Deep Brain Stimulation of the Cuneiform Nucleus for Levodopa-resistant Freezing of Gait in Parkinson’s Disease: Study Design and Rationale

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Disclosures

Dr. Luca: Consultant for and recipient of educational grants from Boston Scientific, Medtronic, and Abbott.

Dr. Jagid: Obtained investigator initiated funding from Boston Scientific for this study. He is a consultant for both Boston Scientific and Medtronic. Additionally he receives funding from Medtronic for research not related to the work presented herein.

Dr(s) Cajigas, Chang, Guest, and Noga have no relevant disclosures.
Introduction

- Freezing of gait (FOG) is a debilitating motor deficit seen in a subset of Parkinson’s Disease (PD) patients that is poorly responsive to standard levodopa therapy or deep brain stimulation (DBS) of established PD targets.

- The proposal of a DBS target in the midbrain, known as the pedunculopontine nucleus (PPN) to address FOG was based on its observed pathology in PD and its hypothesized involvement in locomotor control as a part of the mesencephalic locomotor region (MLR), a functionally defined area of the midbrain that elicits locomotion in both intact animals and decerebrate animal preparations with electrical stimulation.

- Initial reports of PPN DBS were met with much enthusiasm; however, subsequent studies produced mixed results, and recent meta-analysis results have been far less convincing than initially expected.

- A closer review of the extensive MLR preclinical literature, including recent optogenetics studies, strongly suggests that the closely related cuneiform nucleus (CnF), just dorsal to the PPN, may be a superior stimulation site to promote gait initiation.
Methods

• Reviewed current literature regarding the mesencephalic locomotor region in both animals in humans.

• Recent optogenetic studies in mice point to the CnF as being the primary locus for initiating and controlling locomotion (Josset et al., 2018)

• Immunohistochemical staining and electrical stimulation in a decerebrate cat preparation has additionally been used to dissect the contribution of the PPN and CnF to locomotion and provided positive evidence for the role of the CnF in the initiation of locomotion (Opris et al., 2019)

• Given extensive pre-clinical data, we propose to target the CnF rather than the PPN for DBS to alleviate FOG in postural instability and gait difficulty-predominant (PIGD) subtype PD patients.

• We describe the study objectives and design along with major inclusion/exclusion criteria and patient assessments
Mesencephalic stimulus sites evoking locomotion and muscle tone suppression. In this figure, adapted from Takakusaki, 2003, stimulation of the CNF in cats resulted in rhythmic EMG activation pattern of the left (top) and right (bottom) soleus muscles as seen in the EMG trace.
Positions of active electrode contacts in 11 PD patients with gait disorders with bilateral PPN DBS (adapted from Goetz et al., 2018). Contacts are colored based on composite gait score outcomes in patients: Green – good responder; red – bad responder; orange – mild responder; yellow – no evaluation.

A) Contacts overlaid on axial slice T1 MRI at pontomesencephalic junction (PMJ) of brainstem.

B) Upper lateral 3D view of same axial cut in A.

C) Left sagittal view at 6.5mm lateral to midline.

D) Upper lateral 3D view as in B but only showing good responder contacts. The light green contacts posteriorly represent the positions in the two best responder patients with complete alleviation of FOG. The two cyan contacts represent the mean coordinates of the 6 good responder contacts.

(Goetz et al., 2018)
Study Objectives and Purpose

• To assess the extent to which CnF DBS can ameliorate freezing of gait in PD patients with severe, levodopa-resistant gait freezing.
• To determine the optimal stimulation parameters (frequency, pulse, amplitude) to maximize gait performance while minimizing any potential side effects in these patients.
• To evaluate the effect of CnF DBS on other PD symptoms (including pain) and quality of life (QOL).

Study Design

• Prospective, non-randomized, open label, investigation in four (4) participants.
• ClinicalTrials.gov NCT04218526
**Inclusion criteria**

- Confirmed Parkinson’s Disease according to movement disorder neurologist with documented exclusion of other disorders such as fronto-temporal dementia (FTD)/ frontal gait disorder/normal pressure hydrocephalus (NPH)/progressive supranuclear palsy (PSP)
- PD stages 2-3, with predominant axial symptoms: PIGD score >6 (range 0-20)
- Age 40-75 with good response to Levodopa (defined as greater than 20% improvement in UPDRS score)
- FOG refractory to LEVODOPA>600 mg, PIGD UPDRS subscore >4 (range 0-24)
- Absence of major executive dysfunction
- Absence of dementia
- Absence of major medical co-morbidities and other surgical contra-indications

**Assessments**

Pre-op MRI including DTI
Pre-op UPDRS (including PIGD-subscore) off meds, on meds
Post-op UPDRS off meds, on meds
At each visit:
  - FOG Questionnaire (FOGQ)
  - For each of the following stimulation settings: CN L off/CN R off, CN L off/CN R on, CN L on/CN R off, CN L on/CN R on
    1. Timed Up and Go test instrumented with Mobility Lab accelerometers
    2. Stride Length
    3. Velocity
    4. Gait variability measured over a 2-minute walk
  5. UPDRS Part III - Gait and balance assessment
- The Parkinson’s Disease Questionnaire (PDQ-39) and the Parkinson’s Disease Quality of Life Questionnaire (PDQL)
- Gait testing with surface EMG with DBS on/off at study conclusion
Discussion

• We present the study design and rationale for studying this novel DBS target for gait dysfunction, including targeting considerations (ClinicalTrials.gov NCT04218526)

• With FDA IDE and IRB approval, the trial is in the enrollment phase
Summary Points

• The MLR is a physiologically defined area in the midbrain, where low threshold electrical stimulation can initiate and control locomotion in both decerebrate and intact animals.

• Recent studies point to the CnF as being the primary locus for initiating and controlling locomotion.

• We propose a pilot clinical trial which is currently open to recruitment for patients with primary freezing of gait to test this hypothesis.

• Inclusion/Exclusion Criteria and Primary Assessments to be used are described.