Low-Intensity Focused Ultrasound Pulsation for Treatment of Motor Deficits in Parkinson's Disease

NCT04593875

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APPROACH

Participants. Participants will consist of 30 adults, aged 18 to 85 years, diagnosed with Parkinson's Disease (PD).

Subject Recruitment. Subjects will be recruited using flyers and brochures distributed physically and online, as well as from the UCLA Movement Disorder Program in collaboration with Dr. Jeff Bronstein, MD, PhD. A subpage on the Staglin IMHRO Center for Cognitive Neuroscience (henceforth CCN) website will include study information and an interest form to submit contact information if interested. Recruitment mailers will be distributed to doctor's offices and clinics, where patients (or their doctor's office, upon patient's request) can mail us their contact information if interested in the study.

Screening. Participants will be contacted by study staff who will conduct a telephone screening to ensure eligibility and suitability for MRI.

fMRI Validated LIFUP stimulation. We will use a Brainsonix ultrasound system with a transducer that fits in the 20-channel head coil. Participants will have the low-intensity focused ultrasound pulsation (LIFUP) transducer approximately aimed at the internal globus pallidus (GPi) using skin surface fiducials and gently strapped in place to their head. To minimize the ultrasound energy's exposure to air, a gel pad will be placed between the transducer and the participant's scalp. Participants will then be placed into the scanner where head scout scans will be used to guide more precise targeting adjustments. Once targeting is complete, a T1 image will verify the position of the LIFUP transducer and allow for estimation of the spatial location of the sonication beam focus (approximately 5mm long x 7mm diameter). Participants will receive active sonication at one visit and sham sonication at the other, the order of which will be randomized and counterbalanced across participants. The sonication protocol will consist of 20 ultrasound sonications in a 30 s ON, 30 s OFF fashion at 650KHz, Ispta≤720 mW/cm2, 5% duty cycle, 0.5ms pulse width, 73.15mvP-P amplitude, and 100Hz pulse repetition frequency. For sham sonication, the gel pad will block close to all of the ultrasound energy from the transducer. For active sonication, the gel pad will allow the ultrasound energy to pass through. These gel pads are identical in appearance. Resting state fMRI (rs-fMRI) will be collected simultaneously with LIFUP (or sham) sonication.

MRI Data Acquisition: We will use a 3-Tesla Siemens PRISMA scanner. We will collect high-resolution 0.8 mm^3 T1-weighted images, pseudo-continuous arterial spin labeling (PCASL) images, and rs-fMRI images. Total time in the scanner will be approximately 75 minutes each session.

Analysis and Publications. MRI data analysis will begin immediately during data collection, as structural and functional MRI are used to ensure successful targeting of LIFUP sonication. Group level analysis will occur after data from 30 subjects have been collected.

This project has four main aims:

#1: Validate basal ganglia-thalamocortical (BGTC) network perfusion and resting state functional connectivity (rs-FC) is associated with Parkinson's Disease (PD) deficits in cognition and motor impairments.

#2: Use LIFUP to modulate neural activity in the GPi, and PCASL pre- and post- LIFUP to assess up-regulation of BGTC network perfusion.

#3: Measure BGTC network rs-FC before, during, and after LIFUP stimulation.

#4: Assess potential LIFUP-related changes in motor function and their association with changes in perfusion and rs-FC.

PROCEDURES

MRI Analysis. Preprocessing and analyses will be performed using FSL Version 6.0 (www.fmrib.ox.ac.uk/fsl). Structural data will be linearly registered to the standard MNI152 T1 2mm brain. Processing of fMRI data will include correcting for motion artifacts (using framewise displacement, DVARS, within-subject independent component analysis, and outlier removal),

slice timing correction, high-pass temporal filtering (t > 0.01 Hz) unwarping, and spatial smoothing (Gaussian Kernel FWHM = 8mm). Functional data will be linearly registered to stereotaxic MNI space and co-registered with anatomic data for each participant. Subjects with greater than 0.5mm mean framewise displacement will be excluded from analyses. PCASL scans will be transferred to MNI space using non-linear registration in FSL and then linearly registered with anatomic data for each participant.

Stimulation-related fMRI. rs-fMRI will be collected continuously during the LIFUP stimulation paradigms. A block-design model will be used to statistically compare the blood oxygenation level dependent (BOLD) signal during LIFUP stimulation blocks to the BOLD signal during no-stimulation blocks. To examine LIFUP-related network connectivity, we will use a seed-based approach and examine whole brain connectivity with the LIFUP target of interest[69] and compare between stimulation (on-off) conditions using psychophysiological interaction modeling (PPI)[70]. We will also use dynamic connectivity to evaluate changes in connectivity across the course of the LIFUP stimulation paradigm.

RS-fMRI. We will compare rs-FC before and after stimulation. Independent component analyses (ICA) will be used to statistically extract functional networks from each participant's rs-fMRI. Dual-regression analysis will then compare resting state networks between baseline and post-LIFUP to determine the effect of LIFUP on resting state functional connectivity. Age, sex and education will be included as additional regressors.

Perfusion. PCASL is an arterial spin labeling technique that measures cerebral blood flow. It produces a perfusion image with voxel values representing local perfusion rates. Within FSL we will perform a voxel-wise repeated measures analysis between the pre-LIFUP and post-LIFUP PCASL scans. By examining the differences between these two scans, we can determine the effects that LIFUP has on perfusion in the target region and other connected regions. We will also perform a repeated measures analysis of perfusion between conditions (LIFUP vs. sham). By examining subjects receiving sham on visit 2, we can compare pre-sham resting state fMRI and PCASL to the pre-LIFUP values at visit one, to determine the persistence of blood flow effects over a 2-week interval. This will suggest how frequently LIFUP would need to be administered during a more comprehensive clinical trial.

Motor Assessment. Subjects will undergo a motor evaluation with assessments of motor symptoms such as a grooved pegboard task, a 15-second recording of forearm and hand tremor, and dynamometer grip strength measurements. They will also complete The Essential Tremor Rating Assessment Scale (TETRAS) and the Unified Parkinson's Disease Rating Scale (UPDRS). The motor testing portion of the UPDRS will be video-recorded for research staff to review after the session in order to maximize rating accuracy. Any recordings containing participants faces will be exclusively stored locally on UCLA-owned devices kept in a locked room; any video transferred off these devices will first be edited to remove faces and any other identifying information. The original footage will be deleted once this editing is complete. Participants will complete all of these assessments both before and after the MRI/LIFUP portion of each session. We will also ask the participant's partner or caregiver to complete part 1 of the TETRAS during the first virtual session. In addition to the measurements taken during the in-person and virtual sessions, we will ask participants to wear a watch-style device called the Personal KinetiGraph (PKG) starting one week prior to their first in-person session and ending one week after their second in-person session. This device provides round-the-clock monitoring of tremor activity and sleep quality. Additionally, immediately after administering LIFUP or sham stimulation, we will be asking participants open-ended questions about any perceived changes.

Psychological Assessment. After giving informed consent, subjects will be evaluated for cognitive status with the Modified Telephone Interview for Cognitive Status (TICS-M). Subjects will undergo a baseline psychological evaluation at their first in-person visit composed of the State Trait Anxiety Inventory (STAI), Beck's Depression Inventory (BDI), the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS), and the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ). The BDI, the RBDSQ, the "state" portion of the STAI, and an open-ended question about any perceived changes not covered by the inventories will also be completed before MRI/LIFUP at the second in-person session and at both follow-up Zoom sessions. Additionally, the Stanford Sleepiness Scale (SSS) will be completed both before and after each scan session and at each post-LIFUP Zoom session, in

order to control for potential fatigue effects on assessment results. Participants will also be completing a truncated version of the Phenomenology of Consciousness Questionnaire (PCQ) immediately after each scan session, and an experimental probabilistic learning task at each follow-up Zoom session.

STUDY DESIGN

The design is comprised of 2 in-person sessions, a consenting/intake Zoom session, a brief PKG setup Zoom session, 2 post-LIFUP follow-up Zoom sessions, 4 brief follow-up phone calls, and 4 weeks of round-the-clock PKG data collection. All in-person sessions will be held in private rooms on the C-level of the Semel Institute at UCLA, with scans taking place at CCN. All virtual sessions will take place over UCLAHealth HIPAA-secure Zoom. Staff will conduct all Zoom calls and phone calls from private locations to ensure participant confidentiality.

Design Overview

- Pre-screening: upon first contact by the participant, we will conduct an initial screening aimed at ensuring the participant meets inclusion criteria.
- During the intake Zoom session, we will conduct remote consenting procedures and MRI safety screening, and collect data necessary for PKG setup.
- During the remote PKG setup session, we will obtain a Zoom recording of the participant putting on the PKG device and familiarize the participant with the usage of the device.
- During in-person session #1 we will conduct consent procedures, pre-LIFUP behavioral and motor testing, MRI, either LIFUP or sham stimulation during the MRI, and post-LIFUP motor testing.
- During in-person session #2 (two weeks after in-person session #1), we will administer pre-LIFUP behavioral and motor testing, MRI, either LIFUP or sham stimulation (whichever was not received during the first session), and post-LIFUP motor testing.
- 48-72 hours after each in-person session, behavioral testing will be administered, as well as motor testing that can be conducted remotely.
- 4 and 7 days after each in-person session, a brief follow-up call will be conducted.
- Participants will be wearing the PKG device round-the-clock from one week prior to the first in-person session until one week after the second in-person session.
- The independent variable is the type of LIFUP modulation we will perform: active stimulation vs. sham stimulation.
- The dependent variables are: resting-state functional connectivity, perfusion, severity of motor symptoms, severity of psychological symptoms, and performance on the probabilistic learning task.

Detailed Design

Pre-screen: when we are put in contact with a potential participant, we will ask them to undergo a brief screening over the phone. The purpose of this session is exclusively to determine eligibility with respect to the following inclusion and exclusion criteria:

- **Inclusion Criteria:** (i) diagnosis of PD, (ii) age 18-85, (iii) fluent in English, (iv) hearing and vision normal or corrected-to-normal, and (v) willing and able to provide informed consent
- **Exclusion Criteria:** (i) mobility issues requiring use of a wheelchair or walker, (ii) significant cognitive impairment, (iii) history of neurological disorder other than Parkinson's, (iv) history of psychiatric disorders other than sleep disorders, anxiety disorders, and major depressive disorder, (v) pre-PD history of sleep disorders, anxiety disorders, and/or major depressive disorder, (vi) contraindication to MRI, (vii) medication changes within past 6 weeks or planned changes in next 6 weeks, (viii) pregnant or planning to become pregnant, (ix) history of medical event(s) likely to result in neurological abnormalities, (x) uncontrolled diabetes or hypertension, (xi) diagnosis of severe lung, liver, heart, or kidney disease, (xii) history of alcohol or substance abuse (other than nicotine or caffeine)

The only data that will be retained about this screen is whether the participant is currently eligible, ineligible, or eligible at some future date, as well as their necessary contact information and any information necessary to verify MRI safety. No other record will be kept of the contents of the potential participant's answers.

Remote Session 1 [90 minutes]

The aim of this session is to (a) complete informed consent procedures, (b) evaluate cognitive status via the TICS-M (c) complete MRI safety screening procedures, (d) obtain participant demographic and medication information, (e) have caretaker complete part 1 of the TETRAS, and (f) schedule all other sessions

Remote PKG Setup Session [approx. 10 minutes]

The aim of this session is to (a) obtain a recording of the participant putting on the PKG device to ensure correct setup and (b) familiarize the participant with the usage of the device. Participant faces and voices will be removed from recordings before they are transferred from UCLA-owned devices to the UCLAHealth Box server. The PKG device will be worn from one week prior to the first in-person session to one week after the second in-person session. To collect continuous tremor data, the PKG device is to be worn round-the-clock, except for when participant is swimming, showering, syncing the device weekly, or in a LIFUP/MRI session.

In-Person Session 1 [approx. 4.5 hours]

This session will take place one week after the PKG setup session. The aim of this session is to (a) complete pre-LIFUP motor assessments (UPDRS, TETRAS, 1-minute forearm recording, grip strength and grooved pegboard tasks), (b) complete pre-LIFUP psychological assessments (SSS, STAI, RBDSQ, QUIP-RS, BDI), (c) perform neuronavigation-guided LIFUP or sham stimulation during rsfMRI, (d) collect information on any perceived changes immediately post-LIFUP (e) collect pre-LIFUP high res T1w, PCASL, and rsfMRI scans and post-LIFUP PCASL and rsfMRI scans, (f) complete post-LIFUP motor assessments (UPDRS part 3, TETRAS part 2, grip strength and grooved pegboard tasks), and (g) complete post-LIFUP psychological assessments (SSS, PCQ).

Post-LIFUP Remote Session 1 [60 minutes]

This session will take place 48-72 hours after the first in-person session. The aim of this session is to (a) complete post-LIFUP motor assessments that can be administered remotely (UPDRS parts 1, 2, and 4, TETRAS part 1), (b) complete post-LIFUP psychological assessments (SSS, BDI, RBDSQ, STAI-State, probabilistic learning task), and (c) collect information on any perceived changes not covered in the motor and psychological assessments.

In-Person Session 2 [approx. 4 hours]

This session will take place two weeks after the first in-person session. The aim of this session is to (a) complete pre-LIFUP motor assessments (UPDRS, TETRAS, 1-minute forearm recording, grip strength and grooved pegboard tasks), (b) complete pre-LIFUP psychological assessments (SSS, STAI-State, RBDSQ, BDI), (c) perform neuronavigation-guided LIFUP or sham stimulation during rsfMRI, (d) collect information on any perceived changes immediately post-LIFUP, (e) collect pre-LIFUP PCASL and rsfMRI scans and post-LIFUP PCASL and rsfMRI scans, (f) complete post-LIFUP motor assessments (UPDRS part 3, TETRAS part 2, grip strength and grooved pegboard tasks), and (g) complete post-LIFUP psychological assessments (SSS, PCQ).

Post-LIFUP Remote Session 2 [60 minutes]

This session will take place 48-72 hours after the first in-person session. The aim of this session is to (a) complete post-LIFUP motor assessments that can be administered remotely (UPDRS parts 1, 2, and 4, TETRAS part 1), (b) complete post-LIFUP psychological assessments (SSS,

BDI, RBDSQ, STAI-State, probabilistic learning task), and (c) collect information on any perceived changes not covered in the motor and psychological assessments.

Four-day Post-LIFUP Follow-Up Calls [approx. 5 min each]

These calls will take place four days after each in-person session. The aim of these calls is to collect information on any perceived changes since the LIFUP session or the post-LIFUP Zoom session.

One-week Post-LIFUP Follow-Up Call 1 [approx. 10 min]

This call will take place seven days after the first in-person session. The aim of these calls is to (a) collect information on any perceived changes since the LIFUP session or prior follow-up sessions, and (b) walk the participant through the process of syncing the PKG device in order to ensure successful data transfer.

One-week Post-LIFUP Follow-Up Call 2 [approx. 10 min]

These calls will take place seven days after each in-person session. The aim of these calls is to (a) collect information on any perceived changes since the LIFUP session or prior follow-up sessions, and (b) walk the participant through the process of syncing the PKG device in order to ensure successful data transfer, (c) collect feedback on participant experience with the study, and (d) provide instructions for returning the PKG device.