1. TITLE: Optimizing Motor Training in Parkinson Disease through Neural Mechanisms

Running Head: Optimizing Motor training in PD through Neural Mechanisms
Principal Investigator: Madeleine E. Hackney, Ph.D.

June 14, 2016

2. **Abstract**:
Persons with Parkinson's disease (PD) have impaired mobility, which adversely affects their quality of life. The effectiveness of adapted tango dance, in which participants both lead (internally guide: IG) and follow (externally guide: EG) movement has been demonstrated (Hackney & Earhart 2009, 2010). To improve outcomes in those with PD, the underlying neural mechanisms for both motor impairments and improvement must be investigated. IG and EG movements have distinct neural patterns. Individuals with PD have trouble with IG movement but this problem is helped by strategies employed while "leading". During "following", participants with PD can exploit multiple external cues, which facilitate movement in PD, because EG tasks bypass the basal ganglia (Freedland et al., 2002).

Using a randomized controlled trial design, we will begin with an functional Magnetic Resonance Imaging (fMRI) investigation. We will examine neural correlates of a clinically-used foot-tapping task, during IG and EG conditions in older persons with and without PD. Then, we will assess the relative effectiveness of IG versus EG training used in an adapted tango class, compared to a behavioral control (health education) for improved mobility and foot tapping. Participants with PD will be assessed for disease severity, and will receive tests of outcome measures while "OFF" and "ON" medications, 1 week before training, and 1 week and 1 month after training. Participants must attend 20 lessons of IG or EG adapted tango in 12 weeks, taught by an experienced instructor. In an fMRI scanner, we will assess participants for improved foot tapping after training and investigate changes in activation in specific neural circuits in conjunction with training effects upon mobility.

Our long-term goal is to optimize motor training for persons with PD by understanding lower limb motor circuitry in PD as well as neural changes in circuitry through which training is effective.

3. Introduction and Background/Significance

Impairments in Parkinson's Disease: PD affects 1 million Americans and has formidable personal and socioeconomic costs (>$34 billion/year) that are increasing.[10] PD cases are expected to double by 2030.[11] PD impacts the VHA health care system with 1.65% prevalence, compared to ~1% in the general population and 50% of these people use VHA as their only source of health care. Persons with PD report 3-4 points lower on the Short-Form 36 physical and mental health-related quality of life (QOL) than those with diabetes, heart disease, and stroke.[12] Because of impaired gait, balance and mobility, people with PD often experience falls which leads to withdrawal from activities, low self-esteem and poor mood.[13] In one study, 70% of PD patients fell within one year and 50% had a repeat fall the next year.[14] Multiple motor symptoms, including postural instability, gait impairment, turning difficulty and dual-tasking problems rob patients of QOL.[1] Turning, gait initiation, and walking through doorways or other tight spaces can trigger freezing, i.e., a stoppage during gait [15], which affects 53% of patients who have had PD 5 years and more.[16] Adverse changes to gait while dual-tasking are greater in those with PD than those without.[17] [18] Shorter stride length, and slower gait speed while performing a cognitive dual task may result from an underlying cognitive impairment, which is common in PD.[19] A co-morbidity of mild cognitive impairment is associated with greater falls risk in

older people with PD.[20] Spatial cognition, [21] set-switching, [22 23] executive function and attention [24] are impaired in those with PD, which may affect their mobility. However, exercise programs may improve cognition, [25] reduce rates of "near falling",[26] and fall incidence [27] in persons with PD.

Treatment of PD Mobility Impairment: Pharmacology and surgery do not fully address the needs of those with PD.[2] Effective motor rehabilitation is necessary[28], and should be safe, participant-friendly, promote high adherence and have demonstrated efficacy in improving disease severity, mobility and QOL. Traditional exercise programs often suffer from high attrition rates because of high patient task demand and lack of social interaction.[29] Ideally, exercise activities should engage and sustain interest, because 60% of all Americans older than 65 do not achieve recommended daily amounts of physical activity.[30] Activity levels in individuals with PD are even further reduced.[31]

Several mobility programs are effective (e.g., movement strategies, dance, tandem biking, tai chi) for people with PD [8 32-35]. Better mechanistic understanding of beneficial exercise effects could improve the design of targeted motor rehabilitation interventions for particular symptoms (e.g., freezing, bradykinesia, and various disease stages of PD). This information would be of great clinical significance to veterans and others with motor impairment of all etiologies, as well as due to PD.

In the last five years, the PI has published a series of studies of training in adapted Argentine-tango (adapted tango) dance showing gains in mobility and balance, maintained one month later in individuals with PD (Hoehn & Yahr stages II-IV).[3-5 36-38] Participant-friendly, adapted tango had low attrition (15%) demonstrating patient acceptance and feasibility with a diverse patient population. In classes, participants alternated between two motor training approaches: a) leading, consisting of internally guiding (IG) movement plans, and b) following, consisting of responding to external guidance (EG). While feasibility and promising outcomes have been demonstrated, previous studies were not designed to make inferences about the causal mechanisms of this intervention. Of interest now is what leading and following, in isolation, contribute to the observed benefits, because evidence shows IG and EG tasks activate distinct neural pathways, which may impact training effects.

Internally and Externally Guided Movement Strategies: Qualities of effective rehabilitative programs are found in both IG and EG training within the context of adapted tango. For example, training for postural instability is most effective if dynamic balance practice and continual adjustment to environmental demands are incorporated.[39] Specifically for individuals with PD, having complex movements broken down into simpler elements by the teacher, done in any dance pedagogy, may facilitate motor performance.[8] Synchronizing movement to rhythm, inherent to dance, may enhance movement speed.[40] A partner may enhance balance as even light touch contact can augment postural control.[41] Nevertheless, there are key differences between IG and EG training that may affect training gains in mobility, as well as the neural circuitry that drives IG and EG movement.

Leading, which uses internally guided cognitive and motor skill, is thought to involve employing a "movement strategy" that demands increased focus on movement plans and mentally rehearsing and/or preparing for movement. Leaders must determine precise spatiotemporal movement parameters of a dance sequence. As such, leading may pose a challenge for individuals with PD, given that they have deficient executive control, specifically in cognitive processes involved in planning and executing complex, goal-directed behavior.[42] However, movement strategies involving strong cognitive involvement and planning are associated with mobility improvements.[8] For example, focusing on critical movement aspects (e.g., longer steps, quicker movements) helps individuals with PD to achieve nearly normal speed and amplitude.[15] Thus, IG training may be helpful for PD patients.

The observed improved function gained via adapted tango in individuals with PD may also be due to the multiple external cues used in this training. Abundant evidence demonstrates benefits of rehabilitative exercise that exploits external cueing and specifically targets neural systems that

support balance [35] [43]. When following (EG training), participants focus on external cues, which may access CTC circuitry and bypass the basal ganglia.[9] External cuing has improved movement initiation [44] [45]. Other research showed that people with PD have faster reaction times when externally cued compared to self-initiated movement.[46] Importantly, during EG partnered movement, such as that engaged during following in adapted tango, the participant is not required to plan precise spatiotemporal parameters of movement (e.g., direction, length of step, timing, and amount of rotation). From moment to moment the follower receives movement guidance from the leader via tactile and, to a lesser extent, visual cues. Because followers are not devoting attentional resources to planning movement, potentially they can attend more to their postural control.

Because of the benefits of both IG and EG training, we will investigate the relative effectiveness of IG (leading) and EG (following) training, within the context of adapted tango, for improved mobility and functional performance in comparison to a behavioral control (health education), in Aim 2. We postulate that mobility gains will be greater in those who participate in IG training if selecting and planning movements is fundamental to gains. However, if training with concentrated external cueing is most effective, we expect to see greater mobility improvements in those who participate in EG training.

Neural Mechanisms of Mobility Training: IG and EG training may impact the neural circuitry that drives IG and EG movement. However, little is known about the neural mechanisms underlying motor and cognitive improvements as a result of rehabilitative training in individuals with PD. A study utilizing positron emission tomography (PET) showed improved vocal intensity after training in the Lee Silverman Voice Training (LSVT®) LOUD program for speech improvement. These motor improvements were correlated with modification in motor, auditory, and prefrontal areas but there was no effect on the basal ganglia.[47] However, in healthy participants, increased activity in the putamen was noted using PET when tango movements were performed to a metered beat.[48] In a related finding, after a week of tango lessons, healthy individuals exhibited increased activity of supplementary motor (SMA) and premotor cortices during imagined walking.[49]

Underlying mechanistic commonalities may exist amongst a variety of therapies that effectively target symptoms of individuals with PD.[50] In the case of deep brain stimulation, stimulating the subthalamic nucleus is thought to suppress abnormal downstream network activity produced by the malfunctioning basal ganglia.[51] If the mechanism of improvement resulting from motor training is similar, there may be a reduction in abnormal neural activity along the STC (putamen, ventral anterolateral thalamus, rostral SMA and primary motor cortex). Alternatively, with effective treatment, there may be enhanced compensatory capabilities within the CTC (cerebellum, ventral posterolateral thalamus, lateral premotor cortex and somatosensory cortex).[52] Another possibility could be increased activity in the basal ganglia, which has been demonstrated to be hypoactive in drug-naïve individuals in early stages of PD.[53]

Neural Mechanisms of Internally and Externally Guided Movement in PD: Knowledge about neural changes that may occur after repeated and targeted training with IG and EG tasks will allow us to develop better rehabilitation training strategies for those with PD. In healthy individuals performing EG finger-tapping tasks, the CTC circuit is primarily recruited, while during IG tasks the STC circuit is primarily recruited. [6] [54] [55] Given that there is dysfunction of the basal ganglia, which is involved in the STC circuit, people with PD have difficulty internally generating movement [7] [56]. PD may influence STC and CTC circuits on a task-specific basis. For example, during EG movements, people with PD activate the CTC network in a way that is very similar to controls; however, in PD patients, both the CTC and STC are activated during IG tasks.[6] In keeping with the idea of increased compensatory activity/connectivity of cerebellar circuits during IG tasks, striato-cortical and striato-cerebellar connections are weaker in individuals with PD than in controls, while cortico-cerebellar connections

are strengthened.[57] As a compensatory response, those with PD tend to recruit the CTC circuit to perform IG tasks increasingly with time.[55]

Studies investigating IG and EG movement typically have examined finger-tapping tasks.[6 55] Studies that clarify mechanisms of lower limb control are rare. There are differences in the brain functional anatomy between hand and foot movements.[58] Therefore, to understand the mechanisms underlying impairments and training effects in whole-body balance and mobility tasks, lower limb neural activity must be investigated within the context of IG and EG tasks in individuals with and without PD. Thus we will employ foot-tapping, a task that is used in clinical practice to assess lower limb motor control, and also a task that has been adapted to functional neuroimaging. In Aim 1, we will investigate and identify neural correlates of performing a foot-tapping task in participants with PD, compared to age-matched controls. This will allow us to examine the neural circuitry involved in lower limb motor control in persons with PD. Keele et al. (1985)[59] demonstrated that finger-tapping, forefoot-tapping and heel-tapping are highly correlated, suggesting a common underlying mechanism. Therefore, in keeping with studies employing finger-tapping, we hypothesize that IG and EG lower limb control will be associated with activation of the STC and CTC circuits, respectively, in healthy controls. But, those with PD will activate both the STC and CTC circuits during IG tasks, and only the CTC circuit during the EG task. Information gained from the achievement of Aim 1 will further the knowledge base of the pathophysiology of lower limb control in those with PD.

We will use the information gained in Aim 1 about circuits involved in IG and EG movement to evaluate the effects of targeted training upon those same circuits in a clinical intervention we will test in Aim 2. Importantly, Aim 2 proposes to verify if functional improvement noted on foot-tapping and other mobility measures after IG and EG training is related to changes in the activity of IG and EG neural networks. We will also investigate the resting state functional connectivity (RSfc) of these circuits before and after training, because neural networks are best defined in terms of the structure of temporal interactions between regions.[60] The resting state represents the intrinsic blood oxygen level dependent (BOLD) fluctuations of neural areas. Studying connectivity during resting state provides information related to hemodynamic consequences of slow variations in transient neuronal dynamics.[61] These intrinsic fluctuations have a huge metabolic load, are likely functionally relevant and might be used as a marker of network dysfunction. [62] Persons with PD have altered RSfc in motor areas.[56 63] Examining RSfc of circuits before and after targeted motor training may provide information about the pathophysiology of the disease and its training response. Information gained from Aim 2 will provide bases for recommendations of specific motor strategies within a PD rehabilitative program.

Significance

In 2003, the Under Secretary for Health, Department of VA, Dr. Roswell, stated that veterans aged 75 and older would increase from 4 to 4.5 million and those over 85 would triple to 1.3 million. The prevalence of PD increases to 4% in the oldest age groups.[64] Veterans with PD have relatively heavy disease burden and nearly 80% will be using VHA as their only source of health care.[12] Clearly, more veterans with PD will need effective and enjoyable rehabilitative modalities that encourage social interaction.[65] Group exercise programs effectively rehabilitate motor impairments, are social in nature and are likely to improve QOL in veterans and others with PD.[66]

Through our series of adapted tango studies, which included veterans from WWII, Korea and Vietnam, we showed evidence for improved mobility, balance and QOL in those with PD. Now we aim to increase our knowledge about the pathophysiology of task-specific mobility impairments, specific types of motor training effects and associated changes in brain activity. With information about the relative effectiveness of leading and following in tango training we will know: 1) if there is evidence that either leading or following movement is superior, 2) preliminary evidence related to the effects of each training on executive function, procedural learning and spatial cognition, and 3) neural

structures and pathways that are accessed by each form of training. Another novel aspect is that we will evaluate neural activity of lower limb movements during EG and IG tasks, which is not well understood, nor has it previously been investigated in those with PD.

This work will contribute to generalized motor theories that will impact care and create more efficient motor rehabilitation in these concrete ways: 1) This project is designed to discover general principles related to improving movement, e.g., if the IG group improves more than EG, we will assume such principles extend beyond tango and we would suggest that incorporating planning and initiating movement in mobility intervention may provide greater therapeutic effects. However, if EG improves more than IG, we would suggest cueing during training is essential for benefits. 2) Dance programs for older adults and individuals with PD are growing popular. Clinicians may use positive results from this study to suggest dance as a beneficial avenue for therapy. 3) Increased knowledge about the effects of specific types of motor training on neural circuitry will lead to greater specificity of treatment for individual patients with particular stages of disease and primary symptoms. Also, we will seek to partner with an organization, e.g., the National Parkinson Foundation to develop DVDs and manuals, presenting the training program fundamentals, graded to complexity from which clinicians can extract information relevant to their practice and incorporate as appropriate (http://www.parkinson.org/Improving-Care/Education.) Providing mechanistic basis for successful rehabilitative protocols involving exercise will lend greater support for clinical and community use, and may lead to insurance company support. Demonstrating mechanisms of neural circuitry will provide evidence that training may be effective in ways similar to that of pharmacology and surgical devices, e.g., DBS. This project aims to provide enjoyable treatment while investigating neural mechanisms, upon which future clinical recommendations can be made. Clearly this novel work has potential to impact care and QOL of individuals with PD.

4. Objectives

Statement of Hypotheses and Specific Aims:

In the VHA health care system, Parkinson's disease (PD) presents a high illness burden as a result of compromised mobility and quality of life (QOL).[1] Pharmacological agents and surgical options that alleviate impairments do not fully address needs of those with PD. [2] Motor rehabilitation is effective and lacks the side effects of pharmacology and surgery, but the underlying neural basis for motor improvements is largely unknown. To design better treatments for patients with PD that will improve motor function and QOL, we seek to understand the relationship between improved motor function and neural changes. Over the last 5 years, the PI has tested the efficacy of PD-adapted tango, which improved mobility and QOL in adults with PD after training. Adapted tango is a novel, patient-friendly method of motor rehabilitation in which participants learn to alternate leading (internally guided: IG) and following (externally guided: EG) partnered movement [3-5]. IG and EG motor tasks are likely mediated by striato-thalamo-cortical (STC) and cerebello-thalamo-cortical (CTC) circuitry, respectively in healthy controls.[6] Because PD causes dysfunction in the basal ganglia, patients have difficulty with IG tasks. [7] However, this impairment can be remediated by motor rehabilitation that uses skills similar to those used when "leading" in tango, in which participants engage cognitively in planning and selecting movements.[8] Conversely, abundant evidence shows that external cues, such as those used for "following" during tango, facilitate movement in PD, presumably because EG tasks access CTC circuitry and bypass the basal ganglia.[9] During "following", participants with PD can exploit multiple external cues, which may aid rehabilitative effects**. In individuals with PD, we aim to improve our understanding of lower limb motor control and the circuitry involved (Aim 1), determine the relative effectiveness of targeted IG and EG training, and explore neural mechanisms of mobility improvement through adapted tango (Aim 2).** To accomplish this goal,

first we will use fMRI to investigate neural correlates of lower limb control with a foot-tapping task under IG and EG conditions in veterans with and without PD (Aim 1). Imaging studies have previously employed foot-tapping, which is used clinically to assess lower limb control. To achieve Aim 2, we will 1) evaluate the relative effectiveness of practicing IG movement (leading) versus practicing EG movement (following) versus a behavioral control (health education) for improved mobility and lower limb control, and 2) assess neural activity changes underlying improvements in lower limb control across training groups. The long-term goal is to optimize motor rehabilitative interventions for veterans with PD and understand the neural mechanisms through which the training is effective in order to further improve rehabilitation strategies for this and similar diseases.

Specific Aim 1: **Determine neural correlates of internally guided and externally guided foot-tapping in individuals with and without PD.**

Hypothesis 1: In healthy controls, IG and EG foot-tapping are related to task-specific neural networks of the striato-thalamo-cortical and cerebello-thalamo-cortical circuits, respectively. In those with PD relative to controls, IG foot-tapping will result in increased activation of both the STC (posterosuperior putamen, ventral anterolateral thalamus, rostral supplementary motor area, primary motor cortex) and the CTC (cerebellum (Larsell lobules IV, V, and VI), ventral posterolateral thalamus, primary somatosensory cortex, ventral premotor cortex) circuits. EG foot-tapping will result in increased activation in the CTC circuit only.

Specific Aim 2: Determine the effect, in individuals with PD, of internally guided versus externally guided training compared to a behavioral control on: 1) mobility, and 2) whether improved mobility and foot-tapping performance after training correlate with changes in activation and resting-state functional connectivity patterns in IG and EG foot-tapping networks.

Hypothesis 1: If mobility gains are related to training in planning and selecting movements, then those in IG will demonstrate greater improvements than those in EG or control. If mobility gains are related to exploiting cues during training, then those in EG will demonstrate greater improvements than those in IG or control.
Hypothesis 2: If improved IG foot-tapping performance and mobility (as determined in Aim 2, Hypothesis 1) are related to IG training and planning movement, then we will see IG training-related increased activation in the STC circuit and decreased activation in CTC circuitry. If improved EG foot-tapping performance and mobility are related to EG training and attending to cues, then we will see corresponding increased activation in the CTC circuit.
Hypothesis 3: Resting-state functional connectivity patterns will reflect training effects, with connectivity increases primarily in the STC circuit following IG training and in the CTC circuit after EG training; minimal changes will occur following the control intervention.

5. Study design and Methods

Overview*:* To accomplish Aim 1, we will use functional Magnetic Resonance Imaging (fMRI) to determine neural circuitry underlying IG and EG foot-tapping in 24 veterans with and 24 veterans without idiopathic, mild-moderate PD (Hoehn & Yahr stages II-III). To accomplish Aim 2, we propose a randomized controlled trial to evaluate the relative effectiveness of IG and EG movement to improve mobility in veterans with PD. We will also measure corresponding changes in neural activation during IG and EG foot-tapping, as a result of intervention. Participants will be randomized

to receive EG, IG or behavioral control (BC; health education) training over 12 weeks. Participants will be tested on all outcome measures while “OFF” and “ON” medications at a standardized time of day. We are observing participants in outcome measures while OFF medications in order to avoid dyskinesia, and medication fluctuations that may impact functional activity of networks of interest. Participants will complete outcome measure testing for mobility, QOL, executive function, procedural learning, spatial cognition, and foot-tapping 1 week before training (pre), and 1 week (post) and one month (follow-up) after completing all training. Using fMRI we will also investigate the relationship of changes in neural activation in the participants before and immediately after training.

Measures that will be used in screening and outcome assessments:

Descriptors

Health Screening: Participants will be screened for general health with the Project Health Questionnaire at the first testing session.

Vision: Measurement of visual acuity will be performed with Early Treatment for Diabetic Retinopathy Study acuity chart (ETDRS) at 3 m. Visual impairment will be determined as none (better than Snellen acuity 20/30), mild (between 20/30 and 20/60), moderate (20/60 and 20/200) or severe (greater than 20/200) in the best eye (World Health Organization ICD-10, 2006).

Hearing: All participants will be asked if they use a hearing aid, and if yes, the frequency with which they use it. Pure tone audiometry, using a GSI-61 Clinical Audiometer, will assess hearing sensitivity in an acoustically controlled environment (available at the Atlanta Rehab R&D CoE). Participants will be excluded if pure-tone threshold average sensitivity at 0.5, 1.0, and 2.0 kHz exceeds 40 dB.

Disease Severity: Participants with PD will be evaluated for disease severity at each evaluation with the Movement Disorder Society Unified Parkinson Disease Rating Scale (motor subscale III: UPDRS, Movement Disorder Society 2003) by a qualified and experienced rater blinded to study purposes

Mental Status: Participants will be assessed for mental status with the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005).

Handedness and Leggedness Inventory: Participants will self-report their handedness with the Edinburgh Handedness Inventory to help baseline their movements for analysis. This inventory will indicate whether the participant is dominantly right- or left-handed (Edinburgh Handedness Inventory: Oldfield, R.C., 1971). We will also use the Survey of Handedness and Leggedness (Schneiders, 2010)

Outcome Measures: Participants will undergo a comprehensive battery of motor, cognitive and psychosocial measures to evaluate the efficacy of the intervention. See table 2 for a summary of these measures, which are described in more detail below.

Calendar of Adverse Events: Participants will be given calendars and asked to keep track of ‘adverse events’, including falls and near misses. They will be asked about adverse events once per month, and at each evaluation. Their responses will be recorded.

Motor:

- **Six minute walk test** (6MWT; Guyatt et al., 1985). 6MWT is a valid and reliable measure of overall mobility and physical functioning in older people (Lord&Menz, 2002).
- **Single and Dual Timed Up and Go test** (TUG), (Morris S et al., 2001) - A measure of functional mobility, the TUG (Shumway Cook et al., 2000) has demonstrated validity and reliability. The participant is timed while they rise from a chair, walk 3 m as quickly as possible, turn around and return to the chair. Dual-task ability will be measured with the TUG cognitive (TUGc) and manual conditions (TUGm). In TUGc the participant counts backwards by 3s from a random number between 20 and 100. In TUGm the participant carries a full glass of water. Time ≥15 s for TUG-c and time ≥14.5 s for TUGm indicates impaired dual-task ability and increased fall risk. The PI noted improvements on this measure after adapted tango training within older adults with visual impairment, and in those with PD during piloted data collection completed in October 2011.
- **Four square step test-** clinical test of dynamic standing balance (Dite & Temple 2002). It involves stepping over low objects (2.5cm) and movement in 4 directions. The Four square step test has high sensitivity, specificity and predictive value for identifying differences between groups in a population of older adults.
- **30 second Chair Stand test**: Lower body strength is associated with the ability to perform lifestyle tasks such as climbing stairs, getting in and out of a vehicle or bath, and will be measured with the 30-s chair stand (chair stand) test 15, in which the participant rises from a chair to full standing as many times as possible in 30 seconds.

Postural control & Fall Risk:

- **Berg Balance scale** (BBS; Berg et al., 1995). BBS is a performance-oriented measure of fall risk and balance in older adults, consisting of 14 items rated from 0 to 4. Aim 2 is powered with a predicted 4-point improvement in the BBS because this measure was improved repeatedly to clinical significance in previous studies. The BBS has excellent inter- and intra-rater reliability (0.98-0.99) and a maximum score of 56 possible points
- **Dynamic gait index** (DGI; Shumway-Cook & Woollacott, 1995). 8 items, including walking while changing speed and turning the head, walking over and around obstacles, and stair climbing. DGI scoring is based on a 4-point scale from 0 to 3: 0 indicates severe impairment and a score of 3 indicates normal ability. A total score < 20/24 indicates risk for falling. The DGI has been shown to have inter-rater reliability of .96, test-retest reliability of .96.
- **Fullerton Advanced Balance scale** (Hernandez D, and Rose DJ, 2008). The FAB Scale includes items intended to better identify older adults who may be experiencing increased fall risk as a result of sensory system impairments.
- **Limits of Stability test and other tests of the Neurocom Equitest system** – Evaluated with Neurocom Equitest systems, this computerized posturography test evaluates stability limits in 8 directions with measures of maximum excursion and directional control. Adapted tango training will require participants to move their center of mass beyond their stability limits when stepping; therefore, we expect increased stability limits as a result of training.
- **Gait-** Spatiotemporal parameters of habitual (i.e., preferred, comfortable), backward and fast-as-possible walking will be assessed by a 6 m computerized GAITRite walkway (CIR Systems, Inc. Havertown, PA, USA). Variables of interest include velocity, stride length, and stride variability, which have been improved previously through adapted tango training.

<u>Psychosocial Function</u>

Depression- Two standardized, clinical measures of depression will be administered to all participants.

- **Geriatric Depression Scale-15** (GDS) will evaluate depression in oldest old adults, and has demonstrated high specificity, and predictive value for older adults (Yesavage et al., 1988).
- **Beck Depression Inventory II-** recommended by the American Academy of Neurology, and suitable for screening individuals with PD. A cutoff of 18 is reliable for distinguishing individuals with PD with significant depression.

Incontinence (self-report): ICI-Questionnaire-this questionnaires asks four questions pertaining to how often someone urinates during the day, during the night, whether they have a sudden urge to go to the toilet to urinate, and whether they experience leakage right after feeling that sudden urge. Participants are also asked to rate how much each occurrence bothers them on a scale of 0-10 (0 meaning not at all, 10 meaning a great deal).

Balance confidence: Activities-specific Balance Confidence scale (ABC; Whitney et al., 1998). This questionnaire is filled out by the participant and asks 16 questions related to confidence the participant would feel about "not losing their balance" in various life situations.

Quality of life:

- **Short Form -12-** a widely used measure of general health.
- **Life Space Questionnaire** (LSQ) (Stalvey et al., 1999), LSQ assesses the extent of an older person's mobility and is useful for evaluating interventions designed to enhance mobility.
- **Exit Questionnaire** – (administered only at evaluations occurring directly after completion of training). This non-disease specific instrument consists of items which ask whether the participant enjoyed the classes, whether they would continue, whether they notice improvement in various aspects of physical wellbeing, and a section for open-ended responses (Hackney et al., 2007a, 2007b, Hackney & Earhart, 2009a, 2009b, 2009c, Hackney& Earhart NNR, 2010, Hackney & Earhart, J Nerv Ment Dis, 2010). Standardized measures that capture the same constructs do not exist.
- For those with PD only, the following questionnaires will be administered:
    - **Freezing of Gait questionnaire**- subjective evaluation of perception of freezing of gait phenomenon in the previous week (Giladi et al., 2001)
    - **PDQ-39**- health-related quality of life measure for persons with PD that is validated and widely used.

Participation

- **Impact on participation and autonomy scale-** This is a self-report measure and includes multiple domains of participation along with a strong focus on an individual's autonomy in his/her choices for daily activity participation.
- **Physical Activity Scale for the Elderly**- This scale is an easily administered and scored research instrument that measures the level of physical activity in individuals aged 65 years or older.

<u>Cognitive function</u>

- **Brooks spatial memory task** -The participant is asked to visualize a 4x4 matrix in which the location of numbers 1 through 8 is described. Next, the participant is requested to repeat the numbers' location. Participants practice with three instructions and progress up to 8 instructions. All levels are completed regardless of errors in performance and percentages correct (out of 50) will be used for analysis.
- **Body Position Spatial Task**- We found no standardized measure of whole body spatial working memory, i.e., knowledge of spatial position and ability to navigate in a remembered path. Modeled after the Corsi Blocks [104], the PI developed this task. Instead of pointing to a spatial path of blocks, participants are asked to step in a spatial arrangement. The examiner verbally and visually demonstrates random combinations of 5 possible moves: step forward, step left, step right, quarter turn left, and quarter turn right. The examiner begins with 2 moves and progresses up to a maximum of 9 moves, (maximum correct: 16) with 2 trials per level. Participants continue to the next level if one trial is correctly performed. The test ends when participants miss both trials of a level. Span length and number of correct trials are considered for analyses.
- **Corsi Blocks task-** (Kessels et al., 2008), this is a standardized, valid and reliable test of visuospatial ability
- **California Verbal learning test** (to rule out other possible cognitive deficits not found by the MoCA)
- **Wisconsin card sorting test** (64 cards) (Kongs et al., Western Psychological Services) - This test will probe the effects of EG training because participants will be required to respond and alter their decisions based on cues. The following will be outcome variables: Perseverative errors (fewer errors indicate better ability of the patient to switch to a new concept); Failure to maintain set (fewer failures indicate better ability to sustain course of action); Number of sorts (greater sorts indicate better concept formation.)
- **Color Word Interference Test** (Delis-Kaplan Executive Functions System) - Based on the Stroop, this test of executive function and attentional flexibility will also be administered to test the effects of EG training, because participant needs to inhibit their own responses and examine carefully the message that is being given, in spite of sometimes misaligning information.
- **Tower of London**- This test of organizational planning and decision-making will be administered to explore the cognitive effects of IG training, because the test requires the participant to organize, and plan. We will use the Cambridge Neuropsychological Test Automated Battery-Tower Of London, because of impairments in individuals with PD.100 The participant will be shown two displays of three colored balls. The participant is required to rearrange the balls in the bottom half of the screen to match the arrangement in the top half of the screen. The outcome measures are: number of successfully completed problems, number of problems completed in the minimum number of moves and the total score.

Table 2 provides a synopsis of the measures used in this study.

Table 2: Outcome measures of motor, psychosocial and cognitive function

Motor function	**Instrument/scale**
Functional mobility, strength	6-Minute Walk Test; single and dual task Timed Up and Go, Four-square Step Test, 30 s Chair Stand test
Preferred, backward, fast gait	GaitRite walkway (CIR Systems)

Postural control/ Fall Risk	Dynamic Gait Index, Berg Balance Scale, Fullerton Advanced balance scale
Handedness	Edinburgh Handedness Inventory
Psychosocial function	**Instrument/scale**
Depression	Geriatric Depression Scale-15; BDI-II
Incontinence- self report	ICIQ
Balance confidence	Activities Balance Confidence Scale
Quality of life	Life Space Questionnaire, Incontinence IQ, Short Form 12 PD ONLY: PDQ-39; Freezing of Gait
Participants' program enjoyment/satisfaction (Immediately post-training only)	Exit questionnaire- Evaluates participant satisfaction with physical activity programming, (Hackney & Earhart, *in press*).
Self-report measure encompassing multiple domains of participation; a strong focus on an individual's autonomy in his/her choices for daily activity participation	Impact on Participation and Autonomy questionnaire
Participation in physical activity amongst older adults	Physical Activity Scale for the Elderly
Cognitive function	**Instrument/scale**
Spatial ability span	Brooks spatial working memory task (Brooks, 1967)
Body-position spatial ability span	Body position spatial task
Level achieved, trials completed	Corsi blocks
Verbal memory	California Verbal Learning test
Executive function, task switching, response to cues	Wisconsin card sorting test
Task switching, inhibition, attentional flexibility	Color Word Interference Test
Planning, initiation, procedural learning	Tower of London
Procedural learning	Serial reaction time task

Screening

All participants will be screened for general health with a Project Health Questionnaire. All procedures will be videotaped. We will screen for both PD-related and non-PD related impairments that could compromise the study's results. Therefore, while all outcome measures and scans will be performed in both the ON and the OFF state, mental status, sensory impairments, and depression will be

screened during optimal performance conditions: the ON state. However, we will assess disease severity in both ON and OFF states because some outcome measures could be confounded by antiparkinsonian medications. We will also assess disease severity before all outcome measure evaluations.

Mental status: We will exclude individuals with known diagnoses of dementia or vascular cognitive impairment, and screen for mental status with the Montreal Cognitive Assessment (MoCA)[74], which has been recommended by the Parkinson Study Group.[75] We expect to exclude some individuals who pass the MoCA yet have severe primary memory deficits, possibly because of a PD/Alzheimer's disease overlap. Therefore, we will also administer memory testing with delayed recall on the California Verbal Learning Test. [76] [77]

Disease Severity: A qualified and experienced rater, blinded to study purposes, will rate participants with PD for disease severity with the Movement Disorders Society Unified Parkinson Disease Rating Scale Motor Subscale III [77](UPDRS) in videotaped assessments. Participants must have Hoehn & Yahr staging II-III. Participants will be evaluated for disease severity with the UPDRS at the beginning of all evaluations. Participants will also complete the Freezing of Gait questionnaire, a subjective evaluation of perception of freezing of gait (FOG) in the previous week.[78] Participants will be considered "freezers" if they answer > 1 on item 3 of the FOG questionnaire, which indicates freezing frequency of more than once per week.[79]

Sensory impairment: To screen for sensory impairments that could affect movement, we will screen for peripheral neuropathy, vision and hearing. We will screen for **peripheral neuropathy** with the 5.07-10g Semmes Weinstein monofilament method and the vibration on-off method in a clean open space, using established criteria.[80] Participants will be screened for best corrected/aided **visual acuity** better than 20/70 in the better eye (World Health Organization International Classification of Disease-10, 2006); Measurement will be performed with intake screening & chart review. Dr. Hackney will administer the Early Treatment in Diabetic Retinopathy Study Acuity test. Given the role that auditory cues will play in both evaluation (scanning will employ an auditory cue) and treatment (tango dance employs music), we will also screen participants for adequate **hearing.**

Depression: Participants will be screened for untreated depression with the BDI-II, recommended by the American Academy of Neurology, and suitable for screening individuals with PD.[81] A cutoff of 18 is reliable for distinguishing individuals with PD with significant depression.[82] If participants are excluded for depression, but then receive treatment, they may be rescreened and considered for study recruitment.

Ongoing screening for fMRI: Participants will be screened with standard procedures for fMRI eligibility during an initial telephone screen. Then, before every scanning session, participants will answer a standard questionnaire to insure safety during the procedures and adherence to fMRI inclusion and exclusion criteria. Participants will be evaluated for disease severity with the MDS-UPDRS at the beginning of all evaluations.

Specific Aim 1: Determine neural correlates of internally guided and externally guided foot-tapping in veterans with and without PD.

Rationale: We will examine brain activity involved in internally and externally guided lower limb movement, in order to characterize circuitry, which we hypothesize will be targeted by the IG and EG training proposed in Aim 2. Adapted tango has been shown to improve gait and mobility measures;

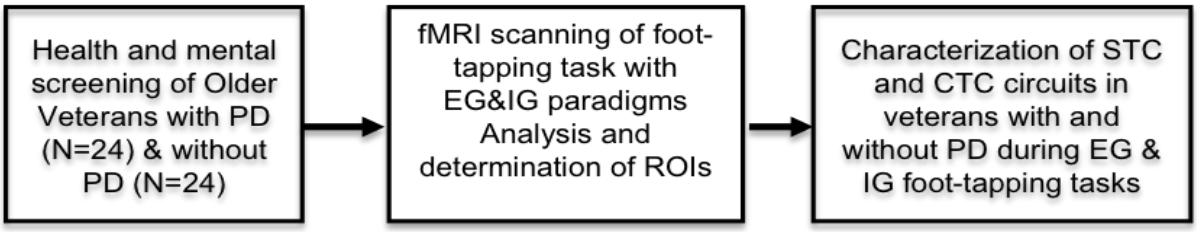
therefore, adapted tango should include the recruitment of neural systems of lower limb control. Foot-tapping involves lower limb control, and is an action that occurs in adapted tango training. Foot-tapping is also a measure of motor dysfunction on the UPDRS, and its circuitry has been investigated in fMRI studies of healthy controls [58] and individuals with PD.[85] However, lower limb neural control of circuitry involved in externally and internally guided movements is not well studied. As such, we will use foot-tapping to provide a window into brain activation during IG and EG lower limb movements. With Aim 1, we seek to identify circuits and structures involved in IG and EG lower limb movement, in veterans with PD in comparison to age-matched controls. We believe that IG and EG lower limb circuitry will have similarities to that observed with finger tapping tasks because Keele at al (1985)[59] demonstrated that finger tapping, forefoot tapping and heel tapping are highly correlated. Therefore, we **hypothesize** that during **IG tasks**, the STC (posterosuperior putamen, ventral anterolateral thalamus, rostral supplementary motor area (SMA), and primary motor cortex) will be activated in controls. During **EG tasks** the CTC (cerebellum Larsell lobules IV, V, and VI), ventral posterolateral thalamus, primary somatosensory cortex, and the ventral premotor cortex) will be more active relative to rest in controls. We predict that in PD patients, during IG tasks, both the STC and CTC circuits will be activated, while only the CTC circuit will be functionally activated during EG tasks.

Rationale for hypothesized areas within circuits during IG and EG tasks:

For **IG networks**, we expect to see activation in the following areas: the posterosuperior putamen, because dopamine depletion in PD most adversely affects this part of the putamen, which is also less functionally connected to important motor structures i.e., the rostral SMA, in individuals with PD relative to controls;[61] the ventral anterolateral thalamus because of its projections from the basal ganglia and because it is part of the IG network outlined by Lewis et al. (2007)[6] and Sen et al. (2010)[55]; the rostral SMA, because of its involvement in motor preparation and initiation[56], and its activation during foot flexion/extension [58]: the primary motor cortex, because of its activation during foot movements [58] and IG tasks in people with PD.[56]

For **EG networks**, we expect to see activation in the following areas: Larsell lobules IV, V, and VI of the cerebellum, because these areas were functionally activated during cued foot movement in controls [58]; the ventral posterolateral thalamus, because of its projections from sensory areas and cerebellar inputs, and because it is part of the circuit outlined by Lewis et al. (2007)[6] and Sen et al. (2010)[55]; the primary somatosensory cortex, for its involvement in cued movement, both tactile and visual, with its expected localization being medial for foot movement; the ventral premotor cortex, because of its involvement in decision making based upon somatosensory signals, [86] activity that mirrors the actions of viewed subjects,[87] and because of its response to externally cued stimuli.[88]

Specific Aim 1:
Experimental Plan

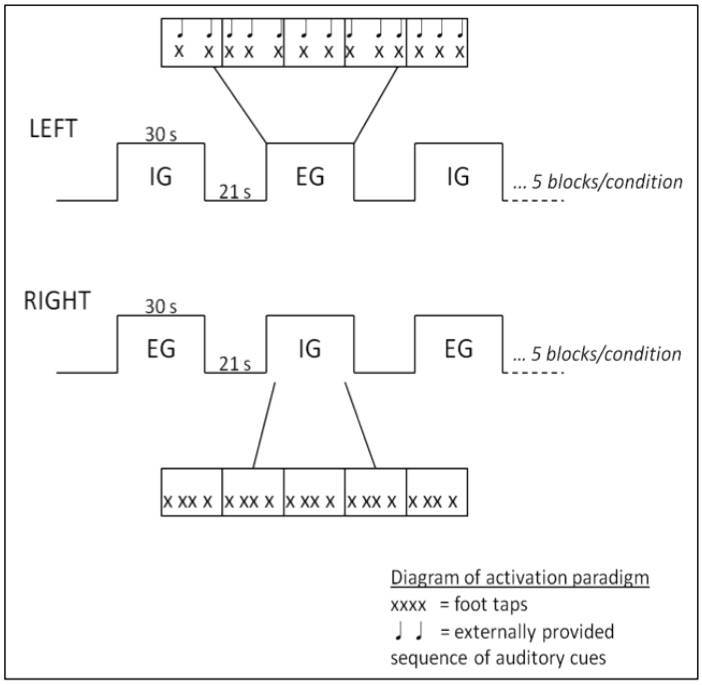


FMRI Data acquistion for Aim 1: 24 older veterans with PD and 24 veterans without PD will be scanned for approximately 1 hour inside the scanner. MR images will be acquired on a 3T Siemens Magnetom Trio TIM scanner with a 32-channel receiver array head coil. BOLD fMRI scans will be acquired with a conventional Echo Planar Imaging (EPI) sequence with Field of View (FOV) =220

mm, TR/TE/FA =2000 ms/24 ms/80°; forty-seven 3mm sagittal slices (no slice gap); 3mm x 3mm in-plane resolution, and band width of 2414 Hz/pixel; Parallel Imaging: GRAPPA factor 2, 24 phase encode reference lines. Prospective real-time motion correction [89] will be used with all EPI fMRI scans to minimize motion artifacts. A whole-brain 3D T1-weighted MPRAGE sequence (FOV=230 mm; TR/TI/TE/FA=2250 ms/900 ms/3 ms/9°; 0.9mm x 0.9mm x 1mm resolution) will provide anatomic detail. All scans will be acquired with parallel imaging: (GRAPPA; acceleration factor = 2; 24 (for EPI) and 36 (for MPRAGE) phase encoding reference lines). A Biopac (Goleta, CA) respiration belt and finger pulse oximeter will be used to acquire physiological waveforms time-locked to fMRI acquisition.

Activation paradigm design: Participants with PD will be scanned while ON and OFF their anti-parkinsonian medication at least 12 h after their last dopaminergic medication, a functionally defined "OFF"; [90] thereby maximizing the ability to see a therapeutic effect. Participants will spend about 1 h total in the scanner. The scanning protocol, including time spent in the scanner, will be clearly explained to all participants, and it will be verified that every participant fully understands and is prepared for the scanning procedure. Standard operating procedures for fMRI involves checking with participants throughout to make sure they are comfortable with scanning procedures and participants are removed from the magnet at any point should they require it. The experimenter or technologist will have frequent verbal contact with the participant throughout the scanning session to assure participant comfort.

For ~20 minutes, participants will perform IG and EG sequences of foot-tapping movements inside the scanner using established methods [85]. As such, the task will involve unilateral ankle dorsiflexion, to a maximum of 30º in a wooden apparatus with movements blocked by IG or EG condition. Participants will be provided foam padding and towels to restrain head motion. Participants'' knees will be flexed to approximately 135º with a soft roll under the knees. An assistant will verify task performance timing and amplitude, as well as monitor for synkinesia from the other limb. If the patient is unable to keep the other limb still, the data will be excluded. Based on pilot scans that we recently collected in 15 individuals with stage II and III PD, we expect 20% attrition for excessive head movement. However, these participants were scanned while ON meds, which generally increases the presence of dyskinesia. Because we will a) test participants OFF meds, b) screen for excessive head and lower limb tremor, and c) target recruitment in order to account for 20% attrition, we expect to retain a sample size that will allow us to detect effects and make meaningful comparisons. Ankle range of motion will be recorded with an MR-compatible potentiometer and amplitude will be averaged over each condition. Absolute timing error will be determined by the potentiometer also, by comparing the timing of every other change in acceleration, with the ideal timing sequence. Thus, the time course of changes in acceleration will be effectively considered the timing of the participants' taps. Error will be averaged from the accumulated absolute value of the tapping errors which either over- or under-shoot the ideal timing. Tapping will occur at a frequency of 0.5 - 2 Hz,



Activation paradigm: In 30 s EG blocks, participants will tap their feet in response to externally provided auditory cues. In 30s IG blocks, participants will tap their feet in pre-learned rhythms. 21 s of rest will occur between IG and EG blocks. There will be 5 blocks per condition

given that individuals with PD demonstrate marked tapping performance deterioration above 2 Hz, in terms of increased movement rate, decreased amplitude and loss of movement phase.[91]

IG and EG foot-tapping tasks: Before entering the scanner, participants will be given approximately 20 minutes to learn one of three unique, 6-s rhythmic sequences of IG and EG foot-tapping. These rhythmic sequences will be similar to those learned during both the IG and EG trainings, i.e., slow and quick beats arranged in different sequences to form differing rhythmic pattern (See "Adapted Tango"). In the EG condition, foot-tapping will be paced by auditory cues from MR-compatible headphones. In the IG condition, because the actual response rate will vary slightly by participant, we will quantify timing interval consistency based on each individual's tap-by-tap deviation from an established "ideal timing" rhythm that will be instructed before entering the scanner. We will determine each participant's average IG response rate (in taps/s) across all IG task blocks in the session, and then calculate the expected amount of time between sequential taps (quick or slow) based on this rate. We then will calculate the deviation from this expected tap time for each pair of sequential foot taps. Finally, we will average all deviations to determine the amount of variation there is in a participant's tapping pace within the scanning session.

In the scanner, participants will be asked to repeat the given foot-tap sequence continuously for 30 s/block. Sequence order will be counterbalanced across participants. IG and EG movement blocks of 30 s will alternate with 21 s of absolute rest. There will be 5 movement blocks and 6 rest blocks per foot, per condition (IG or EG). Both legs will be tested separately. See diagram illustrating the activation paradigm.

fMRI Data Preprocessing for SA1: Data will be processed using Statistical Parametric Mapping Software (SPM8; Wellcome Department of Imaging, Neuroscience, London, UK). Preprocessing steps include head motion correction, co-registration of functional and structural data within sessions, and co-registration of structural data across sessions. Each individual subject's structural and functional data will be spatially normalized to the SPM-standard T1 template, which is in Montreal Neurological Institute (MNI) space. Spatially normalized images will be smoothed with a 5mm full-width-at-half-maximum (FWHM) Gaussian kernel. Low frequency drifts will be removed with a temporal high-pass filter (0.006 Hz). The fMRI scans will be acquired with prospective real-time motion correction.[89] This sequence will correct for volume-to-volume (image-to-image) motion less than 3mm by updating the gradients real-time during scan acquisition. If for a given volume the residual motion after motion correction (estimated as the maximal voxel displacement by the image registration algorithm) is more than 3mm (one voxel dimension) that volume will be discarded during analysis and treated as missing at random (MAR) during statistical signal processing. If more than 10% of the volumes in the fMRI time-series have to be discarded due to the criteria mentioned above, the subject data will likely be discarded from analyses. In previous studies examining a similar foot-tapping task while OFF, PD head movement (0.46 mm ± 0.26 mm in either direction) was not much different from controls (0.56 mm ± 0.26 mm).[85] However, we will recruit for 20% attrition, to account for unsuitable data.

Specific Aim 2: Determine the effect, in veterans with PD, of internally guided versus externally guided training compared to a behavioral control on: 1) mobility, and 2) whether improved mobility and foot-tapping performance after training correlate with changes in activation and resting-state functional connectivity patterns in IG and EG foot-tapping networks.

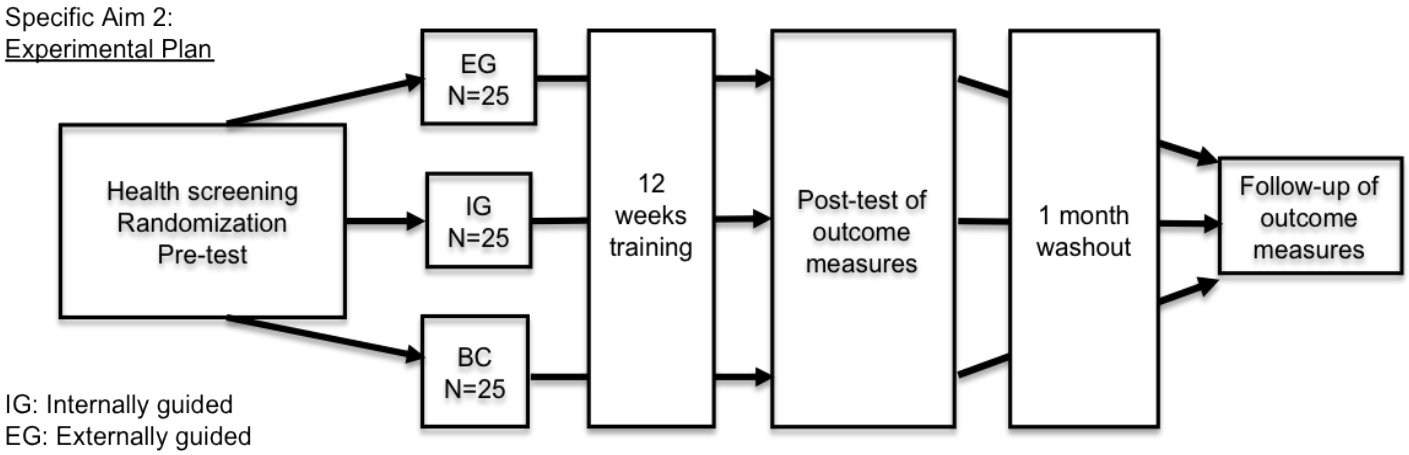
Rationale: As outlined in Background, there are differences in IG and EG training that may lead to distinct effects upon mobility; therefore, Aim 2 will tease out the relative effectiveness of IG and EG

adapted tango training for functional gains in mobility. Aim 2 will also determine whether improved mobility and foot-tapping performance after training correlate to changes in activation and resting state functional connectivity (RSfc) patterns in the IG and EG foot-tapping networks identified in Aim 1. Because we hypothesize that IG and EG adapted tango will target their respective foot-tapping networks, we expect improvements in each to correlate to changes in activation patterns in the corresponding network. Specifically, improved functional performance after IG training will lead to increased activation within the STC network while improved functional performance after EG training will lead to increased activation within the CTC network.

We will also determine how RSfc in the IG and EG foot-tapping networks is affected by training. A network perspective of PD is essential to understand the pathophysiology of the disease because the neurochemical alteration in the basal ganglia propagates throughout many dense striato-cortical connections, altering the activity in each successive brain region [61] and because the pathology is widely distributed. [94] RSfc MRI allows investigation of large-scale functional networks at whole-brain level based on temporal correlation of spontaneous fluctuations in the BOLD signal at a low frequency (<0.1 Hz). Few studies have used this technique to characterize network activity in PD. [61] Previous research has shown abnormal patterns of RSfc of motor planning in premotor areas and execution networks (motor cortex) in PD patients.[56 57 63 95] By scanning the same participants before and after training, we hypothesize that if we observe improved foot-tapping after IG training, we will see increased STC connectivity and if we see improved foot-tapping after EG training we will see increased CTC connectivity. We postulate no changes will be noted in IG and EG foot-tapping networks after training in the behavioral control group.

Participant Randomization for Aim 2

After screening and consent), participants will be randomized to one of three groups (IG, EG or the behavioral control (BC, Education)). Participants will not be blinded to treatment group, but the instructors of the interventions will be blinded to performance on all outcome measures, and raters of all functional performance measures will be blinded to treatment group. The PI will train raters, qualified research assistants, in proper administration of all measures.



Intervention: IG and EG training in adapted tango classes for participants with PD

Dosage: Participants shall receive 1.5 hours of progressive IG or EG adapted tango dance, or BC, a health education class 2 days/week for 12 weeks, with a goal of 20 completed lessons, in the Atlanta

VA Rehabilitation R&D Center's 41 ft x 34 ft Movement Studies Lab. To examine neural circuitry in conjunction with intervention, an effective dose of that intervention must be used, i.e., one with demonstrated improvements in mobility and balance via outcome measures of interest.[5] Twenty sessions were used previously and were effective at improving mobility (See preliminary studies). We expect 20 lessons over 12 weeks will provide enough therapy for both functional improvements to manifest as well as neurological changes to have occurred, because one month after training cessation, observations revealed maintained gains in the absence of treatment.[5] Thus, all participants must complete all 20 lessons to include their data in analyses. Participants will have ample opportunity to complete 20 lessons: there will be 4 lessons offered per week for 12 weeks (48 total sessions). If necessary, make up sessions will be offered. To date, we have experienced ~15 % attrition. Notably, in a recent pilot study in Atlanta examining intensive tango, there was 0% attrition.

Adapted tango: Composed of simple steps, tango involves frequent movement initiation and cessation, multi-directional perturbations and varied rhythms. Participants focus on trunk control and stepping strategies, coordination, somatosensory awareness, attention to partner, path of movement, and aesthetics. Sessions will begin with a typical dance class warm-up consisting of breathing, limbering and postural alignment to upbeat music. Novel step elements will be introduced every class period. Those with PD will partner with an individual without PD. After novel step introduction, the instructor will present rhythmic training, which is indispensable to partnered dancing. Participants will learn 'typical' rhythms from tango and Latin dances, based upon the system of quicks (Q) and slows (S), ubiquitously used in ballroom dance training to understand the temporal relationship of movement to music. Two quick beats equal one slow beat. Accompanying new rhythms to simple moves first allows transfer of the rhythm to more complex steps. Thus, the instructor will physically introduce rhythms by having participants clap, then tap a foot, then march in place and then walk to the rhythm.

In the last third of class, the new step of the day will be reviewed and added on to previously learned steps. We will maintain manageable class sizes (e.g., no more than10 pairs of participants with PD and partners) to maximize safety. Participants will dance with new partners (without PD) every 10 minutes, a widely practiced method designed to enhance learning in partnered dance lessons. Steps will be performed in an adaptation of the traditional ballroom frame, holding each other's bent elbows, maintaining forearms parallel to the floor. During the 20 classes, participants will be randomized to either IG or EG roles, i.e., to leading or to following. Leaders (randomized to IG group) will always dance as leaders, and followers (randomized to EG group) as followers.

Those in IG training will choose direction, timing and amplitude of each successive step. Those in EG will learn to attend to sensory cues for movement direction, timing and amplitude of steps, communicated from their partner to them via the frame and center of mass. Choreographic biomechanical patterns will be very similar between IG and EG training. The only difference between leading and following will be whether or not external guidance of movement is provided, after steps are learned.

The instructor and healthy assistants, trained in spotting techniques, shall carefully monitor all participants' safety. Participants will be encouraged to take regular breaks. Spouses, friends and caregivers will serve as dance partners. Also with methods used several times previously by the PI, student volunteers recruited from surrounding colleges and universities will serve as assistants and dance partners. The PI will educate student volunteers about PD- and aging-related posture and gait problems, proper assistance techniques to use for balance loss and methods for monitoring balance and anticipating falls.

Behavioral Control (BC) Condition: Participants will attend group health education sessions as per Wolf et al., (1996)[96] adapted to the needs and interests of individuals with PD. They will engage in

interactive small group, large group and partnered learning. Discussion will be greatly encouraged. Emory medical students as well as experts from Emory School of Medicine and other local universities or organizations will present information. Student volunteers will participate in these sessions by moderating the lectures, assisting with the presentation of information and leading discussions. Participants in this training will be instructed not to change their habitual exercise routines. After completing health education, participants may be assigned to an IG or EG training class but will not undergo evaluations.

Outcome Measures of Functional Performance (Aim2, Hypothesis 1):
Measures of motor function, PD QOL and explanatory measures of executive function, procedural learning, and spatial cognition will be conducted at evaluations (pre, post and 1 month follow-up). All evaluations will be performed in the safety-monitored Movement Analysis Laboratory at the Atlanta VAMC. All outcome measures will be directly measured with an instrument or self completed by the participant, except for BBS and other scales judged by a trained rater, which will be videotaped for a blinded and qualified rater (e.g., trained physical therapy students or research assistants) not involved with the project otherwise.

Primary measure of motor function: The Berg Balance scale (BBS) [97]

Secondary measures of motor function
- **Fullerton Advanced Balance test**
- **6 minute walk test**
- **Single and Dual Timed Up and Go test** [99]
- **Limits of Stability test**
- **Gait**- assessed with a 6 m computerized GAITRite walkway (CIR Systems, Inc. Havertown, PA, USA).

Explanatory variables
Participant QOL and satisfaction with program
- **PD Questionnaire-39 (PDQ-39)Exit Questionnaire** – (administered only at post-test within one week of completion of training). [3-5 36-38 70]

Executive function, procedural learning, and spatial cognition
We will investigate aspects of executive function, procedural learning, and spatial working memory to characterize more effectively the therapy's impact. The following cognitive measures are explanatory evaluative instruments: **Executive function:** Three standardized tests of executive function will be used:
- **Wisconsin card sorting test (64 cards)** (Kongs et al., Western Psychological Services)
- **Color Word Interference Test** (Delis-Kaplan Executive Functions System)
- **Tower of London**- from Cambridge Neuropsychological Test Automated Battery-Tower Of London, because of impairments in individuals with PD.[100]

Procedural learning: Procedural learning will be used as a predictor for those who will benefit more from EG training, which makes use of automatic processes already learned. Procedural learning ability will be measured with the **Serial Reaction Time Task**,[101]. Procedural learning becomes more impaired with disease progression. [102]

Spatial Cognition*:* Remembering spatial patterns and relationships to others is essential in dancing, and true of both IG and EG training The **Body Position Spatial Task** and **Corsi Blocks** test (previously described) will be also used as tests of spatial ability.

If we note improved cognition in conjunction with mobility improvement in both IG and EG groups, future studies will investigate neural areas related to the particular construct with fMRI. If we note cognitive improvements in one type of training, but not another, we will have additional information related to mechanisms by which particular forms of training are effective.

Procedures and Outcome Variables of Aim 2, Hypotheses 2 and 3:
The same fMRI data acquisition, activation paradigm and preprocessing procedures, outlined in Aim 1, will be used for participants in each of the IG, EG and BC groups to determine BOLD activation (Hypothesis 2) while performing IG and EG tasks. We will also perform RSfcMRI data acquisition and preprocessing (Hypothesis 3), detailed here:

Resting state functional connectivity MRI procedures: At each scanning session, we will collect approximately 9 minutes of fMRI data from participants as they rest quietly in the scanner. Participants will be provided foam padding and towels to restrain head motion, while they look at a gray screen. They will be instructed to keep their eyes open, not to think of anything in particular, nor to fall asleep. Examiners will monitor the participants' eyes in a mirror and prevent them from falling asleep. We plan to compare changes in RSfc of the STC and the CTC pathways before and after IG and EG partnered training. The particular regions examined will be determined through analyses conducted on imaging data collected in Aim 1. We will also investigate whether these changes in functional connectivity correlate with improvement on the UPDRS and on IG and EG foot-tapping.

Resting State Functional Connectivity Image Data Preprocessing for Aim 2, Hypothesis 3:
RSfc data will be preprocessed to correct for head movements, linear drift, and physiological noise (pulse, respiration) and will be normalized to standard space. It is likely the first 8-10 scans will be discarded to account for saturation effects and for adaptation of participants to a novel situation. The RETROICOR algorithm will remove physiological noise arising from main frequency peaks of cardiac and respiratory fluctuations.[105] Cardiac and respiratory function will be monitored with a photoplethysmograph on the left index finger and a respiratory belt around the abdomen. BOLD signal changes arising from low frequency fluctuations of cardiac and respiratory waveforms will be detrended using established methods. [106] The physiological noise corrected data will be low-pass filtered (cutoff frequency: 0.1 Hz) to further isolate low frequency resting state BOLD fluctuations.[107]

Potential Pitfalls/Alternative Approaches

1. If no differences are noted between IG training and EG training on outcome measures, but results match those of the original therapy [3-5], we will know that leading and following alone are likely as effective as the original dual, (interdigitated) IG/EG training for improving mobility. To inform motor rehabilitation, we will then suggest patients and providers have a choice of training type: follow cues, or plan and self-initiate movement. As we are not directly observing a dual IG-EG form of training in comparison to EG and IG, observed in isolation, we cannot determine whether EG or IG is better than dual IG-EG. Switching between leading and following in dual training demanded 'set-switching', impaired in individuals with PD.[22 23] Future Merit proposals will examine the effects of set-switching on neural pathways, and conduct a definitive comparison of IG, EG and dual IG/EG training, by building on data gained from this project. An alternative approach is investigating sequential forms of treatment, i.e., IG then EG training, and comparing the cumulative effects to training in isolation. If, as predicted by our

hypotheses, connectivity patterns do reflect training effects, with connectivity increases primarily in the STC circuit following IG training and in the CTC circuit after EG training, then both circuits may need to be upregulated therapeutically. Future studies will determine optimal doses of each to make evidence-based guidelines for therapy.

2. While hand movement neural activity is relatively well studied, far less is known about brain activity of foot movements.[58] We are making assumptions about brain activity in foot movements based upon hand literature. Given that the foot and hand differ in localization of representation in the sensorimotor cortex, [109] foot cortical control may differ fundamentally from that of the hand. Future work via the VA Merit system will more definitively characterize lower limb motor control, in conjunction with motor training for veterans with PD.

3. This project is novel in key domains: 1) the investigation of foot-tapping in IG and EG paradigms in PD is novel; 2) investigating IG and EG training effects on mobility and especially cognition is novel; 3) changes in neural activation in conjunction with training will be examined for the first time. Based on information we gather from this study, in the future we will conduct targeted studies to continue investigating cognitive differences and changes in neural activation between groups.

4. Future investigations will more definitively investigate what form of training, IG or EG, is best at a particular stage of disease, and for individual patients with particular symptomatology.

Risk to Subjects

Sources of Materials: For blinded ratings and patient confidentiality, all measurement data will be coded. Patient records will be stored in a locked cabinet in a locked office and will be accessible only to the PI. Computer-based records will be maintained on a secure network with password protection. Collection, analyses and use of these data will be exclusively for research purposes.

Potential Risks:

Risk of breach of confidentiality: One risk of participating in this study is the chance of a breach of confidentiality. **Protection against risk of breach of confidentiality:** The study team will try its best to prevent this by coding all measurement data. Patient records will be stored in a locked cabinet in a locked office and will be accessible only to the Principal Investigator at the Atlanta VA Medical Center. Computer-based records will be maintained on a secure network with password protection at the Atlanta VA Medical Center. Collection, analyses and use of these data will be exclusively for research purposes. Videotapes of each trial will be available only to study personnel and kept in a file cabinet in a secure office at the Atlanta VA Medical Center. Permission to share video images and/or use these images as part of professional/scientific presentations will be obtained during the informed consent process.

Protection against risk of breach of confidentiality with fMRI data:

Neuroimaging Core Facilities: The Emory Neurology Department (in coordination with the VAMC) has dedicated approximately 700 sq ft of space for a functional neuroimaging laboratory called the Brain Imaging, Rehabilitation and Cognition (BIRC) Laboratory under the direction of Dr. Bruce Crosson (mentor/co-investigator). For data housing and analysis, the lab contains a high capacity (20

terabyte) storage system as well as 5 multi-processor Linux data analysis workstations, all of which reside on a private gigabit ethernet network within the Emory domain. Only *approved VA personnel* are allowed to access this data, as it is administered and maintained by the VA Rehabilitation R&D Center of Excellence in Atlanta. Data security is maintained through need-only permissions and access control, while secure, encrypted backups maintain integrity and longevity of datasets. Importantly, all data will be *non-identified and scrubbed of all 18 HIPAA identifiers.* All servers are housed in secure server rooms, monitored 24x7 by electronic video and security personnel. Dr. Bruce Crosson will offer mentorship on this project and will give Madeleine Hackney, the PI, unfettered access to lab resources. While completing the proposed research study, Dr. Hackney will complete fMRI analysis at the neuroimaging lab and have the benefit of the use of its testing rooms, technicians and data storage capabilities.

Physical risks: Physical activity interventions for PD-related motor impairments pose minimal risk of fatigue, and the possibility of delayed onset muscle soreness. However, previously we have not had complaints or reports of soreness resulting from physical activity associated with partnered dance programs for people with PD, for older frail adults with low vision, or for those with mental illness. The intervention to be employed, adapted tango, has previously been demonstrated to be effective at reducing fall risk as measured by a standardized balance scale, but all efforts will be made to ensure the safety of participants. Every participant will be frequently encouraged and reminded to take breaks *ad libitum* during testing and classes. Also, during all testing and classes, the PIs, the teacher trainees and trained assistants will continually monitor participants for: fatigue, instability and other reasons for discontinuing evaluations or training.

Plans to minimize adverse physical sequelae during the intervention:

The following procedure, which was previously successful with other dance interventions for people with PD and oldest-old adults with low vision will be employed to minimize risk of falls and ensuing physical sequalae:

During classes participants will be continually monitored by the teacher trainee and trained assistants for fatigue and instability. The trained assistants will be instructed that their primary purpose is to prevent falls or other adverse events. Furthermore, to avoid accident outside of the class time, participants will be instructed not to practice the dance steps they learn at home or elsewhere outside of the class. Participants will be instructed to practice dance steps only when supervised by the instructor and assistants. Participants will be asked about their fall history at each observation, monthly during the intervention and all events will be documented.

Plans to minimize risks during Imaging:

No one with deep brain stimulator implants will be allowed to participate in imaging.

The risks associated with the imaging procedure are the same as those associated with conventional MRI. Specifically, movement or heating of metallic implants is a potential risk, and so subjects will be extensively screened to exclude people with metallic implants, fragments, or pacemakers. Some individuals experience claustrophobic reactions in the scanner. Subjects will be informed of this prior to the study, but because it is difficult to predict who will have such a reaction, this is not a specific exclusion criterion. During the scans themselves, any subject experiencing claustrophobia will be removed from the scanner immediately. There is no invasive component to this study; therefore, discomfort, bruising, and/or infection are not risks.

There may be additional risks associated with scanning at 3T, which we address:

Effect of the static field: The FDA has approved for routine clinical use, scanners up to 4.0 T. The system that we will be using is FDA approved. There is no conclusive evidence for irreversible or hazardous bioeffects to acute, short-term exposures of humans up to 2.0 T (Shellock and Kanal, 1996). Studies have indicated some side-effects at 4.0 T, namely unusual sensations including nausea, vertigo, and metallic taste (Schenck, 1991). However, there is no evidence that this is either irreversible or harmful. If subjects experience unusual sensations, they will be withdrawn.

Effect of the gradient field: MRI operates by rapidly changing small additional fields, called gradients. By Faraday's induction law, a changing magnetic field will induce electrical currents in any conductor. Thus, rapid cycling of the gradient field can induce peripheral nerve stimulation. However, this is not substantially different at higher magnetic fields since the gradients are separate from the main magnet. Should participants experience peripheral nerve stimulation (e.g., tingling or twitching), the principal investigator and staff will withdraw the participant from the study.

Effect of the RF electromagnetic field: The fundamental principle of MRI is that protons are excited by sending in an RF pulse at their resonant frequency for the magnetic field. The FDA provides guidelines for the safe use of MR systems, which includes specific recommendations for how much RF power is safe. They use the "specific absorption rate," or SAR. The SAR is the mass normalized rate at which RF power is coupled to biologic tissue and is typically indicated in units of watts per kilogram (W/kg) (NRCP, 1986). The FDA provides recommendations for two alternative safe levels of exposure to RF energy during MR procedures, primarily to control the risk of systematic thermal overload (heating) and local thermal injury. These are (FDA, 1988):

(a) The exposure to RF energy below the level of concern is an SAR of 0.4 W/kg or less averaged over the body, and 8.0 W/kg or less spatial peak in any 1 g of tissue, and 3.2 W/kg or less average over the head;

OR

(b) The exposure to RF energy that is sufficient to produce a core temperature increase of 1 deg C and localized heating to no greater extent than 38 deg C in the head, 39 deg C in the trunk, and 40 deg C in the extremities, except for patients with impaired systemic blood flow and/or perspiration.

We will adhere to the recommendations for the head, which is also monitored by Siemens' built-in monitor.

Potential Benefit to the Subject and Others:

Given great personal and financial costs of PD-associated movement and balance deficits, strategies are clearly needed to address these impairments. With the guidance of a partner, an individual without PD, individuals with PD may be afforded the ability to focus on key aspects of mobility- dynamic and static postural control, while expanding their motor repertoire. Participants and their caregivers may enjoy taking part in the intervention. If an intensive adapted-tango therapy improves physical function and quality of life in persons with PD, it could decrease fall risk, and reduce the associated injury and mortality. There is little information about cortical and sub-cortical changes in neural activity in those with PD that may accompany improved function resulting from

rehabilitative modalities. This study will be a first step in obtaining crucial information about brain activity during lower limb function, and plastic adaptations resulting from rehabilitative modalities in individuals with PD.

Importance of Knowledge to be gained:

PD affects approximately 1 million Americans, 90% of which are older than 60 years. As the US population ages, cases of PD are predicted to nearly double by 2030 (Dorsey et al., 2007). Persons with PD have a 3.2 fold greater hip fracture risk than those without (Melton et al., 2006). The cost of care for hip fractures in PD is approximately $192 million per year in the United States alone (Melton et al., 2006). Quality of life issues are at stake. This work proposes to illumine information about brain function that is crucial to continued progress in rehabilitative care of those with Parkinson Disease. The pilot study and hypothesis-generating experience gained from this pilot work has the potential to impact greatly care and quality of life of older persons with and without PD.

Relevance to Health Issues: There are extreme personal, financial and social costs associated with falls in older adults and PD in the US. However, increased physical and social activity can lengthen the span of robust function in older adults and those with PD. Results from this project will contribute to improved management of care for those with PD through enhanced knowledge about brain function during lower limb movement.

6. Participant Selection

Recruitment and Informed consent:

Recruitment: We will recruit 140 adults aged 40-85, with PD stages II-III and 24 age-matched controls*.* Individuals without PD (controls) will be recruited from the Atlanta VAMC RR&D CoE's registry, the VA's VINCI database, as well as at senior living communities with whom the PI has a relationship. All patient information will be stored on VA secure servers (room 3A 105) of the Atlanta VA Medical Center. Only authorized study team members will have access to this information because it will be stored on a private directory with limited access and password locked file.

We will request a partial HIPAA waiver to identify potential participants for recruitment purposes from IRB and related approvals from the local VA R&D committees. We will then obtain a list from the VA Movement Disorders clinic including patients likely to have a PD diagnosis, and send them a letter, with the director's signature informing them about the study. Drs. Marian Evatt and Stewart Factor, among others, will assist. A follow-up call will be placed within two weeks of the veteran likely having received the letter. A telephone screen will determine eligibility for participating in fMRI. Also, study fliers will be posted in the medical center and a PowerPoint slide ad will be broadcast throughout the medical center closed circuit TV system, such that veteran self-referrals are possible. To aid recruitment efforts, the PI will initiate meetings with community providers to explain the research goals, and request them to send a letter describing the study to patients who may qualify and have interest. The PI and staff will also visit PD community support and educational groups to present information to potential participants. Specifically, the PI will present information about the study to potential subjects at the 10+ support groups meeting monthly, organized by the GA chapter of the American Parkinson Disease Association and other PD organizations. The PI will also draft information about the trial to be included in the APDA and other PD organizations' newsletters and informational material, as well as the Michael J Fox, foxfinder website for clinical trials in PD.

Though all efforts will be made to recruit from the veteran population served at AVAMC, to meet recruitment goals, it may be necessary to extend recruitment to non-veterans or veterans served by the Emory healthcare system. If so, we will then obtain a list of names from the Emory electronic Medical Records (EeMR) database that includes patients with a diagnosis of idiopathic PD,

and will then send a letter from a staff neurologist at the Movement Disorder program and Emory Movement Clinic, Emory School of Medicine. A follow-up call from the PI will be placed after the letter is likely to have been received by the subject (e.g., 10+ days after sending the letter). With IRB approval, the Emory Movement clinic will include this trial in a "pocket list" of trials for persons with PD.

Informed consent: The Emory University IRB and the VA R&D committee will approve the consent form and all recruiting materials. After being screened on the telephone for eligibility to participate in fMRI, interested potential participants will be invited to the Atlanta VAMC Rehab R&D center. To reduce veteran burden, transportation will be provided for all subjects to and from evaluations. At the first visit, the PI will present information about the study to potential participants with an approved script. In a private room devoted to research, subjects will give informed consent after the PI provides an overview of the study's protocol, associated risks and benefits and subjects have given a verbal summary demonstrating they understand study requirements. At recruitment, study procedures for the fMRI component (Aims 1 & 2) and/or the intervention component (Aim 2) will be explained in great detail. All participants' questions will be answered. Subjects will be given a copy of the consent. Participants will not be excluded for race, ethnicity or sex and will reflect the makeup of metro Atlanta.

Human Subjects Involvement and Characteristics:

Participants: Participants will be individuals age 18 - 85 with and without PD from the Atlanta VAMC as well as other communities. During fiscal year 2010, 500 veterans with PD were seen at the Atlanta VAMC and satellite clinics. As VA funded research is conducted for the benefit of veterans, we will prioritize their recruitment by first exhausting all available means by which we can identify, approach and recruit veterans for this study. After we exhaust all possible resources to recruit veterans with PD, we anticipate extending recruitment to university based movement disorders clinics and community clinics. We will do so because we intend to recruit 140 participants with PD, and 40% will be women, which reflects female representation in the PD population.[71] The greater Atlanta region had 650,000 people age 55 and over in the 2000 US Census (US Census Bureau). As the older population is expected to double by 2015, and given a PD prevalence of 1.5% of the population age 65 and older, we estimate there to be more than 4000 people with PD in the greater Atlanta area. Emory University, the Atlanta VAMC affiliate, has a Movement Disorders unit that follows more than 2000 patients with PD each year.

We are targeting those aged 40-85 with stages II and III. Forty is the upper limit for young onset PD,[72] which will effectively insure that we recruit individuals with idiopathic PD only. Eighty five years is an upper age limit because of vascular, hemodynamic, morphometric and neural changes with aging.[73] A prior study conducted by the PI involved 78 individuals with PD, 70% of whom were under the age of 70 and 83% were stages II-III [18], which suggests that our intended recruitment for an intervention will be attainable.

Table 4: Inclusion/Exclusion Criteria for All Participants (Controls and those with PD)

Inclusion	Exclusion
• Age 18 - 85 years	• Deep brain stimulator implants, Metallic implants, fragments, or pacemakers
• Willingness to spend 1-h in a scanner	• MoCA score < 21
• Able to walk with or without an assistive device ≥10 feet	• Pure-tone threshold sensitivity > 40 dB

• Best corrected/aided acuity better than 20/70 in the better eye	• Peripheral neuropathy
• Absence of dementia or vascular cognitive impairment	• Untreated Major Depression
• Absence of primary memory deficits	• History of stroke, or traumatic brain injury

Inclusion/Exclusion Criteria for Participants without PD (Controls): In addition to the criteria noted in table 2, these participants must not have PD.
Inclusion/Exclusion Criteria for Participants with PD: In addition to the criteria noted above in Table 2, **participants with PD** must have clinical diagnosis of "definite PD",[83], based upon established criteria,[84] and must have presented with asymmetric symptoms that included at least 3 of the cardinal signs of PD (rigidity, bradykinesia, tremor, postural instability). Each PD participant also must show clear symptomatic benefit from PD medications, e.g., levodopa.

7. Statistical Analyses

Power Analysis for Specific Aim 1: We anticipate that 20 participants in each group (total n=40) will be necessary to detect an adequate effect size at 80% power based on studies conducted to determine reasonable sample sizes for fMRI studies.[92] Twenty-four participants per group will be recruited to accommodate 20% attrition. Analysis of variance (ANOVA) will be used to determine and distinguish circuits involved in IG and EG foot-tapping networks in participants with and without PD. The ANOVA will be sensitive to between subjects effect sizes of f=0.45 (F1, 38= 4.098), with a power of 0.80 at α=.05.

Statistical Analysis Plan for Aim 1

- **Participant characteristics**: Descriptive statistics will describe groups, including disease severity and duration for those with PD. T-tests will compare means (e.g., age, mental status) of participants with and without PD. Data analyses will be completed in SPSS (v. 19).
- **Functional performance measures:** Foot-tapping absolute timing error and average amplitude will be compared between groups with t-tests. These measures will also be correlated to fMRI data.
- **fMRI Brain Activation Analyses:** Following preprocessing and normalization to standard space, activation maps for the IG and EG tasks versus rest will be determined for each subject on a voxel by voxel basis. Regressors of interest will model IG and EG blocks of foot movement for each limb separately. Head motion parameters will be included as additional regressors. A similar approach has been used previously in PD.[85] First level contrast maps (betas) for the IG and EG tasks versus rest derived in each subject will be submitted to a second-level, random-effects analysis with subject as a random factor. Second-level t-maps will be thresholded at $p < .05$, corrected for multiple comparisons using the false discovery rate (FDR) method.[93] These activation maps will be used to define circuitry for IG and EG foot-tapping. Average percent signal change for the IG and EG tasks (relative to rest) for each participant will be extracted from the centers of gravity of the activated regions and submitted to hierarchical regression analyses to determine whether they correlate with behavioral measures (absolute timing errors and average amplitude of foot-tapping). Disease severity and duration of illness will be covariates for individuals with PD. **The primary outcome measure will be average percent signal change** for the IG and EG tasks (relative to

rest) to determine and distinguish circuits involved in IG and EG foot-tapping networks in participants with and without PD.

Power Analyses for Aim 2

Hypothesis 1: Power calculations for Aim 2 are based upon an assumed 4-point improvement and effect sizes > 0.8 on the BBS after 12 weeks of adapted tango, which was attained previously (see Preliminary Studies), and the minimal detectable change on the BBS in parkinsonism is 2.84 points.[68] Therefore, with a total sample size of 63 participants (21 participants in each of 3 groups: IG, EG, and BC) a repeated measures (RM) ANOVA with 3 levels of repeat will be sensitive to between-within interaction main effect size of f(v) = 0.44 ($F_{4,114}$= 2.45) with a power of 0.80 at α=.05**.** Post hoc sensitivity to effects between groups will be d = 0.90, and within groups, d_z = 0.65. To reflect an anticipated 20% attrition, we will recruit an additional 4 participants per group. Thus we will recruit 25 participants per group, for a total of 75 individuals with PD recruited for Aim 2**. Hypothesis 2:** 25 participants per group will be sufficient to detect effects for the imaging (activation and resting state) components of Aim 2 as well, based on studies conducted to determine reasonable sample sizes for fMRI studies,[92] that demonstrate at least 20 participants in each group are necessary. **Hypothesis 3:** Differences in RSfc have been noted between different groups of individuals with PD in sample sizes of 16 per group;[63] therefore, with 25 individuals per group, we will be able to detect differences between groups.

Statistical Analysis Plan for Aim 2, Hypothesis 1, 2 and 3:

- **Participant demographics:** Descriptive statistics will characterize groups. One-way ANOVA will determine differences, if any, between groups on baseline measures.
- **Behavioral Outcome measures:** A 3 group (IG, EG, BC) x 3 time (pre, post test, follow-up (1-month later)) RM ANOVA will be used to detect main effects. Appropriate post hoc tests will be used to determine within- and between-group differences, p<0.05, for **BBS, the primary outcome** measure upon which Aim 2 is powered. Statistical tests run on all secondary variables will be corrected for multiple comparisons.
- **Brain Activation Analyses for Aim 2, Hypothesis 2:** Similar to Aim 1 procedures, average percent signal change for IG and EG tasks (relative to baseline) for each participant will be extracted from the centers of gravity of the activated regions and submitted to hierarchical regression analyses to determine whether they correlate with behavioral measures (foot-tapping absolute timing errors and average amplitude). Disease severity and PD duration will be covariates. To determine the effects of time and training status we will submit the percent signal change to a 3 group (IG, EG and BC) X 2 time (pre, post) RM ANOVA. Post-hoc analyses will be corrected for multiple comparisons. The **primary outcome** will be t-contrast maps and effect size maps from ANOVA, which will be evaluated for changes in STC and CTC circuits.
- **Brain Connectivity Analyses for Aim 2, Hypothesis 3**: In Aim 2, Hypothesis 3, we will examine RSfc for increases or decreases as a function of training type and evaluate changes for correlations with improvement on behavioral outcomes. We will use regions of interest ROIs) informed by IG and EG foot-tapping fMRI analyses in Aim 1. Seed ROIs will be 10mm spheres around centers of gravity of clusters of activation in the group level activation maps for IG and EG foot-tapping, in STC areas (posterosuperior putamen, ventral anterolateral thalamus, rostral SMA, and primary motor cortex) and CTC areas (cerebellum Larsell lobules IV, V, and VI, ventral posterolateral thalamus, primary somatosensory cortex, and the ventral premotor cortex). Seed ROIs gained from the foot-tapping task provide one path of inquiry into neural network changes that may occur after training. As RSfcMRI analyses can be extended to other important areas of brain function, we will also use behavioral measures, which may have changed (e.g., spatial

cognition) to determine other ROIs for interrogation of changes in RSfc. For all participants, we will use Pearson's correlation (*r),* to correlate the time series from the seed ROIs with the time series of all other brain voxels. R-maps will undergo Fisher's r to z transformation and will be entered into a 2nd level random effects analysis for between group comparison using one way ANOVA in SPM8. T maps will be thresholded at p<.005 (Z>2.6). Correction for multiple comparisons will be carried out at cluster level according to random fields theory.[108] Age will be a nuisance covariate in all statistical analysis. To account for head motion-related spurious differences in functional connectivity levels, a nuisance regressor based on the total amount of movement will be included in the design. To determine the effect of time and training status on each group, the z scores will be submitted to a 3 group (IG, EG, BC) x 2 time (pre, post) RM ANOVA. Post hoc analyses will be corrected for multiple comparisons. The **primary outcomes for Aim 2, Hypothesis 3** will be changes in average connectivity strength across STC and CTC circuits, as measured by average cross correlation coefficient between the seed regions of the circuits.

8. Adverse Event Reporting

All adverse events will be immediately reported to the IRB and VA Review committees following the guidelines for reportable events and using the Reportable Events Form on the eIRB website.

9. Data and Safety Monitoring plan

Data Management

Safeguards are established to ensure the security and privacy of participants' study records. The information collected from participants in this study has a low potential for abuse, since the data do not address sensitive issues. Nevertheless, appropriate measures are taken to prevent unauthorized use of study information. For blinded ratings and patient confidentiality, all measurement data will be coded. Patient records will be stored in a locked cabinet in a locked office and will be accessible only to the PI, and patient recruiter at the Atlanta VA Medical Center. The files matching participants' names and demographic information with research ID numbers are kept in a separate locked room and are stored in a locked file that uses a different key from that of all other files. Computer-based records will be maintained on a secure network with password protection. Only study personnel have access to these files. All data, collected at any location, will be fully de-identified. Collection, analyses and use of these data are exclusively for research purposes. Regular meetings will be held with research assistants to review accrual, data entry, and examine the database for outliers or database entry errors. After the study is completed, procedures for long-term storage of VA data will be followed.

Neuroimaging Core Facilities: The Emory Neurology Department (in coordination with the Atlanta VAMC) has dedicated approximately 700 sq ft of space for a functional neuroimaging laboratory,the Brain Imaging, Rehabilitation and Cognition (BIRC) Laboratory under the direction of Dr. Bruce Crosson (mentor/co-investigator). For data housing and analysis, the lab contains a high capacity (20 terabyte) storage system as well as 5 multi-processor Linux data analysis workstations, all of which reside on a private gigabit ethernet network within the Emory domain. Only *approved VA personnel* are allowed to access this data, as it is administered and maintained solely by the VA Rehabilitation R&D Center of Excellence in Atlanta. Data security is maintained through need-only permissions and access control, while secure, encrypted backups maintain integrity and longevity of datasets. Importantly, all data will be *non-identified and scrubbed of all 18 HIPAA identifiers.* All servers are

housed in secure server rooms, monitored 24x7 by electronic video and security personnel. Dr. Bruce Crosson will offer mentorship on this project and will give Madeleine Hackney, the PI, unfettered access to lab resources. While completing the proposed research study, Dr. Hackney will complete fMRI analysis at the neuroimaging lab and have the benefit of the use of its testing rooms, technicians and data storage capabilities.

MRI systems reside at the Emory Wesley Woods Center for Systems Imaging with which Dr. Hackney will have access due to her academic affiliation with Emory University. The MRI unit consists of a Siemens Medical Solutions (Malvern, PA) 3.0 Tesla Trio MRI scanner, a full body scanner (60 cm bore) with Sonata gradient set (gradient amplitude of 40mT/m, maximum slew rate of 200T/m/sec, minimum gradient rise time of 200 microseconds). The system is actively shielded and is equipped with 32 RF channels and the total imaging matrix (TIM) suite. Multiple coils are available for the systems, including a 12 channel head matrix coil, 8 channel head coil, 4 channel carotid coil and a 24 channel spine coil. It runs the latest Siemens VB17 software and has a number of advanced Siemens product sequences including SWI, BLADE, Diffusion Tensor Imaging & Tractography, Auto Align feature for reproducible slice positioning based on a 3D MR brain atlas, BOLD imaging and in-line analysis suite with 3D PACE realtime motion correction and single and multi-voxel spectroscopy. Stimulus/response controls for behavioral tasks concurrent with fMRI are supported by an array of hardware specifically designed to allow investigator flexibility and precision. Visual presentation is provided by a high resolution LCD projection system (1400x1050 SXGA, 4200 lumens, 1300:1 contrast ratio) delivered from the back of the suite onto a custom fit screen mounted within the bore behind the participant's head. Audio presentation is provided by an Avotec Silent Scan 3100 that has been calibrated to maintain sound pressure levels that are dependent directly on input (flat frequency response +/- 4dB, 200-4500Hz range). A fiber-optic ergonomic bilateral button response system from Psychology Software Tools exists, as well as a control unit to support custom response shapes (joysticks, steering wheels, wands) from Current Designs. All of the hardware is connected through a single switch that signals TTL trigger pulses and allows connectivity to an investigator's laptop with any non-proprietary connections (USB, 1/8" minijack audio, VGA & DVI). A dedicated stimulus and response monitoring computer running Eprime 2.0 and Presentation stimulus programming software also exists.

Safety Monitoring

As aforementioned, the risks due to participation in this research are minimal. To minimize the potential risk of fatigue during testing and classes, participants will be allowed frequent breaks. To minimize the risk of dizziness or loss of balance during the mobility tests, trained research assistants trained in fall prevention maneuvers will closely monitor and guard the participant during testing.

For fMRI the following procedures will be put into effect:

<u>Imaging:</u>
No one with deep brain stimulator implants will be allowed to participate in imaging.
The risks associated with the imaging procedure are the same as those associated with conventional MRI. Specifically, movement or heating of metallic implants is a potential risk, and so subjects will be screened to exclude people with metallic implants, fragments, or pacemakers. Some individuals experience claustrophobic reactions in the scanner. Subjects will be informed of this prior to the study, but because it is difficult to predict who will have such a reaction, this is not a specific exclusion criterion. During the scans themselves, any subject experiencing claustrophobia will be removed from

the scanner immediately. There is no invasive component to this study; therefore, discomfort, bruising, and/or infection are not risks.
There may be additional risks associated with scanning at 3T, which we address:

Effect of the static field: The FDA has approved for routine clinical use, scanners up to 4.0 T. The system that we will be using is FDA approved. There is no conclusive evidence for irreversible or hazardous bioeffects to acute, short-term exposures of humans up to 2.0 T (Shellock and Kanal, 1996). Studies have indicated some side-effects at 4.0 T, namely unusual sensations including nausea, vertigo, and metallic taste (Schenck, 1991). However, there is no evidence that this is either irreversible or harmful. If subjects experience unusual sensations, they will be withdrawn.

Effect of the gradient field: MRI operates by rapidly changing small additional fields, called gradients. By Faraday's induction law, a changing magnetic field will induce electrical currents in any conductor. Thus, rapid cycling of the gradient field can induce peripheral nerve stimulation. However, this is not substantially different at higher magnetic fields since the gradients are separate from the main magnet. Should participants experience peripheral nerve stimulation (e.g., tingling or twitching), the principal investigator and staff will withdraw the participant from the study.

Effect of the RF electromagnetic field: The fundamental principle of MRI is that protons are excited by sending in an RF pulse at their resonant frequency for the magnetic field. The FDA provides guidelines for the safe use of MR systems, which includes specific recommendations for how much RF power is safe. They use the "specific absorption rate," or SAR. The SAR is the mass normalized rate at which RF power is coupled to biologic tissue and is typically indicated in units of watts per kilogram (W/kg) (NRCP, 1986). The FDA provides recommendations for two alternative safe levels of exposure to RF energy during MR procedures, primarily to control the risk of systematic thermal overload (heating) and local thermal injury. These are (FDA, 1988):

(a) The exposure to RF energy below the level of concern is an SAR of 0.4 W/kg or less averaged over the body, and 8.0 W/kg or less spatial peak in any 1 g of tissue, and 3.2 W/kg or less average over the head;

OR

(b) The exposure to RF energy that is sufficient to produce a core temperature increase of 1 deg C and localized heating to no greater extent than 38 deg C in the head, 39 deg C in the trunk, and 40 deg C in the extremities, except for patients with impaired systemic blood flow and/or perspiration.

We will adhere to the recommendations for the head, which is also monitored by Siemens' built-in monitor.

9. References & Appendices

1. Muslimovic D, Post B, Speelman JD, et al. Determinants of disability and quality of life in mild to moderate Parkinson disease. *Neurology* 2008;70(23):2241-7.
2. Tsai ST, Lin SH, Chou YC, et al. Prognostic factors of subthalamic stimulation in Parkinson's disease: a comparative study between short- and long-term effects. *Stereotact Funct Neurosurg* 2009;87(4):241-8.
3. Hackney ME, Kantorovich S, Levin R, et al. Effects of tango on functional mobility in Parkinson's disease: a preliminary study. *J Neurol Phys Ther* 2007;31(4):173-9.
4. Hackney ME, Earhart GM. Effects of dance on movement control in Parkinson's disease: a comparison of Argentine tango and American ballroom. *J Rehabil Med* 2009;41(6):475-81.
5. Hackney ME EG. Effects of Dance on Gait and Balance in Parkinson Disease: A Comparison of Partnered and Non-Partnered Dance Movement. *Neurorehabilitation and Neural Repair* 2010;24(4):384-92.

6. Lewis MM, Slagle CG, Smith AB, et al. Task specific influences of Parkinson's disease on the striatothalamo- cortical and cerebello-thalamo-cortical motor circuitries. *Neuroscience* 2007;147(1):224-35.
7. Low KA, Miller J, Vierck E. Response slowing in Parkinson's disease: a psychophysiological analysis of premotor and motor processes. *Brain* 2002;125(Pt 9):1980-94.
8. Morris ME, Iansek R, Kirkwood B. A randomized controlled trial of movement strategies compared with exercise for people with Parkinson's disease. *Mov Disord* 2009;24(1):64-71.
9. Freedland RL, Festa C, Sealy M, et al. The effects of pulsed auditory stimulation on various gait measurements in persons with Parkinson's Disease. *NeuroRehabilitation* 2002;17(1):81-7.
10. Noyes K, Liu H, Li Y, et al. Economic burden associated with Parkinson's disease on elderly Medicare beneficiaries. *Mov Disord* 2006;21(3):362-72.
11. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 2007;68(5):384-6.
12. Gage H, Hendricks A, Zhang S, et al. The relative health related quality of life of veterans with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;74(2):163-9.
13. Bloem BR, Grimbergen YA, Cramer M, et al. Prospective assessment of falls in Parkinson's disease. *J Neurol* 2001;248(11):950-8.
14. Bloem BR, Hausdorff JM, Visser JE, et al. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord* 2004;19(8):871-84.
15. Morris ME, Huxham F, McGinley J, et al. The biomechanics and motor control of gait in Parkinson disease. *Clin Biomech (Bristol, Avon)* 2001;16(6):459-70.
16. Nieuwboer A, Dom R, De Weerdt W, et al. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. *Mov Disord* 2001;16(6):1066-75.
17. O'Shea S, Morris ME, Iansek R. Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Phys Ther* 2002;82(9):888-97.
18. Hackney ME, Earhart GM. The Effects of a Secondary Task on Forward and Backward Walking in Parkinson's Disease. *Neurorehabil Neural Repair* 2009.
19. Leroi I, Collins D, Marsh L. Non-dopaminergic treatment of cognitive impairment and dementia in Parkinson's disease: a review. *J Neurol Sci* 2006;248(1-2):104-14.
20. Camicioli R, Majumdar SR. Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-Year Prospective Cohort Study. *Gait Posture* 2010;32(1):87-91.
21. Possin KL, Filoteo JV, Song DD, et al. Spatial and object working memory deficits in Parkinson's disease are due to impairment in different underlying processes. *Neuropsychology* 2008;22(5):585-95.
22. Cools R, Barker RA, Sahakian BJ, et al. Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain* 2001;124(Pt 12):2503-12.
23. Werheid K, Koch I, Reichert K, et al. Impaired self-initiated task preparation during task switching in Parkinson's disease. *Neuropsychologia* 2007;45(2):273-81.
24. Hausdorff JM, Doniger GM, Springer S, et al. A common cognitive profile in elderly fallers and in patients with Parkinson's disease: the prominence of impaired executive function and attention. *Exp Aging Res* 2006;32(4):411-29.
25. Cruise KE, Bucks RS, Loftus AM, et al. Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurol Scand* 2011;123(1):13-9.
26. Ashburn A, Fazakarley L, Ballinger C, et al. A randomised controlled trial of a home based exercise programme to reduce the risk of falling among people with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78(7):678-84.
27. Protas EJ, Mitchell K, Williams A, et al. Gait and step training to reduce falls in Parkinson's disease. *NeuroRehabilitation* 2005;20(3):183-90.

28. Gage H, Storey L. Rehabilitation for Parkinson's disease: a systematic review of available evidence. *Clin Rehabil* 2004;18(5):463-82.
29. Qutubuddin AA, Cifu DX, Armistead-Jehle P, et al. A comparison of computerized dynamic posturography therapy to standard balance physical therapy in individuals with Parkinson's disease: a pilot study.
NeuroRehabilitation 2007;22(4):261-5.
30. Macera CA, Ham SA, Yore MM, et al. Prevalence of physical activity in the United States: Behavioral Risk Factor Surveillance System, 2001. *Prev Chronic Dis* 2005;2(2):A17.
31. Toth MJ, Fishman PS, Poehlman ET. Free-living daily energy expenditure in patients with Parkinson's disease. *Neurology* 1997;48(1):88-91.
32. Earhart GM. Dance as therapy for individuals with Parkinson disease. *Eur J Phys Rehabil Med* 2009;45(2):231-8.
33. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair* 2009;23(6):600-8.
34. Hackney ME, Earhart GM. Tai Chi improves balance and mobility in people with Parkinson disease. *Gait Posture* 2008;28(3):456-60.
35. Kadivar Z, Corcos DM, Foto J, et al. Effect of step training and rhythmic auditory stimulation on functional performance in Parkinson patients. *Neurorehabil Neural Repair* 2011;25(7):626-35.
36. Hackney ME, Earhart GM. Health-related quality of life and alternative forms of exercise in Parkinson disease. *Parkinsonism Relat Disord* 2009;15(9):644-8.
37. Hackney ME, Earhart GM. Short duration, intensive tango dancing for Parkinson disease: an uncontrolled pilot study. *Complement Ther Med* 2009;17(4):203-7.
38. Hackney ME, Earhart GM. Effects of dance on balance and gait in severe Parkinson disease: a case study. *Disabil Rehabil* 2010;32(8):679-84.
39. Hirsch MA, Toole T, Maitland CG, et al. The effects of balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease. *Arch Phys Med Rehabil* 2003;84(8):1109-17.
40. Howe TE, Lovgreen B, Cody FW, et al. Auditory cues can modify the gait of persons with early-stage Parkinson's disease: a method for enhancing parkinsonian walking performance? *Clin Rehabil* 2003;17(4):363-7.
41. Jeka JJ. Light touch contact as a balance aid. *Phys Ther* 1997;77(5):476-87.
42. Kliegel M, Phillips LH, Lemke U, et al. Planning and realisation of complex intentions in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2005;76(11):1501-5.
43. Nieuwboer A, Rochester L, Muncks L, et al. Motor learning in Parkinson's disease: limitations and potential for rehabilitation. *Parkinsonism Relat Disord* 2009;15 Suppl 3:S53-8.
44. Dibble LE, Nicholson DE, Shultz B, et al. Sensory cueing effects on maximal speed gait initiation in persons with Parkinson's disease and healthy elders. *Gait Posture* 2004;19(3):215-25.
45. Jiang Y, Norman KE. Effects of visual and auditory cues on gait initiation in people with Parkinson's disease. *Clin Rehabil* 2006;20(1):36-45.
46. Ballanger B, Thobois S, Baraduc P, et al. "Paradoxical kinesis" is not a hallmark of Parkinson's disease but a general property of the motor system. *Mov Disord* 2006;21(9):1490-5.
47. Narayana S, Fox PT, Zhang W, et al. Neural correlates of efficacy of voice therapy in Parkinson's disease identified by performance-correlation analysis. *Hum Brain Mapp* 2010;31(2):222-36.
48. Brown S, Martinez MJ, Parsons LM. The neural basis of human dance. *Cereb Cortex* 2006;16(8):1157-67.
49. Sacco K, Cauda F, Cerliani L, et al. Motor imagery of walking following training in locomotor attention. The effect of "the tango lesson". *Neuroimage* 2006;32(3):1441-9.
50. Asanuma K, Tang C, Ma Y, et al. Network modulation in the treatment of Parkinson's disease. *Brain* 2006;129(Pt 10):2667-78.

51. Trost M, Su S, Su P, et al. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. *Neuroimage* 2006;31(1):301-7.
52. Yu H, Sternad D, Corcos DM, et al. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage* 2007;35(1):222-33.
53. Spraker MB, Prodoehl J, Corcos DM, et al. Basal ganglia hypoactivity during grip force in drug naïve Parkinson's disease. *Hum Brain Mapp* 2010;31(12):1928-41.
54. Taniwaki T, Okayama A, Yoshiura T, et al. Functional network of the basal ganglia and cerebellar motor loops in vivo: different activation patterns between self-initiated and externally triggered movements. *Neuroimage* 2006;31(2):745-53.
55. Sen S, Kawaguchi A, Truong Y, et al. Dynamic changes in cerebello-thalamo-cortical motor circuitry during progression of Parkinson's disease. *Neuroscience* 2010;166(2):712-9.
56. Wu T, Long X, Wang L, et al. Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. *Hum Brain Mapp* 2011;32(9):1443-57.
57. Wu T, Wang L, Hallett M, et al. Effective connectivity of brain networks during self-initiated movement in Parkinson's disease. *Neuroimage* 2011;55(1):204-15.
58. Sahyoun C, Floyer-Lea A, Johansen-Berg H, et al. Towards an understanding of gait control: brain activation during the anticipation, preparation and execution of foot movements. *Neuroimage* 2004;21(2):568- 75.
59. Keele SW, Pokorny RA, Corcos DM, et al. Do perception and motor production share common timing mechanisms: a correctional analysis. *Acta Psychol (Amst)* 1985;60(2-3):173-91.
60. He BJ, Shulman GL, Snyder AZ, et al. The role of impaired neuronal communication in neurological disorders. *Curr Opin Neurol* 2007;20(6):655-60.
61. Helmich RC, Derikx LC, Bakker M, et al. Spatial remapping of cortico-striatal connectivity in Parkinson's disease. *Cereb Cortex* 2010;20(5):1175-86.
62. Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci* 2004;16(9):1484-92.
63. Baudrexel S, Witte T, Seifried C, et al. Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease. *Neuroimage* 2011;55(4):1728-38.
64. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006;5(6):525-35.
65. Simpson J, Haines K, Lekwuwa G, et al. Social support and psychological outcome in people with Parkinson's disease: Evidence for a specific pattern of associations. *Br J Clin Psychol* 2006;45 (Pt 4):585-90.
66. Goodwin VA, Richards SH, Taylor RS, et al. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2008;23(5):631-40.
67. Perera S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54(5):743-9.
68. Lim LI, van Wegen EE, de Goede CJ, et al. Measuring gait and gait-related activities in Parkinson's patients own home environment: a reliability, responsiveness and feasibility study. *Parkinsonism Relat Disord* 2005;11(1):19-24.
69. Carey K, Montez-Rath ME, Rosen AK, et al. Use of VA and Medicare services by dually eligible veterans with psychiatric problems. *Health Serv Res* 2008;43(4):1164-83.
70. Hackney ME, Earhart GM. Social partnered dance for people with serious and persistent mental illness: a pilot study. *J Nerv Ment Dis* 2010;198(1):76-8.
71. Wooten GF, Currie LJ, Bovbjerg VE, et al. Are men at greater risk for Parkinson's disease than women? *J Neurol Neurosurg Psychiatry* 2004;75(4):637-9.
72. Schrag A B-SY, Brown R, et al. Young-onset Parkinson's disease revisited- clinical features, natural history, and mortality. *Mov Disord* 2004;13(6):885-94.

73. Samanez-Larkin GR dEM. Group comparisons: imaging the aging brain. *Soc Cogn Affect Neurosci* 2008;3(3):290-7.
74. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-9.
75. Chou KL, Amick MM, Brandt J, et al. A recommended scale for cognitive screening in clinical trials of Parkinson's disease. *Mov Disord* 2010;25(15):2501-7.
76. Delis DC KJ, Kaplan E et al. *California Verbal Learning Test: Second Edition*. San Antonio: Psychological Corporation, 2000.
77. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23(15):2129-70.
78. Giladi N, McDermott MP, Fahn S, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology* 2001;56(12):1712-21.
79. Nieuwboer A, Kwakkel G, Rochester L, et al. Cueing training in the home improves gait-related mobility in Parkinson's disease: the RESCUE trial. *J Neurol Neurosurg Psychiatry* 2007;78(2):134-40.
80. Perkins BA, Olaleye D, Zinman B, et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care* 2001;24(2):250-6.
81. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2007;22(8):1077-92.
82. Silberman CD, Laks J, Capitao CF, et al. Recognizing depression in patients with Parkinson's disease: accuracy and specificity of two depression rating scale. *Arq Neuropsiquiatr* 2006;64(2B):407-11.
83. Racette BA, Rundle M, Parsian A, et al. Evaluation of a screening questionnaire for genetic studies of Parkinson's disease. *Am J Med Genet* 1999;88(5):539-43.
84. Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55(3):181-4.
85. Katschnig P, Schwingenschuh P, Jehna M, et al. Altered functional organization of the motor system related to ankle movements in Parkinson's disease: insights from functional MRI. *J Neural Transm* 2011;118(5):783-93.
86. Romo R, Hernandez A, Zainos A. Neuronal correlates of a perceptual decision in ventral premotor cortex. *Neuron* 2004;41(1):165-73.
87. Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci* 2004;27:169-92.
88. Lewis PA, Wing AM, Pope PA, et al. Brain activity correlates differentially with increasing temporal complexity of rhythms during initialisation, synchronisation, and continuation phases of paced finger tapping. *Neuropsychologia* 2004;42(10):1301-12.
89. Thesen S, Heid O, Mueller E, et al. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magn Reson Med* 2000;44(3):457-65.
90. Langston JW, Widner H, Goetz CG, et al. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;7(1):2-13.
91. Stegemoller EL, Allen DP, Simuni T, et al. Rate-dependent impairments in repetitive finger movements in patients with Parkinson's disease are not due to peripheral fatigue. *Neurosci Lett* 2010;482(1):1-6.
92. Mumford JA, Nichols TE. Power calculation for group fMRI studies accounting for arbitrary design and temporal autocorrelation. *Neuroimage* 2008;39(1):261-8.
93. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002;15(4):870-8.
94. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24(2):197-211.

95. Wu T, Wang L, Chen Y, et al. Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. *Neurosci Lett* 2009;460(1):6-10.
96. Wolf SL, Barnhart HX, Kutner NG, et al. Reducing frailty and falls in older persons: an investigation of Tai Chi and computerized balance training. Atlanta FICSIT Group. Frailty and Injuries: Cooperative Studies of Intervention Techniques. *J Am Geriatr Soc* 1996;44(5):489-97.
97. Berg K, Wood-Dauphinee S, Williams JI. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. *Scand J Rehabil Med* 1995;27(1):27-36.
98. Lord SR, Menz HB. Physiologic, psychologic, and health predictors of 6-minute walk performance in older people. *Arch Phys Med Rehabil* 2002;83(7):907-11.
99. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the Timed "Up & Go" test in people with Parkinson disease. *Phys Ther* 2001;81(2):810-8.
100. McKinlay A, Grace RC, Kaller CP, et al. Assessing cognitive impairment in Parkinson's disease: a comparison of two tower tasks. *Appl Neuropsychol* 2009;16(3):177-85.
101. Keele S IR, Mayr U, et al. The cognitive and neural architecture of sequence representation. *Psychol Rev* 2004;110:316-39.
102. Muslimovic D, Post B, Speelman JD, et al. Motor procedural learning in Parkinson's disease. *Brain* 2007;130(Pt 11):2887-97.
103. Brooks LR. The suppression of visualization by reading. *Q J Exp Psychol* 1967;19(4):289-99.
104. Kessels RP, van den Berg E, Ruis C, et al. The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment* 2008;15(4):426-34.
105. Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn Reson Med* 2000;44(1):162-7.
106. Bianciardi M, Fukunaga M, van Gelderen P, et al. Sources of functional magnetic resonance imaging signal fluctuations in the human brain at rest: a 7 T study. *Magn Reson Imaging* 2009;27(8):1019-29.
107. Gopinath K, Ringe W, Goyal A, et al. Striatal functional connectivity networks are modulated by fMRI resting state conditions. *Neuroimage* 2011;54(1):380-8.
108. Worsley KJ, Taylor JE, Tomaiuolo F, et al. Unified univariate and multivariate random field theory. *Neuroimage* 2004;23 Suppl 1:S189-95.
109. Buccino G, Binkofski F, Fink GR, et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 2001;13(2):400-4.
110. Oldfield, R.C.. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*,1971;9: 97-113.
111. Schneiders, et. al., A valid and reliable clinical determination of footedness. *PM&R*, 2010; 2: 835-841.

10. Devices: N/A.