EXERCISE AND PARKINSON'S: COMPARING INTERVENTIONS AND EXPLORING NEURAL MECHANISMS

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A Introduction

A1 Study Abstract

Parkinson disease (PD) is a progressive, neurodegenerative disorder that affects 1-1.5 million people in the United States. Difficulty with walking has been recognized as one of the earliest signs marking onset of disability in people with PD [1]. Walking difficulties and other symptoms are not fully addressed by current treatment approaches [2, 3], making clear the need for additional approaches. Exercise is one such approach. Current literature supports use of exercise as an adjunct to traditional treatments for improving gait, balance, and quality of life [4]. The primary aims of the proposed work are to compare the effects of three community based exercise programs on locomotor function and to determine whether and how these interventions alter the function and connectivity of locomotor control networks in the brain. To this end, we will utilize task-based functional magnetic resonance imaging (fMRI) and resting state functional connectivity (rs-fc) MRI to assess brain function and connectivity before and after the exercise interventions.

One hundred twenty people with PD will be randomly assigned one of *three* community-based exercise groups: tango dancing, treadmill training *or stretching (control)*. Tango has been chosen because evidence suggests tango may be superior to a more traditional exercise program for improving gait, balance and quality of life [5, 6]. Treadmill training has been chosen because studies suggest that it can improve gait and quality of life [7]. *Stretching has been chosen for the control group because it is an intervention that does not directly target walking and will allow us to control for the social and attentional aspects of participating in group exercise.* Each group will receive 3 months of intervention, attending tri-weekly one-hour group classes. Each participant will be evaluated at three time points over 6 months. MRI and behavioral measures will be conducted with participants OFF medication, with behavioral measures also assessed ON medication.

A2 Primary Hypothesis

Hypothesis 1a: *Both tango and treadmill training will improve forward walking performance, but only tango will improve backward walking performance. Walking performance in the stretching group will not change.*

Hypothesis 1b: *Tango and treadmill training will similarly improve disease severity. Tango will result in larger improvements in balance and quality of life compared to treadmill training and stretching.*

Hypothesis 2a: *Following tango, a differential BOLD signal increase will be observed in the premotor area, supplementary motor area, and putamen during both imagined forward walking and imagined backward walking; following treadmill training, BOLD signal will increase in the primary somatosensory cortex and cerebellum during imagined forward walking, but not during imagined backward walking. No BOLD signal changes will occur in the stretching group.*

Hypothesis 2b: *BOLD signal changes will be directly related to changes in actual locomotor performance.*

Hypothesis 3a: *Following tango, resting state functional connectivity of the premotor area, supplementary motor area, and putamen will increase; following treadmill training, resting state functional connectivity of the primary somatosensory cortex and cerebellum will increase. No changes will occur in the stretching group.*

Hypothesis 3b: *Changes in resting state functional connectivity of the locomotor control network will be directly related to changes in actual locomotor performance. No changes will occur in the stretching group.*

A3 Purpose of the Study Protocol

B Background

B1 Prior Literature and Studies

SIGNIFICANCE

Parkinson disease (PD) is the second most common neurodegenerative disorder, affecting 1-1.5 million Americans. PD is characterized by numerous non-motor and motor symptoms including gait dysfunction. Gait dysfunction is of particular concern in PD as it is most often the first area of difficulty reported by people with PD and is thought to represent the leading edge of disability [1]. As such, the emergence of gait difficulty is considered a red flag and there is a clear need to develop interventions that can effectively address gait deficits such as reduced speed and reduced stride length [2, 3]. These gait difficulties have been noted in PD not only for forward walking, but also for backward walking, where gait speed and stride length are even more reduced relative to healthy controls [4, 5]. While pharmacological and surgical approaches to the management of PD can help to partially alleviate some gait problems, they do not completely address the issue, indicating a need for additional and complementary approaches to the treatment of gait in PD. Numerous studies have demonstrated the effectiveness of exercise as a complementary treatment for improving gait function in PD. Among the exercise approaches known to improve walking function, tango and treadmill training have recently emerged as two promising therapies for improving gait while also providing benefit with respect to disease severity and quality of life (for reviews see [6-8]). While these studies have been helpful in identifying possible intervention approaches for improvement of gait dysfunction, they have done little to elucidate the neural mechanisms by which the improvements are occurring and have not directly compared tango to treadmill training.

One of the difficulties in understanding the role of exercise interventions in improved gait function for individuals with PD is that the underlying neural mechanisms responsible for gait-related disturbances in PD are not well understood. Our lack of understanding of the locomotor network may be due in part to the difficulty in collecting imaging data during locomotion. Because of the difficulty in accurately using brain imaging techniques to examine online locomotion, imagined walking has been used to gain a functional understanding of the neural correlates of gait in both healthy controls [9, 10] and

populations with neurological disorders [11, 12]. In healthy controls, la Fougère et al. [9] compared real walking using positron emission tomography to imagined walking during functional magnetic resonance imaging and concluded that while some differences were apparent in the final motor pathways, the two tasks resulted in activation of very similar locomotor networks. The advent of resting state functional connectivity, which assesses activity at rest and therefore eliminates the need to evoke real or imagined locomotor behaviors, presents another viable means of assessing locomotor networks using imaging. Rs-fcMRI, as its name implies, measures activity at rest and only requires that participants lie quietly in the scanner. Rs-fcMRI focuses on spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal at rest. These spontaneous fluctuations are not random, but rather are correlated among functionally related regions. Previous rs-fcMRI results have shown correlations equal to those seen during task-based MRI [13, 14]. These spontaneous fluctuations show coherence across areas of the brain known to be not only functionally related, but also anatomically connected as demonstrated by studies combining rs-fcMRI with diffusion tensor imaging (a technique used to trace white matter tracts) [14]. Rs-fcMRI identifies related networks within the resting state BOLD data, providing insight regarding the neuronal activation patterns of different brain regions and reflecting the amount of functional communication between these regions [15]. Rs-fcMRI techniques have been used to successfully identify several networks, including the visual, auditory, default mode, and motor networks, among others [15, 16]. Rs-fcMRI methods have also been employed in groundbreaking studies examining connectivity in disease states such as Alzheimer disease, schizophrenia, depression, and several others yielding key advances in our understanding of these conditions (for review see [16]). Rs-fcMRI holds great promise as a potential biomarker for progression of disease, elucidating compensatory mechanisms associated with disease processes, informing targeting of neurosurgical treatments, and investigating new treatment strategies. Although used successfully in many other populations with neurological disorders, rs-fcMRI has been little utilized to date to study PD. We are excited about the possibility of utilizing rs-fcMRI to study individuals with PD. We will combine measures of imagined walking (Aim 2) with measures of resting state functional connectivity (Aim 3) to gain a fundamental understanding of the human locomotor control network in PD and how it is altered by exercise. Both the imagined and the resting state tasks have the benefit of not requiring any actual motor output from the participants, thus limiting the extent to which the effects of the disease on movement production might confound the data collection process.

Tango and PD

Over 50% of the general population does not achieve recommended daily levels of physical activity [17], and activity levels in those with PD may be lower than those of individuals without PD [18]. As such, development of exercise programs that are enjoyable and engaging, thus promoting regular participation, is critical. Dance may be a highly suitable intervention as it incorporates many features recommended as key components of exercise programs for those with PD [19] in a format that is engaging, motivating and social [20]. Evidence from our studies over the past five years supports the beneficial effects of tango on balance, quality of life, disease severity, and most importantly for the present proposal, locomotor performance. We have repeatedly demonstrated improvements in both forward and backward walking, with increases in gait velocity of approximately 0.1 m/s following tango [21-24]. This is not surprising, as the basic tango step for the leader is forward walking and for the follower is backward walking. In our classes, we have men and women dance both the leader and the follower roles equally to ensure that all participants get similar experiences

moving in both directions.

We have recently completed a 12-month tango intervention study which suggests that in addition to improved gait, participation in tango may convey several other substantial benefits including reduced disease severity and a slowed progression of disability over the long term [25]. Our earlier work also suggests that tango may be superior to some forms of traditional exercise for those with PD [21]. However, the traditional exercise program used for comparison to tango in our earlier work was modeled on community-based classes offered in the St. Louis area that were considered the current standard of care. This traditional exercise program did not include many of the elements now recommended for a PD-specific exercise program. In the present application, we propose to compare tango to an intensity-matched treadmill training program designed to specifically target locomotor function in people with PD.

Very few studies have examined the neural underpinnings of dance or the effects of tango dancing on brain activity. Brown et al. [26] utilized task-based fMRI to study brain activity during production of tango-like leg movements performed to music by healthy young subjects lying supine in the scanner. This study specifically implicated the putamen in the control of dance movements performed to a metered and predictable beat. This work informs our hypotheses (2a and 3a) that locomotion-related activity and connectivity of the putamen will increase following tango training in people with PD. To our knowledge, the only study to utilize neuroimaging before and after tango training is that of Sacco et al. [27], who also studied healthy young controls. Following one week of tango training, participants showed increased activation of the supplementary motor area (SMA) and premotor area (PMA) during imagined forward walking as compared to baseline. This study informs our hypotheses (2a and 3a) that locomotion-related activity and connectivity of the SMA and PMA will increase following tango training in people with PD.

Treadmill Training in PD

Over the past decade, there have been several studies examining the effects of treadmill training on gait in people with PD. These studies have consistently shown improvements in forward walking velocity following training, regardless of the training paradigm or training schedule used (for review see [7, 8]). These improvements are, similarly to tango, on the order of 0.1 m/s. Some have also noted improvements in balance [28] and quality of life [29] with treadmill training, though these aspects have been investigated on a very limited basis and are not addressed by most studies. Treadmill training has the advantage of being task specific, as walking is the focus of the intervention. *We will utilize traditional forward walking treadmill training, though we recognize that multi-directional treadmill training including backward and sideways walking has been utilized successfully in people with PD [30]. Multi-directional training is beyond the scope of this proposal, however, as we aim to determine the effects of traditional treadmill training.* Very recent evidence suggests that low intensity treadmill training with more minutes per session may be superior to higher intensity training with fewer minutes per session [31, 32]. As such, we have chosen to implement treadmill training at a speed matched to preferred overground walking speed in our proposal. We will utilize a low intensity treadmill training approach which will not only follow in line with the latest available evidence, but also allow us to keep the intensity of the treadmill training similar to that of the tango classes.

To our knowledge, there are currently no studies that have utilized neuroimaging to examine the effects of treadmill training in PD. This represents a major gap in the literature and an obvious hole in our understanding of the mechanisms of action of treadmill training in PD. Aims 2 and 3 will address this critical knowledge gap. Despite the lack of literature in PD, there is currently a small body of literature describing changes in neural activity following treadmill training in other populations including those with stroke, spinal cord injury, and hemispherectomy [33-35]. These studies have noted increases in activity in the primary somatosensory cortex following treadmill training in people with spinal cord injuries [35] and strokes [33]. Furthermore, increases in cerebellar activity following treadmill training were seen preferentially in those participants with spinal cord injury for whom overground walking performance improved [35] to the point of being functional. These studies inform our hypotheses (2a and 3a) that activity and connectivity of the primary somatosensory cortex and cerebellum will increase following treadmill training in PD.

Exercise and Imaging: A Multi-Faceted Approach
The proposed direct comparison of tango to treadmill training is critical as it will put these two emerging forms of therapy head-to-head in order to determine their differential effects on actual locomotor performance (Aim 1), on brain activity during imagined walking (Aim 2), and on resting state functional connectivity of the locomotor control network (Aim 3) in people with PD. The combination of neuroimaging with exercise interventions is novel and will fill important gaps in our knowledge regarding basic locomotor control in PD and the mechanisms by which different exercises might convey benefit with respect to locomotor function. Previous neuroimaging work in different populations, as well as prior work in PD examining the effects of either tango or treadmill training on locomotion, sets the stage for this exciting work. Our use of different interventions along with two different neuroimaging techniques makes for a powerful and multi-faceted approach that will yield an extremely rich data set capable of addressing multiple gaps in our current knowledge.

B2 Rationale for this Study

Effective treatment of locomotor dysfunction in PD is essential, as gait difficulty is an early and major contributor to disability. The proposed study will provide important insights into the effects of different modes of exercise on locomotor function in PD, filling current knowledge gaps and guiding future design and delivery of optimal exercise interventions. This work is innovative because it: 1) uses a community-based exercise approach, 2) examines dance as a novel form of exercise and directly compares it to traditional treadmill training and *stretching*, 3) tests participants OFF medication to allow more accurate assessment of disease severity, and 4) utilizes two distinct neuroimaging approaches, in conjunction with interventions, to explore potential mechanisms of the effects of exercise on both brain function and brain connectivity.

C Study Objectives

C1 Primary Aim

SPECIFIC AIM 1: To determine the effects of tango, treadmill training, and s*tretching (control)* exercise on locomotor function and other aspects of PD. The primary variable for this aim is gait velocity. Additional gait variables of interest are stride

length, stride length variability, gait asymmetry, interlimb coordination, freezing of gait questionnaire scores, and six minute walk test distance. A secondary aim is to compare the effects of the different interventions on disease severity, balance, and quality of life.

C2 Secondary Aim

SPECIFIC AIM 2: To determine the effects of tango, treadmill training *and stretching* on brain activity assessed by task-based fMRI blood oxygen level dependent (BOLD) signal during imagined walking.

SPECIFIC AIM 3: To determine the effects of tango, treadmill training *and stretching* on resting state functional connectivity of the locomotor control network assessed by rs-fc MRI.

C3 Rationale for the Selection of Outcome Measures

To our knowledge, there are currently no studies that have utilized neuroimaging to examine the effects of treadmill training in PD. This represents a major gap in the literature and an obvious hole in our understanding of the mechanisms of action of treadmill training in PD. Despite the lack of literature in PD, there is currently a small body of literature describing changes in neural activity following treadmill training in other populations including those with stroke, spinal cord injury, and hemispherectomy [33-35]. These studies have noted increases in activity in the primary somatosensory cortex following treadmill training in people with spinal cord injuries [35] and strokes [33]. Furthermore, increases in cerebellar activity following treadmill training were seen preferentially in those participants with spinal cord injury for whom overground walking performance improved [35] to the point of being functional. These studies inform our hypotheses (2a and 3a) that activity and connectivity of the primary somatosensory cortex and cerebellum will increase following treadmill training in PD.

D Investigational Agent

None

E Study Design

E1 Overview and Design Summary

This study will directly compare tango dancing and treadmill training, to each other and to a control group that participates in a stretching program to determine their effects on gait and function in people with PD. One hundred twenty people with PD will be randomly assigned one of three community-based exercise groups: tango dancing, treadmill training or stretching (control). Each group will receive 3 months of intervention, attending one-hour group classes. Each participant will be evaluated at three time points over 6 months. MRI and behavioral measures will be conducted with participants OFF medication, with behavioral measures also assessed ON medication. We will utilize

brain imaging techniques to examine how participation in these exercise programs modifies brain function. The information gained will inform the development of optimal exercise interventions, and perhaps other treatment approaches, designed to specifically target walking problems in PD.

Screening phone call - 15-20 minutes - on medicaion
Pre-Intervention Evaluation - 4.5 hours - off medication
3 exercise sessions per week for 12 weeks - 1 hour each - on medicaion
Post Intervention Evaluation Visit - 4 hours - off medication
Follow-Up Evaluation - 12 weeks after conclusion of exercise class - 2 hours (no fMRI) - off medication

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

1) at least grade 3/5 strength and normal joint ranges of motion in both legs
2) vision corrected to 20/40 or better
3) able to walk independently for 10 feet with or without an assistive device
4) normal gross somatosensory function in the feet (2-point discrimination, vibration, joint kinesthesia, and light touch)
5) no history of vestibular disease
6) no evidence of dementia (MMSE ≥ 26, and AD8 ≤ 2 [36, 37]).

PD diagnostic criteria include those used for clinically defined “definite PD”, as previously described by Racette et al. [38] based upon established criteria [39-41]. Each participant must have had clear benefit from levodopa and meet the above inclusionary and exclusionary criteria. All participants will complete the Kinesthetic and Visual Imagery Questionnaire (KVIQ-20)[42] with an additional four question imagined gait task assessment. This test is used to assess ability to imagine motor tasks and has been previously used in PD [43]. Participants with a mean KVIQ-20+gait subsection score more than one standard deviation below the mean of an age-matched healthy cohort (Earhart lab, pilot data) will be excluded from the study. We anticipate that individuals in Hoehn and Yahr stages of I-III will participate. Informed consent will be obtained from each participant.

2.a Exclusion Criteria

1) Serious medical problem (aside from PD)
2) Use of neuroleptic or other dopamine-blocking drug
3) Use of drug that might affect balance, like a benzodiazepine
4) Evidence of abnormality on brain imaging (previously done for clinical evaluations-not part of this research)
5) History or evidence of other neurological deficit, such as previous stroke or muscle disease
6) History or evidence of orthopedic, muscular, or psychological problem.

In addition to the above state inclusion and exclusion criteria, all subjects will complete the MRI Procedure Screening Form with no contra-indications for MR participation.

Indication of any of the following will require follow-up with Dr. Perlmutter and will most likely result in exclusion from the study.
1) Pregnancy
2) Aneurysm clip(s)
3) Cardiac pacemaker
4) Implanted cardioverter defibrillator (ICD)
5) Electronic implant or device
6) Magnetically-activated implant or device
7) Neurostimulation system
8) Spinal cord stimulator
9) Internal electrodes or wires
10) Bone growth/bone fusion stimulator
11) Cochlear, otologic, or other ear implant
12) Insulin or other infusion pump
13) Implanted drug infusion device
14) Any type of prosthesis (eye, penile, etc.)
15) Heart valve prosthesis
16) Eyelid spring or wire
17) Artificial or prosthetic limb
18) Metallic stent, filter, or coil
19) Shunt (spinal or intraventricular)
20) Vascular access port and/or catheter
21) Radiation seeds or implants
22) Swan-Ganz or thermodilution catheter
23) Medication patch (Nicotine, Nitroglycerine)
24) Any metallic fragment or foreign body
25) Wire mesh implant
26) Tissue expander (e.g., breast)
27) Surgical staples, clips, or metallic sutures
28) Joint replacement (hip, knee, etc.)
29) Bone/joint pin, screw, nail, wire, plate, etc.
30) IUD, diaphragm, or pessary
31) Dentures or partial plates
32) Tattoo or permanent makeup
33) Body piercing jewelry
34) Hearing aid (Remove before entering MR system room)
35) Other implant _____
36) Breathing problem or motion disorder
37) Claustrophobia Ethical Considerations

2.b Subject Recruitment Plans and Consent Process

The principal investigator and research team will identify potential participants from the Washington University School of Medicine’s Movement Disorders Center's database of more than 2200 people with idiopathic PD, from the Volunteers for Health database or via the movement disorders webpage (http://neuro.wustl.edu/patientcare/clinicalservices/movementdisorders/movementdisordersclinicals). Individual's identified as meeting the study criteria will be initially approached either by letter or a phone call. If interest is expressed by the individual a

phone interview will be conducted to explain the study and identify individuals that meet the inclusion criteria. Any individual qualifying for inclusion based on the information supplied during the phone interview, will be invited to participate in the study. Informed consent will be obtained from each subject by a member of the study team prior to starting the experiment. All study team members have enrolled and consented both PD patients as well as control participants in the past.

During the consent process, it will be emphasized that participation in this or any other study in our lab is done on a voluntary basis only. The investigator completing the consent procedure will verbally state and make reference to the written statement about withdrawing from the study at any time.

A copy of the consent form will be provided to all participants.

2.c Randomization Method and Blinding

Participants will be assessed during the week prior to starting the intervention (pre-intervention), the week following completion of the intervention (postintervention), and three months after completing the intervention (follow-up) (Figure 1). At the preintervention visit participants will be notified as to whether they were randomized to the tango, treadmill or stretching group. Randomization sequences will be generated a priori by an independent statistician. Prior to commencing exercise all participants will undergo a physical examination and will be required to complete an on medication screening graded exercise test per previously established protocols [44-46] in order to determine whether or not they can exercise safely. All groups will receive 12 weeks of exercise, meeting 3 times per week for one hour each session. The exercise groups will thus participate in 180 minutes of exercise per week, meeting the CDC guidelines for physical activity[17]. All groups will exercise in community-based group settings to ensure that participants have similar experiences with respect to social interactions associated with participating in a group exercise class. Participants will be assigned to groups using a process of stratified blocked randomization. Self-selected forward gait velocity measured at baseline will be used to stratify participants into three categories: <1.1 m/s, 1.1-1.3 m/s, and >1.3 m/s. These strata have been chosen based upon our preliminary data from 60 individuals tested OFF medication. The average velocity for this group was 1.2 +/- 0.1 m/s (mean +/- SD). Thus the middle stratum includes individuals within one SD of the mean and the upper and lower strata include individuals more than one SD above or below the mean, respectively. Each stratum will be randomized to the 3 groups using a block size of 10 to ensure that there is no temporal bias and guarantee that the number of participants at each level of walking performance who enter each study arm is the same.

2.d Risks and Benefits

There are no identifiable legal, social, or psychological risks associated with participation in the proposed studies. The identifiable risks are minimal and we are aware of no alternative procedures that can provide the same information.

The potential risks to subjects are: a) effects of withholding overnight medication, b) loss of confidentiality, c) stumbling during locomotion, d) falling into the safety harness during testing on the treadmill, e) mechanical injury involving moving apparatus, f)Skin irritation from surface electrode preparation or rubbing of the electrodes on your skin during data collection may occur. g) fatigue associated with long periods of exercise and MRI

scanning, h) dizziness after the MRI, i)claustrophobic reaction to being in the MRI tube and j) effects of the loud noise generated by the MR scanning sequence.

We do not yet know the full extent to which exercise may benefit people with Parkinson disease. Recent evidence suggests that the benefits may include improvements in physical function as well as quality of life. This study will allow us to determine what the benefits may be and if different types of exercise have different benefits.

This project will be the first to directly compare tango to treadmill training and will explore the neurophysiologic changes in brain function and connectivity following these two different forms of exercise. The information gained will provide critical insights regarding the relative merits of the two exercise approaches for improving function in people with PD and add to our understanding of the potential mechanisms by which these interventions convey their respective benefits. If the three interventions both impart improvements in function and do so through very different effects on the brain, as hypothesized, this would suggest that both interventions are beneficial and that a combination of exercise might be more effective than either intervention alone as different aspects of locomotor control may be targeted. This could lead to future studies comparing different combination approaches to exercise rather than single mode exercise programs. Future work could examine the effects of different doses of exercise or different exercise intensities, the effects of long-term participation in exercise, and the retention of benefits through inclusion of follow-up evaluations. The imaging techniques proposed herein will also lay the groundwork to allow us to answer many other questions regarding locomotor control mechanisms in PD. The potential implications of this work are vast and the proposed study will set the stage for much future research.

2.e Early Withdrawal of Subjects

Based upon our previous intervention studies, we anticipate an attrition rate of approximately 15-20% due to dropouts or failure to complete the required minimum of 85% of classes.

2.f When and How to Withdraw Subjects

Individuals may withdraw at any time during the duration of the study

2.g Data Collection and Follow-up for Withdrawn Subjects

No follow-up will be completed for withdrawn subjects

E3 Study Drug

None

F Study Procedures

F1 Screening for Eligibility

Possible participants will be screened via a phone interview. The screening process will identify if the individual meets the inclusion criteria stated above and does not meet any of the exclusion critera.

F2 Schedule of Measurements

Time requirements:
Screening phone call - 15-20 minutes - on medicaion
Pre-Intervention Evaluation - 4.5 hours - off medication
3 exercise sessions per week for 12 weeks - 1 hour each - on medicaion
Post Intervention Evaluation Visit - 4 hours - off medication
Follow-Up Evaluation - 12 weeks after conclusion of exercise class - 2 hours (no fMRI) - off medication

Screening phone call
Following the consent process we will complete an MRI screening form. If the individual is not excluded from completing an MRI scanning session we will continue with the screening process.

In addition, all eligible participants must be able to perform the imagined gait tasks in the MRI at or above a previously determined threshold. All participants will complete the Kinesthetic and Visual Imagery Questionnaire (KVIQ-20) (Malouin, et al, 2007) with an additional four question “imagined” gait task assessment (Pickett, Peterson & Earhart, 2012). The KVIQ-20 is used to assess vividness of mental imagery during motor tasks and has been previously used with PD patients (Heremans, et al, 2011). Participants with a mean KVIQ-20 + gait subsection score more than one standard deviation below the mean of an age matched healthy cohort (data recently collected in Dr. Earhart’s lab) will be excluded from the study.

Any individual who is accepted for the study based on the above will be given a packet of questionnaires to complete at home and continue on following the procedure below. This portion will be completed with a researcher who is blinded to the individual's group assignment. The specific questionnaires that will be included in the packet are as follows:
Epworth Sleepiness Scale
Non-Motor Symptom Questionnaire
Stages of Readiness to Exercise Questionnaire
Fall History Questionnaire
Footedness/Handedness Questionnaire
Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults
Activities Balance Confidence (ABC) Scale
Geriatric Depression Scale (GDS)
Prospective & Retrospective Memory Questionnaire (PRMQ)

Visit 1 (pre-test):
Prior to commencing any exercise all participants will undergo a physical examination and will be required to complete an on medication screening graded exercise test per previously established protocols (Schenkman, M., et al., 2008; Christiansen, C.L., et al., 2009; Katzel, L.I., et al., 2001) in order to determine whether or not they can exercise.

A single 90 minute fMRI session will be completed first. During this session, participants will have 2 structural scans: a T1-weighted (T1W) sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=15°, 1.0 mm3 voxels, 8:09 min) and a T2-weighted (T2W) fast spin echo (TR=3200

ms, TE=455 ms, 1.0 mm3 voxels, 4:43 min). Two functional connectivity scans will be acquired via BOLD sensitized fMRI (TR=2200 s, TR=25 ms, 4.0 mm3 voxels, 7-min runs of 194 frames). During these scans, participants will remain still and keep their eyes closed. Participants will be visual monitored via an eye tracking device during data acquitions and will be given an emergency indicator which can be pressed at any time to stop the scans. During the imagined walking component 9 minutes of eco-planar imaging data will be acquired (TR=2200ms, TE=2.5ms, 4 mm3 voxels) will be acquired while the participant views the cue or null condition on a mirror mounted to the head coil.

All individuals will then complete the following battery of questionnaires and assessments(approximately 90 minutes):
Montreal Cognitive Assessment
Wechsler Test of Adult Reading (WTAR)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Trail Making Test
Stroop Test
Go-No-Go (GNG)
Verbal Fluency
RMswitch task
Frontal Systems Behavior Scale (FrSBe)

All individuals will complete the clinical assessments listed below as well as gait and balance testing consisting of the following (approximately 1 hour):
RMswitch task
Go-No-Go (GNG)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Mini Mental Status Exam (MMSE)
The New Freezing of Gait Questionnaire (nFOG_Q)
Mini BESTest
The Smell Threshold Kit
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)
Five times sit to stand (5xSTS) - 6 minute walk (6MWT) - 9 Hole Peg Test (9HPT)
PDQ-39
Forward preferred speed, forward fast, backward, tandem and dual task walking on a GAITRite computerized walkway system.
Spatiotemporal gait assessment will be completed simultaneously with the GaitRITE assessment.

Exercise training begins:

Each Participant will be assigned to a group (treadmill training, tango dance training or stretching) using a process of stratified blocked randomization and notified of their group assignment following their initial visit. This is necessary as walking speed must first be assessed prior to group assignment.

Within one week of the initial visit, the training sessions will begin. All groups will receive 12 weeks of exercise, meeting 3 times per week for one hour each session. The exercise groups will thus participate in 180 minutes of exercise per week, meeting the CDC guidelines for physical activity. All groups will exercise in community-based group

settings to ensure that participants have similar experiences with respect to social interactions associated with participating in a group exercise class

The individual groups will complete 1 hour of training following the protocol listed below:

Tango Training: Tango classes will be modeled on those of our previous studies, and will include a brief warm up and a cool down, with 45 minutes of the hour devoted to tango specifically as described previously in our lab. Participants will dance both leading and following roles and will change partners frequently in order to ensure that everyone spends time moving forward and backward and gets experience dancing with many different partners. Partners will be individuals without PD and will include spouses and caregivers of those with PD as well as healthy volunteers.

Treadmill Training: The treadmill training group will have the same warm up and cool down period as the tango group with 45 minutes of the hour devoted to walking on the treadmill. Participants will walk on the treadmill at their own self-selected comfortable pace. Overground walking speed will be reassessed every 2 weeks and treadmill speed adjusted as needed to ensure that it continues to match overground walking speed. This model of treadmill training was chosen for two reasons: 1) to be of comparable intensity to the tango class where the basic dance step is walking done at preferred pace and 2) because recent evidence suggests that training at preferred speed for longer durations is more effective in enhancing gait than training at higher intensity for shorter blocks of time. The periodic reassessment of overground preferred speed and subsequent adjustment of treadmill speed will help to ensure that the treadmill training is also progressive in nature and in that way mirrors the progressive nature of the tango classes as much as possible.

Stretching Group: The stretching class will also have the same warm up and cool down as the other groups, with 45 minutes devoted to stretching and flexibility exercises taken from the Be Active and Fitness Counts programs.

Post-Intervention Evaluation (4 hours):
This assessment will be completed off medication and will exactly mirror the pre-intervention assessment with the following exceptions:
No KVIQ/GIQ
No physical examination and medical screening.
No consent documents and payment forms.

Follow-Up Evaluation - 12 weeks after exercise classes have ended (2 hours):
This assessment will be completed off medication and will NOT include an MRI session. All other components completed in the post-intervention evaluation will be repeated.

F3 Forms to be completed prior to first visit

Following the phone screening session, all individuals who are accepted for the study will be sent the following assessments and questionnaires in the mail

Epworth Sleepiness Scale
Non-Motor Symptom Questionnaire

Stages of Readiness to Exercise Questionnaire
Fall History Questionnaire
Footedness/Handedness Questionnaire
Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults
Activities Balance Confidence (ABC) Scale
Geriatric Depression Scale (GDS)
Prospective & Retrospective Memory Questionnaire (PRMQ)

F4 Visit 1 - Pre-Intervention Evaluation

Prior to commencing any exercise all participants will undergo a physical examination and will be required to complete an on medication screening graded exercise test per previously established protocols (Schenkman, M., et al., 2008; Christiansen, C.L., et al., 2009; Katzel, L.I., et al., 2001) in order to determine whether or not they can exercise.

A single 90 minute fMRI session will be completed first. During this session, participants will have 2 structural scans: a T1-weighted (T1W) sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=15°, 1.0 mm3 voxels, 8:09 min) and a T2-weighted (T2W) fast spin echo (TR=3200 ms, TE=455 ms, 1.0 mm3 voxels, 4:43 min). Two functional connectivity scans will be acquired via BOLD sensitized fMRI (TR=2200 s, TR=25 ms, 4.0 mm3 voxels, 7-min runs of 194 frames). During these scans, participants will remain still and keep their eyes closed. Participants will be visual monitored via an eye tracking device during data acquitions and will be given an emergency indicator which can be pressed at any time to stop the scans. During the imagined walking component 9 minutes of eco-planar imaging data will be acquired (TR=2200ms, TE=2.5ms, 4 mm3 voxels) will be acquired while the participant views the cue or null condition on a mirror mounted to the head coil.

All individuals will then complete the following battery of questionnaires and assessments(approximately 90 minutes):
Montreal Cognitive Assessment
Wechsler Test of Adult Reading (WTAR)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Trail Making Test
Stroop Test
Go-No-Go (GNG)
Verbal Fluency
RMswitch task
Frontal Systems Behavior Scale (FrSBe)

All individuals will complete the clinical assessments listed below as well as gait and balance testing consisting of the following (approximately 1 hour):
RMswitch task
Go-No-Go (GNG)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Mini Mental Status Exam (MMSE)
The New Freezing of Gait Questionnaire (nFOG_Q)

Mini BESTest
The Smell Threshold Kit
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)
Five times sit to stand (5xSTS) - 6 minute walk (6MWT) - 9 Hole Peg Test (9HPT)
PDQ-39
Forward preferred speed, forward fast, backward, tandem and dual task walking on a GAITRite computerized walkway system.
Spatiotemporal gait assessment will be completed simultaneously with the GaitRITE assessment.

F5 Intervention

Each Participant will be assigned to a group (treadmill training, tango dance training or stretching) using a process of stratified blocked randomization and notified of their group assignment following their initial visit. This is necessary as walking speed must first be assessed prior to group assignment.

Within one week of the initial visit, the training sessions will begin. All groups will receive 12 weeks of exercise, meeting 3 times per week for one hour each session. The exercise groups will thus participate in 180 minutes of exercise per week, meeting the CDC guidelines for physical activity. All groups will exercise in community-based group settings to ensure that participants have similar experiences with respect to social interactions associated with participating in a group exercise class

The individual groups will complete 1 hour of training following the protocol listed below:

Tango Training: Tango classes will be modeled on those of our previous studies, and will include a brief warm up and a cool down, with 45 minutes of the hour devoted to tango specifically as described previously in our lab. Participants will dance both leading and following roles and will change partners frequently in order to ensure that everyone spends time moving forward and backward and gets experience dancing with many different partners. Partners will be individuals without PD and will include spouses and caregivers of those with PD as well as healthy volunteers.

Treadmill Training: The treadmill training group will have the same warm up and cool down period as the tango group with 45 minutes of the hour devoted to walking on the treadmill. Participants will walk on the treadmill at their own self-selected comfortable pace. Overground walking speed will be reassessed every 2 weeks and treadmill speed adjusted as needed to ensure that it continues to match overground walking speed. This model of treadmill training was chosen for two reasons: 1) to be of comparable intensity to the tango class where the basic dance step is walking done at preferred pace and 2) because recent evidence suggests that training at preferred speed for longer durations is more effective in enhancing gait than training at higher intensity for shorter blocks of time. The periodic reassessment of overground preferred speed and subsequent adjustment of treadmill speed will help to ensure that the treadmill training is also progressive in nature and in that way mirrors the progressive nature of the tango classes as much as possible.

Stretching Group: The stretching class will also have the same warm up and cool down as the other groups, with 45 minutes devoted to stretching and flexibility exercises taken from the Be Active and Fitness Counts programs.

F6 Visit 2 – Post-Intervention Evaluation

A single 90 minute fMRI session will be completed first. During this session, participants will have 2 structural scans: a T1-weighted (T1W) sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=15°, 1.0 mm3 voxels, 8:09 min) and a T2-weighted (T2W) fast spin echo (TR=3200 ms, TE=455 ms, 1.0 mm3 voxels, 4:43 min). Two functional connectivity scans will be acquired via BOLD sensitized fMRI (TR=2200 s, TR=25 ms, 4.0 mm3 voxels, 7-min runs of 194 frames). During these scans, participants will remain still and keep their eyes closed. Participants will be visual monitored via an eye tracking device during data acquitions and will be given an emergency indicator which can be pressed at any time to stop the scans. During the imagined walking component 9 minutes of eco-planar imaging data will be acquired (TR=2200ms, TE=2.5ms, 4 mm3 voxels) will be acquired while the participant views the cue or null condition on a mirror mounted to the head coil.

All individuals will then complete the following battery of questionnaires and assessments(approximately 90 minutes):
Montreal Cognitive Assessment
Wechsler Test of Adult Reading (WTAR)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Trail Making Test
Stroop Test
Go-No-Go (GNG)
Verbal Fluency
RMswitch task
Frontal Systems Behavior Scale (FrSBe)

All individuals will complete the clinical assessments listed below as well as gait and balance testing consisting of the following (approximately 1 hour):
RMswitch task
Go-No-Go (GNG)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Mini Mental Status Exam (MMSE)
The New Freezing of Gait Questionnaire (nFOG_Q)
Mini BESTest
The Smell Threshold Kit
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)
Five times sit to stand (5xSTS) - 6 minute walk (6MWT) - 9 Hole Peg Test (9HPT)
PDQ-39
Forward preferred speed, forward fast, backward, tandem and dual task walking on a GAITRite computerized walkway system.
Spatiotemporal gait assessment will be completed simultaneously with the GaitRITE assessment.

F7 Visit 3 – Follow-up

A follow-up visit will be scheduled for 12 weeks after the final exercise class has been completed.

All individuals will complete the following battery of questionnaires and assessments (approximately 90 minutes):
Montreal Cognitive Assessment
Wechsler Test of Adult Reading (WTAR)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Trail Making Test
Stroop Test
Go-No-Go (GNG)
Verbal Fluency
RMswitch task
Frontal Systems Behavior Scale (FrSBe)

All individuals will complete the clinical assessments listed below as well as gait and balance testing consisting of the following (approximately 1 hour):
RMswitch task
Go-No-Go (GNG)
Spatial Delayed Response Task (SDR)
Nback Working Memory Test (Nback)
Mini Mental Status Exam (MMSE)
The New Freezing of Gait Questionnaire (nFOG_Q)
Mini BESTest
The Smell Threshold Kit
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)
Five times sit to stand (5xSTS) - 6 minute walk (6MWT) - 9 Hole Peg Test (9HPT)
PDQ-39
Forward preferred speed, forward fast, backward, tandem and dual task walking on a GAITRite computerized walkway system.
Spatiotemporal gait assessment will be completed simultaneously with the GaitRITE assessment.

F8 Safety and Adverse Events

8.a Safety and Compliance Monitoring

8.b Medical Monitoring

Effects of medication withdrawal will be monitored via patient report and if the effects are too severe, participation in the study will be terminated prior to the second day of "off medication" testing.

8.c Definitions of Adverse Events

An adverse event is any patient reported

8.d Classification of Events

We do not anticipate any adverse events; however, the following procedures will be followed to minimize the risk.

a) Temporary Worsening of Parkinson's symptoms. A temporary worsening of Parkinson's disease symptoms may result from not taking anti-Parkinson's medication for study evaluations. Once the individual resumes taking their medication, symptoms should return to their typical levels. Effects of medication withdrawal will be monitored and if the effects are too severe, participation in the study will be terminated prior to the second day of "off medication" testing .

b) Loss of confidentiality. Loss of confidentiality is highly unlikely. To safeguard against this, we will comply with all HIPAA regulations. Data will not be identified by subject name. All data will be coded, and code sheets will be stored in locked files.

c) Stumbling during locomotion. Subjects will be closely attended by a physical therapist during walking. Walking will be performed in a large, open space and the therapist will be prepared to assist subjects who may stumble. It is therefore unlikely that subjects will experience falls during testing or will be injured as the result of a fall.

d) Falling into safety harness. During testing on the treadmill, subjects will wear a modified parachute harness connected to an overhead beam that is rated to support heavy loads. A subject who falls will be supported fully by the harness and is therefore unlikely to be injured. Subjects will also be able to hold the support guides which will help them to stabilize balance during treadmill testing. In addition, the treadmill will be equipped with redundant safety features to prevent subject injury and allow immediate cessation of treadmill movement at the touch of a button.

e) Mechanical injury involving moving apparatus. The treadmill is equipped with a safety switch that, when pressed, will immediately stop treadmill movement. The treadmill is also equipped with a break that can be applied at any time. Treadmill design is such that accelerations and decelerations are not abrupt, but are smooth, non-jarring transitions. Furthermore, it will be laboratory policy that: 1) the PI or another lab member will always be the first test subject for any new protocol and 2) on the day of an experiment, the exact protocols to be used will first be run without a subject to ensure proper system function.

f)Skin irritation may be prevented by notifying investigators of any potential allergens due to adhesive or alcohol (i.e. skin preparation).

g) Fatigue. The proposed study involves one-hour exercise training sessions. Rest breaks will be provided as frequently as needed but you still are likely to be tired

afterwards. Some of the proposed studies involve stretching, stepping or walking for periods of time up to 60 minutes and this may result in fatigue for some subjects. Rest breaks will be provided as frequently as possible and no subjects with history or indication of orthostatic hypotension will be admitted to the studies. Fatigue during the MRI may also occur. We will maintain contact with the participant through out the session to monitor them. Additionally we can remove the individual from the scanner if they report being too sleepy to continue.

h) Dizziness. At the completion of the test, when the subject may be a little dizzy, investigators will walk very near the subject to the outer room and make sure the subject is not dizzy before he/she is dismissed.

i) Claustrophobia. All individuals will be screened for previous claustrophobic experiences prior to participation. During the scanning sequence all participants will have an emergency squeeze bulb in their hand that, when squeezed, will notify the researchers of their distress. We will immediately remove the individual from the scanner at this time.

j) Loud noise. While inside the magnet, subjects will be able to communicate with the investigators through an intercom. To help protect the participant's hearing two levels of hearing protection will be worn by all participants. Ear plugs will be inserted into the ear and outer headphones will be placed over your ears. Also, they will be given an alarm device to press if the intercom system should be ineffective because of the loud noises. This alarm will create a definite signal to the investigators that the subject wishes to communicate or exit. If a test is in progress, the test will be stopped and investigators will either speak to the subject using the intercom or enter the room and take the patient out of the magnet.

The risks associated with these studies are minimal. Participant safety will be continuously monitored by the PI during experimental sessions and participants will be advised of how to contact the PI if they have any concerns that arise outside of these sessions.

8.e Reporting Procedures

Any adverse events will be reported to the local IRB immediately and will trigger an immediate review, like the annual review described previously, to determine what changes need to be made and whether the study should continue or conclude.

8.f Adverse Event Reporting Period

Patients will be followed for 12 weeks following their final exercise session. Adverse events will be documented throughout this period.

8.g Post-study Adverse Event

Any advent reported to the investigators following the conclusion of the study will be documented and reviewed.

G Statistical Plan

G1 Sample Size Determination and Power

Using PASS software (NCSS, LLC, Kaysville, UT), *we have powered each aim based upon preliminary data.* Our primary variable of interest in Aim 1 is gait velocity. Average forward gait velocity +/- SD was 1.2 +/- 0.1 m/s and average backward gait velocity was 0.6 +/- 0.1 in a sample of 60 individuals with PD (H&Y = 2.4 +/- 0.2) tested OFF medication in our laboratory over the past year for a different study. The study has been powered to be able to detect differences of 1 SD, or 0.1 m/s, which is equivalent to an effect size of 0.4. Changes of 0.1m/s or more in gait velocity have been reported previously following both tango [22-24] and treadmill training [8, 29, 61, 62]. *With an effect size of 0.4, 27 participants per group will provide 89% power to detect differences between or within groups using two-tailed tests at a significance level of 0.05.* Based upon additional preliminary data from our lab, we have determined that this sample size is also more than sufficient to adequately power our secondary variables in Aim 1 (MDS-UPDRS-III, mini-BESTest, PDQ-39).

Aims 2 and 3 have been powered based upon preliminary data from our lab and sources in the literature. For Aim 2, our preliminary data from controls before and after a single session of treadmill training indicate an effect size of 0.91 for change in beta weights using the cerebellum as an exemplar region (pre = -0.094 +/- 0.111, post = 0.418 +/- 0.116, Figure 9) during imagined forward walking. We recognize that responses in those with PD may be less pronounced than in controls and as such have used a very conservative effect size of 0.45, half the size of the effect observe in controls, for our power calculation. Our preliminary data from people with PD (n=8) imagining forward walking indicate a beta weight of -0.075 +/- 0.097, which is comparable to the value obtained from young controls at baseline. Utilizing the data from the sample with PD and an estimated effect size of 0.45, 18 subjects per groups will provide 80% power to detect differences between groups and 88% power to detect within group differences. Significant findings of differential BOLD signal changes have been localized in PD populations during similar imagined walking MRI paradigms with a total of 12 PD participants per group [59], further supporting that our proposed sample size is likely adequate. For Aim 3, utilizing rs-fcMRI (Figures 7,8) to determine correlations between regions in the locomotor control network, we have powered the study to enable detection of differences in correlation coefficients of 0.1 (mean correlation = 1.0, SD = 0.1, p = 0.05, effect size = 0.44, per data from Wu et al. 2009 and our own preliminary data). We will have 80% power to detect between group differences and 88% power to detect within group differences with 18 subjects per group.

Based upon our previous intervention studies [23], we anticipate an attrition rate of approximately 15-20% due to dropouts or failure to complete the required minimum of 85% of classes. We also expect MRI related complications due to head motion in roughly 30% of tested individuals. *This estimate is based upon our preliminary data from individuals with PD (Fig. 4, 5) where we lost 24% of scans due to head motion greater than 2mm of translation or rotation during a scan.* As such, we will recruit 40 subjects per group to account for attrition and data loss due to head motion and still obtain the needed final sample sizes for each aim. *For Aim 1 dropouts will be handled utilizing intent to treat analyses with the last observation carried forward. Dropouts will be excluded from analyses in Aims 2 and 3 as full imaging data are needed from two time points.*

G2 Interim Monitoring and Early Stopping

The protocol will also be evaluated and the risk to benefit ratio assessed twice annually.

G3 Analysis Plan and Statistical Methods

For **Aim 1**, we will employ a repeated measures ANOVA with group (tango, treadmill, and *stretching*) and time (pre-intervention, post-intervention, *and follow-up*) as factors to determine whether and how these interventions impact gait velocity, our primary variable for Aim 1. Similar analyses will also be performed for secondary variables of interest, including the MDS-UPDRS-III, mini-BESTest, and PDQ-39. *As a secondary analysis for gait velocity, MDS-UPDRS-III, and mini-BESTest, we will determine percent difference between OFF and ON medication values at pre-intervention and post-intervention time points and compare these difference values using RM ANOVAS with group and time as factors. (If prescribed medications change over the course of the study then levodopa equivalent daily dose will be included as a covariate in these analyses.) This will allow us to determine if response to medications was different before vs. after intervention and whether this effect differed between groups.* Analyses will be conducted using NCSS software (NCSS, LLC, Kaysville, UT). All imaging analyses will be conducted using Brain Voyager (Brain Innovation, Maastricht, The Netherlands) and custom written Matlab (MathWorks, Natick, MA) software. For **Aim 2**, we will apply random effects general linear model analysis using forward and backward imagined tasks as individual contrasts. A false discovery rate (FDR) correction will be used to compensate for multiple comparisons. BOLD signal changes within the previously specified regions of interest will be compared for pre- and post-intervention conditions. Additionally, the three groups will be compared to each other in the post-intervention condition using RFX ANCOVA. For **Aim 3**, we will use an independent component analysis (ICA) to examine the strength of the correlation coefficients for anatomical regions identified as part of the locomotor control network. The strength of these correlations before vs. after intervention will be compared via two-tailed RM ANOVAs with group and time as factors. Finally, we will correlate BOLD signal changes during the imagined walking tasks (Aim 2) and changes in connectivity (Aim 3) with changes in motor performance.

G4 Missing Outcome Data

For Aim 1 dropouts will be handled utilizing intent to treat analyses with the last observation carried forward. Dropouts will be excluded from analyses in Aims 2 and 3 as full imaging data are needed from two time points.

H Data Handling and Record Keeping

H1 Confidentiality and Security

All data and data monitoring will be kept strictly confidential according to HIPAA regulations. Results will be coded and the code sheets will be stored in locked files.

H2 Training

All investigators involved with this study will complete safety training, HIPPAA requirements and will undergo yearly training by the PI in data handling and safeguarding.

H3 Case Report Forms and Source Documents

Any adverse events will be reported to the local IRB immediately and will trigger an immediate review to determine what changes need to be made and whether the study should

H4 continue or conclude.Records Retention

Data will not be identified by participant name. All data will be coded, and code sheets will be stored in locked files behind a locked door. Records will be stored for a minimum of seven years.

H5 Performance Monitoring

Participant safety will be continuously monitored by the PI and participants will be advised of how to contact Dr. Earhart if they have any concerns that arise outside of these sessions. Data quality will also be assessed on an ongoing basis, as data will be processed immediately after each experimental session. In addition, Dr. Earhart and Dr. Perlmutter will conduct a twice yearly review of data to ensure that the studies are progressing in a timely manner. The protocol will also be evaluated and the risk to benefit ratio assessed twice annually. All data and data monitoring will be kept strictly confidential according to HIPAA regulations. Results will be coded and the code sheets will be stored in locked files.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan & Auditing and Inspecting

The risks associated with these studies are minimal, as detailed in the Human Subjects Research section of the application. Participant safety will be continuously monitored by the PI and participants will be advised of how to contact Dr. Earhart if they have any concerns that arise outside of these sessions. Data quality will also be assessed on an ongoing basis, as data will be processed immediately after each experimental session. In addition, Dr. Earhart and Dr. Perlmutter will conduct a twice yearly review of data to ensure that the studies are progressing in a timely manner. The protocol will also be evaluated and the risk to benefit ratio assessed twice annually. Any adverse events will be reported to the local IRB immediately and will trigger an immediate review to determine what changes need to be made and whether the study should continue or conclude. All data and data monitoring will be kept strictly confidential according to HIPAA regulations. Results will be coded and the code sheets will be stored in locked files.

J Study Administration

J1 Funding Source and Conflicts of Interest

DHHS, National Institutes of Health

J2 Subject Stipends or Payments

All participants will be paid $75 for each completed MRI session and $50 for the follow-up evaluation The maximum possible compensation amount equals $200.

Individuals able to begin an MRI session but who withdraw during the session will be compensated $25 for their time.

J3 Study Timetable

Table 2. Project Timeline	Year 1	Year2	Year3	Year4	Year5
Standardize Protocol train Personnel	X				
Recruit Participants	X	X			
Evaluate Participants	X	X	X	X	
Deliver Exercise Interventions		X	X	X	
Data Entry/Verification	X	X	X	X	
Analyze Data				X	X
Prepare & Submit Manuscripts					X

K Publication Plan

Preparation and submission of manuscripts is projected to occur in the fifth year of the study.

L Attachments **(attached to HRPO document)**

L1 Informed consent documents

One consent document version for all participants.

L2 Questionnaires or surveys

Epworth Sleepiness Scale
Non-Motor Symptom Questionnaire
Stages of Readiness to Exercise Questionnaire
Fall History Questionnaire

The New Freezing of Gait Questionnaire (nFOG_Q)
Mini Mental Status Exam (MMSE)
Five times sit to stand (5xSTS) - 6 minute walk (6MWT) - 9 Hole Peg Test (9HPT)
PDQ-39
Footedness/Handedness Questionnaire
Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)
Kinesthetic and Visual Imagery Questionnaire (KVIQ) & Gait Imagery Questionnaire (GIQ)
Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire for Older Adults
Activities Balance Confidence (ABC) Scale
Mini BESTest
Montreal Cognitive Assessment
Wechsler Test of Adult Reading (WTAR)
Trail Making Test
Stroop Test
Verbal Fluency
Geriatric Depression Scale (GDS)
Frontal Systems Behavior Scale (FrSBe)
Prospective & Retrospective Memory Questionnaire (PRMQ)

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