Human Subjects Protocol

VA Puget Sound IRB

Genetic influences on response to gait rehabilitation in Parkinson's disease

MIRB# 01566

Funding Agency: Department of Veterans Affairs

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Abstract

Objective(s) and Hypotheses:
The aging Veteran population, together with high exposure to Agent Orange or other herbicides during military service, has made diseases such as Parkinson's disease (PD), currently affecting more than 80,000 Veterans, a major health issue in the Veterans' health system. Mobility and cognitive limitations are a common problem in PD and are associated with significant disability, increased fall risk, reduced quality of life, and increased caregiver burden. While less is known about its benefit on cognition, physical therapy has proven to be an effective treatment to mitigate mobility limitations, though the response to rehabilitation interventions is highly variable. The proposed research will inform our understanding of the impact of certain genetic profiles associated with learning impairments on motor and cognitive benefits in response to gait rehabilitation, and will provide an important foundation for more personalized and improved gait rehabilitation programs for different subgroups of PD patients.
The long-term goals of this research are: (Aim 1) to determine if certain genetic variants associated to learning impairments impact the motor and cognitive benefit experienced in response to physical rehabilitation in Veterans with Parkinson's disease (PD), and (Aim 2) to use that knowledge to identify subpopulations of patients that may require rehabilitative strategies tailored to their genotype to optimize physical rehabilitation.
Research Design:
To achieve these goals we will enroll 30 Veterans with PD (10 in each of the genotype groups carriers of BDNF-Met66, carriers of APOE-ε4 (N=10) and those not carrying either of those variants) in a 10-week moderate intensity gait training program consisting of 2 times per week treadmill training with verbal cues for gait quality. Aim 1 will examine the association between variants in 2 genes known to affect cognition and motor learning (APOE-ε4 and BDNF-Met66), and motor improvements after gait training. Aim 2 will examine the effect of APOE-ε4 and BDNF-Met66 genetic variants on cognitive changes in response to this training program.
Methodology
For Aim 1 we will sensitively and objectively assess changes in walking form, during and after training using state-of-the-art quantitative gait analysis, and compared between three genotype groups.
For Aim 2 we will measure cognitive performance pre- and post-training using a brief, targeted battery aimed at assessing attention, processing speed, executive function, and learning/memory, the domains more affected, and more likely to improve with physical exercise in PD.
Relevance to VA Mission
The results of this project will enhance our knowledge regarding the influence of different genetic profiles in the response to physical rehabilitation in Veterans with PD, and will generate supporting data that will translate to more personalized and effective rehabilitation programs for people with PD.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

PD- Parkinson's Disease

APOE- Apolipoprotein E

BDNF- Brain-Derived Neurotrophic Factor

AD- Alzheimer Disease

VHA- Veterans Health Administration

NCI- No Cognitive Impairment

MCI- Mild Cognitive Impairment

PD-D- Parkinson's Disease Dementia

MDS-UPDRS- Movement Disorders Society Unified Parkinson's Disease Rating Scale

MoCA- Montreal Cognitive Assessment

WPDR- Washington Parkinson State Registry

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1.0 Study Personnel

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2.0 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, behind Alzheimer's disease (AD). Over 4 million people worldwide are diagnosed with PD (1, 2) and its prevalence is expected to double by 2030, when it is estimated that more than 1 million Americans will carry a diagnosis of PD. Since 2010, PD is recognized by the Department of Veterans Affairs as a service connected condition, associated with exposure to Agent Orange or other herbicides during military service, affecting approximately 80,000 United States Veterans. **Gait impairment and increased risk of falls in PD.** Gait disturbance is one of the most consequential motor symptoms experienced by individuals with PD, contributing to increased risk

of falls (3), and resulting in increased disability (4), reduced quality of life (5), and increased caregiver burden (6). The impact of gait impairment on people with PD, their caregivers, and the healthcare system make gait a critical therapeutic target. Although gait impairment is not typically a presenting sign, its prevalence increases with disease progression. Within 3 years of diagnosis, over 85% of people with PD develop gait problems (7). Unfortunately, this debilitating symptom remains difficult to treat. Typical gait abnormalities include reduced speed, shortened step length, and increased stride-to-stride variability. Gait impairment worsens with disease progression, when festination and freezing can emerge, contributing to an increased risk for falls (3).

Falls while walking and their associated morbidity and mortality present a significant and growing challenge at both individual and societal levels (8, 9). The diagnosis of PD contributes to more falls than any other chronic disease and imposes a heavy burden in people over 65 years (10). Healthcare for fall-related injuries has a significant impact on the provision of care within the Veterans Health Administration (VHA). Administrative data from 1997 through 2001 indicate that over 60,000 unique patients received services for fall-related injuries, with over 20,000 patients receiving care for fall-related injuries in 2001 alone (11). Within the VHA alone, the annual cost of the initial outpatient visits associated with fall-related injuries was estimated at nearly 3.3 million dollars (11). Acknowledging this important issue, the VA's National Center for Patient Safety worked with the Veterans Integrated Service Network 8 Patient Safety Center of Inquiry (VISN 8 PSCI) and others to develop a toolkit designed to aid facilities to develop comprehensive fall and injury prevention programs (12).

Cognitive impairment in PD. Although PD was once considered a disorder of movement alone, cognitive impairment is now recognized as a common and consequential non-motor feature of the disease (13). People with PD can be classified as having no cognitive impairment (PD-NCI), mild cognitive impairment (PD-MCI), or dementia (PD-D) based on neuropsychological assessment and the impact on functional independence (13, 14). Similarly to gait impairment, cognitive impairment is very prevalent in people with PD. PD-MCI is present in approximately 25% of PD patients at the time of diagnosis, with an estimated cross-sectional prevalence of up to 60% (14, 15). Nearly 80% develop dementia during the course of the disease (16). PD is associated with deficits in executive function, attention, memory, language, and visuospatial abilities (13).

Interestingly, associations between cognition and gait have been demonstrated among older adults with and without cognitive impairment, and the combination of cognitive and gait impairments may accelerate functional decline (17, 18). In PD, gait disturbance is associated with cognitive impairment; for example there is a higher prevalence of falls among PD patients with cognitive impairment compared to those without cognitive impairment. Also, deficits in both global cognition and specific executive functions (processing speed) in patients with PD have been consistently associated with more severe postural instability and gait abnormalities, as measured by composite scores from the Unified Parkinson's Disease Rating Scale (UPDRS) (23). Together, these studies demonstrate a complex pattern of associations between gait impairment and specific cognitive domains. However, we have a limited understanding of the impact of cognitive dysfunction in PD on walking, particularly complex walking tasks that are critical to day-to-day mobility.

Rehabilitation as treatment for gait and cognitive impairment in PD. Since gait impairment in PD is typically minimally responsive to other treatments, rehabilitation is a critical part of its clinical management. While gait impairment may be initially improved by pharmacological and surgical approaches, their efficacy declines with disease progression. Antiparkinsonian medications improve gait speed and stride length but have mixed effects on stride-to-stride variability, which has been associated with falls in PD (19, 20). In addition, medications do not reliably reduce festination and freezing of gait, which can emerge with disease progression. A recent systematic review demonstrated that physical therapy can improve walking in people with

PD (21). Two common approaches to gait training for people with PD are treadmill training and training with a cognitive cueing strategy, both of which can effectively improve gait in people with PD (21). Exercise programs involving walking have also been shown to improve cognition in older adults (22), and there is some early evidence to suggest that such programs may also improve cognition in PD (23-26). In particular, gait training programs that incorporate walking at moderate aerobic intensity have the potential to improve both gait and cognitive impairments in PD.

The capacity for learning is fundamental to successful rehabilitation. Learning, like memory, is often defined as either procedural or declarative in nature, though this distinction likely oversimplifies these complex processes. Procedural, or implicit, learning develops gradually through repetition, does not require conscious awareness, and is expressed through improved performance. Despite the proposed role of the basal ganglia in procedural motor learning, people with PD do demonstrate preserved acquisition and retention of procedural motor learning (27). Practice improves motor performance in people with PD (28). However, research from both upper extremity (29) and postural control tasks (30) suggests people with PD may require more practice than healthy individuals in order to achieve similar performance gains, consistent with reduced efficiency of learning. In contrast to procedural learning, declarative, or explicit, learning requires awareness and attention, and results in knowledge that can be consciously recalled and verbalized. Impairments in declarative learning have been demonstrated among people with PD during both cognitive (31) and motor tasks (32). Research suggests that both procedural and declarative learning are impaired in PD, and both types of learning may be more affected in people with PD who have cognitive impairments (33). Treadmill training is a form of gait rehabilitation that emphasizes procedural motor learning, while cognitive cueing emphasizes declarative motor learning (i.e., verbal instructions to focus on walking), thus we believe a combination of both strategies should be used when treating PD patients.

Gap in knowledge to be addressed. PD is a heterogeneous disorder with considerable inter-individual differences in clinical features, disease course, and treatment response, which can be due to disease processes and other clinical variables, but also by other factors such as genetics. Currently, rehabilitation approaches do not take into account an individual's genetic profile, which may impact learning and therefore mediate the response to rehabilitation. Two genes that have been shown to play an important role in motor learning are the genes coding for brain-derived neurotrophic factor (*BDNF*) and apolipoprotein E (*APOE*). The BDNF protein is involved in neuronal survival and synaptic plasticity (34) and a variant in the *BDNF* gene (Val66Met), carried by approximately 30% of European-Americans has been associated with greater error in motor learning in healthy individuals (35) and appears to impact rates of motor learning on a locomotor adaptation task in individuals with cerebrovascular accidents (36). This variant results in 18 to 30% less activity-dependent secretion of the BDNF protein (37). On the other hand, the *APOE* gene encodes a glycoprotein that plays an important role in neuronal repair and synaptic remodeling. Genetic variation in this gene (*APOE*-ε4) is a well-known risk factor for AD, but has also been associated with motor decline (explained mostly by a loss in muscle strength) (38) and abnormal gait (shorter stride length and greater dual-task related disturbances in stride length) (39), in the elderly. Recently, we and others have shown that the *APOE*-ε4 allele is associated with poorer performance on specific cognitive domains in PD (40). Therefore, understanding the effect of genetic variants on the physical and cognitive improvement in response to training is an essential first step to investigate this relationship

Relevance of this project:

Understanding the impact of these genetic variants on physical and cognitive improvements in response to gait rehabilitation is critical to personalize the rehabilitation prescription for patients with PD. Our long-term goal is to identify genetic subgroups of patients with PD with differential response to different rehabilitation approaches. If such subgroups exist, we can then target effective and personalized rehabilitation strategies to each subgroup.

A greater understanding of the benefits on gait and cognitive impairments after rehabilitation training, and how genetic variants may be in involved in learning will not only help Veterans with PD, but will also inform our understanding of this relationship in Veteran populations that also experience both gait and cognitive impairment due to other neurologic diseases or injuries such as AD or traumatic brain injury respectively.
We are rapidly approaching an era when understanding the impact of genetic variations will help physical therapists and other rehabilitation professionals better identify individual differences in symptom manifestation, treatment response, and overall patient wellness. Providing better tools for stratifying individual patients will undoubtedly enhance the impact of rehabilitation.

3.0 Objectives

Parkinson's disease (PD) is a heterogeneous neurodegenerative condition that currently affects over 4 million people worldwide and, as a service connected condition, affects approximately 80,000 United States Veterans (2, 41, 42). Gait impairment is common in patients with PD, resulting in increased disability (4), reduced quality of life (5), and increased risk of falls (3). As PD progresses, gait impairment is typically minimally responsive to pharmacological or surgical interventions, making rehabilitation an essential aspect of clinical care in this patient population. Physical therapy is a key component of the rehabilitation process; specifically gait training on a treadmill results in short-term improvement in gait speed and physical endurance in PD (21). It is well-known that patient responses to rehabilitation interventions are variable despite apparent similarities in impairment profiles (21). An important factor that could impact the outcome of rehabilitation is cognitive function. Cognitive impairment, often underdiagnosed, is also a very common symptom and has been shown to affect mobility in PD (10). In many patients with PD, numerous aspects of learning, including motor learning, are impaired, suggesting that one factor contributing to variable rehabilitation response is the ability to consistently learn and implement learning-related changes in order to gain and sustain gait improvements. We believe that those Veterans with learning impairments may not receive as much benefit from routine gait rehabilitation and, if this is true, we may need to develop and tailor training programs to specifically target these individuals. We believe that the inter-individual heterogeneity in treatment response in PD can be explained not only by disease process and other clinical variables, but also by an impact from genetic factors. Increasing evidence suggests genetic variation is associated with brain plasticity and motor learning (35, 38); thus studying these genetic factors may help to differentiate subsets of Veterans with PD based on their response to rehabilitation and therefore identify optimal rehabilitation approaches for each subgroup. The proposed work will focus on variants in two genes (the *APOE*-ε4 and *BDNF*-Met66 alleles), which are postulated to play important roles in cortical plasticity and neural repair, thus having an effect on learning and cognition. We aim to understand whether genetic variants in these genes are associated with motor and cognitive outcomes in response to gait rehabilitation in Veterans with PD. **We hypothesize that Veterans with PD who carry an *APOE*-ε4 or *BDNF*-Met66 allele will demonstrate smaller improvements in gait (Aim 1) and cognition (Aim 2) during/after a 10-week gait treadmill-training program.** We will test these hypotheses through the following specific aims:

SPECIFIC AIM 1: **Determine the effect of genotype on motor learning in response to gait rehabilitation among Veterans with PD**. Aim 1 is designed to test the hypothesis that motor learning is reduced in those carrying *APOE*-ε4 or *BDNF*-Met66. We will compare the effect of a 10-week gait treadmill-training program on motor learning, defined as increased walking speed from pre-training (0 weeks) to 2 weeks into training and to post-training (10 weeks), between the three genotype groups. Secondary hypotheses will determine the effect of genotype on: (1) the retention of motor learning changes (from post-training (10 weeks) to follow-up (16

weeks)); and (2) the transfer of motor learning from the trained walking task (straight line walking at a self-selected speed) to more complex walking tasks (dual-task walking and turning while walking) from pre-training to post-training..

SPECIFIC AIM 2: **Determine the effect of genotype on cognitive changes in response to gait rehabilitation among Veterans with PD**. We will compare the effect of a 10-week gait treadmill-training program on cognition in each of the three genotype groups. Changes in cognition will be assessed by comparing performance on cognitive tests from pre-training (0 weeks) to post-training (10 weeks).

4.0 Resources and Personnel

All data collection procedures for this study will be conducted at the VA Puget Sound in Seattle, WA.

The physical therapy will be performed at the gym located in building 103, Room 1106, or Room 510 (Building 1). The gait and balance testing will be done at the RR&D Center Motion Analysis Laboratory located in Building 100, Room 1D-118D, Room 510 (Building 1) or Physical Therapy Gym Building 103, Room 1106. Lastly, all interviews and neuropsychological evaluations will be performed in Room 130 at the Clinical Research Unit (CRU), Room 510 (Building 1), or Physical Therapy Gym Building 103, Room 1106.

Under the supervision of the PI: the research assistant will be responsible for conducting recruitment, screening, consenting and scheduling study procedures. The research assistant will also perform cognitive testing under the supervision of a neuropsychologist. Physical therapists will be in charge of gait training as well as gait analysis. The PI and co-investigator will be primarily responsible for data analysis and interpretation. (See more details about the Study personnel above (1.0))

We have also a collaborator in RR&D, William Ledoux, who will help with facilitating the use of the Motion Analysis Laboratory and data collection and analysis. The assessments however will be performed using our system, a portable APDM Movement Monitoring Solutions system (APDM, Inc.) which is more efficient for the measurements we will be collecting.

5.0 Study Procedures

5.1 Study Design

To achieve these aims we will enroll thru the WPDR 30 Veterans with PD (10 subjects in each the three genotype groups: (1) at least one BDNF-Met66 allele, (2) at least one APOE-ε4 allele and (3) no Met66 nor ε4 allele) in a 10-week moderate intensity gait training program consisting of 2 times per week treadmill training with verbal cues for gait quality. Genotypes will be available thru the WPDR and recruitment will be targeted for those groups of patients.
Aim 1 will examine the association between variants in 2 genes known to affect cognition and motor learning (APOE-ε4 and BDNF-Met66), and motor improvements after gait training. Aim 2

will examine the effect of APOE-ε4 and BDNF-Met66 genetic variants on cognitive changes in response to this training program.
Participation in this study involves a total of 22 visits to the VA Puget Sound (**Table 1**). These visits will occur over approximately 16 weeks, for a total of ~28 hrs.
In the rare event that we cannot meet our targeted number, we will contact and recruit non-Veterans also enrolled in WPDR.

Visit 1, the baseline assessment, will include:

1) An interview to collect key demographic variables (such as gender, age, height, weights, etc.) as well as information about the disease, medications, etc.
2) A visit with a neurologist to test the severity of PD motor signs using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).
3) Questionnaire to assess fall history including the number of recent falls, circumstances, causes, and associated injuries
4) Questionnaire about physical activity levels using the International Physical Activity Questionnaire
5) A quick series of clinical tests of balance and gait including the Mini-Balance Evaluation Systems Test (mini-BEST), the 6-minute walk test, the Activity Specific Balance Scale Test, a Sensorimotor and Vision screen, and the Dynamic Gait Index (DGI).
6) A neuropsychological assessment using a brief, targeted battery of test including both paper and pencil and computerized measures. We will perform this in a quiet environment in the Clinical Research Unit (CRU) (room 130), Room 510 (Building 1), or building 103, room 1106, also at the VA Puget Sound Healthcare System.
7) A more quantitative balance and walking assessment using an APDM Movement Monitoring Solutions system (APDM, Inc.), which uses six inertial sensors attached to the wrists, feet, pelvis, and trunk to quantify body movements during mobility tasks. These tasks will include walking back and forth across a 7-m course for one minute. Two trials each will be performed under single-task (walking only) and dual-task walking (walking while performing serial-3 subtractions). We will do this at the VA RR&D Center Motion Analysis Laboratory (building 100, room 1D-118D at the VA Puget Sound, Room 510 (Building 1), or Physical Therapy Gym Building 103, Room 1106)
8) Additional questionnaires concerning sleep and quality of life including the Parkinson's disease sleep scale (PDSS-2), the Epworth Sleepiness Scale (ESS), and the Parkinson's disease questionnaire (PDQ-8).

This first visit will take approximately 4 hrs.
Visits 1 through 20 will take place over 10 weeks, with 2 visits a week focused on a gait training program. Every patient will participate in the same rehabilitation program conducted at the physical therapy gym (building 103, room 1106 at the VA Puget Sound), or Room 510 (Building 1). Each training will take 1 hour. The program will involve two weeks of light intensity training on a treadmill with special focus on improving gait form, followed by 8 weeks of monitored, self-controlled moderate to vigorous intensity gait training on a treadmill, always using verbal cues for gait quality provided regularly throughout the gait training sessions.

Visit 4 and **visit 20** will also include the same balance and walking assessments previously described in the baseline visit 1 (the mini-BEST, DGI, MDS-UPDRS, and the quantitative assessment), with **visit 20** also including neuropsychological assessments. Thus visit 4 will take an additional 1 hour while visit 20 will take an additional 2 hours.

Visit 21 will take place approximately 6 weeks after you complete the rehabilitation program. This visit will only include the balance and walking assessments (again both the mini-BEST, DGI, MDS-UPDRS, and the quantitative assessment), for a 1 hour duration.

Table 1. Summary of protocol for proposed research.

	Pre-training (Baseline)	Start Training	Short-term Motor learning	Post-training	Follow-up (Retention)
Week	0	1	2	10	16
Gait training		weeks 1-10, 2x/week			
AIM 1: Gait assessment	X		X	X	X
AIM 2: Neuropsych. assessment	X			X	

Risks

The potential risks of the proposed study are low, and this research is entirely non-invasive. Where potential risks have been identified, we have taken steps to mitigate them. Participants may find some of the questions in the baseline assessment (e.g., regarding medical co-morbidities) are sensitive and may perceive this as an invasion of privacy. Participants will not be required to answer any questions that they do not choose to answer. For both Aims, participants will be asked to perform a variety of motor and cognitive tasks. During testing, participants may become fatigued. Participants will be able to rest as needed in order to complete tasks. Testing and gait training may result in some slight muscle soreness after walking. People with PD have a greater risk of falling than older adults without PD. We have taken great care to reduce the risk of falling. We will have 2 licensed physical therapists, and at least one will be present for all assessment and training sessions. All subjects will wear a gait belt and trained investigators will walk with them to guard against loss of balance and falls. Also, during gait training, a harness system for the treadmill will be available to reduce the risk of falls. We will monitor participants throughout the assessment and training sessions for any fatigue or soreness. Finally, because sessions will be 1-2 hours in length, water and a variety of snacks will be offered and available to participants throughout the sessions.

5.2 Recruitment Methods

Recruitment.

Recruitment will be done thru the Washington Parkinson Disease Registry (WPDR, MIRB#01023) using an Institutional Review Board (IRB) approved letter that describes the research study and provides contact information for the study. WPDR will contact Veterans that meet the requirements to participate in the study from an existing cohort of Veterans with PD who are already part of the registry. Potential participants will then contact the investigator of this project and will be screened by phone to determine their eligibility for this research. Eligible individuals will be scheduled for their baseline visit at a mutually agreeable time and will be sent a confirmation letter that includes a copy of the

informed consent document to review prior to study participation. The informed consent will detail the purpose, procedures, risks, and benefits of the research. Upon arrival in the laboratory for their baseline visit, the PI or appropriate study personnel will review the informed consent and answer any questions.
Results from the telephone screening will be kept in our database and shared with the WPDR to make further recruitment efforts for similar projects more efficient. For this purpose, we have filled out and submitted a request for waiver or alteration of the informed consent process form.

The WPDR will approach 60 individuals with the goal of recruiting a total 30 participants with PD, 10 subjects in each the following three groups: (1) at least one BDNF-Met66 allele, (2) at least one APOE-ε4 allele and (3) no Met66 nor ε4 allele. The genotypes will be available thru the WPDR and therefore will be used by WPDR during the recruitment to target those patients that fall in each of these three groups. In the rare event that we cannot meet our targeted number, we will contact and recruit non-Veterans also enrolled in WPDR.

Payment.
Veterans will be offered compensation in return for the time and effort for a total of $175: $25 for the assessment at 2 weeks, $50 for the assessment at 10 weeks and $100 for the assessment 6 weeks after the program is done. Payments may be issued in cash or check (participant preference). We believe that the last assessment (6 weeks after the training finishes) is the most time consuming as participants are no longer coming to the VA for their training program and will just come here to do the assessment. The data from the last visit will help answering a very important question, which is the duration of the benefit provided by the training program. Thus we have assigned the last visit with the highest monetary compensation.

Checks will be mailed about 6-8 weeks after each visit, or cash payments can be collected through the agent cashier at the VA Puget Sound approximately 6-8 weeks after each visit.

5.3 Informed Consent Procedures

The informed consent will detail the purpose, procedures, risks, and benefits of the research. Upon arrival in the laboratory, the PI or appropriate study personnel will review the informed consent and answer any questions. We will strive to ensure that all individuals understand the nature of the study. The decisional capacity of all prospective participants will be assessed by study personnel, in consultation with a study clinician, at the baseline visit. The assessment will be based on four key elements: the person's ability to 1) communicate a choice, 2) understand the relevant information, 3) appreciate a situation and its consequences, and 4) reason rationally, as described in detail in Appelbaum, N Engl J Med, 2007. Those individuals who are deemed to have impaired decisional capacity will not be enrolled in the study. Each individual will be told that they can choose not to participate in the study, that they can withdraw at any time, and that if they decide not to participate, it will in no way alter their medical care. Individuals who consent to participate in the study will be asked to sign the informed consent document

and will be given a copy of the signed form. All study personnel will complete the necessary human subjects' protections training per VA policy.

5.4 Inclusion/Exclusion Criteria

Patients will have to:

1. Meet UK Brain Bank (UKBB) criteria for the diagnosis of PD (modified so that having more than one affected relative was not considered an exclusion criteria);
2. Have a Hoehn & Yahr score of ≤ 3.
3. Have the ability to walk 400 m without physical assistance from a device or another person.
4. Do not have other health conditions (e.g., orthopedic, cardiopulmonary) that impact the ability to safely participate in a moderately intense gait training program.

We will exclude those patients with a clinical diagnosis of dementia.

WPDR will first contact patients for recruitment that meet these inclusion criteria based on information recorded at their last visit in the WPDR database (UKBB criteria and Hoehn & Yahr are available for all patients). Once those patients interested in participating contact a staff member for this project, we will ask questions about their ability to walk and other health conditions during the phone screening. Finally eligibility will be determined after the patients perform the baseline visit where they will undergo a clinical and neuropsychological assessment by a neurologist and a neuropsychologist. At this visit we will make sure patients still meet UKBB criteria and Hoehn & Yahr requirements, as well as assess the ability to walk without physical assistance and their cognitive function. After the baseline evaluation, the neurologist and the neuropsychologist will review the results from all the assessments and generate a consensus clinical diagnosis of non-demented/demented and those diagnosed as demented will not be enrolled in this study.

5.5 Study Evaluations

Demographics: Sex, age, height, weight, ethnicity (incl. Hispanic origin), education, year of initial PD diagnosis, co-morbid medical diagnoses, and medications (PD & non-PD).

Clinical characteristics & quality of life: The severity of PD motor signs will be quantified using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Fall history will be assessed using a questionnaire including the number of recent falls, circumstances, causes, and associated injuries. Physical activity levels will be assessed using the International Physical Activity Questionnaire. Clinical tests of balance and gait will include the Mini-Balance Evaluation Systems Test (mini-BEST), the Activity specific balance confidence scale, a sensorimotor and vision screen, the 6-minute walk test, and the Dynamic Gait Index (DGI). Quality of life questionnaires will include the PDSS-2, PDQ-8, and the ESS.

Gait Training Intervention: All 30 individuals will attend a 10-week training program at the physical therapy gym at the VA Puget Sound, consisting of 1-hour sessions, twice a week (**Table 1).** The program will involve light intensity training on a treadmill with special focus on improving gait form for 2 weeks, followed by 8 weeks of monitored, self-controlled moderate to vigorous,

intensity gait training on a treadmill, with verbal cues for gait quality provided regularly throughout the gait training sessions. Adding verbal cues will incorporate declarative (explicit) in addition to procedural (implicit) learning processes. Feedback about the training speed achieved will be provided at the end of each 5-minute block.

Balance and Walking Assessment: (AIM 1) Walking will be assessed at the VA RR&D Center Motion Analysis Laboratory in a 1 hour session at 4 time points (**Table 1**): 0 weeks (baseline), 2 weeks (short-term motor learning changes), 10 weeks (long-term motor learning changes, immediately post-training), and 16 weeks (retention of motor learning, follow-up) using a wearable inertial sensor system. Motor learning will be assessed using gait speed during self-paced walking from baseline to 2 weeks (short-term motor learning changes) and from baseline to 10 weeks (long-term motor learning changes).
Objective spatiotemporal parameters of walking will be measured with the portable APDM Movement Monitoring Solutions system (APDM, Inc.), which uses six inertial sensors attached to the wrists, feet, pelvis, and trunk to quantify body movements during mobility tasks. We have used the APDM inertial sensor system extensively to quantify balance and gait in people with PD and other older adult populations, with data collection completed for >20 people with PD and >90 people with mild cognitive impairment or early AD. Participants will walk back and forth across a 7-m course for one minute. Two trials each will be performed under single-task (walking only) and dual-task walking (walking while performing serial-3 subtractions), allowing us to quantify changes in both straight-line walking and 180 degree turns under conditions of increasing cognitive load. Motor learning will be assessed using the primary outcome of gait speed during straight-line walking under single-task conditions. Therapists will be blinded to the subjects' genotyping status.

Secondary analyses: We will also measure retention and transfer of motor learning. Retention of motor learning will be assessed by differences in walking speed from post-training (10 weeks) to follow-up (16 weeks) time points (**Table 1**). Transfer of motor learning from a simple walking task (self-paced straight-line walking on a treadmill) to complex walking tasks (turning, dual-task walking) that are commonly impacted by PD will be assessed by the change in walking speed during complex walking tasks from pre-training to post-training time points.
Secondary walking measures to inform the mechanisms underlying any gait changes will assess specific gait domains (43-45) and will include step time, step time variability, step time asymmetry, and arm swing range of motion. These gait measures will be calculated in both single-task and dual-task walking conditions. In the dual task condition, performance of the serial-3 subtraction task will be audio recorded and the number of responses (correct and incorrect) will be tallied offline. Cognitive task performance will be measured as the correct response rate (number of correct responses per second), with number of correct responses and percent of correct responses (number of correct responses / total number of responses * 100%). Turns will be quantified using peak turning velocity as the primary measure, with turn time and number of steps required to turn as secondary measures for turning.

Neuropsychological Assessment: (AIM 2) Cognitive performance will be measured at baseline (0 weeks) and post-training (10 weeks) (**Table 1**) using a brief, targeted battery aimed at assessing learning/memory, executive function, attention and processing speed. The battery will include both paper and pencil and computerized measures, and is approximately 45 minutes in length. When needed, we will minimize learning effects by using different versions of the same test pre- and post-training program. The battery includes:

1) Story recall (46): This measure of episodic verbal memory consists of an auditory presentation of a brief story, followed by immediate and delayed recall conditions.

Multiple validated equivalent versions of this measure are available and will be presented in a counterbalanced, randomized order.

2) Frontal Assessment Battery (47): This battery assesses a broad sampling of executive functions (abstract reasoning, phonemic verbal fluency, motor programming, interference, response inhibition) with minimal subject and time burden. It has been used in clinical trials and in pre- and post-intervention designs without apparent practice effects (48, 49).
3) Flanker Inhibitory Control and Attention Test (50): This computerized task is part of the NIH Toolbox and is derived from the Attention Network Test. It examines the participant's ability to inhibit visual attention to irrelevant stimuli.
4) Semantic verbal fluency (51): Semantic verbal fluency consists of asking the participant to produce as many words as possible in one minute that belong to a given semantic category.
5) Pattern Comparison Processing Speed Test (52): This computerized task from the NIH Toolbox measures choice reaction time by asking participants to quickly determine whether two visual stimuli are the same or different.
6) Dimensional Change Card Sort Test (50): The Dimensional Change Card Sort Test is a computerized measure of executive function/set shifting from the NIH Toolbox. A target is presented on the screen which must be matched to one of two choices, shape or color. During "switch" trials, the participant must quickly adapt to new rules for matching (e.g., first color, then shape, then color), with little feedback on how to do so.
7) Montreal Cognitive Assessment (MoCA) (53): The MoCA is a brief assessment of global cognitive abilities, including orientation, attention, memory, language, abstract reasoning, and visuospatial items. The MoCA has been shown to be a suitably accurate, brief test when screening for cognitive impairment in PD.

5.6 Data Analysis

Descriptive analyses at baseline will be used to examine participant characteristics and demographic variables and compare them across the sample and by genotype, including age, sex, height, education, disease duration, disease severity, physical activity levels cognitive task performance and global cognition. Histogram and quantile-quantile plots will be generated for each variable and transformation will be used when necessary to improve the fit to normality. **Aim 1**: The primary hypothesis that motor learning is reduced in those carrying *APOE* or *BDNF* genetic variants compared to those without *APOE*-ε4 or *BDNF*-Met66 genotypes will be tested using repeated-measures analysis of variance (ANOVA) with one within-group factor, time point (0 weeks, 2 weeks for short-term motor learning; 0 weeks, 10 weeks for long-term motor learning) and one between-group factor, genetic group (*BDNF*-Met66 group, *APOE*-ε4 group, no Met66 nor ε4 allele group) to examine changes in the primary outcome measure for walking, gait speed. The secondary hypothesis examining the effect of genotype on retention of motor learning changes will be tested using repeated-measures ANOVA with one within-group factor, time point (10 weeks, 16 weeks follow-up) and one between-group factor, genetic group to examine changes in gait speed. The secondary hypothesis examining the effect of genotype on the transfer of motor learning from the trained walking task (straight line walking at a self-selected speed) to more complex walking tasks will be tested using repeated-measures ANOVA with one within-group factor, time point (0 weeks, 10 weeks) and one between-group factor, genetic group to examine changes in gait speed for dual-task walking and peak turning velocity for turning while walking. For all analysis, unadjusted models will be used. We will consider adjusting for age, height, cognitive task performance (for dual-task) or global cognition if any of these factors are shown to be different between genotype groups.

Aim 2: The primary hypothesis that those carrying *APOE* or *BDNF* genetic variants will experience reduced improvement in cognitive performance in different domains compared to those with *APOE*-ε4 or *BDNF*-Met66 genotypes, will be tested using a repeated-measures analysis of the covariance (ANCOVA), with visit (0 weeks, 10 weeks) as the within-group factor and genetic group (*BDNF*-Met66 group, *APOE*-ε4 group, no Met66 nor ε4 allele group) as the between-group factor for each of the tests, with adjustment for important covariates: age, disease duration and years of education.
All analyses will be perform using commercially available software (Stata, version 14.0; StataCorp).

5.7 Withdrawal of Subjects

This is not a treatment study; withdrawing or being terminated from this study will not have an impact on participant safety. Our recruitment and screening processes are designed to identify individuals who can tolerate 10 week of gait training, but a study clinician or the PI may withdraw a participant without their consent if he or she feels that it is not in a participant's best interest to continue in the study or if they are unable to complete the study procedures. For example if the participant develops knee pain that cannot be appropriately managed by decreased training intensity.
All data previously collected from participants who withdraw, or are withdrawn, will be kept and may be used in the study data analysis. Participants may withdraw at any time by informing the Research Coordinator and/or the PI.

6 Reporting

All safety information on Adverse Events (AEs), Serious Adverse Events (SAEs), unanticipated events or problems, and protocol deviations will be collected. This information will be collected at study visits and whenever participants call to report a problem. It will be collected on VA IRB forms (Report of a SAE and/or Problem Form), or Report of Problems (ROP) Form as well as a study form.
If we become aware of relevant findings or information that may affect participants' health or welfare we will contact participants by phone and/or a letter to notify them.

7 Privacy and Confidentiality

See section 9.0

8 Communication Plan

Not a multi-site study

9.0 Information Security and Data Storage/Movement

Electronic data with PHI/sensitive information will be stored on the secure server at the VA Puget Sound. These data will only be accessed by authorized study personnel. Hardcopies of VA sensitive data and documents with PHI will be stored in a locked file cabinet in a locked office at the VA Puget Sound (Seattle). Study files/data with PHI or sensitive information will not be sent off-site. This is a locked facility to which only study investigators have access. Identifiable data will not be transmitted, transported, or stored on portable media or laptops outside of the VA, and the data will only be accessed by authorized VA study staff. We will notify the Information Security Officer of the location of the hardcopy data/files via the Data Inventory form. If study data is improperly used or disclosed we will notify the ISO and Privacy Officer within one hour of becoming aware of the issue.

Participants who are enrolled in this study will be given a unique study identification number that will be used to code all research materials obtained. The link between the participant name and their study identification number will be kept on a password protected computer in a locked office.

All research materials will utilize only the study identification number. The baseline assessment (demographic information, lower extremity screening, mobility testing, and PD motor symptom severity) will be performed using a standardized data collection sheet that will be stored in a secured location. Motion capture data that are used to characterize walking will be stored in an electronic file that is accessible only using proprietary software and stored on a password protected computer in a locked office. Audio recordings collected during the serial subtraction task in the balance and walking assessment will also be kept both physically in a locked file cabinet and electronically on the secure VA server. Participants will not be identified by name at any stage of data analysis nor in any presentation or publication resulting from these studies

Since patients are enrolled in the WPDR, data will be shared back to the WPDR for recruitment of future research studies. Since all patients will be enrolled in the Parkinson's Genetic Research Study (The PaGeR Study, MIRB #00088 PI: Cyrus Zabetian) we will keep their data and link it to their bio-specimen. This will allow for samples and data to be shared together

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