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Project Title:	Utilizing Neural Signatures and Virtual Reality to Advance DBS Programming
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Study Funder: Michael J. Fox Foundation for Parkinson's Research
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PROJECT GOAL: Falls related to postural and gait impairments and freezing of gait (FOG) occur in nearly 80% of Parkinson's disease (PD) patients and are the greatest motor-related contributor to health care costs and the primary reason for transition to dependent care settings among PD patients.[1-3] Despite their prevalence in the daily lives of PD patients, identifying FOG episodes in a clinical[4,5] or laboratory[6,7] environment is challenging. Consequently, the neural signature underlying FOG remains elusive.[6,8] A necessary step in treating FOG is characterizing neural activity within the basal ganglia during FOG episodes. An approach to evaluate the neural signals associated with FOG includes recording the neural activity in the area of the subthalamic nucleus (STN) or globus pallidus internus (GPi) from implanted deep brain stimulation (DBS) leads.[7,9-11] The proposed project combines the most advanced virtual reality (VR) technology and neural recording techniques to identify specific neural correlates of FOG while patients physically walk through a virtual environment, **V**irtual-**Ga**it **T**ask (V-GAIT), that simulates motor and cognitive\limbic triggers.

Objective: To identify the corresponding neural signatures of FOG associated with motor and cognitive\limbic triggers.

Fifteen individuals with PD will complete the V-GAIT modules while synchronized kinematic and neural data from the DBS lead within the STN or GPi are recorded. The kinematic data will be utilized to identify the timing of FOG episodes in the neural data. The neural correlates of FOG in the ON and OFF medication states within each domain will be evaluated.

METHODOLOGY AND APPROACH

The V-GAIT platform utilizes a VR headset to deliver high fidelity realistic virtual environments resembling a home environment while the participant walks on an omnidirectional treadmill. Briefly, the VR headset provides a realistic display with high resolution and refresh rate, wide field of view, and color clarity currently available. The 360-degree moving platform allows the user to naturally walk and turn in any direction. The 3-dimensional linear and angular position of the head, waist, and both feet are tracked using motion sensors that are embedded in the headset, waist belt, and foot straps. To ensure safety, a supported harness is worn by the user. To monitor overall exertion and provide a proxy for stress, a heart rate monitor is integrated into the V-GAIT platform.

V-GAIT Module: This module replicates a home, including a kitchen. The tasks will include, but not be limited to, walking in hallways will have digital doorways which reduce the width of the passageway and a virtual room where participants will appear to walk on an elevated platform to trigger anxiety-induced FOG.

INCLUSION/EXCLUSION CRITERIA

Participants: Fifteen individuals with idiopathic PD will be recruited for the study. Individuals who have previously undergone DBS surgery with the Medtronic Percept BrainSense DBS system will complete the protocol while neural data from the DBS electrodes are streamed.

Inclusion Criteria:

- Clinical diagnosis of idiopathic PD
- Previous implantation of Percept DBS system as standard of care for their PD treatment

- Self-reported response of one or greater on question #3 of the FOG-Q
- Ability to ambulate independently for a minimum of 10 minutes
- Ability to provide informed consent

Exclusion Criteria:

- Neurological disease other than PD
- Musculoskeletal impairment that affects one's ability to ambulate for 15 minutes continuously
- Presence of active and untreated psychiatric symptoms meeting Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) criteria for Axis-I disorder. Depression and anxiety are very common in patients with Parkinson's disease and are often mitigated as part of routine care. Depression and anxiety will not preclude study participation
- Cognitive impairment meeting Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV) criteria for dementia on formal neuropsychological evaluation
- Current alcohol or substance abuse
- Hearing or visual impairment precluding VR use
- Lack of fluency in English which may invalidate certain tests

RESEARCH DESIGN AND METHODS

Individuals with the Medtronic Percept DBS system will be medically stable status post DBS surgery prior to enrollment.

Screening: Potential participants will be identified and screened by a member of the study team. They will undergo an in-person informed consent process. They will also complete a familiarization session with the VR headset and treadmill. The Percept system allows for continuous streaming of LFP data from the implanted device.

V-GAIT Assessments: Participants will perform two assessment sessions. During the sessions, the participants will complete the V-GAIT as outlined in Table 1. The sessions can be performed consecutively on the same day or on separate days depending on patient tolerance and preference.

Table 1: Assessment States

	DBS State	PD Medication State
Session 1	Off	Off
Session 2	Off	On

DATA COLLECTION PROCEDURES

Neural Recording Procedures: The proposed study design will enable synchronized recordings to be made in the form of LFP from the six or eight channels of implanted DBS lead(s), as well as IMU sensors from the V-GAIT platform to quantify gait-related behaviors using a commercial EEG recording platform. The physiological and sensor data will be synchronized to motor task and gait-related activities and events associated with participant performance on the V-GAIT paradigm through additional analog and digital ports using a low voltage electrical current (1.5 mA) through surface electrodes placed on the participant's neck.

Behavioral Tasks: The Unified Parkinson's Disease Rating Scale (UPDRS) will be conducted by a rater blinded to medication state.

DATA ANALYSIS

Biomechanical Data Analysis: All data will be recorded and analyzed off-line using custom-scripts in Matlab using the Chronux toolbox to examine changes in oscillatory neural activity time-locked to FOG episodes identified with the kinematic data from the body worn motion sensors in the motion capture area. The 3D position data of each foot will be utilized to determine steps and other biomechanical stepping variables FOG episodes will be identified utilizing the data from the body-worn motion sensors.
Neural Data Analysis: Neural data will be detrended and passed through a moving window line noise subtraction algorithm to remove drifting baseline and continuous noise artifacts, respectively. From the Percept device, 6 electrode pair combinations, 3 combinations per DBS lead, will be recorded directly with the Percept communicator. 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 multi-taper method with a 100 ms, 50 ms overlap moving window, 2.5 Hz frequency resolution, and 1 taper.
Local Field Potential (LFP) Outcomes: The relationship of synchronization and desynchronization changes in oscillatory activity within the delta, theta, alpha, beta and/or gamma bands as well as the power of high-frequency oscillations (200+ Hz) will be calculated in relation to all events identified with the kinematic data, i.e. normal walking and FOG episodes. Power spectral densities will be used to determine the power and confidence bands of oscillatory activity across frequencies during these events.
Statistical Analysis: Neural data outcomes, average power within alpha, beta, and/or gamma frequency bands, will be quantified using descriptive statistics during FOG episodes and during periods of functional walking while performing the V-Gait modules. Within and across participant analyses will determine the degree of consistency and similarity of the neural signal during FOG episodes between each medication state (ON and OFF).

Confidentiality: CCF study investigators will have sole access to the study data. To protect confidentiality, participants' data will be identified only by coded subject number and stored in a secure location in a de-identified manner. A password-protected, electronic record linking subject numbers with identifying information will be maintained in a password-protected folder on a secure server and only CCF-based study investigators will have access to this file. Data analysis will be conducted by the study investigators in consultation with biostatistics, where appropriate. Dissemination of the results will largely involve aggregate data, although individual data points may be used where illustrative. All dissemination of the study findings will maintain confidentiality and include only de-identified data, except in the situation where express written permission has been obtained from the participant in advance.

Adverse Events and Safety: A Data Safety Monitoring Board (DSMB) will oversee this Phase I study. Non-conflicted members in the following areas: neurology, neurosurgery, statistics and bio-ethics will be recruited. Additionally, the Principal and Co-Investigators, along with the rest of the research team, will continuously monitor subject safety and data integrity. Adverse events and Unanticipated Problems will be reviewed by the Principle and Co-Investigators. If an Adverse Event occurs, it will be recorded on the Adverse Event Summary Sheet, and this will be submitted along with the Adverse Event Report in accordance with the stated time limitations. No clinical electrophysiological or imaging report will be generated as the experiments performed do not constitute diagnostic studies. However, if an unexpected finding is observed during the electrophysiological analysis, the appropriate clinical consults will be ordered.

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