The Impact of Exercise on Subthalamic Nucleus Neural Activity in Parkinson's Disease

Study Protocol

NCT05905302

Document Date 2/14/2023

Posted 9/16/2025

APPROACH

Fifteen PwPD utilizing the Percept PC DBS system will be enrolled for this project. Briefly, all patients will be at least six-months post bilateral DBS surgery with DBS parameters clinically optimized for at least three months prior to enrollment. To reduce possibility of a cardiac adverse event during the proposed exercise sessions, the American College of Sports Medicine (ACSM) Pre-exercise Screen[1] will be performed prior to exercise (see Protection of Human Subjects for details). We anticipate an ample population of PwPD eligible for recruitment as neurosurgeons within the Center for Neurological Restoration (CNR) perform 200 bilateral STN DBS surgeries annually. The Percept platform is rapidly becoming the system of choice due to ease of programming.

Following all pre-screening, participants will complete three visits on 3 separate days. For **Visit 1**, participants will complete the informed consent process, establish resting heart rate (HR; supine x5 min), be fitted to the cycle to ensure proper mechanics, complete ~5-10 minutes of FE and VE to ensure safety and understand cycle operation, complete 5-10 familiarization force-tracking trials,[2] and have order of FE or VE assigned for Visit 2 and 3 via a computerized randomization scheme. Target HR will be calculated using the Karvonen method[3] [(Max HR-Resting HR) x (60%-80%) + Resting HR]; max HR will be estimated as (220-age).[4] Figure 1 provides an overview of the experimental paradigm for Visit 2 and 3.

For **Visit 2 and 3,** PwPD will arrive OFF antiparkinsonian medication and On-DBS. The 130-minute experimental session will be divided into four epochs: 1) On-DBS, 2) Off-DBS, 3) Off-DBS + Exercise and 4) Post-exercise. Neural activity from the STN will be continuously recorded from both DBS electrodes <u>for the entire 130-minute session.</u>

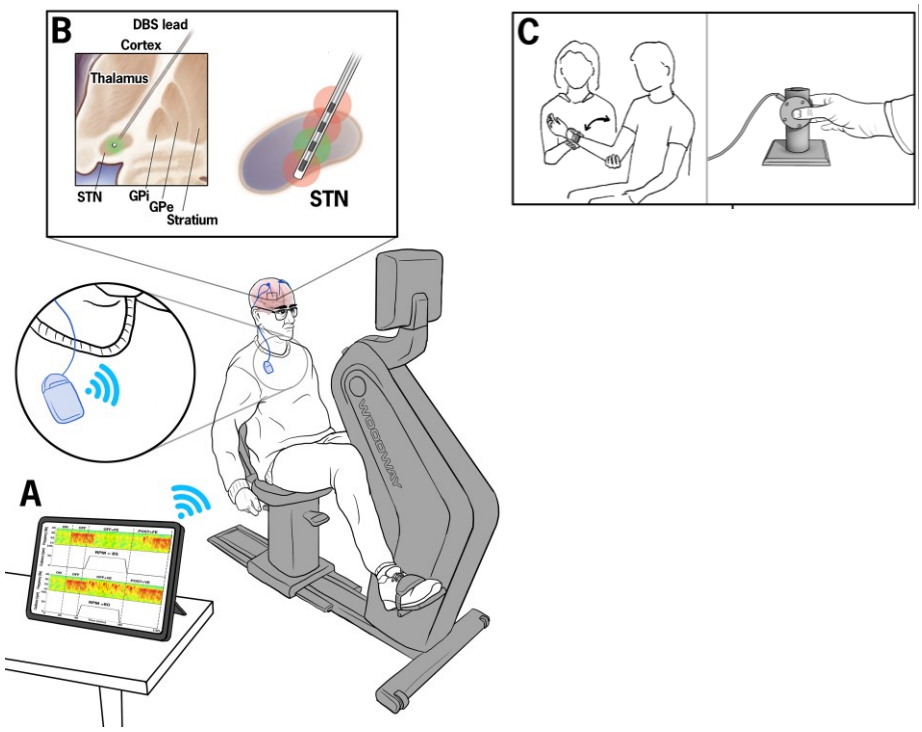

Figure 1: *Illustration of experimental protocol and equipment utilized to obtain LFPs from STN-DBS implanted in PD patients during exercise. (A) Percept PC system is integrated into the implantable pulse generator (IPG) shown in circle insert and continuously transmits LFPs in real time wirelessly to a storage device (tablet) (B) Illustration of the DBS lead implanted in the subthalamic nucleus (STN) and surrounding basal ganglia nuclei (C)Assessments, MDS-UPDRS-III and force-tracking, will be performed at 3 time points during an experimental session.*

To ensure proper autonomic and hemodynamic response to exercise, BP will be taken before, during (minute 20), and following cool-down. During exercise sessions, pedaling torque, cadence and HR will be continuously recorded at 60Hz and rate of perceived exertion (RPE) will be recorded every 10 minutes using our previous methods.[5] The main exercise set (40 min) and HR (60-80% of HHR)[6] will be identical across FE and VE. The single manipulated independent variable is pedaling cadence. For the VE group, maximum cadence will be limited to 60rpms. During FE, with assistance of the motor, cadence will be maintained between 80-90rpms.[6] This approach replicates previous human and animal exercise paradigms and will lead to clear interpretation of the effect of cadence on STN neural activity and upper extremity motor function.

Forced-exercise (FE) Cycle and Session: To deliver the FE intervention, a suite of sensors is integrated into a standard stationary cycle to monitor system and rider status. The inertia wheel, brake and brake controller

were replaced with three core components: servomotor, motor-drive, and programmable controller. While the motor augments pedaling rate in the FE mode, participants actively contribute to pedaling as they must exercise within their specified target HR range. The control algorithm automatically adjusts assistance or resistance during FE based on the user's continuously-monitored torque production and heart rate thus allowing the system to maintain an effective therapeutic cadence while the user maintains their target heart rate.

Voluntary Exercise (VE) Session: During the VE session, individuals will complete the main exercise set at a cadence of no greater than 60rpms[6] on the same stationary cycle while in its standard voluntary mode. In the event that a participant's voluntary rate is >60rpms, resistance will be applied to ensure cadence is maintained and target HR is reached. In standard voluntary mode the motor control assistance algorithm is disabled and the cycle functions as a typical resistance based stationary cycle. During the VE exercise session, pedaling torque, cadence and HR will be continuously recorded at 60Hz and RPE will be recorded as in the FE session.

DATA COLLECTION

Local Field Potentials (LFP) Recordings: Neural activity of the STN will be gathered bilaterally for the duration of each 130-minute visit. Medtronic's BrainSense Indefinite Streaming platform will provide LFP data from Medtronic 3389 electrode model or SenSight directional leads. For the **On-DBS epoch**, LFPs from contact pairs surrounding the stimulating contact (0-2, 0-3, 1-3) for each hemisphere will be recorded (2 channels total).[7] In the **Off DBS, Exercise and Post-exercise epochs,** LFPs will be recorded between contact pairs 0-2, 0-3, 1-3 bilaterally resulting in simultaneous recordings of 3 channels per hemisphere (6 channels total). All LFP recording will be sampled at 250Hz and low-pass filtered (0-100Hz) and streamed via Bluetooth to the Medtronic tablet (Figure 1A&B). While in the Off DBS epoch, the bipolar channel with highest peak power in the beta band (13–35 Hz) during rest in each hemisphere will be selected for further analyses. This selection is based on previous studies demonstrating a significant correlation between contact-pair location in the sensorimotor portion of the STN and beta power.[8] **LFP outcomes**: Prior to calculation of outcomes, windows containing movement artifacts will be visually identified by large fluctuations in the time series and high amplitude broadband activity in the spectrogram and removed from further analysis. Triggered spectrograms will be calculated for each trial using the multitaper method with a 500 ms, 250 ms overlap moving window, 2.0 Hz frequency resolution, and 1 taper. Relative power will be obtained for each subject and frequency by normalizing the absolute power by its average across time for each channel. This approach will facilitate comparison across subjects, whose absolute signal magnitude can vary by one or two orders of magnitude. The relationship of synchronization and desynchronization changes in oscillatory activity within the frequency bands of interest, delta, theta, alpha, beta and gamma bands, will be calculated across each of the four epochs within an experimental session. Along with average power, moment-to-moment dynamics of the band power, e.g., beta bursts, will be assessed in each condition as previous data indicate beta burst activity during continuous movement is related to PD bradykinesia.[9] Dr. Miller Koop will lead the collection and analysis of LFP data.

Force-tracking: Upper extremity motor control will be assessed during the performance of a force-tracking task used previously with older adults[10,11] and PwPD.[2,12] Patients will use a precision grip (thumb and index finger) with the dominant hand to exert an isometric force against a six-degree of freedom force transducer (Figure 1C) affixed to an adjustable experimental table. The greatest force produced in the F_Z axis (grip force) during a five second trial will be considered their maximum voluntary contraction (MVC). To ensure consistent motor task demands across the four data collection timepoints, target tracking force will be 20% of their MVC for a given session. During the force-tracking task, participants match their grip force to the target force as accurately as possible; a monitor simultaneously displays target force and patient produced grip force.

Force-tracking Outcomes: Force data will be filtered with a phase-symmetric low-pass filter employing Woltring's algorithm using existing Matlab analysis programs.[13,14] The primary outcomes will be time within the target range (TWR) and relative root mean square error (RRMSE). The TWR is calculated by determining the time the patient's force trace is within ±2.5% of the target line. The TWR provides an overall accuracy measure of force-tracking. To account for differences in the amplitude of the target force (e.g. inter-patient and intra-patient variability due to stimulation or exercise status), the RRMSE will be used as a method of normalizing

performance relative to force amplitude. Where, $F_T(t)$ is the target force provided to the patient, $F_0(t)$ is the force produced by the patient, T trial time.

Aim 1: To determine the effects of two modes of high intensity exercise, FE and VE, on the pattern of neural activity within the STN.
Statistical Analysis: Average band powers (delta, theta, alpha, beta and gamma) will be calculated at rest for 90 seconds in the Off DBS session immediately prior to exercise and immediately following FE and VE sessions. Mixed effect models will be utilized for each band power to determine if band powers at rest while Off DBS are significantly reduced following high intensity exercise (primary outcome), and to determine if the FE reduces band power significantly more than VE (secondary outcome).

Aim 2: To determine the relationship between changes in STN neural activity associated with FE and VE on upper extremity motor function and clinical symptoms of PD.
Statistical Analysis: The force-tracking outcomes, including TWR, will be calculated for all trials. Data from the Off DBS and Off DBS + Post Exercise sessions will be used for the primary analysis. Mixed effects models will be utilized to determine if force tracking performance improves following either exercise mode compared to Off-DBS and secondary analysis will be conducted to determine if FE improves force tracking more than VE. Clinical data from the same time points will be evaluated to determine the overall clinical response to high intensity exercise and any differential effects of exercise mode (FE vs. VE). Mixed models will be adjusted for confounding characteristics determined a priori, including sex, education, and PD severity. Model assumptions and model fit will be assessed, and variables will be transformed, as needed.

Inclusion Criteria:

a) Adult with a diagnosis of PD by a movement disorders neurologist
b) Previous placement, at least six months, of bilateral Medtronic Precept DBS as standard of care treatment for their PD.
c) Stable and clinically optimized DBS parameters for three months prior to enrollment.
d) Demonstrate the ability to safely mount and dismount a recumbent exercise cycle with an upright back.
e) Willingness to withhold antiparkinsonian medication and DBS stimulation.
f) Exercise clearance using the American College of Sports Medicine (ACSM) Pre-participation Health Screen
    a. If the ACSM screen recommends medical clearance, the subject must obtain medical clearance by their health care provider prior to participation.
    b. Those who choose not to obtain physician clearance will not be eligible for participation.

Exclusion Criteria:

a) Diagnosis of dementia or any neurocognitive impairment that compromises the ability to provide informed consent.
b) A musculoskeletal issue that limits one's ability to cycle
c) Neurological disease other than Parkinson's disease (i.e. multiple sclerosis, stroke) that impacts motor or cognitive function
d) Uncontrolled cardiovascular risk factor such as a current cardiac arrhythmia, uncontrolled hypertension, untreated deep vein thrombosis, etc.

REFERENCES

1. Riebe D, Franklin BA, Thompson PD, et al. Updating ACSM's recommendations for exercise preparticipation health screening. *Med Sci Sports Exerc*. Nov 2015;47(11):2473-9. doi:10.1249/MSS.0000000000000664
2. Frankemolle AM, Wu J, Noecker AM, et al. Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. *Brain*. Mar 2010;133(Pt 3):746-61. doi:10.1093/brain/awp315
3. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn*. 1957;35(3):307-15.
4. Fox SM, 3rd, Naughton JP. Physical activity and the prevention of coronary heart disease. *Prev Med*. Mar 1972;1(1):92-120. doi:10.1016/0091-7435(72)90079-5
5. Rosenfeldt AB, Rasanow M, Penko AL, Beall EB, Alberts JL. The cyclical lower extremity exercise for Parkinson's trial (CYCLE): methodology for a randomized controlled trial. *BMC Neurol*. Apr 24 2015;15:63. doi:10.1186/s12883-015-0313-5
6. Ridgel AL, Vitek JL, Alberts JL. Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair*. Jul-Aug 2009;23(6):600-8. doi:10.1177/1545968308328726
7. Medtronic. Percept PC Neurostimulator with Brainsense Technology: DBS Sensing White Paper. . 2021
8. Horn A, Neumann WJ, Degen K, Schneider GH, Kuhn AA. Toward an electrophysiological "sweet spot" for deep brain stimulation in the subthalamic nucleus. *Hum Brain Mapp*. Jul 2017;38(7):3377-3390. doi:10.1002/hbm.23594
9. Syrkin-Nikolau J, Koop MM, Prieto T, et al. Subthalamic neural entropy is a feature of freezing of gait in freely moving people with Parkinson's disease. *Neurobiol Dis*. Dec 2017;108:288-297. doi:10.1016/j.nbd.2017.09.002
10. Voelcker-Rehage C, Alberts JL. Age-related difference in working memory and force control under dual-task conditions. *Aging, Neuropsychology, and Cognition*. 2006;13:1-19.
11. Voelcker-Rehage C, Alberts JL. Effect of motor practice on dual-task performance in older adults. *J Gerontol B Psychol Sci Soc Sci*. May 2007;62(3):P141-8. doi:10.1093/geronb/62.3.p141
12. Alberts JL, Voelcker-Rehage C, Hallahan K, Vitek M, Bamzai R, Vitek JL. Bilateral subthalamic stimulation impairs cognitive-motor performance in Parkinson's disease patients. *Brain*. Dec 2008;131(Pt 12):3348-60. doi:10.1093/brain/awn238
13. Voelcker-Rehage C, Alberts JL. Age-related changes in grasping force modulation. *Exp Brain Res*. Sep 2005;166(1):61-70. doi:10.1007/s00221-005-2342-6
14. Voelcker-Rehage CS, A.J.; Alberts, J.L. Age-related Differences in Working Memory and Force Control under Dual-task Conditions. *Aging, Neuropsychology and Cognition*. In Press;