Study title: Combining Transauricular Vagus Nerve Stimulation with Physical Therapy Interventions for Individuals with Parkinson's Disease

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Patient Population:

**We will recruit, screen, and enroll up 20 subjects in this study.

Inclusion Criteria:

1. 1.Diagnosis of Parkinson's Disease by a board-certified Neurologist, or by a Nurse Practitioner or Physician Assistant under the supervision of a Neurologist.
2. 2. Age between 35 and 80 years
3. 3. No walking aids
4. 4. Stable medication 4 weeks prior to the study
5. 5. No falls in the past 6 weeks
6. 6. Must have a neurologist or movement disorder specialist willing to approve and monitor their participation in the 'off' state' period of the study**

****Clinically Defined "Off" State:** Patients with Parkinson's disease have motor and cognitive fluctuations that can impact the interpretation of assessments performed in different medication states. To address this, we will conduct the initial evaluation in the practically defined off medication state, defined as when the participants have refrained from taking their PD medications for a period exceeding 12 hours. In this off medication state, we aim to observe and measure changes in the cardinal PD symptoms: tremor, rigidity, bradykinesia, and dyskinesias. These observations will be made using the physical and cognitive assessments described below. This approach is vital to our study as it allows us to investigate the effects of the intervention in isolation. To mitigate any potential discomfort or adverse effects, this will be done under the careful supervision of our clinical team, which is supervised by Dr. Harrison Walker, who is a neurologist specializing in the treatment of individuals with Parkinson's Disease. Additionally, we will obtain consent from the participants provider to ensure that they are safe to withhold PD medications for 12 hours prior to enrolling the participant in our study. *To further ensure participant safety, we will require that the participant has someone drive them to and from their clinic visits when they are in the clinically defined off state.* We will ensure participant safety and comfort throughout the evaluation sessions, intervening immediately if any adverse effects are observed. By focusing on the clinically defined 'off' medication state, we hope to gain a clearer understanding of the standalone effects of the brain stimulator on the symptoms and progression of Parkinson's disease. The findings of this study may contribute to future developments in the management and treatment of this debilitating condition.

Exclusion criteria:

1. 1. Moderate-severe cognitive impairment (MoCA <20)
2. 2. Diagnosed severe depression
3. 3. Antidepressive or antipsychotic medication
4. 4. Participation in a VNS study in the past year
5. 5. Disabling bradykinesia to ensure patients are able to participate in intensive physiotherapy (based on clinical impression and in accordance to UPDRS part III item 14 - to be administered in clinic)
6. 6. Prior history of cardiovascular, neurological or musculoskeletal disorders known to interfere with testing PD features
7. 7. Implanted medical device of any type, (8) history of seizures, (9) peripheral neuropathy including temporal mandibular disorders and Bells Palsy
8. 8. Vasovagal syncope.

9. 9. Pregnancy
10. 10. non-English speaking

Screening & Informed Consent

- Participants who have been deemed eligible for this study will attend an in-person session at either UAB SRC room R027, Community Health-19 building, or at Lakeshore.
- Upon arrival, the study coordinator/designated personnel will perform a more in depth screen for eligibility
- The participant must also pass cognitive screening (MoCA) and a motor screen (MDS-UPDRS Part III), however this will be completed after informed consent.
- If eligible, the study coordinator/designed personnel will consent the participant, using the Informed Consent form
- After informed consent has been obtained, the participant will undergo cognitive screening using the Montreal Cognitive Assessment. The Montreal Cognitive Assessment (MoCA) is a brief screening test that assesses various cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientations. The MoCA is used to detect mild cognitive impairment (MCI), a condition that can precede the onset of dementia and monitor changes in cognitive function over time. If the participant scores <25/30 on this assessment, they will be excluded from the study.
- -After informed consent, the participant will also undergo motor screening using the MDS-UPDRS Part III. The Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III is a comprehensive clinical assessment tool designed to evaluate the motor function in patients with Parkinson's disease. This segment of the scale involves a clinician-scored evaluation of motor skills, which includes assessments of speech, facial expressions, tremors, rigidity, finger dexterity, hand movements, rapid alternating movements, leg agility, arising from a chair, posture, gait, postural stability, and body bradykinesia. The UPDRS will be administered by a Movement Disorder Society-certified assessor. If the participant has disabling bradykinesia based on clinical impression and in accordance to UPDRS part III item 14, they will be excluded from the study.
- Each participant that is eligible for the study will undergo a 5-minute trial of taVNS (after obtaining consent) to ensure that they can tolerate the intervention. If they are unable to tolerate the intervention, they will be excluded from the study.
- At the conclusion of this session, participants will be scheduled for an Initial Assessment visit. See below for details.

Randomization Protocol:

- To ensure that randomization is blinded, we will use a computer-generated randomization sequence.
- After obtaining informed consent, we will randomize eligible participants into one of two groups.
    - GROUP 1: active taVNS + exercise (details provided below)
    - GROUP 2: non-active taVNS + exercise (details provided below)

Treatment Protocol:

Initial Assessment (2 hours)

**Prior to the Initial Assessment, enrolled participants will receive an email from the study coordinator outlining the requirements of the clinically defined "off" state.

Outcome Measures: At the first study study visit, Outcome Measure (OM) assessment will be conducted for ALL participants. Outcome measures (all previously validated in PD) will include the following:

Physical Assessments:

1. MDS-UPDRS - Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III is a comprehensive clinical assessment tool designed to evaluate the motor function in patients with Parkinson's disease. This segment of the scale involves a clinician-scored evaluation of motor skills, which includes assessments of speech, facial expressions, tremors, rigidity, finger dexterity, hand movements, rapid alternating movements, leg agility, arising from a chair, posture, gait, postural stability, and body bradykinesia. The UPDRS will be administered by a Movement Disorder Society-certified assessor.
2. 6-minute walk test (6MWT) - The 6-minute walk test (6MWT) is a simple, commonly used test to assess exercise capacity and functional mobility in individuals with Parkinson's Disease. During the 6MWT, the participant will be asked to walk as far as possible for six minutes in a straight line along a flat, hard surface. The participant's heart rate, blood pressure, and oxygen saturation will be monitored during the test. The distance that the participant is able to walk within the six minutes is recorded and is used as a measure of exercise capacity and functional mobility.
3. 10-Meter Walk Test (10MWT) - The 10 meter walk test (10MWT) is a clinical assessment tool used to measure gait speed in individuals with PD. The test is used to evaluate the functional mobility and gait speed of patients. During the 10MWT, the participant will be asked to walk a distance of 10 meters (about 33 feet) at their usual walking speed. The time it takes to complete the distance is recorded and the gait speed is calculated by dividing the distance by the time taken to complete it.
4. Mini-Balance Evaluation Systems Test (Mini-BESTest) - The Mini-BESTest (Balance Evaluation Systems Test) is a standardized, performance-based assessment tool used to evaluate balance and mobility in individuals with PD. It is designed to assess multiple aspects of balance, including anticipatory postural adjustments, reactive postural control, sensory orientation, stability in gait, and dynamic balance during functional tasks. The Mini-BESTest consists of 14 items, including tests of static and dynamic balance, sensory integration, and gait. The test takes approximately 15-20 minutes to administer.
5. Functional Gait Assessment (FGA) - The Functional Gait Assessment (FGA) is a standardized evaluation tool used to assess an individual's gait, balance, and risk of falling. This 10-item test evaluates walking ability under various conditions, including walking with a narrow base of support, walking with eyes closed, walking backwards, and changes in gait speed.
6. Modified Clinical Test of Sensory Integration and Balance (mCTSIB) - The CTSIB (Clinical Test of Sensory Integration of Balance) is a clinical assessment tool used to evaluate the ability of an individual to maintain balance under different sensory conditions. The test assesses the integration of sensory information from the visual,

somatosensory, and vestibular systems that are necessary for maintaining postural stability and balance during standing and walking. During the CTSIB test, the participant will be asked to stand on a firm or foam surface with their eyes open or closed. The test administrator observes the participant's postural sway and records their ability to maintain balance.

Cognitive Assessments:

1. Delis-Kaplan Executive Functioning System (DKEFS) Trails Test - The Delis-Kaplan Executive Function System (DKEFS) is a neuropsychological test battery that assesses various aspects of executive function, including cognitive flexibility, inhibition, and problem-solving. The trails test assesses visual attention and task switching. Participants will be asked to draw lines connecting numbers and letters in sequential order as quickly and accurately as possible.
2. Delis-Kaplan Executive Functioning System (DKEFS) Color Word Interference Test - The Color Word Interference test assesses selective attention and response inhibition. Participants will be asked to name the ink color of printed words while inhibiting automatic reading of the word itself.
3. Delis-Kaplan Executive Functioning System (DKEFS) Verbal Fluency Test - the Verbal Fluency Test assesses language-based executive function. Participants will be asked to generate as many words as possible within a given category (e.g., animals) or starting with a specific letter. These tests are commonly used in clinical settings to assess executive function and may help detect potential cognitive impairments or changes in cognitive function over time.
4. Digit Span Memory Test (DSMT) - The Digit Span Memory Test is a neuropsychological test that assesses working memory. Participants will be presented with a series of numbers and asked to repeat them back in the same order (Digit Span Forward) or in reverse order (Digit Span Backward). The test takes approximately 5-10 minutes to complete
5. Digit Symbol Substitution Test (DSST) - The Digit Symbol Substitution Test (DSST) is a neuropsychological test that assesses cognitive processing speed and attention. Participants will be presented with a series of symbols paired with digits and asked to match as many symbols to their corresponding digits as possible within a set time limit. The test takes approximately 5-10 minutes to complete.
6. MoCA - The Montreal Cognitive Assessment (MoCA) is a brief screening test that assesses various cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientations. The MoCA is used to detect mild cognitive impairment (MCI), a condition that can precede the onset of dementia and monitor changes in cognitive function over time.
7. Flanker test - The Flanker test is a cognitive task designed to measure attention and inhibitory control abilities. This test will be performed on an iPad or computer, and will measure reaction time (how quickly participant respond to stimuli), and accuracy. It provides insight into how well the participant can maintain attention on a central task while ignoring distracting information. This test will take approximately 5-10 minutes to administer. Results will be used to assess the effectiveness of the exercise intervention.

Questionnaires:

1. PROMIS-NeuroQOL questionnaires - The Patient-Reported Outcomes Measurement Information System (PROMIS) NeuroQOL is a questionnaire designed to assess health-related quality of life as it relates to cognitive function. Participants will be asked to complete a series of questions related to cognitive abilities such as memory, attention, and processing speed. The questionnaire takes approximately 10-15 minutes to complete and is administered by a trained healthcare professional. The results of the PROMIS-NeuroQOL may help identify potential cognitive impairments or changes in cognitive function over time.
2. Short Form-36 (SF-36) - The SF-36 is a questionnaire designed to assess health-related quality of life. Participants will be asked to answer questions related to their physical and mental health, including their ability to perform daily activities, their level of pain and discomfort, and their emotional well-being. The questionnaire takes approximately 5-10 minutes to complete and is administered by a trained healthcare professional. The results of the SF-36 may help identify areas of concern and inform healthcare providers about the participant's overall health status. Results will be used to assess the effectiveness of the exercise intervention.
    1. In the case of identification of severe depression or risk, the research team member administering the questionnaire will immediately notify the principal investigator. The principal investigator or a suitably qualified co-investigator will then review the participant's responses to confirm the initial assessment. If the investigator agrees with the initial assessment, they will notify the participant's clinician about the situation within 24 hours, or as soon as possible if the risk appears immediate. We will inform the participant about our concerns and our intention to contact their clinician.

Blood Draw:

- -In order to investigate the presence of the Val66Met polymorphism in our participants, we will collect a blood sample (10mL or 2 teaspoons) for genetic analysis.
- -Trained phlebotomists will collect approximately 10 ml (2 tablespoons) of blood from each participant using standard venipuncture techniques.
- -The blood samples will be stored securely and transported to a laboratory for analysis using polymerase chain reaction (PCR) and/or sequencing methods to determine the presence or absence of the Val66Met polymorphism.

Participants will be compensated with a $100 clincard at the conclusion of this visit.

Treatment (over the course of 4-6 weeks, 1 hour sessions, up to 3 sessions/week)

- During treatment clinic visits, participants who are randomized into the active taVNS + exercise group will receive 15 minutes of active taVNS prior to treatment.
- Participants who are randomized into the non-active taVNS + exercise group will receive 0 mA of current for 15 minutes prior to treatment.
- To implement the non-active condition, participants will still undergo the same electrode placement procedure as those in the active taVNS group, with the electrodes placed in the ears. However, the taVNS device will be set to a 0 mA (no stimulation) during the non-active condition. Participants will be informed prior to the stimulation that they may or may not feel anything during the session, and that just because they do not feel anything does not mean that they are not receiving stimulation.

- All participants will be guided through low intensity, high amplitude exercises led by a trained exercise specialist.
- The exercise intervention proposed involves the supervision of a trained exercise specialist at all times during the treatment session
- The use of a gait belt will further ensure the participant's safety by providing additional support and stability during exercise
- The proposed exercise intervention will be conducted by a trained exercise specialist who has expertise in assessing and managing potential risks associated with exercise interventions. This will ensure that the intervention is safe for the participant and will minimize the risk of injury or adverse events
- After each treatment session, participants will be asked post-intervention questions to evaluate potential side effects of the taVNS treatment and exercise (see below):
    - 1. Since our last session, have you experienced any unusual physical symptoms such as dizziness, fatigue, muscle soreness, shortness of breath, or heart palpitations?
    - 2. Have you experienced any unusual discomfort or pain in the ear where the taVNS device was applied?
    - 3. Have you noticed any changes in your sin around the area where the taVNS device was applied, such as redness, swelling, or rash
    - 4. Have you felt any changes in your mood, like feeling more anxious, depressed, or irritable since the last session?
    - 5. Have you noticed any changes in your ability to concentrate or remember things?
    - 6. Have you experienced any other side effects or symptoms that you believe may be related to the taVNS treatment or exercise program?
- If a participant reports experiencing any adverse effects, they will be advised to seek appropriate medical attention. We will also document all reported side effects.
- Participants will wear a heart rate monitor during each treatment session to monitor and record heart rate response to exercise.
- Participants will be asked to answer a series of questions about the tolerability of the taVNS treatment & exercise intervention via a RedCap survey.

Re-Assessment (2 hours)

**Prior to the re-assessment, enrolled participants will receive an email from the study coordinator outlining the requirements of the clinically defined "off" state.

- All participants will complete outcome measure assessment after completion of the protocol, including re-administration of the Montreal Cognitive Assessment (**MoCA**), Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale(**MDS-UPDRS**), 6-minute walk test (**6MWT**), mini-Balance Evaluation Systems Test (**Mini-BESTest**), Functional Gait Assessment (**FGA**), the modified Clinical Test of Sensory Integration and Balance (**mCTSIB**), Delis-Kaplan Executive Functioning System (**DKEFS**), Digit span test (DST), Digit symbol substitution test (DSST), Flanker test, **PROMIS-NeuroQOL**, the Short Form-36 (**SF-36**)
- Additionally, participants will complete a qualitative interview to assess tolerability and feasibility of the treatment provided in this study. The interview will be recorded and transcribed on a HIPPA compliant platform and will be stored in a secure database. Audio and transcription will be analyzed at the conclusion of the study.
- Participants will be asked to answer a series of questions about the tolerability of the taVNS treatment & exercise intervention via a RedCap survey.

Participants will be compensated with a $100 clincard at the conclusion of this visit.

Follow-up (2 hours)

- All participants will complete outcome measure assessment after completion of the protocol, including re-administration of the Montreal Cognitive Assessment (**MoCA**), Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale(**MDS-UPDRS**), 6-minute walk test (**6MWT**), mini-Balance Evaluation Systems Test (**Mini-BESTest**), Functional Gait Assessment (**FGA**), the modified Clinical Test of Sensory Integration and Balance (**mCTSIB**), Delis-Kaplan Executive Functioning System (**DKEFS**), Digit span test (DST), Digit symbol substitution test (DSST), Flanker test, **PROMIS-NeuroQOL**, the Short Form-36 (**SF-36**)
- Prior to follow-up, enrolled participants will receive an email from the study coordinator outlining the requirements of the clinically defined "off" state.

Participants will be compensated with a $100 clincard at the conclusion of this visit.

Statistical Analysis:

To assess feasibility, we will track recruitment rate, retention rate, adverse events, and compliance. We will obtain patient feedback to gather insight about the acceptability and usability of this intervention. We will perform paired t-tests to compare the mean outcome measure values of the treatment and control groups to estimate effect size.