Official Title: Physical Therapy and Deep Brain Stimulation in Parkinson Disease

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I. Specific Aims

The purpose of this study is to examine the safety, feasibility, and preliminary efficacy of PT in people with PD with STN-DBS. We expect that participants with STN-DBS in the PT group will not report more adverse effects than those in the control group. Furthermore, we hypothesize that those in the PT group will complete at least 80% of prescribed PT sessions. We also expect that those in the PT group will demonstrate improvements in balance and gait while those in the control group will demonstrate no change or a decline in balance and gait.

Specific Aim 1: To determine the safety of an 8-week PT intervention in people with STN-DBS. The primary variable of interest for safety is the number of adverse events (e.g. falls, orthopedic injuries).

Hypothesis 1: We hypothesize that participants with STN-DBS plus PT will not report more adverse effects than those with STN-DBS only.

Specific Aim 2: To determine the feasibility of an 8-week PT intervention in people with STN-DBS. The primary variable of interest for feasibility is adherence to the PT intervention, measured as a percentage of PT sessions completed.

Hypothesis 2: We hypothesize that participants with STN-DBS will complete at least 80% of prescribed PT sessions.

Specific Aim 3A: To evaluate the preliminary efficacy of PT on balance in people with STN-DBS. The primary variable of interest is the Balance Evaluation Systems Test (BESTest) total score.

Hypothesis 3A: We hypothesize that participants with STN-DBS plus PT will demonstrate improvements in balance while those with STN-DBS only will demonstrate no change or a decline in balance.

Specific Aim 3B: To determine the preliminary efficacy of PT on gait in people with STN-DBS. The primary variables of interest is preferred-pace gait velocity.

Hypothesis 3B: We hypothesize that participants with STN-DBS plus PT will demonstrate improvements in preferred-pace gait velocity while those with STN-DBS only will demonstrate no change or a decline in gait.

II. Background and Significance

Subthalamic nucleus deep brain stimulation (STN-DBS) effectively reduces tremor, rigidity, and bradykinesia in people with Parkinson disease (PD)[1], but the effects of STN-DBS on postural instability and gait are less clear. Postural stability initially improves following STN-DBS[2–4]; however, these benefits may not endure. For example, worsened postural responses were observed in individuals six months post-DBS surgery[5] , and STN-DBS did not improve balance in individuals with PD with abnormal quiet stance prior to surgery[6].

Further, despite positive initial effects of STN-DBS on postural instability and gait difficulty (PIGD), PIGD progressively worsened and within two years was more impaired than before surgery[7]. Finally, falls may increase after STN-DBS surgery[8]. With respect to gait, STN-DBS is effective in improving spatial parameters (e.g. stride length), but does not seem to change temporal parameters. Stride-to-stride variability, known to be impaired[9] in PD, was unchanged following STN-DBS[10]. More importantly, approximately 42% of individuals post-STN-DBS subjectively reported worsened gait when on medication[11].

Deficits in balance and gait may lead to falls, fall-related complications, and physical inactivity in people with PD[12]. These negative effects are thought to lead to a 'malignant' form of PD in which there is reduced quality of life and increased risk for mortality[12]. While people who have had STN-DBS often experience reductions in tremor, rigidity, and bradykinesia, surgical management of PD may not be effective in ameliorating impairments in balance and gait. In fact, investigators have reported that DBS may worsen balance, which may accelerate an individual's decline toward 'malignant' PD. To this end, recent studies indicate physical activity levels did not increase after STN-DBS[13–15]. This finding should not go unnoticed as physical activity may have a disease modifying effect, slowing the progression of motor disability[16]. As of 2011, approximately 70,000 people with PD have undergone DBS[17], with the annual number of DBS procedures for PD totaling between 8,000-10,000[18]. In addition, investigators are now studying the effects of STN-DBS in people with early PD[19–21]. The procedure appears to be safe and effective in this population, which will increase the number of surgical candidates. With the number of people with PD expected to double to more than 8 million by 2030[22], the number of those receiving DBS is expected to substantially increase.

Given the expected rise in STN-DBS procedures and potential for worsening of postural instability and gait deficits, there is a clear need for interventions that prevent these negative complications of STN-DBS.

Physical therapy, delivered using various treatment approaches (e.g. treadmill training, balance training), is effective in reducing postural instability and improving spatiotemporal gait characteristics among individuals with PD who do not have DBS[23]. To our knowledge, there are no studies to date that assessed the impact of PT for those with PD who have DBS. In fact, the current standard of care following STN-DBS does not include PT. Current care post-DBS includes pharmacologic management and monitoring of DBS settings, which are optimized based on Unified Parkinson's Disease Rating Scale motor subsection (UPDRS III) scores. Despite the introduction of substantial changes to neural activity in areas of the brain governing movement with DBS, formal movement training or assessment of functional mobility and safety are not provided after surgery. As such, patients may not experience significant improvements in postural stability and gait following surgery, and may be at increased risk for falls, fall-related complications, and development of a sedentary lifestyle. Physical therapy is a personalized intervention that can be used to address specific movement impairments that remain even when patients are on optimal regimens of medication and DBS. There is an urgent need to determine if PT is effective in improving postural stability and gait performance over time following STN-DBS. If the intervention is safe and feasible, future studies could evaluate the efficacy of PT for gait and balance deficits in this population before and/or immediately post-surgery, increasing the potential impact of this research.

III. Methods

Participants

Participants will be recruited from the community.

Inclusion Criteria: Participants with PD will be ≥30 years of age and have a neurological diagnosis of PD. PD diagnostic criteria include those used for clinically defined "definite PD", as previously described by Racette et al.[24] based upon established criteria[25–27]. Each must have had clear benefit from levodopa and meet the other inclusionary and exclusionary criteria below.

All participants will meet the following inclusion criteria:

1) At least one year post-surgery for STN-DBS for PD

2) No evidence of dementia (MMSE ≥ 24)[28].

Exclusion Criteria:

1) Serious medical problem (aside from PD)

2) History or evidence of other neurological deficits, such as previous stroke or muscle disease

3) History or evidence of orthopedic, muscular, or psychological problem that prevents participation in either intervention

4) Inability to walk 10 meters with or without assistive device

Measures

Adverse Events: Adverse events will be measured using a questionnaire administered on a weekly basis.

Feasibility of PT: Feasibility of PT sessions will be measured by the number of sessions attended relative to the total possible number of sessions (i.e., 16).

Preliminary Efficacy:

Balance: To assess balance, each participant will complete the Balance Evaluation Systems Test (BESTest). This is a 27-item assessment that requires the participant to complete a variety of balance tasks like standing on one leg, walking with changes in speed, and standing on foam with eyes closed. The total possible score ranges from 0-100% with higher scores indicated better balance.

Gait: To assess gait, participants will walk at their preferred pace across a GAITRite walkway, which will determine their gait velocity in centimeters per second. Higher gait velocities are associated with better walking ability.

Protocol

A phone screen will be used to screen study candidates for eligibility. All eligible participants will be scheduled to start the study as soon as they are able at a time that is convenient to both the participant and the research team.

Baseline Testing

Baseline testing will be conducted with participants in two conditions: 1) OFF stimulation / OFF medication, 2) ON stimulation / ON medication. These conditions will be tested on two separate days within one week of each other and the order of conditions will be randomized. The OFF stimulation / OFF medication and ON stimulation / ON medication testing sessions will occur on two separate days to avoid fatigue. Regardless of testing condition, upon arriving for the first laboratory visit, informed consent will be obtained from each participant.

Informed Consent and MMSE: Participants will be consented in a private room with only the participant and study team members present. Participants will first receive a verbal explanation of the study and then be given as much time as they wish to read the consent form and ask any questions they may have. Participants will provide written informed consent prior to commencing study participation.

The Mini-Mental Status Examination (MMSE) will be conducted first only in the ON stimulation / ON medication condition. If the participant scores less than 24/30, the participant will be excluded from further participation at this time. If the score is 24 or above, the baseline assessment will proceed. After completing the MMSE in the ON stimulation / ON medication condition, each participant will complete the battery of balance, walking, and motor function tests.

For the OFF stimulation / OFF medication condition, participants will arrive to the laboratory in the practically defined off-state of their medication cycle (i.e. ≥ 12 hours since last dose). The deep brain stimulators will be turned off and the participant will then wait 45 minutes until the physical assessment begins. After 45 minutes, each participant will complete a battery of balance, walking, and motor function tests.

Upon completion of the baseline visits, the participant will be randomized to either the intervention or control group.

Intervention

Within one week of the initial visit, for the participants assigned to the PT group, the PT intervention will begin. Participants in the PT group will receive 8 weeks of the intervention, meeting 2 times per week for one hour each session.

Physical Therapy: This intervention will mirror traditional physical therapy for individuals with PD and will include exercises designed to improve balance, gait, and lower extremity strength. Balance exercises will follow a framework outlined by Schoneburg and colleagues[29] targeting quiet stance, anticipatory and reactive postural adjustments, and dynamic postural control. Quiet stance exercises might include, but are not limited to, standing on a firm surface with eyes closed, standing on a foam surface with eyes closed, and standing in tandem (one foot in front of the other). Anticipatory postural adjustment exercises might include, but are not limited to, standing on one leg, sit-to-stand, and trunk rotation in standing with feet planted. Reactive postural adjustment exercises might include, but are not limited to, standing with perturbations from the physical therapist while on firm and foam surfaces and leaning forward, backward, or laterally and taking a step to regain balance when needed. Dynamic postural control exercises might include, but are not limited to, walking with head turns side-to-side, walking while bouncing a ball, and walking around

an obstacle course. During every balance exercise, a physical therapist will be guarding the participant, who will be wearing a gait belt for safety. The gait belt will reduce the risk of falling by enabling the physical therapist to maintain contact with the participant at all times. Balance exercises following a similar framework improved balance and reduced falls in people with PD without STN-DBS. Balance exercises will be chosen using a decision tree to ensure exercises are sufficiently challenging to maximize the potential effect. For example, if a person is able to stand with feet together on a firm surface without significant sway on observation, the participant will then be asked to close their eyes to increase the challenge. Gait training exercises will include treadmill walking and practice with cueing strategies (e.g., auditory, visual) to improve gait and reduce freezing of gait. Treadmill walking will start at the participant's comfortable pace (measured during overground walking) and progress weekly provided the participant is able to tolerate it. Tolerance of treadmill walking will be determined by the observation of gait quality during treadmill walking and the participant's rating of perceived exertion (RPE) using Borg's Scale. If a participant's RPE rating exceeds 15 (i.e. Hard (heavy)) or the physical therapist determines that the gait quality is poor, the treadmill walking will be stopped. The treadmill is equipped with a wrist-band that, if detached from the treadmill, will stop the treadmill. Furthermore, there are two buttons on the treadmill that will allow the participant or physical therapist to stop the treadmill at any time. Each participant will be oriented to these safety features prior to starting treadmill walking. Both treadmill walking and cueing have been used to reduce gait variability and improve spatiotemporal gait parameters in people with PD without STN-DBS. To gain more information about how participants perceive the fatigue and challenges associated with each exercise, we will use a numeric rating scale (NRS). Participants will be asked on a scale of 0-10 how fatiguing and challenging they feel each exercise was after completing it. The attachment (NRS) will be shown to the participant each time the question is asked. Each participant's ratings will be recorded on the physical therapy intervention protocol document. Finally, participants in the physical therapy group will be provided a home exercise program (HEP). The HEP will be designed to maintain or improve lower extremity strength. Lower extremity strengthening exercises will include repeated sit-to-stand, heel raises in standing, hip abduction, and standing half squats. Participants will receive a detailed handout that includes instructions on how to correctly and safely complete each exercise. Participants will perform the HEP twice weekly on days in which they are not attending a physical therapy session. Additionally, participants in the PT group will be asked to complete the HEP twice weekly during the 4 weeks between the post-test and follow-up assessments. Participants will track performance and completion of the HEP using the HEP Checklist. During the intervention, the forms will be returned to the study team at each physical therapy session. During the 4-week follow up period, each participant in the PT group will return the forms at the follow-up assessment visit. In addition to physical therapy, participants will be allowed to adjust anti-PD medication and STN-DBS settings as determined by their neurologist. To measure safety, participants assigned to the PT group will complete an Adverse Events tracking form with the physical therapist weekly during the intervention.

Control Group

The control group will not receive a prescribed physical therapy intervention and will be instructed to go about their daily lives as usual. They will be asked to avoid making changes to their daily routine or usual exercise program. Participants will be allowed to adjust anti-PD

medication and STN-DBS settings as determined by their neurologist. To measure safety, those assigned the control group will be called weekly and will complete the Adverse Events tracking form over the phone with a member of the study team.

Follow-Up Testing

The 8-week and 12-week follow up visits will occur as soon as possible after the intervention is completed. The same protocol completed at baseline will be followed for this assessment. Again participants will be tested in the OFF stimulation / OFF medication and ON stimulation / ON medication conditions on two separate days. The OFF stimulation / OFF medication visit will last approximately 3 hours and the ON stimulation / ON medication visit will last approximately 2 hours.

Randomization Method

Participants will be randomly assigned (1:1 ratio) to either the PT intervention group or the control group in a consecutive fashion using an internet randomization scheme generator. A study team member will write the group assignment number on a piece of paper wrapped in tin foil. This will be placed in an opaque envelope and sealed. After participants complete both baseline assessment they will be allowed to open the envelope to determine their group assignment.

Safety and Adverse Events

The research team will do everything possible to ensure safety of all participants over the course of this study. Potential adverse events related to this study may include falls with serious injury, major cardiovascular incidents, or serious injuries associated with physical activity. The Adverse Event tracking form will be completed weekly with every participant. The adverse event most likely to occur in this study is a participant fall due to walking. Members of the research team will all be trained in fall prevention and will closely monitor all participants throughout all aspects of the study in case of a need to assist with balance to prevent a fall. In the case of a serious adverse event, emergency medical care will be sought immediately if needed. Any serious adverse events will be reported to the local IRB in accordance with their policies and procedures.

These risks will be addressed in the following ways:

a) Effects of withholding overnight and morning anti-PD medications: Participants may experience a temporary worsening of your Parkinson's disease symptoms as a result of not taking their anti-Parkinson's medication for study evaluations. Once taking the medication, the symptoms should return to their typical levels. Effects of medication withdrawal will be monitored and if the effects are too severe, participants will immediately take their medication. At that point, the study will be discontinued.
b) Effects of turning off deep brain stimulators: Participants may experience a temporary worsening of your Parkinson's disease symptoms as a result of turning off the deep brain stimulators for study evaluations. Once we turn the stimulators on, the symptoms should return to their typical levels. Effects of stimulation withdrawal will be monitored and if the effects are too severe, participants will immediately have their stimulators will be turned on. At that point, the study will be discontinued.

c) Loss of confidentiality: Loss of confidentiality is highly unlikely. To safeguard against this, we will comply with all HIPAA regulations. Data will not be identified by subject name. All data will be coded, and code sheets will be stored in locked files.
d) Stumbling during locomotion: Participants will be closely attended by a physical therapist during the assessment and physical therapy intervention. Walking, during the assessments, will be performed in a large, open space and the therapist will be prepared to assist participants who may stumble. Walking during the intervention will be performed on a treadmill and participants will be instructed to hold onto the railing for stability and will be guarded by a physical therapist to reduce fall risk. The treadmill is equipped with several safety features that allow the participant or physical therapist to stop the treadmill immediately. Each participant will be oriented to the safety features prior to commencing treadmill walking and these will be reviewed at each intervention session. It is therefore unlikely that participants will experience falls during testing or will be injured as the result of a fall. If a fall were to occur, the physical therapist will provide immediate first aid as needed using a first aid kit within the Movement Science Research Center. The physical therapist will also assess for the need for emergency medical care and will call 314-362-4357 (Washington University Security Services) to arrange for emergency transportation to the Barnes Jewish Hospital Emergency Department as needed.
e) Falling during locomotion: Participants will be closely attended by a physical therapist and/or trained assistant who will ensure the safest of conditions. It is unlikely that participants will experience falls during assessment or exercise or will be injured as the result of a fall. If a participant appears unsteady, breaks will be encouraged or testing will be terminated. If a fall were to occur, the physical therapist will provide immediate first aid as needed using a first aid kit within the Movement Science Research Center. The physical therapist will also assess for the need for emergency medical care and will call 314-362-4357 (Washington University Security Services) to arrange for emergency transportation to the Barnes Jewish Hospital Emergency Department as needed.
f) Fatigue: Rest breaks will be provided as frequently as possible.
g) Muscle soreness: Rest breaks will be provided as frequently as possible.
h) Skin irritation from activity monitor: Participants will be instructed in how to correctly don and doff the monitors. The participants will also be instructed in how to monitor for any skin irritation that might be associated with wearing the monitors. Participants will be instructed that if they have noticeable skin irritation (i.e. redness, discomfort) they should doff the monitors.
i) Fatigue and/or loss of balance during home exercise program: The home exercise program will include only 3 exercises: sit-to-stand, standing heel raises, and standing partial squats. Regarding fatigue, participants will be instructed to rest if they feel fatigued during the exercise program. The participants will be educated in how to perform these exercises correctly and safely. The physical therapist will require that participants demonstrate safe performance of the exercise before clearing them to do the home exercise program. For sit-to-stand, participants will be instructed to place a chair against a wall so that the chair doesn't have room to move backward thus avoiding a potential fall. For both the heel raises and squats, participants will be instructed to only do these exercises when holding on to a counter or sink at home that is fixed to the wall. This will provided stable upper extremity support minimizing the risk for any loss of balance.
j) Major cardiac event during physical activity: The cardiac risks in this study are minimal because the exercise intervention will not be of high intensity. To ensure that the risk is minimal, we will obtain a physician's note prior to the start of intervention that clears each participant for participation. Further, for those in the PT group, we will measure vital

signs before treatment and before and after aerobic activity like treadmill walking. If a participant's vital signs are found to be outside of normal for that specific participant, aerobic exercise will not be performed and we will contact the physician to determine how to proceed. If a participant demonstrates or reports symptoms associated with a cardiac event, the intervention will stop and the physical therapist will contact emergency medical personnel.

Benefits

It is unclear whether participants will benefit from participating in this study. This study will help to determine whether physical therapy might be a useful treatment option for people with PD who have DBS.

Interim Monitoring and Early Stopping

Safety will be monitored throughout the study. If it is noted that the physical therapy intervention is unsafe (i.e. more than 2 falls across multiple individuals are occurring **within** the intervention sessions), the research team will meet to determine whether or not it is safe to continue. We will not conduct an interim data analysis to determine whether the study should continue.

Statistical Analysis Plan

The total number of adverse events will be reported for each group allowing for qualitative comparisons.

Adherence will be reported for both attendance of PT and control sessions and will be expressed as percent of sessions completed.

Balance and gait data will be analyzed using mixed models with repeated measures or appropriate non-parametric test as appropriate to test for main effects of group (PT, control) and time (baseline, 8-weeks) and group*time interactions ($\alpha \leq 0.05$).

If there are baseline differences in demographic variables (e.g. age, gender, years since PD diagnosis, years since DBS), we will use these variables as covariates in the analyses.

Power

To our knowledge, there are no intervention studies that specifically examined the efficacy of physical therapy on balance in people with PD with STN-DBS. Given that this is a pilot study, the authors chose an effect size that would be meaningful and required to support moving forward with a larger trial. As such, with a medium effect size of 0.25 (Cohen's *f*)[30] and an alpha level of 0.05, 14 participants per group will provide 82% power to detect significant differences between or within groups for the primary preliminary efficacy outcome (i.e., BESTest). Factoring in a potential for 20% dropout attrition rate based on prior studies, we plan to recruit 17 participants per group. This pilot study is not powered to detect significant differences in the number of adverse events between groups.

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