variables and post-test measures of fatigability and CF will be assessed using Pearson product-moment correlation coefficients with statistical significance accepted at $p \leq 0.05$. Spearman ranked correlation coefficients will be substituted if non-normality is found.

Secondary Analysis: Following univariate analysis of the primary outcome and ANCOVA of the secondary outcome, multivariate analysis will be performed to examine relationships between baseline or demographic variables that potentially influence study outcomes.

Scope and Boundaries of Proposed Study

VO_2 On-Kinetics

Defining the exercise intensity domain within which VO_2 on-kinetic measurements are made is important because the characteristics of responses are affected by the domain of exercise intensity used to perturb the subject. Many cross-sectional investigations have demonstrated an inherent within-subject slowing of the phase-II time constant (τ) with increasing exercise intensity.[144,152–155] Thus, it seems that increased exercise intensity slows the phase-II time constant. The goal of Aim 2 is to determine if the phase-II time constant during the 10MWT is significantly faster following OLT training. Our Aim 2 hypothesis is that OLT training will positively impact the phase-II time constant (i.e., faster). Since we anticipate that the majority of our subjects will attain a higher absolute exercise intensity (i.e., increased speed and VO_2) during the post-intervention 10MWT than in the pre-intervention 10MWT it is likely that our measurement paradigm for VO_2 on-kinetics biases us against showing a training effect on the phase-II time constant. This is a potentially conservative bias. We will mitigate the bias that walking velocity has on the phase-II time constant by using an ANCOVA model to analyze our second aim and by using walking velocity as a covariate in this model.

Constant work rate exercises, regardless of the modality (bike, treadmill, constant load muscle contractions), allow for variance within the physiology of the person to be studied in relative isolation, as the ATP turnover rate is held steady. During the 10MWT subjects may display slight fluctuations in speed, thus reducing the steadiness of the

exercise perturbation. Kern et al 2014 studied VO_2 on-kinetics during a 6MWT in 258 subjects of different varied health status. Out of 258 completed 6MWT, mono-exponential modeling of the rest-to-work transition succeeded for 220 samples, an 85% success rate. Reasons cited for lack of model fit in the remaining 15% were lack of a plateau in VO_2, pauses for rest breaks, and excessive fluctuations in speed.[22] Additionally, studies by Jones et al 2007 and Turnes et al 2014 demonstrated that pacing strategy in the initial few minutes of an exercise bout can influence the speed of the on-kinetic response at the rest-to-work transition.[156,157] To avoid these potential pitfalls we will record distance and velocity at 1-minute intervals throughout the 10MWT and will exclude any tests from the analysis where minute-by-minute velocity fluctuations exceed 10% above or below the mean. The purpose of this exclusion is to minimize the influence of speed changes on VO_2 on-kinetics modeling throughout our sample.

The methods used in this study have many advantages. These include convenience to the subject and reduced testing time. The biomechanical and spatiotemporal profile of overground walking in people with PD is altered by treadmill walking.[158,159] Our OLT program was designed to enhance overground ambulation specifically. Thus, measurement of the cardiorespiratory response specifically associated overground ambulation is relevant to our overarching theoretical framework that places a high value on the influence of task and environmental constraints on the characteristics of the overall movement solution (its' cardiorespiratory signature duly considered).[160]

Literature Review

Prevalence and Economic Impact of Parkinson's Disease

Parkinson's disease is a complex disorder featuring neurodegeneration in the central and peripheral nervous system.[132,161–163] Second in prevalence only to Alzheimer's disease, an estimated 160 per 100,000 people 65 years of age or older have PD.[1] In the United States, annual medical costs such as nursing home care were approximately $12,800 per patient/year above those not having PD.[164] Indirect costs such as reduced employment associated with PD are estimated to be $10,000 per patient/year.[164] Age is considered to be the greatest risk factor for developing PD.[164–166] When considered alongside the projected expansion of the older adult population, these data portend a rise in the prevalence and economic burden of PD in coming years.

Etiology and Clinical Picture of Parkinson's Disease

PD is hypothesized to result from a complex interplay of genetic and environmental factors.[163] Individuals with PD experience both motor and non-motor symptoms. Clinically identifiable motor symptoms include bradykinesia, resting tremor, rigidity, and postural instability.[107] Clinically identifiable non-motor symptoms include fatigue, depression, olfactory loss, apathy, cognitive impairment, sleep disturbance, pain, and autonomic dysfunction.[167] Life expectancy is shortened by PD,[168] however, treatment with dopamine-based drugs typically ameliorates initial motor symptoms, thus forestalling functional decline,[169–171] Pharmacological treatment has no effect on underlying disease progression.[81,171] In recent years, exercise prescription has become a core component of disease management strategy.[81,171]

Walking Limitations in Parkinson's Disease

Gait issues are prominent in PD. Difficulty with walking is one of the earliest clinical problems reported by members of this patient population.[172] Walking is not a single action, rather, it is an array of behaviors expressed to solve varying mobility needs across various environments. Multiple aspects of overall ambulatory ability (i.e., long distance, short distance, maneuverability, turning, safety, initiation) are compromised in people with PD. The classic gait pattern in PD is characterized by slow walking speeds, reduced step length, faster cadence with shuffling steps, stooped posture, and decreased angular movement of the lower extremities.[115,173–177] Furthermore, in PD, time spent in stance and double support phase is increased along with reduced amplitude and altered coordination of arm swing.[173,176,178,179] Additionally, joint power production and propulsive force are diminished during walking in people with PD.[180,181] Sustainability of gait in PD is often compromised as well, possibly due to a combination of increased energetic cost of walking[4,88] and an inability to meet these relatively high energetic demands because of diminished cardiorespiratory fitness.[11] The confluence of these limitations in walking pose a barrier to activities of daily living[172] and may pose a barrier to physical activity, a relevant factor given that exercise and a physically active lifestyle may slow or halt the progression of the disease.[79,81,105]

Interventions for Overall Walking Ability in Parkinson's Disease

Pharmacological therapies ameliorate gait deficits initially, but their positive effects are lessened in later stages of the disease thus placing increased importance upon non-pharmacological rehabilitative interventions for maintenance of functional mobility.

A variety of movement-based interventions to improve general walking ability have been studied in PD. These include tango, dancing, cycling, LSVT BIG, multidimensional physical training, treadmill training, resistance exercise for the lower extremities, Tai Chi, yoga, boxing, and balance and gait training[80]. Rationale for such interventions vary, with some attempting to facilitate motor learning and others targeting impairments thought to constrain performance.

A recent systematic review and meta-analysis of randomized controlled trials for gait training conducted by Ni et al. examined pooled treatment effects of a variety of modalities on a variety of gait related outcomes.[80] Across multiple modalities, the authors found small-to-medium significant effects for changes in TUG, comfortable walking speed, fast walking speed, cadence, and stride/step length. In contrast, the authors found small-to-medium, but non-significant effects for changes in double leg support time, dynamic gait index, 6MWT distance, and freezing of gait questionnaire. These data are encouraging because they support the notion that gait performance is mutable in PD. However, optimal methods for specific walking outcomes (such as endurance walking performance) have not been established in PD and it appears that distinct programs may be effective for some aspects of gait but ineffective for other aspects.[80,114] Consequentially, individuals with PD and their care team are recommended to seek multiple treatment modalities to improve different aspects of walking, each targeting a specific impairment or an isolated component of movement performance.[80,114] Approaching gait rehabilitation in this manner may be time-consuming and burdensome

and is inconsistent with established training paradigms used in other neurological populations.[12,182]

Endurance Walking Performance Following Exercise-Based Interventions

In the systematic review conducted by Ni and colleagues, only randomized control trials were included.[80] Consequentially, only 9 studies were reviewed that reported on changes in 6MWT total distance. Ni et al. concluded that there was insufficient evidence to support any single intervention strategy for improving endurance walking performance in PD, which is most commonly measured by the 6MWT. This conclusion is concerning, given the fact that the sustainability of gait over prolonged distances is often compromised in individuals with PD.[2,3,88–92] In PD, difficulty with sustained ambulation is associated with motor symptoms severity and self-reported fatigue,[53,103] and may pose a barrier to engagement in life activities. Given the importance of walking endurance for daily life, we were interested in gaining a more comprehensive picture of the evidence-base regarding changes in walking endurance following different types of exercise-based treatments in PD. Specifically, we wanted to know what information could be gleaned regarding magnitudes of effects for changes in 6MWT total distance and secondary outcomes concerning balance performance, strength, aerobic fitness, and physiological function that may underly walking performance improvements following various exercise-based interventions. Additionally, we were interested in surveying the exercise protocols employed to ascertain if intervention design was guided by movement performance concepts and/or specific theorized effects, or if protocol selection was more so driven by convenience or community access. Table 1 provides

review of studies that have addressed changes in endurance walking performance following exercise-based interventions in PD. Studies were included if they included the 6MWT as an outcome measure, employed an exercise-based intervention, and involved individuals with PD.

Table 3: Review of exercise intervention studies for people with PD that included the 6MWT as an outcome measure.

Author and Year	*Stated Study Rationale and Aim*	*Study Design and Details and Study Flow*	*Sample Characteristics: N, Age, and Disease Severity*	*Intervention Details*	*Key Outcome Measures*	*Key Findings*
Burini et al., 2006[48]	Rationale -Equivocal evidence for optimal physiotherapy practice in PD. -Purported benefit of aerobic training but relatively little evidence on effects. Aim -Compare effects of aerobic training to effects of group-based Qigong exercise in mild-to-moderate PD.	-Randomized controlled cross-over trial of aerobic training versus Qigong exercises. -G1: test 1, 7 weeks aerobic training, test 2, 2-month washout period, test 3, 7 weeks Qigong, test 4. -G2: test 1, 7 weeks Qigong exercise, test 2, 2-month washout period, test 3, 7 weeks aerobic training, test 4.	G1 -N=11 -Age: 65.7(7) -Hoehn and Yahr: II/III G2 -N=11 -Age: 62.7(4) -Hoehn and Yahr: II/III	Aerobic Training Program -Leg cycle ergometer training 3x/week, 7 weeks, 20 sessions total. -Exercises: 10 mins low-intensity warmup. 30 mins at 50-60% heart rate reserve. 10 mins gradual recovery and stretching. Qigong Exercise Program -Group classes 3x/week, 7 weeks, 20 sessions total, 50-minutes each. -Exercises: breathing, stretching, trunk and neck rotations, balance training in upright position. Static balance practice at limits of limb range of motion.	-6MWT -Borg Scale during 6MWT -Leg cycle ergometer CPET	-6MWT total distance increased following aerobic training in both groups (G1: +35m; G2: +62m), but changed marginally following Qigong in both groups. -Borg scores during 6MWT were significantly reduced following aerobic training in both groups, but not following Qigong in both groups. -Peak VO2 decreased following aerobic training in both groups (G1: -1.9 ml/kg/min; G2: -3.4 ml/kg/min), and increased following Qigong in both groups (G1: +1.4 ml/kg/min; G2 +1.7 ml/kg/min).
Dibble et al., 2006[54]	Rationale -Existent sarcopenia and eccentric and concentric strength deficits in PD that may lead to mobility deficits. -Only 3 previous studies providing evidence of effects of resistance training in PD. Aim -Compare effects of high-force eccentric resistance training to effects of standard-care general exercise training in mild-to-moderate PD.	-Randomized controlled trial of high-force eccentric resistance training versus standard-care general exercise training. -Groups were matched for age and disease severity. -G1: pretest, 12-weeks high-force eccentric exercise, posttest. -G2: pretest, 12-weeks standard care general exercise training, posttest.	G1 -N=10 -Age: 64.3(9.6) -Hoehn and Yahr: 2.5(0.5) G2 -N=9 -Age: 67(10.2) Hoehn and Yahr: 2.5(0.7)	G1: High Force Eccentric Resistance Training -3x/week, 12-weeks, 45-60 mins each session. -All components identical to G2 with exception of lower extremity resistance training mode (high force eccentric ergometer training substituted) G2: Standard Care General Exercise Training -3x/week, 12-weeks, 45-60 mins each session. -Light calisthenics, stretching, treadmill walking, leg cycle ergometer training, machines and free weights for legs and arms.	-6MWT -Quadriceps muscle volume -Knee extensor isometric force testing -Stair ascent -Stair descent	-6MWT total distance increased substantially in G1 (119.04m 95% CI [34.46-203.60]) and marginally in G2 (19m 95% CI[-39.98-76.98]). -Quadriceps muscle volume for both legs increased in G1 (more affected: 43.32cm^3 95% CI [13.05-73.59]; less affected: 44.19cm^3 95% CI [12.66-75.91]) and changed equivocally for both legs in G2. -Average torque production increased more substantially in G1 than in G2. -Stair ascent and descent times increased more substantially in G1 than in G2.
Hackney and Earhart, 2008[55]	Rationale -Purported benefit of Tai Chi for improving balance performance in PD, but lack of high-quality evidence. Aim -Compare effects of Tai Chi to effects of no-treatment in mild-to-moderate PD.	-Randomized controlled trial of Tai Chi training program versus no-treatment control. -G1: pretest, 13 weeks Tai Chi training, posttest. -G2: pretest, 13 weeks no-treatment, pottest.	G1 -N=13 -Age: 64.9(8.3) -Hoehn and Yahr: 2 G2 -N=13 -Age: 62.6(10.2) -Hoehn and Yahr: 2	G1: Tai Chi Training -1-hour lessons, 2x/week, 13 weeks, 20 lessons total. -Structured, progressive lessons from experienced instructor focusing on first and second circles of Yang Short Style of Cheng Manching. -G2: No Treatment -Subjects received no exercise treatment from study personnel.	-6MWT -Berg Balance Scale	-6MWT total distance increased in G1 (+44.4m) and showed virtually no change in G2 (+0.8m). -Berg Balance Scale improved 7% in G1 and deteriorated by -1% in G2.
van Eijkeren et al., 2008[56]	Rationale -Physical activity is important in PD. -Nordic walking provides a full body workout and is accessible.	-Single arm, pre-experimental study examining immediate and long-term effects of a	G1 -N=19 -Age: 67	G1: Nordic Walking Training -1-hour sessions, 2x/week, for 6 weeks.	-6MWT	-6MWT total distance increased significantly in G1. -In subset of 9 subjects from G1 tested again 5 months following

	-Preliminary data show beneficial effects of Nordic walking, but do not follow patients long-term after study ends. <u>Aim</u> -Assess the immediate and long-term effects of a Nordic walking exercise program in mild-to-moderate PD.	Nordic walking exercise program. -G1: pretest, 6 weeks of Nordic walking training, posttest. -A subset of 9 subjects from G1 were tested again 5 months after completion of the program.	-Hoehn and Yahr: 1.6 (average)	-Warm-up, practicing Nordic walking competence, improving intensity and distance of Nordic walking, cool down.		completion of the program, 6MWT total distance increases were retained. -Magnitude of changes were not reported, only parameters of statistical significance. -Visual inspection of bar graph indicates that magnitude of increase was 50-80m.
Skidmore et al., 2008[53]	<u>Rationale</u> -Treadmill walking may be beneficial in PD, but previous studies have used complex methods such as body-weight support or variable tasks during treadmill training. <u>Aim</u> -Assess the safety, feasibility, and effects of a progressive treadmill aerobic training program in moderate PD.	-Single arm, pre-experimental study examining the safety, feasibility, and effects of progressive treadmill aerobic training. -G1: pretest, 12 weeks treadmill training, posttest	<u>G1</u> -N=5 -Age: 67(8) -Hoehn and Yahr: 2.9(0.7)	<u>G1: Progressive Treadmill Aerobic Training</u> -3x/week for 12 weeks. -Initial training parameters: 10-20 total minutes of treadmill walking at no greater than 40-50% heart rate reserve. -Every 2 weeks duration was progressed by 5 min and intensity was progressed by adding 0.1mph of speed and/or 1% incline. -Intensity was capped at 70% heart rate reserve for safety reasons. -Handrails were used only for balance and not body weight support.	-6MWT -Treadmill CPET	-6MWT total distance increased in G1 (+44m) and approached statistical significance. -Peak VO2 on treadmill CPET increased slightly in G1 (+1.42 mL/kg/min) but changes were variable and did not approach statistical significance. -Peak Ambulatory Workload capacity during treadmill CPET increased by 26% in G1 (+1.54 METs) and changes were statistically significant.
Pelosin et al., 2009[160]	<u>Rationale</u> -Poor walking economy in PD may be related to altered biomechanics of gait. -Treadmill training seems beneficial in PD, but its impact on overground gait, metabolic walking economy, and generalized exercise economy remains understudied. <u>Aim</u> -Analyze the effects of treadmill training on cardiopulmonary function, walking economy, and generalized exercise economy in mild PD.	-Single arm, pre-experimental study examining the effects of treadmill training on cardiopulmonary function, overground walking, walking economy, and general exercise economy in mild-to-moderate PD. -G1: pretest, 4 weeks training, posttest, follow-up test 30 days after completion.	<u>G1</u> -N=10 -Age: 69.2(5.6) -Hoehn and Yahr: no greater than 2.5	<u>G1: Treadmill Training</u> -3x/week, 4 weeks, 12 sessions total. -Initial training parameters: 30 mins walking at 2km/h -Every 3 days of treatment the treadmill speed was increased by 0.5km/h	-6MWT -Treadmill submaximal CPET (used to assess movement economy, not aerobic capacity) -Leg cycle ergometer submaximal CPET (used to assess movement economy, not aerobic capacity)	-6MWT total distance increased in G1 and this effect was retained at 30 days post-training (statistical significance was reported but not magnitude of change) -Visual inspection of graph indicates that magnitude of increase in 6MWT total distance 60-80m. -Oxygen consumption and respiratory rate significantly decreased during treadmill CPET in G1 and this change was largely retained at 30 days follow-up. -Heart rate during treadmill CPET significantly decreased in G1 and the effect was minimally retained at 30 days follow-up. -No statistically significant changes in metabolic parameters during leg cycle ergometer CPET were found in G1.
Frazzitta et al., 2009[58]	<u>Rationale</u> -Efficacy of auditory and visual cuing during rehabilitation in PD has been shown. -Efficacy of treadmill training in PD has also been shown. -No studies have assessed treadmill training in association with auditory or visual cues in PD. <u>Aim</u>	-Randomized controlled trial of treadmill training with visual and auditory cues verses traditional (overground) training with visual and auditory cues. -G1: pretest, 4 weeks treadmill training with	<u>G1</u> -N=20 -Age: 71(8) -Hoehn and Yahr: only participants with a score of 3 admitted. <u>G2</u> -N=20 -Age: 71(7)	<u>G1: Treadmill Training with Visual and Auditory Cues</u> -20 min sessions, 7x/week, 4 weeks, 28 sessions total. -Initial training parameters: 60% maximal walking speed for 2 training sessions. Belt speed increased thereafter by 0.05 stride cycles/second every 3 days.	-6MWT	-6MWT significantly increased in G1 (+130m). -6MWT significantly increased in G2 (+57m).

	-Compare the effects of treadmill training with auditory and visual cues to the effects of traditional (overground) training with visual and auditory cues in moderate PD.	visual and auditory cues, posttest. -G2: posttest, 4 weeks traditional training with visual and auditory cues, pottest.	-Hoehn and Yahr: only participants with a score of 3 admitted.	-Visual cue: Continuous step target goals on TV screen in front of treadmill with accuracy feedback on each step. -Auditory cue: synchronized with visual cues at 0.5 c/s. <u>G2: Traditional Training with Visual and Auditory Cues</u> -20 min sessions, 7x/week, 4 weeks, 28 sessions total. -Training performed overground. -Visual cue: lines spaced on ground according to each subjects' stride length. Spacing increased 0.05 m every 3 or 4 days. -Auditory cue: Musical beat same as G1 (0.5 c/s).		
Hackney and Earhart, 2009[59]	<u>Rationale</u> -Dance may be a feasible and enjoyable activity that promotes health benefits in general and mobility benefits specifically to people with PD. -The effects of dance on balance and gait is relatively understudied in PD. <u>Aim</u> -To compare the effects of programs consisting of Tango dance, Waltz/Foxtrot dance, and non-treatment, in individuals with mild-to-moderate PD.	-Randomized controlled trial comparing the effects of Tango, Waltz/Foxtrot, and non-treatment. -G1: pretest, 13-week progressive tango protocol, pottest. -G2: pretest, 13-week Waltz/Foxtrot protocol, pottest. -G3: pretest, 13-week no intervention, pottest.	<u>G1</u> -N=14 -Age: 66.8(2.4) -Hoehn and Yahr: 2(0.2) <u>G2</u> -N=17 -Age: 68.2(1.4) -Hoehn and Yahr: 2.1(0.1) <u>G3</u> -N=17 -Age: 66.5(2.8) -Hoehn and Yahr: 2.2(0.2)	<u>G1: Progressive Tango Lessons</u> -20 sessions completed in 13 weeks. Professionally instructed Tango lessons in a group setting. <u>G2: Waltz/Foxtrot Lessons</u> -20 sessions completed in 13 weeks. Professionally instructed Waltz/Foxtrot lessons in a group setting. <u>G3: No Intervention</u> -Subjects received no exercise treatment from study personnel.	-6MWT -Berg Balance Scale	-6MWT total distance significantly increased in G1 (+49.1m). -6MWT total distance significantly increased in G2 (+59.4m). -6MWT decreased slightly in G3 (-7.5m). -Berg Balance Scale scores increased significantly in G1 (+4) -Berg Balance Scale scores increased significantly in G2 (+3.9) -Berg Balance Scale scores decreased slightly in G3 (-1.2)
Schilling et al., 2010[119]	<u>Rationale</u> -Neuromuscular deficits are debilitating in PD and interventions to ameliorate the deficits in PD are needed. -Despite variable methodology in terms of exercise programming, studies of resistance training in PD are encouraging. -Precise resistance training parameters need to be studied in PD. <u>Aim</u> -To examine the effects of a moderate volume, high-load 8-week resistance training intervention on lower-body strength and functional mobility in mild-to-moderate PD, and to examine the relationship of strength to neuromuscular function.	-Randomized controlled trial of moderate volume, high-load resistance training versus standard care control (delayed intervention). -Groups were gender matched during the randomization process. -G1: pretest, 8-weeks of moderate volume, high-load resistance training, pottest. G2: pretest, 8-weeks of no-intervention, pottest.	<u>G1</u> -N=8 -Age: 61.3(8.6) -Hoehn and Yahr: 2-2.5 <u>G2</u> -N=8 -Age: 57(7.1) -Hoehn and Yahr: 1-2.5.	<u>G1: Moderate-Volume, High-Load Resistance Training</u> -2x/week, 8-weeks. -Training activities: Warm-up, 3 sets of 5-8 repetitions for leg press, seated leg curl, and calf press. -Loads were targeted and progressed so that volitional fatigue was reached at the end of the 3rd set for each exercise. -Emphasis on lifting the weights as fast as possible with good form and returning to start positions in a slow and controlled manner. <u>G2: No-Intervention</u> -Advice was given for subjects to continue their current activities and were given an opportunity to complete the training intervention after the study period.	-6MWT -Maximal strength assessed via leg press (1-RM).	-6MWT total distance increased in G1 (+49.2m) -6MWT total distance increased in G2 (+25.1m) -Maximal strength relative to body mass increased in G1 (+1.2kg/kg) which corresponded to a 29% increase. -Maximal strength relative to body mass did not change in G2.
Chaiwanichsiri et al., 2011[61]	<u>Rationale</u> -Treadmill training is commonly used and effective in PD. -Auditory cueing may be beneficial as well. -Treadmill training with musical cueing could be effective, but is relatively understudied. <u>Aim</u>	-Randomized controlled trial of treadmill training with musical cues versus treadmill training without musical cues versus home-based overground walking program.	<u>G1</u> -N=10 -Age: 67.1(4) -Hoehn and Yahr: II-III <u>G2</u> N=10	<u>G1: Treadmill Training With Musical Cues</u> -8 weeks total: treadmill training 3x/week, 30 mins per session, home walking program 3x/week 30 mins per session. -Training activities:	-6MWT	-6MWT total distance increased in G1 (+43.6m). -6MWT total distance increased in G2 (+23.1m). -6MWT distance increased in G3 (+13m).

	-To compare the effects of 3 forms of training. 1) Treadmill training with musical cues. 2) Treadmill training without musical cues. 3) Home-based overground walking program.	-G1: pretest, 8 weeks treadmill training with musical cues, posttest. -G2: pretest, 8 weeks treadmill training without musical cues, posttest. -G3: pretest, 8 weeks home-based overground walking program, posttest.	-Age: 67.9(6.3) -Hoehn and Yahr: II-III G3 N=10 -Age: 68.6(5.2) -Hoehn and Yahr: II-III	-10 mins stretching followed by 20 mins treadmill walking with musical cues or 20 mins overground walking with musical cues. G2: Treadmill Training Without Musical Cues -8 weeks total: treadmill training 3x/week, 30 mins per session, home walking program 3x/week 30 mins per session. -Training activities: -10 mins stretching followed by 20 mins treadmill walking or 20 mins overground walking. G3: Home-Based Overground Walking Program -8 weeks total: overground walking 6x/week, 30 mins per session. -Training activities: -10 mins stretching followed by 20 mins overground walking.		
Canning et al., 2012[62]	Rationale -The evidence base for treadmill training in PD is encouraging, but comes mainly from laboratory trials. -Semi-supervised home-based treadmill training may be more feasible and accessible but is understudied in PD. Aim -To examine the feasibility, safety, immediate effectiveness, and long-term effectiveness of a home-based treadmill training program in mild PD.	-Randomized controlled trial of home-based treadmill training versus standard care control (advice to maintain current level of physical activity). -G1: pretest, 6-week home-based treadmill training, posttest, follow-up test 12 weeks from baseline. -G2: pretest, 6 weeks no-intervention, posttest, follow-up test 12 weeks from baseline.	G1 -N=9 (posttest), 8 (follow-up test) -Age: 60.7(5.9) -Hoehn and Yahr: I=II G2 N=9 -Age: 62.9(9.9) -Hoehn and Yahr: I-II	G1: Home-Based Treadmill Training -30-40 min sessions, 4x/week, 6 weeks. -First initial 7 sessions were supervised in participants' homes. -Training activities: -5-minute warm up consisting of slow walking, sit-to-stand exercises and stretching exercises. -Treadmill walking training portion. -5 min cool down identical to warm up activities. -Participants were required to hold handrails to ensure safety. -Treadmill speed progressed from 60% of their average 6MWT speed to 80% of the 6MWT speed. -Cognitive and manual tasks were introduced at week 4 to challenge stride length regulation. -Emphasis was placed on taking long strides. G2: No-Intervention -Advice was given to subjects to maintain their current level of physical activity.	-6MWT	-6MWT total distance increased from baseline in G1 at week 6 (+13.3m) and at week 12 (+26.1m) -6MWT total distance increased from baseline in G2 at week 6 (+18.1m) and at week 12 (+48.4m)
Duncan and Earhart et al., 2012[183]	Rationale -Testing participants off-medication may provide a more accurate picture of underlying disease processes. -Institution-based dance programs have been encouraging, but community-based programs are more accessible, and their effects need to be examined over long time-periods. Aim -To determine the effects of a long-term community-based dance program in people with PD, with all testing performed off-medication.	-Randomized controlled trial of Tango versus no-intervention. -G1: pretest, 12-months Tango classes, posttest. -G2: pretest, 12-months no intervention, posttest.	G1 -N=26 -Age: 69.3(1.9) -Hoehn and Yahr: 2.6 (0.1) G2 -N=26 -Age: 69 (1.5) -Hoehn and Yahr: 2.5 (0.1)	G1: Tango Classes -1 hours Argentine Tango classes, 2x/week, 12 months. G2: No Intervention -Subjects instructed to go about their usual activities.	-6MWT -MiniBESTest	-6MWT total distance was maintained in G1 -6MWT total distance decayed in G2. -MiniBESTest performance improved significantly in G1. -MiniBESTest performance decayed in G2.
Rose et al., 2013[65]	Rationale -Many forms of rehabilitation have been studied in PD, but optimal methods have yet to be established. -Motoric and metabolic challenge during training may be beneficial in PD.	-Single-arm, pre-experimental study of body-weight supported progressive high-intensity locomotor training in moderate PD.	G1 -N=13 -Age: 53-75 -Hoehn and Yahr: 2-3	G1: Body-Weight Supported Progressive High-Intensity Locomotor Training -60-min sessions, 3x/week, 8 weeks total. -Training activities: Motor block, fitness block, mix block.	-6MWT	-6MWT total distance increased in G1 by 10.6% (+61m).

	-High-intensity and type-specific locomotor training may be effective in PD, but may need to be delivered with body-weight support to be feasible. <u>Aim</u> -To evaluate the effect of body-weight supported progressive high-intensity locomotor training in moderate PD.	-G1: pretest, 8 weeks of body-weight supported progressive high-intensity locomotor training, posttest.		-Motor block: variation in body-weight support, variation in stepping patterns, speeds, inclines, jumping on and off treadmill, interspersed 5-15 sec sprints with 50% body-weight support. -Fitness block: 5-10 mins steady-state walking or running with 50% body-weight support at approximately 70-80% estimated heart rate capacity. -Mix block: training for high-speed running and aerobic performance in interval bouts; 5 sets of running for 60 seconds with 30 second rest periods.		
Shulman et al., 2013[28]	<u>Rationale</u> -Exercise rehabilitation is becoming more popular in PD. -Methodological issues across the evidence base constrain development of evidence-based exercise guidelines in PD. <u>Aim</u> -To compare the efficacy of 3 types of physical exercise in mild-to-moderate PD. 1) Higher-intensity treadmill training. 2) Lower-intensity treadmill training. 3) Stretching and resistance training.	-Randomized controlled trial of higher-intensity treadmill training, lower-intensity treadmill training, and stretching/resistance training. G1: pretest, 12 weeks of higher-intensity treadmill training, posttest. G2: pretest, 12 weeks of lower-intensity treadmill training, posttest. G3: pretest, 12 weeks of stretching and resistance training, posttest.	<u>G1</u> -N=23 -Age: 66.1 (9.7) -Hoehn and Yahr: 2-3 <u>G2</u> -N=22 -Age: 65.8 (11.5) -Hoehn and Yahr: 2-3 <u>G3</u> -N=23 -Age: 65.3 (11.3) -Hoehn and Yahr: 2-3	<u>G1: Higher-Intensity Treadmill Training</u> -15-30 min sessions, 3x/week, 12 weeks, 36 sessions total. -Training activities: Sessions initially consisted of 15 mins of treadmill walking at 40-50% maximal heart rate reserve and progressed as tolerated to 30 mins of treadmill walking at 70-70% heart rate reserve. <u>G2: Lower-Intensity Treadmill Training</u> -15-30 min sessions, 3x/week, 12 weeks, 36 sessions total. -Training activities: Sessions initially consisted of 15 mins of treadmill walking at self-selected pace and progressed to 50 minutes of treadmill walking at 40-50% heart rate reserve. <u>G3: Stretching and Resistance Training</u> -15-30 min sessions, 3x/week, 12 weeks, 36 sessions total. -Training activities: muscle strengthening activities consisted of leg presses, leg extensions and leg curls. 2 sets of 10 repetitions were performed for each exercise. Loads were progressed throughout the program as tolerated. -Stretching exercise comprised trunk rotations, hip abductions, and stretches of the hamstrings, quadriceps, calves, and ankles.	-6MWT -Treadmill CPET -Muscle strength assessed via leg press and single-leg leg extension (1-RM).	-6MWT total distance improved in G1 by 6.3% (+77ft), in G2 by 11.6% (+161ft), and in G3 by 9.1% (+107ft). -Peak VO2 during treadmill CPET changed +8.1% in G1, +6.7% in G2, and -0.2% in G3. -Strength assessed via leg press changed +3.5% in G1, +1.6% in G2, and +15.7% in G3. -Strength assessed via single-leg leg extension changed +7.7% in G1, +3.6% in G2, and +15.7% in G3.
Frazzitta et al., 2014[67]	<u>Rationale</u> -Evidence suggests that intensive rehabilitation is beneficial in PD and that BDNF release may be involved as a mechanism. -Only 2 studies have measured BDNF levels in PD. <u>Aim</u> -To assess whether intensive rehabilitation treatment reduces motor disability and increases BDNF serum levels in patients in the early stages of PD.	-Randomized controlled trial of intensive rehabilitation versus no-rehabilitation in clinically probable patients with PD who were all taking the same drug; rasagiline. -G1: Baseline blood and functional test, initiate 28 days of treatment, day 10 blood test, day 20 blood test, day 28 blood test and functional test. -G2: Baseline blood test, initiate 28 days no	<u>G1</u> -N=14 -Age: 67(5) -Hoehn and Yahr: 1-1.5 (clinically probable diagnosis) <u>G2</u> -N=10 -Age: 65(4) -Hoehn and Yahr 1-1.5 (clinically probable diagnosis)	<u>G1: Intensive Rehabilitation Treatment</u> -4 weeks of inpatient physiotherapy, 3 daily 1-hour sessions, 5x/week. -Daily session 1: cardiovascular warm-up, relaxation exercises, muscle stretching, spinal, scapular, and pelvic mobility drills, postural changes in supine position. -Daily session 2: balance drills with stabilometric platform followed by treadmill training with visual and auditory cues (30 mins treadmill training at ≤60% heart rate reserve, progressive increase in speed throughout 28 days up to treadmill speed of 3.5km/h). -Daily session 3: Occupational therapy focused on daily living activities.	-6MWT (G1 only) -Berg Balance Scale (G1 only) -Serum BDNF levels at baseline, day 10, day 20, and day 28	-6MWT total distance increased significantly in G1 (+94m). -Berg Balance Scale scores increased 11% in G1. -in G1, serum BDNF levels were elevated from baseline values by 15.7% at day 10, by 19.2% at day 20, and by 14.5% at day 28. -No significant changes in serum BDNF levels were observed in G2 at any time point.

		rehabilitation, day 10 blood test, day 20 blood test, day 28 blood test. -No functional testing in G2, blood test only.		G2: No Rehabilitation -Subjects received no rehabilitation treatment from study personnel.		
Kelly et al., 2014[68]	Rationale -Resistance and endurance training both are effective in PD, but knowledge of the intervention-induced cellular changes in skeletal muscle involved in this effect remain unknown. Aim -To test the adaptability of PD muscle to high intensity exercise training in mild-to-moderate PD.	-Single arm pre-experimental study of the effects of high-intensity exercise training in mild-to-moderate PD. -G1: Pretest, 8 weeks high-intensity training, mid-test, 8 weeks high-intensity training, posttest.	G1 -N=15 Age: 66.5(6) -Hoehn and Yahr: II and III	G1: High-Intensity Exercise Training -35-45 min sessions, 3x/week, 16 weeks. -Training activities: -5 min warm up on treadmill or leg cycle ergometer. -Progressive resistance training of 3 sets of 8-12 repetitions of leg press, knee extension, chest press, overhead press, lat pull down. -Loads for resistance training were progressed when subjects could complete first full 12 repetitions in first 2 sets. -In lieu of rest breaks between sets, subjects performed one or two sets of either push-ups, step-ups, lunge, side lunge, modified dip for 45-60 sec, or a 60 sec interval on a treadmill or stationary leg cycle ergometer. -Intensity was maintained above 50% heart rate reserve during session. -3 sets of abdominal crunches per session were also performed.	-6MWT -Single leg balance test (duration) -Maximal voluntary leg power via bilateral knee extension. -Skeletal muscle histological assessment via thigh biopsy. -Relative motor unit activation during sit-to-stand test.	-6MWT total distance increased significantly in G1 (+43.1m) -Single leg balance duration increased significantly in G1 (+34%) -Leg power increased significantly in G1 (+42%) -Myofiber hypertrophy occurred in G1 (type 1 fibers: +14%; type 2 fibers +36%). -Mitochondrial respiratory complex activity increased G1 in both subsarcolemmal and intermyofibrillar fractions (complex I: +45-56%; complex IV: +39-54%). -Relative motor unit activation during a sit-to-stand task decreased in G1 (-30%)
Nadeau et al., 2014[184]	Rationale -Treadmill training is beneficial in PD. -Manipulating the incline of the treadmill during training may provide the challenge necessary to promote further gains in walking ability. Aim -To compare the effects of 3 training programs in mild-to-moderate PD. 1) Treadmill training with progressive speed and incline increases. 2) Treadmill training with progressive speed increases. 3) No treadmill training with light exercise.	-Randomized controlled trial of speed- and incline-based treadmill training versus speed-based treadmill training versus no treadmill training with light exercise. -G1: Pretest, 24-week speed- and incline- based treadmill training, posttest. -G2: Pretest, 24-week speed-based treadmill training, posttest. -G3: Pretest, 24-week light exercise training, posttest.	G1 -N=11 -Age: 60.1(6.8) -Hoehn and Yahr: 1.95(0.15) G2 -N=12 -Age: 64(6.6) -Hoehn and Yahr: 1.92(0.2) G3 -N=11 -Age: 64.3(5.6) -Hoehn and Yahr: 1.86(0.23)	G1: Speed and Incline Based Treadmill Training -1-hour sessions, 3x/week, 24 weeks. -Training activities: -Heart did not exceed 75% age-predicted maximum. -Speed and incline were progressed throughout training. -5 min warm-up and cool-down. -45 mins treadmill walking. G2: Speed Based Treadmill Training -1-hour sessions, 3x/week, 24 weeks. -Training activities: -Heart did not exceed 75% age-predicted maximum. -Speed was progressed throughout training. -5 min warm-up and cool-down. -45 mins treadmill walking. G3: Light Exercise Training -1-hour sessions, 3x/week, 24 weeks. -Low intensity exercises including: -Tai Chi exercises -Latin dance exercises -Resistance band exercises -coordination exercises. -Seated exercises with progressive amplitude of movements.	-6MWT	-6MWT total distance increased moderately in G1 (+28.7m). -6MWT total distance increased significantly in G2 (+43.5m) -6MWT total distance increased moderately in G3 (+22.1m)
Güngen et al., 2017[72]	Rationale	-Single-arm pre-experimental study on the	G1 -N=34	G1: Pulmonary Physiotherapy	-6MWT	-6MWT total distance increased in G1 (+33.7m)

	-Respiratory complications in PD may lead to decreased effort capacity. -The effects of pulmonary rehabilitation in PD are understudied. <u>Aim</u> -To evaluate the effects a pulmonary physiotherapy protocol in mild-to-moderate PD.	effects of pulmonary physiotherapy. -G1: pretest, 12-week pulmonary physiotherapy program, posttest.	-Age: 68.21(12.2) -Hoehn and Yahr: 1.4 (0.4)	-12-week program with pulmonary physiotherapist consisting of diaphragmatic pulmonary exercises.		
Ferraz et al., 2018[74]	<u>Rationale</u> -Exercise is beneficial in PD, but no evidence exists to support one program over another. <u>Aims</u> -To examine the effects of functional training, leg cycle ergometer training, and Kinect Adventures exergaming in mild-to-moderate PD.	-Randomized controlled trial of functional training, leg-cycle ergometer training, and Kinect Adventures exergames. -G1: pretest, 8 weeks of functional training, posttest. -G2: pretest, 8 weeks of leg cycle ergometer training, pottest. -G3: pretest, 8 weeks of Kinetic Adventures exergaming, posttest.	<u>G1</u> -N=22 -Age: 71 (66-75) -Hoehn and Yahr: 2.5-3 <u>G2</u> -N=20 -Age: 67 (64-71) -Hoehn and Yahr: 2-3 <u>G3</u> -N=20 -Age: 67 (66-68) -Hoehn and Yahr: 2-2.5	<u>G1: Functional Training</u> -50-min sessions, 3x/week, 8 weeks total. -Training activities: 10 mins stretching, 5 mins calisthenics, 30 mins functional training (gait with obstacles, stairs and ramps, sitting and standing exercise, side gears, balance activity on platform, activities with balls, step exercises, foot tip exercises, reaching activities, gait training) -5 mins breathing exercises. <u>G2: Leg Cycle Ergometer Exercise</u> -50-min sessions, 3x/week, 8 weeks total. -Training activities: 10 mins stretching, 5 mins calisthenics, 30 mins biking (progressed from 50% heart rate reserve to 75% heart rate reserve across intervention time period). -5 mins breathing exercises. <u>G3: Kinect Adventures Exergames</u> -50-min sessions, 3x/week, 8 weeks total. -Training activities: 10 mins stretching, 5 mins calisthenics, 30 mins exergaming (stepping side-to-side, jumping in place) -5 mins breathing exercises.	-6MWT	-6MWT total distance increased in G1 (+36.8m). -6MWT total distance increased in G1 (+35m). -6MWT total distance increased in G1 (+35.8m).
Landers et al., 2019[75]	<u>Rationale</u> -Aerobic, resistance, and balance training are efficacious in PD. -People with PD might benefit from a combination of these modalities. -The safety, feasibility and efficacy of high-intensity multimodal exercise has not been vetted in PD. <u>Aim</u> -To determine whether a high-intensity multimodal exercise boot camp was feasible, safe, and more beneficial than a low-intensity exercise program in mild-to-moderate PD.	-Randomized controlled trial of high-intensity multimodal exercise versus low-intensity exercise. -G1: pretest, 8 weeks of high-intensity multimodal exercise, pottest. -G2: pretest, 8 weeks of low-intensity exercise, posttest.	<u>G1</u> -N=14 -Age: 63.5(10.9) -Hoehn and Yahr: 1-3 <u>G2</u> -N=13 -Age: 64.6(6) -Hoehn and Yahr: 1-3	<u>G1: High-Intensity Multimodal Exercise</u> -90-minute sessions, 3-4 days/week, 8 weeks total. -Training activities: -30 mins of aerobic exercise (treadmill, overground walking, stair climber, bike, recumbent bike, rowing machine) at 70-80% age-predicted HR max. Rest intervals were permitted early in the program but were progressively removed. -30 mins of resistance exercise (chest, back, trunk, upper extremity, lower extremity). Lighter loads (50-70% 1-RM) with higher repetition ranges (3 sets of 10-14 reps) were initially used. Loads were increased (70-70% 1-RM), and repetition ranges decreased (3 sets of 8-10 reps), progressively throughout program. -15 mins balance exercises (anticipatory postural control, reactive postural control, dynamic gait, sensory orientation) -15 mins active rest and stretching -Minimal rest throughout entire session. <u>G2: Low-Intensity Exercise</u> -60-minute sessions, 3-4 days/week, 8 weeks total.	-6MWT (both on-medication and off-medication)	-6MWT total distance increased in G1 both on-medication (+35.1m) and off-medication (+38.3m). -6MWT total distance increased in G2 both on-medication (+35.4m) and off-medication (+46.3m).

				-Training activities: -15 mins of aerobic exercise (treadmill, overground walking, stair climber, bike, recumbent bike, rowing machine) at 50-65% age-predicted HR max. Rest intervals were permitted early in the program but were progressively removed. -15 mins of resistance exercise. Light exercises were initially used (1 set of 10-15 reps) in first 2 weeks. Machine and free-weight exercises, as in G1, were introduced in week 3, but loads (50% 1-RM) and repetition ranges (1 set of 10-15 reps) were restricted. -10 mins balance exercises (step touch task). -10 mins passive stretching. -A total of 10 mins rest was interspersed during sessions.		
Rawson et al., 2019[76]	<u>Rationale</u> -Group classes using treadmill, dance, and stretching are safe, feasible, and efficacious in PD. -Direct comparisons of interventions would further our understanding of intervention specific effects. <u>Aim</u> -To evaluate the effects of 1) tango training, 2) treadmill walking, and 3) stretching exercise classes on gait and balance in mild-to-moderate PD.	-3-arm controlled trial of tango training, treadmill walking, and stretching exercise classes. -G1: pretest off-medication, 12 weeks of tango training, posttest off-medication. -G2: pretest off-medication, 12 weeks of treadmill walking, posttest off-medication. -G1: pretest off-medication, 12 weeks of stretching exercise, posttest off-medication	<u>G1</u> -N=39 -Age: 66.73(9.52) -Hoehn and Yahr: 1-4 <u>G2</u> -N=31 -Age: 68.52(9.54) -Hoehn and Yahr: 1-4 <u>G3</u> -N=26 -Age: 66.18(7.3) -Hoehn and Yahr: 2-4	<u>G1: Tango Training</u> -1-hour sessions, 2x/week, 12 weeks total. -Training activities: -Warm-up/cool-down consisting of deep breathing exercise, trunk rotations, side-to-side neck movements, walking in a circle, side bending stretch, bending over to touch knees. -Argentine tango focusing initially on basic steps and progressing to more complex steps throughout the program. <u>G2: Treadmill Walking</u> -1-hour sessions, 2x/week, 12 weeks total. -Training activities: -Warm-up/cool-down consisting of deep breathing exercise, trunk rotations, side-to-side neck movements, walking in a circle, side bending stretch, bending over to touch knees. -Treadmill training with walking speed set to match preferred overground walking speed. -Speeds reassessed every week. -Social interaction encouraged in group setting. <u>G3: Stretching Exercise</u> -1-hour sessions, 2x/week, 12 weeks total. -Training activities: -Warm-up/cool-down consisting of deep breathing exercise, trunk rotations, side-to-side neck movements, walking in a circle, side bending stretch, bending over to touch knees. -Gentle stretching and whole-body flexibility exercises designed for people with PD. -Support given in sitting and standing to minimize balance challenge.	-6MWT -MiniBESTest	-Increases in 6MWT total distance and MiniBESTest in G1 were small (magnitude values not reported). -Increases in 6MWT total distance and MiniBESTest in G2 were small (magnitude values not reported). -Increases in 6MWT total distance and MiniBESTest in G3 were small (magnitude values not reported).

Fernandes et al., 2020[77]	Rationale -Poor cardiovascular autonomic function in PD increases prevalence of cardiovascular disease and mortality. -Exercise is a well-established tool for improving cardiovascular function, but its effects in PD are largely unexplored. -It remains unknown if high-intensity interval training is superior to moderate-intensity continuous training in PD. Aim -To assess the effects of high-intensity interval training and moderate-intensity continuous training in mild-to-moderate PD.	-Randomized controlled trial of high-intensity interval training versus moderate-intensity continuous training. -G1:	G1 -N=12 -Age:67.6(8.9) -Hoehn and Yahr: 1.9 G2 -N=9 -Age: 69.8(7.7) -Hoehn and Yahr: 1.5	G1: High-Intensity Interval Training -45 min sessions, 3x/week, 12 weeks total. -Training activities: -4 min warm up of treadmill walking at RPE of 9. -21 mins of interval treadmill training (1 min active intervals of walking/jogging at RPE 15-17; 2 min recovery intervals of walking at RPE 9-11). -20 mins calisthenics/balance exercises. G2: Moderate-Intensity Continuous Training -50 min sessions, 3x/week, 12 weeks total. -Training activities: -4 min warm up of treadmill walking at RPE of 9. -26 mins treadmill walking/jogging at RPE 11-14. -20 mins calisthenics/balance exercises.	-6MWT -Endothelial reactivity measured via forearm occlusion and measures of blood flow volume during reactive hyperemia.	-6MWT total distance increased in G1 (+10.4%). -Endothelial reactivity increased in G1 (+4.05%). -6MWT total distance remained the same in G2. -Endothelial reactivity decreased in G2 (-1.29%).
Sherron et al., 2020[78]	Rationale -Use of slow-rhythm auditory cues during treadmill walking in PD may increase stride length, while use of fast auditory cues during overground walking may increase cadence. -Pairing treadmill training aimed at improving spatial aspects of gait (stride length) with overground training aimed at improving temporal aspects of gait (cadence) may correct multiple aspects of disordered walking in PD. Aim -To describe the effects of sequentially combined treadmill and overground training in PD; specifically, slow tempo rhythmic auditory cueing on a treadmill followed by fast temp rhythmic auditory cueing during overground walking.	Single arm case-series pilot study of a novel pairing of treadmill and overground gait training designed to address multiple aspects of spatiotemporal gait disorder in PD. -Px1: pretest, 6 weeks of intensive gait training, posttest. -Px2: pretest, 6 weeks of intensive gait training, posttest. -Px3: pretest, 6 weeks of intensive gait training, posttest.	Px1 Age: 72 Hoehn and Yahr: II Px2 Age: 66 Hoehn and Yahr: II Px3 Age: 75 Hoehn and Yahr: II	Px 1-3: Intensive Gait Training -6 weeks total. Px 1 and 3 completed 15 sessions. Px 2 completed 16 sessions. Sessions were 1 hour in length. -Training Activities: -10-20 mins treadmill walking with auditory metronome set to 85% of Pxs' baseline overground cadence followed by 10-20 mins overground walking with auditory cadence set to 115% of Pxs' baseline overground cadence. -Treadmill speed was gradually progressed over course of program while keeping heart rate below 75% heart rate reserve. -Handrail use was variable between subjects.	-6MWT -MiniBESTest -Spatiotemporal parameters of gait during 6MWT	-In Px1, 6MWT total distance increased (+96.9m), MiniBESTest score did not change, cadence improved (+9.2% (steps/min)), and stride length improved (14.2% cm). -In Px12, 6MWT total distance increased (+71.7m), MiniBESTest score improved by 3 points, cadence improved (+2.7% (steps/min)), and stride length improved (11% (cm)). -In Px3, 6MWT total distance increased (+65.2m), MiniBESTest score improved by 3 points, cadence improved (+6.9% (steps/min)), and stride length improved (11% (cm)).

Table 3 Abbreviations: 6MWT, Six Minute Walk Test; CPET, cardiopulmonary exercise test; 1-RM, one-repetition maximum; BDNF, brain-derived neurotrophic factor.

Review of Studies Addressing Endurance Walking Performance

The studies reviewed in Table 1 employed a variety of interventions including various forms of treadmill training[28,53,58,61,62,65,67,76–78,160,184] (with visual cues, with auditory cues, with incline, with task variation, with body-weight support), various forms of resistance training activities[28,54,119] (differing loads, mode of contraction, exercises, and repetition ranges), multimodal exercise[68,75] (resistance + aerobic + balance + flexibility activities), overground walking programs,[56,61] dance classes,[59,76,183] (tango, waltz/foxtrot), balance training[48,55] (Tai Chi, Qigong), functional gait training,[74] stationary cycle training,[48,74] Nordic walking,[56] pulmonary rehabilitation,[72] and exergaming.[74]

Treadmill training generally yielded positive results for 6MWT total distance, but results varied widely in terms of effect size. Aerobic capacity improved following treadmill training in one study[28] but inconsistently in another.[53] Movement economy measured on a treadmill, but not on a bicycle, improved in tandem with increases in 6MWT total distance following treadmill training in one study, suggesting that movement economy improvements are highly task-specific.[160] Even though lower intensity protocols

have imparted comparable benefits,[28] results from the overall body of literature suggest that treadmill training with a high metabolic intensity may be more efficacious than training at lower intensities. For example, in the study by Canning et al., a low-intensity protocol with mandatory handrail holding was used, which yielded small effects for improvements in 6MWT total distance.[62] Furthermore, the study by Rawson et al., which also employed a low-intensity treadmill protocol, yielded small effects for 6MWT total distance as well.[76] In contrast, in a study by Fernandes and colleagues, a high-intensity treadmill protocol produced favorable results for 6MWT total distance, but a low-intensity training protocol yielded no benefit, suggesting that higher intensity protocols are more beneficial.[77] On another note, a study by Rose et al., which trained a variety of gait-related motor tasks on the treadmill, yielded encouraging results for 6MWT total distance.[65] Most treadmill-based studies progressed the workload and intensity of training, however, the addition of visual and auditory cues seemed to provide additional benefit.[58,67,78] Overall, these results suggest that both metabolic and motoric challenge are necessary elements of successful gait training, even if a treadmill serves as the practice environment.

Dancing classes may be beneficial for long term maintenance of ambulatory ability,[183] and may be well-attended because they are easily accessible in the community, but their immediate impact on 6MWT total distance is inconsistent and small.[59,76,183] 6MWT total distance improved to a small degree after pulmonary rehabilitation, balance training, exergaming, and functional training.[48,55,72,74] Following a progressive Nordic walking program that focused on motor skill and aerobic fitness, 6MWT total distance

improved moderately, suggesting that overground training with a focus on skill acquisition may be beneficial.[56] Encouragingly, subjects in this study retained their improvements in 6MWT total distance 5 months after the completion of the study.[56]

Multimodal activities produced small improvements in 6MWT total distance, but the effects are difficult to interpret due to the deliberate breadth of such interventions.[68,75] Bicycle ergometer training produced small benefits for 6MWT total distance, with variation between studies.[48,74] General resistance training activities, when predominantly focused on the lower extremities, produced consistent and positive effects on muscle strength and power, and seemed to produce small improvements in 6MWT total distance.[28,119] Notably, in response to a high-force eccentric cycling program that specifically targeted the quadriceps muscles, 6MWT total distance improved substantially and these changes occurred in tandem with excellent improvements in muscle strength, power, and balance performance.[54] On interpretation of these results is that the gait-related benefits of resistance training may be most fully realized if strengthening activities focus on force absorption, thus enhancing stability and confidence to move with greater explosiveness.

The results from the 23 studies included in Table 1 suggest that interventions to improve endurance walking performance in PD should be both motorically and metabolically challenging and that walking-specific practice is critical for improving endurance walking performance. Additionally, given the breadth of interventions that did produce favorable changes in 6MWT total distance, it seems that recovery of endurance walking performance in PD may be facilitated by adaptations across multiple systems.

Progression of training intensity and volume seemed to be a common ingredient in successful interventions. The addition of simple auditory and visual cues also seemed to add additional benefits for changes in 6MWT total distance. However, differences in protocols between studies make it difficult to interpret which elements of cueing are most critical for promoting recovery of walking performance.

There is a scarcity of evidence regarding the magnitude of improvement in endurance walking performance that can be expected from walking-specific practice performed exclusively overground. While treadmill training enables walking-specific practice, the treadmill environment differs considerably from an overground environment. Exergaming, dance classes, and balance activities are performed overground, but the motor actions performed during training differ substantially from those that comprise overground walking. Only two studies provide an indication of the effects of walking-specific practice performed exclusively overground, as previously mentioned. Again, in one study, a 6-week progressive Nordic walking program produced moderate improvements in 6MWT total distance.[56] In contrast, in another study an 8-week home-based walking program produced negligible improvements 6MWT total distance[61]. These data highlight a crucial knowledge gap in the gait rehabilitation literature in PD.

Specifically, overground training has been relatively unexplored. This is surprising for two reasons. First, walking in daily-life is performed overground, thus, training that mimics everyday life seems logical. Second, motor learning paradigms emphasize the ongoing interaction between the performer and the environment during the

skill acquisition process,[36] thus, it is surprising that overground paradigms have been so neglected in this patient population.

Performance-Based Framework

Performance-based training frameworks emanate from dynamical system theory.[12] Dynamic systems theory of motor control proposes that a given movement is a function of interacting component of numerous complex systems.[13] Specifically, an individuals' movement at any given point in time is expressed as a solution in response to the interactions between constraints imposed by the task pursued by the organism, constraints imposed from within the organism, and constraints imposed by the environment.[122,123,185,186] Thus, interventions to optimize movement should facilitate an individual's response to the dynamic interplay of constraints that are unique to a specific task and its environmental context. Applying these principles to the context of gait rehabilitation, performance-based frameworks emphasize principles of task specificity, practice variation, and progressive overload in an attempt to promote active exploration of real-world movement solutions and adaptation across multiple body systems responsible for recovery of locomotor function.[12] This approach attempts to account for both physiological adaptation as well as motor learning, as together they may synergistically promote experience-dependent plasticity. Additionally, emphasis on exclusively overground practice flows logically from performance-based concepts, and may facilitate exploration of critical constraint interactions in an ecologically valid practice environment. These concepts have not been fully applied in the context of gait

rehabilitation for individuals with PD and the effects of performance-based interventions are unknown in people with PD.

Fatigue and Fatigability in Parkinson's Disease

Fatigue is a problematic non-motor symptom that is often reported in people with PD.[187–190] Fatigue is a symptom defined as a subjective lack of physical and/or mental energy that is perceived by the individual to interfere with usual or desired activities commonly assessed using self-report questionnaires.[191] In PD specifically, fatigue has been described by many as a sense of exhaustion that is not attributable to drug effects or other medical or psychiatric issues.[189,190] Fatigue is frequently reported in people with PD, often manifesting before patients are diagnosed with the disease, persisting over the course of the disease, and negatively impacting quality of life, even when controlling for other potentially confounding symptoms such as depression, motor symptom severity, and sleep quality.[192–199]

Recently, it has been suggested that the symptom of fatigue should be distinguished from fatigability.[190] Fatigability is an activity-specific construct that describes important elements of functional capacity.[5,52,120,121,200] More precisely, as a function of the duration, intensity, and/or frequency of activity, fatigability describes the magnitude or rate of change over time in the performance of an activity (i.e. performance fatigability) and the change in perceptions of tiredness (i.e. perceived fatigability).[5] Individuals who express greater levels of fatigability, performance or perceived, are likely to be limited in their ability to sustain physically demanding activities due to a more rapid deterioration of performance and greater sense of exertion during activity.

Evidence from exercise studies indicate that both performance fatigability and perceived fatigability are often elevated during whole-body activity in people with PD.[2–4,7,8,10,47,129,133,141,142,201] For example, when compared to healthy controls, it is often reported that individuals with PD are limited during both maximal and submaximal exercise protocols.[7,8,8,10,47,129,133,141,142,201] Additionally, in people with PD, ratings of perceived exertion have often been reported to be higher in comparison to controls at peak exercise, despite lower peak work rates.[10,47] Furthermore, in comparison to controls, ratings of perceived exertion were reported to be higher in individuals with PD while walking at a range of submaximal treadmill speeds,[4] and after a 6MWT.[2] Increased susceptibility to fatigability may, in part, contribute to limitations in sustained overground walking performance often observed in members of this patient population.[2,3]

Cardiorespiratory Impairments and Fatigability in Parkinson's Disease

Fatigability is strongly influenced by the functional status of the cardiorespiratory system. The cardiorespiratory system supports the aerobic energy synthesis needed to maintain muscle contraction. Both cross-sectional and interventional studies have demonstrated a strong relationship between fatigability and cardiorespiratory fitness in individuals of various age ranges and disease states.[42,127,143,202–207] Cardiorespiratory fitness is often reduced in people with PD.[7–10,47,129,133,141,142,201] While this deficit has recently been proposed as an underlying driver of elevated fatigability in this patient population,[11] these relationships are underexplored in the context of gait rehabilitation in PD. For example, Shulman et al. reported concomitant improvements in $\dot{V}O_2$ peak and 6MWT total distance following both lower-intensity and higher-intensity treadmill

training in individuals with PD.[28] In contrast, two studies, one employing stationary cycling training and the other employing progressive treadmill training, reported equivocal changes in VO_2 peak following training despite concomitant improvements in 6MWT total distance. Thus, it remains unknown if intervention induced cardiorespiratory adaptations play an important role in modulation of fatigability and endurance walking performance in people with PD. Addressing this question may yield insight that informs the design of rehabilitation programs aimed at improving walking endurance in people with PD.

Table 4: Excluded participant characteristics.

Participant	Age (years)	Gender	Height (cm)	Weight (kg)	Hoehn and Yahr	More affected side
3	67	F	163	53.7	1.5	R
7	85	M	175.5	86.2	2	L
13	67	F	160.6	95.9	2	L
16	65	F	165.2	54.8	2	L
17	65	M	164.2	84.4	2	R

Abbreviations: M, male; F, female; L, left; R, right.

Table 5: Walking Performance and Fatigability Outcomes for All Participants.

Parameter	**Pretest**	**95% CI**	**Posttest**	**95% CI**	**Pre-Post Change**	**95% CI**	**Cohen's $d_{(unbiased)}$**	**P value**
Total distance (m)	885.9 (157.2)	[786, 985.7]	969.5 (140.9)	[879.9, 1059]	+83.6 (77.5)	[34.3, 132.8]	0.54	0.0033
Performance fatigability index (1/m)	1.2 (0.2)	[1, 1.3]	1.0 (0.2)	[0.9, 1.1]	-0.1 (0.1)	[-0.2, 0]	0.64	0.0029
Pacing index	100 (2.8)	[98.2, 101.7]	99.3 (2.3)	[97.8, 100.8]	-0.7 (2.1)	[-2, 0.7]	0.25	0.2941
Perceived fatigability index (au)	5.3 (1.3)	[4.5, 6.1]	4.9 (1.3)	[4.1, 5.8]	-0.3 (1.6)	[-1.3, 0.7]	0.24	0.4921
Raw perceived tiredness/energy ratings (au)	4.7 (1.4)	[3.8, 5.5]	4.8 (1.5)	[3.9, 5.8]	+0.2 (1.1)	[-0.5, 0.9]	0.11	0.6147

Description: Total distance is in meters (m). Performance fatigability index is in units of 1/m. Perceived fatigability index and raw perceived tiredness/energy ratings are in arbitrary units (au). Pacing index is a ratio, and is therefore unitless.

Table 6: Walking Performance and Fatigability Outcomes for Male Participants.

Parameter	Pretest	95% CI	Posttest	95% CI	Pre-Post Change	95% CI	Standardized Effect Size	P value
Total distance (m)	949.8 (180.4)	[783, 1116.6]	1025.6 (142.9)	[893.4, 1157.7]	+75.8 (81.2)	[0.7, 150.9]	0.44*	0.0486
Performance fatigability index (1/m)	1.1 (0.2)	[0.9, 1.3]	1.0 (0.1)	[0.9, 1.1]	-0.1 (0.1)	[-0.2, 0]	0.63⸸	0.0180ψ
Perceived fatigability index (au)	5.6 (1.1)	[4.7, 6.6]	5.3 (1.2)	[4.2, 6.4]	-0.3 (1.8)	[-2.1, 1.4]	0.24*	0.6738
Raw perceived tiredness/energy ratings (au)	5.3 (1.1)	[4.3, 6.3]	5.4 (1.3)	[4.3, 6.6]	+0.1 (1.2)	[-0, 1.27]	0.08*	0.7663

Description: Total distance is in meters (m). Performance fatigability index is in units of 1/m. Perceived fatigability index and raw perceived tiredness/energy ratings are in arbitrary units (au). A superscript of "⸸" indicates calculation of r using Eq. 3. A superscript of "*" indicates calculation of Cohen's $d_{(unbiased)}$ using Eq. 2. A superscript of "ψ" indicates use of the Wilcoxon signed-rank test in lieu of a paired t-test.

Table 7: Walking Performance and Fatigability Outcomes for Female Participants.

Parameter	Pretest	95% CI	Posttest	95% CI	Pre-Post Change	95% CI	Standardized Effect Size	P value
Total distance (m)	796.4 (44.6)	[741, 851.8]	890.9 (103.7)	[762.1, 1019.7]	+94.5 (79.9)	[-4.7, 193.7]	1.06*	0.0573
Performance fatigability index (1/m)	1.3 (0.1)	[1.1, 1.4]	1.1 (0.2)	[0.9, 1.3]	-0.1 (0.1)	[-0.3, 0]	0.64⏚	0.0431ψ
Perceived fatigability index (au)	4.8 (1.5)	[2.9, 6.7]	4.4 (1.5)	[2.6, 6.2]	-0.3 (1.2)	[-1.8, 1.2]	0.24*	0.5697
Raw perceived tiredness/energy ratings (au)	3.8 (1.3)	[2.2, 5.4]	4 (1.6)	[2, 5.9]	+0.2 (1.1)	[-1.2, 1.6]	0.04⏚	0.8759ψ

Description: Total distance is in meters (m). Performance fatigability index is in units of 1/m. Perceived fatigability index and raw perceived tiredness/energy ratings are in arbitrary units (au). A superscript of "⏚" indicates calculation of r using Eq. 3. A superscript of "*" indicates calculation of Cohen's $d_{(unbiased)}$ using Eq. 2. A superscript of "ψ" indicates use of the Wilcoxon signed-rank test in lieu of a paired t-test.

Documents

Link to ClinicalTrials.gov

To view the parent study registration on ClinicalTrials.gov please use the link below:

https://clinicaltrials.gov/ct2/show/NCT03864393

Medical History Form

George Mason University
Department of Rehabilitation Science
Evaluation of a Power, Agility, and Coordination Program for Individuals with Parkinson's Disease
HEALTH HISTORY FORM

Participant Name:_____ ID #:_____

Date of Birth:_____ *PD Only*: Diagnosis Date:_____

Emergency Contact:_____Relationship:_____Phone #:_____

What is your dominant: *a) Arm*: ☐Right ☐Left *b) Leg*: ☐Right ☐Left

For PD Only: Which limb is more affected by the disease? ☐Right ☐Left Other:_____

SOCIAL/CULTURAL

Race (Please check all that apply)

- ☐American Indian or Alaska Native
- ☐Asian
- ☐Black or African American
- ☐Hispanic or Latino
- ☐Native Hawaiian or Other Pacific Islander
- ☐White

Language (Please check all that apply)

- ☐English understood
- ☐Interpreter needed
- ☐Language you speed most often:_____

Education *(Circle highest grade level completed)*

Grades: 1 2 3 4 5 6 7 8 9 10 11 12

Some College / Technical School

College Graduate

Graduate School

Cultural/Religious: Any customs or religious beliefs or wishes that might affect participation? _____

_____

_____

Living Environment

With whom do you live: _____

Does your home have: *(Circle all that apply)*

Stairs, no railing
Stairs, railing
Ramps
Elevator
Uneven terrain
Assistive devices in bathroom,etc

Do you use: *(Circle all that apply)*

Cane
Walker or rollator
Hearing aids
Glasses
Other:_____

George Mason University
Department of Rehabilitation Science
Evaluation of a Power, Agility, and Coordination Program for Individuals with Parkinson's Disease
HEALTH HISTORY FORM

Participant Name:_____ ID #:_____

Date of Birth:_____ *PD Only*: Diagnosis Date:_____

Emergency Contact:_____Relationship:_____Phone #:_____

What is your dominant: *a) Arm*: ☐ Right ☐ Left *b) Leg*: ☐ Right ☐ Left

For PD Only: Which limb is more affected by the disease? ☐ Right ☐ Left Other:_____

SOCIAL/CULTURAL

Race (Please check all that apply)

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Hispanic or Latino
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White

Language (Please check all that apply)

- ☐ English understood
- ☐ Interpreter needed
- ☐ Language you speed most often:_____

Education *(Circle highest grade level completed)*

Grades: 1 2 3 4 5 6 7 8 9 10 11 12

Some College / Technical School

College Graduate

Graduate School

Cultural/Religious: Any customs or religious beliefs or wishes that might affect participation? _____

_____

_____

Living Environment

With whom do you live: _____

Does your home have: *(Circle all that apply)*

Stairs, no railing
Stairs, railing
Ramps
Elevator
Uneven terrain
Assistive devices in bathroom,etc

Do you use: *(Circle all that apply)*

Cane
Walker or rollator
Other:_____
Hearing aids
Glasses

George Mason University
Department of Rehabilitation Science
Evaluation of a Power, Agility, and Coordination Program for Individuals with Parkinson's Disease
HEALTH HISTORY FORM

GENERAL HEALTH / HEALTH HABITS

Health Rating Please rate your health: Excellent Good Fair Poor

Tobacco use

☐ No

☐ Yes: Cigarettes: # or packs/day_____

Cigars/Pipes: # per day_____

☐ Past Year quit:_____

Alcohol use

How many days per week?_____

How many drinks on an average?_____

Exercise

Do you exercise beyond normal daily activities and chores?

☐ Yes Describe the exercise: _____

How many days/week: _____ How many minutes:_____

☐ No

MEDICAL HISTORY (Please check all medical diagnoses and conditions that apply)

☐ Anemia
☐ Arthritis
☐ Bleeding Disorders
☐ Cancer: _____
☐ Chemical Dependency
☐ Communicable Disease
☐ HIV+ ☐ VRE ☐ MRSA
☐ E Coli ☐ Scabies
☐ Depression
☐ Diabetes
☐ Dizziness
☐ Emphysema
☐ Gout
☐ Heart Disease
☐ High Blood Pressure
☐ Irregular or Rapid Heart Beat
☐ Joint Replacement
☐ Kidney Problems
☐ Osteoporosis
☐ Pacemaker
☐ Parkinson's Disease
☐ Current Pregnancy
☐ Stroke
☐ Thyroid Problem

☐ *Other medical condition not listed above:*_____

CURRENT SYMPTOMS (Please check all symptoms you currently have)

☐ Productive cough
☐ Fever/Chill
☐ Coughing up blood
☐ Night sweats
☐ Nausea/Vomiting
☐ Chest pain
☐ Trouble breathing
☐ Joint pain
☐ Joint stiffness
☐ Rashes or skin changes
☐ Visual changes
☐ Hearing changes
☐ Constipation
☐ Bloody Stools
☐ Pain with urination
☐ Incontinent bladder
☐ Incontinent bowel
☐ Other:_____

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HEALTH HISTORY FORM

FALLS (Please check)

Are you concerned about falling? ☐ Yes ☐ No Have you fallen in the last year? ☐ Yes ☐ No If yes, Date:

Have you fallen more than 2 times? ☐ Yes ☐ No Has any resulted in injury? ☐ Yes ☐ No

---

SURGERIES/HOSPITAL PROCEDURES (Please list the procedure and date)

_____
_____
_____
_____

ALLERGIES / DRUG INTERACTIONS

_____
_____

CURRENT MEDICATIONS

Medication Name	Dose	Frequency	Reason	Time Since Start

Data Collection Sheet

Date:_____ Time of Day: _____ Time of medication:_____ POSS_____ 1

POSSabilities Assessment Pre/Post COSMED turbine:

Assessment Team

BP	HR	Height(in)	Weight(lbs)

Mini-mental Exam	
Hoehn & Yahr Scale	
HHQ	

10 Minute Walk

(COSMed, APDM):

POSS###_Pre/Post_10min

sit: 3 min. stand 4 min. walk 10 min. stand recovery 10 min.

PFS	
Before	After

BP (sit) – 1:00	BP stand – 3:30	BP stand – 5:30		
BP stand – 7:30	BP stand – 9:30	BP at 1:00 recovery	BP at 4:00 recovery	BP at 9:00 recovery

Breaks Taken:

Total distance:

Time delay:

1	2	3	4	5	6	7	8	9	10
11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50

"check mark" in box = lap completed... T1, T2, T2.5, T3, T4, T5, T6, T7, T7.5, T8, T9, T10 in box = tape measurement during lap

Informed Consent

Department of Rehabilitation Science

4400 University Drive, MS 2G7, Fairfax, Virginia 22030
Phone: 703-993--1950; Fax: 703-993-6073

INFORMED CONSENT

Effect of Multimodal Exercise Training on Walking Economy in Individuals with Parkinson's Disease

RESEARCH PROCEDURES

This research study is being conducted to understand the influence of a multimodal overground locomotor training program (OLT) on walking economy and secondary effects with regard to performance fatigability and propulsion during ambulation in individuals with Parkinson's Disease (PD). If you agree to participate, you will be asked to participate in 24 training sessions following an initial evaluation of your health history and functional abilities, including your cardiorespiratory fitness, and motor function including gait. Training sessions will occur twice per week for 12 weeks. Each session will last approximately one hour. You will also be asked to repeat your initial assessment as a final evaluation following the completion of the training sessions.

Examination Procedures

You may be asked to complete the following as part of the pre and post training evaluations:

- Health history questionnaire
- Psychological assessments: used to obtain measurements such as your intellectual function, cognition, memory, judgement, and mood
- Parkinson's disease scales: standardized measures of the course, progression, and severity of PD
- Body composition assessments: measures such as your height and weight
- Fitness assessments: tests and measures of your body's response to physical activity while walking overground, on a treadmill, or cycling on a bike; this often requires wearing a facemask that will collect the air you breathe in and out
- Muscle strength tests: measures of your muscle strength and power which include asking you to push against various types of resistance while wearing sensors over the muscles being used
- Gait and Balance assessments: tests and measures of your walking characteristics and abilities and of your ability to balance during static and dynamic activities; this may include wearing sensors when walking on a platform or treadmill
- Agility, Coordination, and Motor Control Assessments: tests and measures of your ability to plan and execute coordinated movements

The evaluation and assessment will last approximately 90 minutes, one session prior to training and one after training (3 hours of testing total). The testing session will begin with a Health History Questionnaire, Parkinson's Disease scales, psychological state assessment, and assessment of body composition. The order of the remaining assessments will be determined by every other participant drawing a slip of paper with either a 1 or 2 written upon it. When drawing a number from the envelope the chance of drawing either number is 50%.

Training Procedures

The training will involve various forms of exercise designed to address your cardiorespiratory fitness, muscle strength and power, and motor function (including balance and gait). Each training session will last approximately 60 minutes, twice a week for 12 weeks. A heart rate monitor and step watch will be used to monitor intensity and volume during each training session. The heart rate monitor consists of a strap around your chest and wrist watch and the step watch is worn around the ankle.

Videography and photography

Testing and training sessions may be videotaped. During testing, the motion capture system used to analyze gait includes a video component. Video and photographs may be included in the dissemination of results such as research presentations at conferences and in teaching presentations. You have the right to decline videotaping at any session or at any given point while videotaping. Videos will be used for training and teaching purposes. To the extent possible, you will be videotaped in ways that will diminish facial recognition. Video material (photos and videos) will remain on a secure computer and will be deleted after 5 years after the study is completed. You also may request at any time that your videotapes be completely erased immediately either while participating in the study or after your participation has ended.

Re-testing Procedures

At the conclusion of 24 sessions or 12 weeks, you will be retested in the same ways you were tested at the start of the program.

Time Commitments

Participants will need to be available for approximately 1.5 hours of testing prior to and following training for approximately 3 total hours of testing and a total of 24 training sessions (two 60-minute sessions per week for 12 weeks). The total time commitment will be approximately 27 hours.

RISKS

The foreseeable risks or discomforts are similar to the risks that you take when exercising or engaging in moderate physical activity on your own, with or without supervision, at home or in a gym or other facility. The level of exercise or physical activity is in your control, and you will not be asked to engage in any activity that you believe is beyond your ability or tolerance.

You may have some minor discomfort during testing procedures that are similar to any temporary discomfort that you may experience in a routine medical examination or annual physical examination.

You may experience some discomfort from any of the testing or training including muscle fatigue, muscle or joint soreness, and lightheadedness during or in the hours following testing or training. Straining a muscle or spraining a ligament is a very small possibility during testing or training.

You may experience a fall, slip, or trip during testing or training. Every effort will be made to minimize these risks. You will have a research assistant nearby at all times to avoid a fall, slip, or trip.

The risks of exercise testing and supervised training are generally low, although sometimes medical complications do occur. During exercise and moderate physical activity, certain changes in heart rate and rhythm, blood pressure, and respiratory rate are expected, but abnormal or unanticipated changes are small possibilities. Every effort will be made to minimize these risks.

Although rare in occurrence the most serious risks of exercise testing and training include sudden death, heart attack, dizziness, chest pain or tingling in the arm, jaw, or back, shortness of breath, and/or extreme fatigue. Please let the researcher know if you experience any of these symptoms during testing or training activities.

In case of injury during testing or training procedures, the George Mason University research team may provide basic first aid. If appropriate, the staff will call the emergency response team at 911. Neither George Mason University nor the investigators have funds available for payment of medical treatment for injuries that you may sustain while participating in this research. Should you need medical care, you or your insurance carrier will be responsible for payment of the expenses required for medical treatment.

BENEFITS

There are no direct benefits to you as a participant other than to further the research of interventions designed for people with PD.

CONFIDENTIALITY

The data in this study will be confidential, including in publications and reports resulting from the research. All participants will be assigned an identification number after agreeing to participate, and all de-identified data will be stored using this identification number. The signed informed consent and the identification number linking data to individuals will be stored by the lead researcher in a locked cabinet in a locked office along with any other forms or papers that have protected personal or health information. Only members of the research team will have access to this information. The de-identified data could be used for future research without additional consent from participants. Monitors, auditors, the Institutional Review Board, and regulatory authorities may have access to the data for verification of clinical trial procedures without violating the confidentiality of the participants to the extent permitted by law.

PARTICIPATION

Your participation is voluntary, and you may withdraw from the study at any time and for any reason. If you decide not to participate or if you withdraw from the study, there is no penalty or loss of benefits to which you are otherwise entitled. There are no costs to you or any other party except transportation to and from testing or training sessions and parking in compliance with University regulations. You will receive information on how PD has affected your abilities from the testing we will do, and you may or may not improve in these abilities after training.

Your participation in testing or training may be stopped at any time by a member of the research team without your consent for reasons that include a belief by the research team that continued testing or training may affect your health or safety; you are unable to follow or adhere to testing or training instructions; or other administrative reasons that require your withdrawal.

CONTACT

This research being conducted is led by Dr. Andrew Guccione, Department of Rehabilitation Science, at George Mason University. He may be reached at 703-993-4650 for questions or to report a research-related problem. You may contact the George Mason University Institutional Review Board Office at 703-993-4121 if you have questions or comments regarding your rights as a participant in the research.

This research has been reviewed according to George Mason University procedures governing your participation in this research, IRBnet #: **1374615-1**.

CONSENT

I have read this form, all my questions have been answered by the research staff, and I agree to participate in this study.
Please indicate below your preference for videography/photography. This will not affect your participation in the study.

☐ I grant permission to videotape my image and likeness as part of this research study.

☐ I DO NOT grant permission to videotape my image and likeness as part of this research study.

_____ _____

Name **Date of Signature**

_____

Signature

Standardized Mini-Mental State Examination

Name of patient: | DOB: / / | Name of examiner: | Date of test: / /

Standardised Mini-Mental State Examination (SMMSE)

Please see accompanying guidelines for administration and scoring instructions

Say: *I am going to ask you some questions and give you some problems to solve. Please try to answer as best you can.*

1. Allow ten seconds for each reply. **Say:**

   a) *What year is this?* (accept exact answer only) /1
   b) *What season is this?* (during the last week of the old season or first week of a new season, accept either) /1
   c) *What month is this?* (on the first day of a new month or the last day of the previous month, accept either) /1
   d) *What is today's date?* (accept previous or next date) /1
   e) *What day of the week is this?* (accept exact answer only) /1

2. Allow ten seconds for each reply. **Say:**

   a) *What country are we in?* (accept exact answer only) /1
   b) *What state are we in?* (accept exact answer only) /1
   c) *What city/town are we in?* (accept exact answer only) /1
   d) <At home> *What is the street address of this house?* (accept street name and house number or equivalent in rural areas) /1
      <In facility> *What is the name of this building?* (accept exact name of institution only) /1
   e) <At home> *What room are we in?* (accept exact answer only) /1
      <In facility> *What floor of the building are we on?* (accept exact answer only) /1

3. **Say:** *I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes* (say slowly at approximately one-second intervals).

   Ball Car Man

   For repeated use: Bell, jar, fan; bill, tar, can; bull, bar, pan

   Say: *Please repeat the three items for me* (score one point for each correct reply on the first attempt) /3

   Allow 20 seconds for reply; if the person did not repeat all three, repeat until they are learned or up to a maximum of five times (but only score first attempt)

4. **Say:** *Spell the word WORLD* (you may help the person to spell the word correctly). **Say:** *Now spell it backwards please* (allow 30 seconds; if the person cannot spell world even with assistance, score zero). Refer to accompanying guide for scoring instructions (score on reverse of this sheet)

   /5

5. **Say:** *Now what were the three objects I asked you to remember?* /3

   (score one point for each correct answer regardless of order; allow ten seconds)

6. Show wristwatch. **Ask:** *What is this called?* /1

   (score one point for correct response; accept 'wristwatch' or 'watch'; do not accept 'clock' or 'time', etc.; allow ten seconds)

1

7. **Show pencil. Ask:** *What is this called?* /1

   (score one point for correct response; accept 'pencil' only; score zero for pen; allow ten seconds for reply)

8. **Say:** *I would like you to repeat a phrase after me: No ifs, ands, or buts* /1

   (allow ten seconds for response. Score one point for a correct repetition. Must be exact, e.g. no ifs or buts, score zero)

9. **Say:** *Read the words on this page and then do what it says* /1

   Then, **hand** the person the sheet with CLOSE YOUR EYES (score on reverse of this sheet) on it. If the subject just reads and does not close eyes, you may repeat: *Read the words on this page and then do what it says*, a maximum of three times. See point number three in Directions for Administration section of accompanying guidelines. Allow ten seconds; score one point only if the person closes their eyes. The person does not have to read aloud.

10. **Hand** the person a pencil and paper. **Say:** *Write any complete sentence on that piece of paper* (allow 30 seconds. Score one point. The sentence must make sense. Ignore spelling errors). /1

11. **Place** design (see page 3), pencil, eraser and paper in front of the person. **Say:** *Copy this design please.* Allow multiple tries. /1

    Wait until the person is finished and hands it back. Score one point for a correctly copied diagram. The person must have drawn a four-sided figure between two five-sided figures. Maximum time: one minute.

12. **Ask** the person if he is right or left handed. **Take** a piece of paper, hold it up in front of the person and **say** the following: *Take this paper in your right/left hand* (whichever is non-dominant), *fold the paper in half once with both hands and put the paper down on the floor.*

Takes paper in correct hand_____ /1

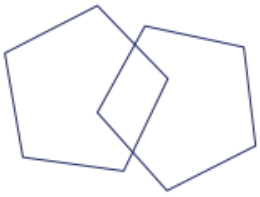
Folds it in half_____ /1

Puts it on the floor_____ /1

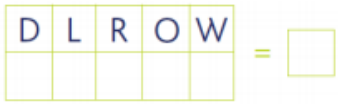
TOTAL TEST SCORE: /30

ADJUSTED SCORE: /

Molloy DW, Alemayehu E, Roberts R. Reliability of a standardized Mini-Mental State Examination compared with the traditional Mini-Mental state Examination. *American Journal of Psychiatry*, Vol. 14, 1991a, pp.102-105.



Time:



CLOSE YOUR EYES

3

Approved IRB Application for Parent Study

GEORGE MASON UNIVERSITY

Institutional Review Board

Application Form

Instructions:

1. CITI certification (www.citiprogram.org) must be completed for all team members at the time of application submission.
2. Complete all sections and required addenda. Submit one complete package via IRBNet.
3. Projects with funding/proposed funding must include a copy of the grant application or proposal.
4. Research may not begin until you have received notification of IRB approval.
5. Handwritten and incomplete forms cannot be accepted.

1. Study Title: Effect of Multimodal Exercise Training on Walking Economy in Individuals With Parkinson's Disease

2. Study Investigators

A. Principal Investigator (*must be faculty/staff and meet PI Eligibility, University Policy 4012*)

Name: Andrew Guccione Department: Rehabilitation Science

Phone: 703-993-4650 E-mail: aguccion@gmu.edu

B. Co-Investigator/Student Researcher

Name: Clint Wutzke Department: Rehabilitation Science

Phone: 703-993-1903 E-mail: cwutzke@gmu.edu

C. Are there additional team members? No ☐ Yes ☒ *If yes, complete Addendum J to list additional team members*

D. Do any investigators or team members have *conflicts of interest* related to the research?

No ☒ Yes ☐ If yes, explain

3. Study Type: ☒ Faculty/Staff Research ☒ Doctoral Dissertation ☐ Masters Thesis ☐ Student Project (**Specify** ☐ Grad or ☐ Undergrad) ☐ Other (Specify)

4. Complete Description of the Study Procedures

A. Describe the aims and specific purpose of the study:

Sustained ambulation is a challenge for individuals with Parkinson's disease (PD) as walking economy is frequently compromised. There are also various disease-related skeletal muscle alterations that may contribute to performance fatigability during ambulation. Concomitantly, individuals with PD experience substantial difficulty maintaining sustained forward progression at push-off during the gait cycle due to diminished force production. Exercise is commonly prescribed for these individuals, though traditional exercise approaches to PD have often applied a "one impairment-one modality" paradigm that addresses each impairment seperatly. Interventions to optimize movement should facilitate an individual's response to the challenge of responding to a complex interplay of constraints that are also specific to a task and its environmental context. Thus, there are multiple concurrent targets for exercise interventions that may not fit easily within a "one impairement-one modality" model. A multimodal intervention is designed to address an array of constraining impairments concurrently. However, the evidence-base for multimodal exercise approaches is still developing and far from conclusive. The purpose of this study is to demonstrate that multimodal overground locomotion training (OLT) can promote walking economy during sustained overground ambulation in individuals with PD, and produce concurrent secondary effects that decrease preformance fatigability and increase propulsion. The aims of this study are to 1)

Evaluate walking economy during sustained overground walking after 12 weeks of multimodal OLT, 2) Evaluate secondary effects of OLT.

B. Provide a COMPLETE description of the study procedures in the sequence they will occur including the amount of time each procedure will *take (attach all surveys, questionnaires, standardized assessment tools, interview questions, focus group questions/prompts or other instruments of data collection)*:

Protocol Overview: Subjects will be recruited from the greater Washington D.C. metro area and Northern Virginia areas by word of mouth, healthcare provider referral, support groups, social media posting, and by posted fliers. The study design and participation will be explained to those who are potentially interested in participating in the study. Individuals interested in participating as subjects will complete initial verbal screening to determine eligbility for inclusion. Those subjects who volunteer to participate will then be consented and enrolled for participation if exclusion and inclusion criteria are met.

Visit 1: (~ 90 minutes) Subjects meeting inclusion and exclusion criteria will be consented and enrolled in the study. They will then be asked to fill out a medical history form. Height and weight measurements will then be taken. The Hoehn and Yahr and Mini-metnal State Exams (described below) will then be administered by an investigator. Subjects will then be randomized as to the order of testing procedure. Randomization will be performed using blocks of two, whereby the first subjects will draw a number (1 or 2) out of an envelope with 1 indicating the 10-minute walk will be performed first and 2 indicating gait lab propulsion testing will be performed first. The next subject enrolled in the study will do the opposite. This testing pattern will continue with the third subject drawing randomly and the fourth subject doing the opposite and so on. These tests will be separated by a sufficient rest period or as long as it takes to set up for the next testing procedure, with a minimum rest period of 10 minutes but less than 20 minutes for consistency between subjects. Those subjects performing the the 10-minute walk test first will be fitted with a portable metabolic unit consisting of a face mask and torso apparatus similar to a backpack. Wearable sensors will be secured with velcro to both arms, trunk, and legs. The walk will take place in a long corridor within the Peterson Health Sciences Building. Prior to starting the test, subjects will stand in a resting position for at least 3 minutes to gain resting metabolic data. They will then be asked to walk as far as they can in 10 minutes. Following the 10-minute walking period, subjects will again stand in a resting position to obtain recovery data. Subjects will then be provided a 10-20 minute resting period during the transition to the second test. For the second test, subjects will be fitted with reflective markers at pre-specified anatomical landmarks used in a standardized gait marker set, for example medial and lateral knee and ankle joints. Electromyography (EMG) sensors will be placed on lower limb muscles. Subjects will then be asked to walk at both their preferred and fast walking speed over a 6 meter platform with embedded force plates. Subjects will be asked to perform as many trials as necessary to collect sufficient force plate data which is anticipated to be between 20-30 passes. Following this test, subjects will be given the opportunity for a rest period if required before ending the testing day. For those subjects who start with the gait propulsion test, the testing order will include the same procedures yet in the reversed order.

Visits 2-25: (~1 hour each) For these visits, subjects will perform an overground multimodal locomotor training protocol. Subjects will train individually with 1-2 trained instructors. Each training session will consist of an initial warm-up period, the main training intervention, and a cool-down period. Subjects will wear a Polar chest strap and a StepWatch (research grade pedometer) during each session to enable instructors to modify training within the session to maintain a target intensity zone. The training protocol covers 12 weeks with two sessions per week for a total of 24 sessions.

Visit 26: (~90 minutes): Subjects will repeat the same testing procedures as they did in visit 1 in the same order as they did, determined by the initial randomization process.

Study Procedures:

10-Minute Walk Test: The purpose of this test is to provide a method of perturbation for measuring both performance and perceived fatigability. Subjects will wear a fitted face mask and a torso unit as part of a portable metabolic unit. Wearable sensors will be secured on the torso, upper and lower limbs to measure gait characteristics. Subjects will rest in a standing position for at least 3 minutes prior to beginning this test to collect baseline data. Subjects will then walk over a level corridor as far as they can over a 10-minute interval or until they have to stop walking. Distance covered will be recorded at at 2.5-minute intervals throughout the test and at the end of the time walked if not the full 10 minutes. Velocity will be computed from the distances covered at the time intervals (meters/sec). The 10-minute walk test will be performed during the pre-intervention testing visit and post-intervention testing visit. At least one member of the research team will conduct the test and give limited cueing throughout the test to ensure proper testing procedure but not excessive motivational encouragement. Following the 10-minute walk period (or total time if ended early) subjects will rest in the standing position to obtain recovery data for at least 6 minutes.

Gait Propulsion Testing: Subjects will be outfitted with reflective markers comprised of a standardized full-body marker set for motion capture analysis. EMG sensors will be placed on muscle bellies of lower limb muscles. To establish the maximum voluntary contraction, subjects will be asked to contract muscles against resistance. Subjects will be asked to stand for system calibration for less than one minute and may be asked to move various limbs through a range of motion to ensure accuracy of the system prior to starting the test. Subjects will then be asked to walk across a 6-meter platform with embedded force plates enclosed by safety rails at their preferred and fast walking speed. Subjects will perform approximately 20-30 passes to ensure sufficient data collection by the force plates as appropriate contact with the force plate must be made for valid measurement. Once sufficient data has been collected, markers and sensors will be removed and the subject will be offered a seated rest period if needed.

Multimodal Exercise Intervention: The intent of the multimodal training intervention is to encompass cardiovascular adaptations and locomotor improvements. Cardiovascular adaptations, as evidenced by improved in AT-VO2, have been demonstrated to improve performance fatigability in other clinical populations. To promote cardiovascular adaptation, training sessions will be adjusted in real-time to achieve a pre-determined target HR zone for each subject. HR will be monitored coninuously during each training session. The target HR

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intensity during training sessions will be 60% of the subjects predicted maximal HR. The target HR zone will be 60% of predicated maximal HR +/- 5%. The subjects predicted maximal HR will be calculated using the formula: 220-age. To promote locomotor improvements, training procedures will include drills based on gait initiation and termination, agility, muscular power, and steady state actions. Drills will be conducted with an emphasis on direction change beyond usual forward progression. As subjects become familiar with the various drills, instructors will gradually increase the complexity, speed, and volume.

Propulsion Measures: For this study, propulsion will be defined by anterior peak positive ground reaction force (GRF) during overground walking. The force plates measure the GRF in response to the force placed upon it by the subject. In conjuction with motion capture analysis, the propulsive phase of gait can be determined and within that phase the anterior peak vector will be calculated. Peak propulsive force will be determined as the maxima (one point) of the anterior GRF.

Performance Fatigability Test Scoring: Performance fatigability is the rate or extent to which tissue, organ, system or total body function (fatigue) declines in response to a given task. After a 10-minute period of quiet rest in the sitting position, subjects will complete the 10-minute walk test. Distance covered will be recorded at the 2.5-minute interval of the test and for the total test. Velocities for the entire test (total distance walked / total minutes of test) and the first 2.5 minutes of the test (distance covered in the first 2.5 minutes / 2.5 minutes) will be calculated. The fractional change in velocity will then be computed as the quotient of total test velocity / 2.5 minute velocity. For example if the total test velocity and the 2.5-minute velocity were both 82 meters/minute, the total test velocity would be 100% of the velocity at 2.5 minutes. However, if the total test velocity were 80 meters/min and the velocity at 2.5 minutes were 82 meters/minute, then the total test velocity would be only .98 of the 2.5-minute velocity. To calculate the performance fatigability score, the fractional change in velocity will be divided by the distance covered. Thus any 2 subjects could have similar change in velocity scores (for example 0.5) but different total distances (100 versus 200 meters). In this case the performance fatigability score for the first subject would be 0.5/100 = 0.005 versus .5/200 = 0.0025. Scores are multiplied by 1000 to facilitate reporting. A small score indicates lower fatigability. Thus, even though the fractional change in velocity was similar for the 2 hypothetical subjects above, fatigability was less in the second subject as demonstrated by a lower performance fatigability score.

Perceived Fatigability Test Scoring: Perceived fatigability is the rate or magnitude of change in feelings of tiredness or weariness (symptoms of fatigue or perceived fatigue) in response to a given task. After the initial 10-minute sitting rest period, subjects will rate their perception of fatigue or vigor using the left side of the Fatigue and Fatigability Scale. Following the 10-minute walk test, subjects will be asked "compared to when you started, how would you rate your level of tiredness now" using the right side of the scale. The left side is considered a measure of fatigue because a change in fatigue was not assessed. The right side is considered to be a rating of fatigability because it assesses the change in tiredness. The score for the change in tiredness is then normalized to the total distance covered to calculate the perceived fatigability score: perceived fatigability = (change in tiredness / total distance walked) x 100 (multiplied by 100 to facilitate reporting and comparison).

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Cardiopulmonary Gas Exchange Analyes: All gas exchange will be collected using a wearable metabolic unit, the COSMED K5© portable cardiorespiratory testing system. The K5 system uses a galvanic fuel cell and non-dispersive infrared sensor for the analysis of oxygen consumption (VO_2) and carbon dioxide expiration (VCO_2) in the inhaled and exhaled air and an optoelectronic reader with a high performance turbine flowmeter to measure flow rate. After the unit warms up for approximately 20-30 minutes, flowmeter, gas, scrubber, and delay time calibrations are performed following manufacturer's recommendations. The two-point gas calibration is completed sampling the ambient air and the gas from a certified tank containing 16% O_2, 5% CO_2, and standard atmospheric Nitrogen. Flowmeter calibration was performed connecting the turbine to a calibrated Hans Rudolph 3-liter syringe and completing six full strokes at a respiratory frequency of 20-25 breaths/min. Delay time calibration was performed with the flowmeter and the sampling line connected to the face mask and by executing six breaths at a given rhythym while breathing in the facemask. The unit uses OMNIA software and has both wireless and bluetooth capabilities. Subjects interface the system by wearing a form-fitting facemask and chest unit. The unit is calibrated prior to each test.

Motion capture system: Our dedicated gait lab includes infrared cameras that capture movements of reflective markers worn by subjects within the volume. Reflective markers will be placed about the subject according to a predetermined full body gait marker model. VICON Nexus software, installed on a PC, is used to collect, identify, and reconstruct the movement data.

EMG sensors for measurement of muscle activity: Noraxon EMG Wireless TeleMyo allows the wireless collection of up to 16 channels of EMG, as well as other analog signals, in real time for up to 300 feet away. The 16 channel DDTS is equipped with EMG preamplifiers, operating in the standalone analog out mode to synchronize with the VICON Nexus software. EMG sensors, DTS EMG probe with EMG lead are attached to Noraxon Dual EMG Electrodes that are secured to the subject's skin over the muscle belly of interest. The sensor and electrode are covered with tape to minimize movement artifacts.

Force plates for GRF measurement: 4 Bertc forceplates are embedded in the center of the 6 meter walkway. The forceplates measure x, y and z axes of the force and moment components, with the output signal fed into an amplifier. This signal output is displayed and recorded into the VICON Nexus software suite.

Wearable sensors for measurement of gait characteristics: APDM wearable sensors contain accelerometers, gyroscopes, and magnetometers. Measurements are collected on the x, y, and z axes at a sample rate of 128 Hz. These sensors are attached to the preselected locations on the subject's body. This data is either wirelessly streamed via an access point and/or logged and stored in the sensor. Participants will also wear a step counter during each training sessions to record the total number of steps taken

Questionnaire:

Medical History Form: Subjects will fill out the medical history form on visit 1.

5

Testing/Forms:

Hoehn and Yahr: The Hoehn and Yahr scale (HY) is a widely used clinical rating scale, which defines broad categories of motor function in Parkinson's disease. This test will be adminstered by the researchers on visit 1.

Standardised Mini-mental State Exam: This test will be administered by researchers on visit 1 and is a 12-point questionnaire that addresses cognitive function.

C. Describe the target population (age, sex, ethnic background, health status, etc.): **The target population includes men and women over the .age of 18 diagnosed with mild to moderate, Hoehn & Yahr (H&Y) stage 1-3, Parkinson's Disease.**

1. Summarize the inclusion/exclusion criteria for participation in the study:
- Inclusion Criteria: age > 18; diagnosis of mild to moderate Idiopathic Parkinson's Disease (H&Y 1-3); able to speak English; able to ambulate with no assistive device
- Exclusion: neurological disease diagnosis other than PD; uncontrolled cardiovascular, pulmonary, neurological, or metabolic disease which may impact the ability to exercise or in which exercise is contraindicated; any medications, such as beta-blockers, that may alter HR or metabolic data; cognitive or psychiatric impairment precluding informed consent or ability to following unstructions; mini-Mental State Examination score <24; pregnancy; inability to ambulate without assistive device

2. Are there any enrollment restrictions based on gender, pregnancy, race or ethnic origins? ☒Yes ☐No If yes, please describe the process and reasons for restriction(s): **Those who are pregnant will be excluded from participation in the study as pregnancy may alter the exercise response and adaption and is possibly unsafe to pregnant females.**

3. Do any researchers listed on the application have a relationship to any of the participants that could unduly influence them to participate (including a teacher/student relationship)? ☐Yes ☒No If yes, please describe the relationship and how any possibility of undue influence will be managed:

4. Estimated number of subjects (may use a range): **20-30 individuals with mild to moderate PD**

5. Estimated amount of total participation time per subject: **Total hours = 27. Approximately 3 hours total for testing (pre and post intervention). Approximately 24 hours for training intervention (2x week/12 weeks)**

D. Where will the study occur (*list all study sites and collaborators*)? **RHBS Functional Performance Laboratory; Peterson Hall. George Mason University Fairfax Campus**

E. Describe other approvals that have been/will be sought prior to study initiation (facility authorizations, biosafety review, IRB approval from collaborating institutions, approval from public school system IRBs, etc.): **This study will be registered and approved on Clinicaltrials.gov**

F. Is this study a clinical trial that requires registration on ClinicalTrials.gov? ☒Yes ☐No If yes, please provide the NCT number assigned to the study: to be forwarded when approved

5. Recruitment and Consent

A. Describe the processes used for selecting subjects and the methods of recruitment including when, how, and by whom the subjects will be recruited (***attach all recruitment materials including flyers, emails, SONA posting, scripts, etc. and please include the IRBNet number of***

the project and the PI's name on all recruitment documents)? **Patients will be recruited using fliers, word of mouth, support groups, social media, physicians and physical therapist referral. Approval will be sought from social media administrators, support groups, physician and physical therapist offices, and other advertising locations prior to advertising.**

B. Describe the consent process including how and where the consent will take place, who will conduct the consent process, information that will be discussed with and distributed to subjects, and how participants will indicate consent even if a waiver of signature is being requested below (*attach all consent documents*): **Potential subjects will have the rationale for the study, study procedures, rights as a human subject, and their ability to terminate participation in the study explained to them. Subjects will have the opportunity to read over the consent form and ask any questions prior to signing. The consent process will take place in a private room in the Functional Performance Laboratory by one of the investigators on the study.**

C. Is a waiver of signature on the Informed Consent being requested? ☐ Yes ☒ No

If yes, complete the following:

1. This waiver is being sought because (*check one*):
   - ☐ The only record linking the subject and the research would be the consent document AND the principal risk would be potential harm resulting from a breach of confidentiality.
   - ☐ The research presents no more than minimal risk of harm to subjects AND involves no procedure for which written consent is normally required outside of the research context.
2. Explain why the waiver of signature is being requested:

6. Privacy & Confidentiality

A. How will the researchers protect the *privacy* of the participants and the *confidentiality* of the data obtained? **Information contained in the database spreadsheet will be identifiable only by a unique identification code. The identification key and data will be accessible only by the Principal and Co-Investigators.**

B. What individually identifiable information will be collected as part of the study data and who will have access to that information? **Identifiable data will include the subject's name, signature, birthday, and medical history. This data willl be listed with the subject's unique identification number on the identification key. This information will be kept in a locked cabinet accessible only to the PI and Co-I, and student investigators.**

C. When will identifiable information/the identification key be destroyed (if applicable)? *Please note that when feasible, the IRB recommends that personal identifiers be destroyed as soon as possible, though research data must be stored for 5 years.* **Signed consent forms and data will be destroyed 5 years after the end of the study. The identification key will be also be destroyed 5 years after the end of the study, though may be destroyed earlier if data collection and analysis are completed sooner.**

D. Where will the data be stored (*Copies of records must be stored on Mason property—for example, in the PI's office*)? **The signed consent form and identification key will be stored in a locked file in the PI's office. Deidentified and non-identifiable data will be kept in a file on a password-protected computer in the Functional Performance Laboratory. Copies of deidentified and non-identifiable data may also be stored on investigators' (PI and Co-Investigators) personal password-protected computers for analysis.**

E. How long will the data be stored (*data must be retained for at least 5 years after the study ends*)? **Deidentified will be stored indefinitely, but for at least 5 years, after the end of the study.**

F. What, if any, are the final plans for disposition/destruction of the data? **The identification key, signed consent forms, or any other identifiable data will be shredded or deleted five years after completion of the study.**

G. Will results of the research be shared with the participants? ☒ Yes ☐ No If yes, describe how this will be accomplished: **Individual results overall will be shared with participants upon request of the participant following completion of data collection and analysis.**

H. Will individually identifiable information be shared with anyone outside of the research team (*If yes, please explain and be sure to include this information in the consent form*)?
☐ Yes ☒ No If yes, please explain:

I. Does the research involve possible disclosure by participants of intent to harm themselves or others or possible disclosure of child abuse or neglect? (*If yes, please explain and be sure to include this information in the consent form*)?
☐ Yes ☒ No If yes, please explain:

7. Risks

A. Summarize the nature & amount of risk if any (*include side effects, stress, discomfort, physical risks, psychological and social risks*): **Risks to the participants in this study are minimal.**
-The participant may experience some discomfort from any of the testing or training including muscle fatigue and/or muscle or joint soreness following testing or training. Straining a muscle or spraining a ligament is a very small possibility during testing or training.
-The risks of the protocol exercise testing and supervised training are low as the testing and training intensity are designed and anticipated to be of moderate intensity or below. As with all exercise intervention, there is minimal risk including risk of falling, dizziness, sudden death, heart attack, chest pain or tingling in the arm, jaw, or back, shortness of breath, and/or extreme fatigue. In case of injury during testing or training procedures, the George Mason University research team may provide basic first aid. If appropriate, the team will call the emergency response team at 911. All of the research team have been trained and certified in CPR/AED administration.

B. Estimate the probability if any (e.g. not likely, likely, etc.) that a given harm may/will occur and its severity: **It is unlikely that a given harm may occur. The testingand training risks are relatively low and all testing is supervised and monitored directly.**

C. What procedure(s) will be utilized to prevent/minimize any potential risks? **Personnel trained in CPR and AED will be present at each testing and exercise testing. Subjects will be monitored at all times during testing and training visually and using heart rate monitors to ensure compliance with target intensity zones. Furthermore, personnel will alter to the balance deficiencies of this population and attendant at all times to the subject to prevent falls if a loss of balance occurs.**

8. Benefits

A. Describe any probable benefits (if any) of the research for the subject(s) (*Do not address compensation in this section*): **There are no known direct benefits of this research.**

B. Describe the benefits to society and general knowledge the study is likely to yield: **The health and social costs of living with chronic illness such as PD to society is quite large, particularly with respect to the myriad secondary conditions that may ensue as a result of chronic decreased mobility. This intervention, if effective, may offer an affordable way for individuals with PD to maintain their health and fitness and accrue the same health-related benefits of physical activity as others.**

9. Financial Information

A. Is there any internal or external funding or proposed funding for this project? ☐Yes ☒No
If yes, funding agency and OSP # (if external funding) ***(attach grant application)***
B. Are there financial costs to the subjects? ☐Yes ☒No If yes, please explain:
C. Will subjects be paid or otherwise compensated for research participation? ☐Yes ☒No
If yes, please respond to the following questions:
1. Describe the nature of any compensation to subjects (cash, gifts, research credits, etc.):
2. Provide a dollar amount/research credit amount, if applicable:
3. When and how is the compensation provided to the subject?
4. Describe partial compensation if the subject does not complete the study:
5. If research credit, what is the non-research alternative to research participation?

10. Special Topics

A. Will the study involve minors? ☐Yes ☒No
If yes, complete addendum A

B. Will the study involve prisoners? ☐Yes ☒No
If yes, complete addendum B

C. Will the study specifically target pregnant women, fetuses, or neonates? ☐Yes ☒No
If yes, complete addendum C

D. Will the study involve FDA regulated drugs (other than the use of approved drugs in the course of medical practice)? ☐Yes ☒No
If yes, complete addendum D

E. Will the study involve evaluation of the safety or effectiveness of FDA regulated devices? ☐Yes ☒No
If yes, complete addendum E

F. Will false or misleading information be presented to subjects (deception)? ☐Yes ☒No
If yes, complete addendum F

G. Will participants be audio or videotaped? ☒Yes ☐No
If yes, complete addendum G

H. Will the research involve other potentially vulnerable participants (e.g. disabled or addicted individuals, populations engaging in illegal behavior)? ☐Yes ☒No
If yes, complete addendum H

I. Will the research be conducted outside of the United States? ☐Yes ☒No
If yes, complete addendum I

11. Investigator Certification

I certify that the information provided in this project is correct and that no other procedures will be used in this protocol. I agree to conduct this research as described in the attached supporting documents. I will request and receive approval from the IRB for changes prior to implementing these changes. I will comply with all IRB policies and procedures in the conduct of this research. I will be responsible for ensuring that the work of my co-investigator(s)/student researcher(s) complies with this protocol. I understand that I am ultimately responsible for the entire conduct of this research.

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