

# **Thalamic deep brain stimulation for spasmodic dysphonia: a Phase I prospective randomized crossover trial**

## **Clinical Research Proposal**

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## **Brief Summary**

Laryngeal Dystonia (LD, also known as spasmodic dysphonia) is a focal, action-specific movement disorder with prominent effects on speech (1-2). Patients with LD lose their ability to speak due to involuntary contractions of their laryngeal muscles. As a result, LD tremendously affects an individual's quality of life by limiting their ability to communicate effectively.

The current standard of care for SD involves botulinum toxin (BTX) injections into the laryngeal muscles. BTX causes a weakness in the injected muscles thereby lessening the spasms (7). The primary neurological problem is not changed but weakening the muscles temporarily diminishes the symptoms. However, BTX therapy is associated with several limitations (7,8). Firstly, the clinical effect produced by BTX is temporary and repeated injections are required approximately every 3 months. Secondly, there is a delay in the onset of benefits provided by BTX injections; this delay results in a sinusoidal symptom curve where SD is optimally controlled for only 30% of a treatment cycle and patients' spasms return prior to the next injection cycle. Furthermore, the injections are very painful and some patients develop antibodies to BTX (7,8). Oral medications used in dystonia, such as anticholinergics, benzodiazepines, and baclofen, provide minimal relief and have numerous side effects at the doses required to influence a patient's voice. Thus, on basis of these limitations, we set out to explore new and innovative strategies to treat SD and provide patients with long-term benefit.

Deep Brain Stimulation (DBS) is a neurosurgical procedure that involves the implantation of electrodes to deliver electrical stimuli to specific brain regions (Figure 1). It is the gold-standard surgical treatment for other movement disorders such as Parkinson's disease and essential tremor (ET). During a DBS procedure, an electrode is inserted very precisely into the brain that is linked to a brain pacemaker implanted in the chest or abdominal wall. When the pacemaker is switched on, a very small electric current passes into the brain, blocking the damaging signals that cause the condition.

## ***Clinical Motivation***

Our team recently studied a small cohort of patients with LD and concurrent ET who underwent DBS for their ET. We found that these patients tremendously improved in their voice as a result of DBS. Scattered case reports are present in the literature of thalamic DBS improving voice in LD and concurrent ET. Based on our recent study and others elucidating the neural circuitry of LD, we are hoping to initiate a Phase 1 DBS trial in pure LD patients (those without essential tremor). This trial will be of international significance, span multiple specialties, and potentially revolutionize the standard of care for these patients.

## **Background**

In essential tremor, the ventralis intermedius (Vim) nucleus of the thalamus is the most common target for deep brain stimulation (DBS) and provides good to excellent results in the majority of patients<sup>3</sup>. Some essential tremor patients also present with laryngeal dystonia (LD), a dystonic movement disorder of the laryngeal muscles. Multiple reports, including ours, have showed that Vim DBS for essential tremor and coincident LD improves voice. Previous reports from the Baylor College of Medicine found that unilateral ViM in essential tremor and coincident LD patients tremendously improved in voice<sup>6</sup>. Furthermore, leaders in the field otolaryngology and speech-language pathology have expressed that the central neurological abnormality observed in LD must be treated, rather than treat the disorder at neuromuscular level (as done with BTX).<sup>6</sup>

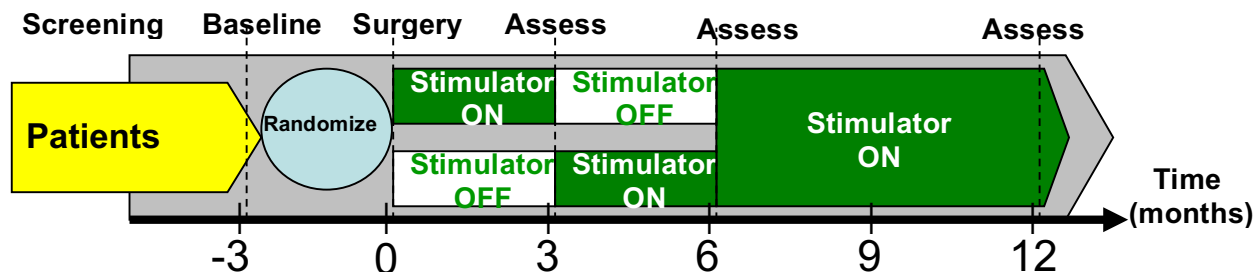
## **Hypothesis**

The ventral intermediate nucleus (Vim) of the motor thalamus receives somatosensory input from the cerebello-thalamic circuit (1-2,9). This circuit is desynchronized in LD as previous studies have shown that the Vim is involved in the motor control of laryngeal musculature (1,9). We believe that neuromodulation of this cerebellar circuit at the Vim will lead to significant vocal improvement in LD patients. We recently targeted the Vim for patients with coincident essential tremor and LD. We found that patients significantly improved in voice,

neurological, and quality of life outcomes; this publication is currently under preparation.

### Study Design

To investigate our hypothesis, we will conduct a prospective, randomized, double-blinded, crossover Phase 1 DBS trial in LD patients. Patients will be randomized to either active or sham-stimulation for 3 months, crossed-over, and conclude with open-label treatment for 6 months. Patient and assessors will be blinded to treatment allocation. Below is a graphical illustration of trial.



Previous Phase 1 trials for new indications of DBS have recruited N=6 patients. We plan to also recruit N=6 patients for this trial from the Pacific Voice Clinic. We will use a computer-generated 1:1 pairwised randomization sequence when the patients are enrolled into the trial, so that similar numbers of patients are recruited to each study group. Patients will be evaluated in a double-blinded manner for their voice and voice-related quality of life. Patients and rating clinicians will be masked to treatment allocation; an unmasked clinician will be responsible for programming the stimulation.

DBS stimulation parameters will be chosen based on standard programming guidelines. Primary endpoints will assess: (1) patient improvement in SD using the Unified Spasmodic Dysphonia Rating Scale (2) assess patient quality of life using the Voice-Related Quality of Life. Patients will also be asked their subjective assessment of each of the settings. Anujan Poologaindran will be administering these scales.

We also will acquire two advanced neuroimaging scans: PET and DTI. The former will allow us to monitor neural network wide changes as a result of DBS. DTI will allow us to determine which white matter tracts are being activated as a result of this surgery. Once pilot\* testing of the PET protocol is completed, patients enrolled in this trial will be asked to obtain a PET scan at end of the 3-month mark and at the 6-month mark (see trial timeline above). DTI scan will only be required pre-operatively. The neuroimaging arm of our surgical trial will add considerable scientific rigour to our trial and helps us further elucidating the neurobiology of this disease.

At the Vancouver General Hospital (VGH), we have a 17-year experience with Deep Brain Stimulation Surgery. As of 2012, we have performed over 400 of these operations including DBS stimulator programming.

### Details of PET Study

Given that it is very difficult to acquire meaningful functional MRI scans with DBS electrodes in the brain, we have decided to acquire functional PET scans to study how DBS changes the speech neural networks in our patients while they talk. In collaboration with UBC Professor Vesna Sossi, a world-leader in PET imaging, we

have decided to investigate the feasibility of applying a very innovative and informative approach to acquiring FDG-PET scans<sup>10</sup> developed by a group from Harvard. The technique is called “fPET-FDG”. Briefly, this involves the participant being intravenously administered with fluorodeoxyglucose (FDG) in saline solution at a constant infusion rate of 0.01 ml/s for 90 mins (duration of a single scan). Venous blood samples will then be collected every 10 min from the other arm during scanning, centrifuged to obtain plasma, and aliquoted in a gamma count that had been calibrated to the PET scanner to measure venous activity during the experiment<sup>10</sup>. This methodology follows the recent publication by the Harvard group which can be found in reference 10 for details.

Ultimately, this methodology overcomes technical limitations in traditional PET methodology (Bolus Method) which involves two scans and two large doses of FDG injection at the start of the experiment. The only caveat is that we will also have to acquire venous blood samples throughout the experiment in this new method. Together with consulting with Dr. Vessna Sossi and her team, we believe that fPET-FDG is most effective approach in answering our scientific question given that we are trying to dynamically measure glucose metabolism during a task and trying to acquire brain scans that closely parallel functional MRI scans.

\*Pilot Test of Scan- Before implementing this methodology into the overall trial, we will pilot this in a healthy control and our most severe trial participant. (Note- Both of them already been recruited as the patient part of the trial has asked a friend to be a healthy control for this scan). The purpose of the pilot testing is to optimize acquisition parameters, optimize the behavioral task, and determine if we will observe meaningful changes using this new fPET-FDG methodology.

\*Scans for The Trial- If the pilot testing is successful, we will implement this new fPET-FDG methodology into our overall trial. Patients will first have a Raclopride-PET Scan to study how dopamine is modulated in their brains with DBS-ON and DBS-OFF. They will then have this new fPET-FDG scan optimized in the pilot testing. Both of these scans will take place at the 3, and 6 month mark of the study (see trial figure for clarification)

### **Adverse Events**

There can be temporary side effects related to the stimulation spreading outside the target area of the brain. These side effects depend on what area of the brain is being stimulated and can include tingling, muscle tightness, double vision, hoarse speech, and dyskinesia. These temporary side effects can be adjusted and resolved by the DBS Clinicians and be minimized. In this study, if any adverse events occur, the patient will be able to contact Dr. Honey on a 24/7 basis. The DTI scan is a standard MRI scan and carries no additional risk to the patient. The PET scan will use ligands that expose the patient to radiation. Each PET scan entails a radiation exposure similar to a single transatlantic 6-hour flight.

### **Significance**

The significance of this research is two-fold: improving the patients’ spasmodic dysphonia symptoms and secondly, providing neurosurgeons with a strategy of treating spasmodic dysphonia. This trial will be of international significance as it is the first time these dystonia patients will be undergoing DBS intervention.

In the past, otolaryngologists have been involved in treating spasmodic dysphonia cases. Our study has the potential to show that perhaps, DBS can be used for pure spasmodic dysphonia as well. This will be the largest study reported in the literature on studying the effects of DBS on spasmodic dysphonia. Based on the limitations of existing treatments, DBS can provide SD patients with a long-term and sustained relief from their voice disorder. Our work has the potential to revolutionize the care provided for these patients.

SD is the third most common focal dystonia followed by cervical dystonia and blepharospasm. This disorder has classically been thought of as a disorder of the laryngeal muscles or of psychogenic origins. Recent neuroimaging studies have emerged indicating the presence of a central neurological abnormality in the basal ganglia of SD patients (6). Thus, our current investigations are aimed at determining the efficacy of DBS for SD.

***Un-randomization:***

In the case of an adverse or unanticipated event during this surgical trial, the patients will be un-randomized completely turned off. However, based on the literature and our 15-year experience, we expect all patients to experience at least some benefit (even if minimal to none) rather than deteriorating.

**Novelty**

DBS therapy has been used in clinical practice for the last 15 years. Recent “indications” for DBS include Alzheimer’s disease, anorexia nervosa, and even obesity. Unlike these disorders, LD is a movement disorder that can follow track of DBS for Parkinson’s disease, essential tremor, and primary dystonia as the surgical gold-standard treatment. We hope to provide a novel neurosurgical treatment for LD and potentially show this is a new “indication”. While existing treatments such as BTX therapy and laryngeal nerve surgery aim to treat SD at the neuromuscular level, our goal is to use DBS to treat the central neurological abnormality that precipitates this voice disorder.

**Statistics**

We will compare the primary (Unified Spasmodic Dysphonia Rating Scale) and secondary endpoints (Quality of Life) at baseline, for the off- stimulation period and the on-stimulation period, with repeated measures ANOVA. For the endpoints in which a significant effect of timepoint ( $p < 0.05$ ) was identified, pairwise comparisons will be performed between each of the three timepoints (baseline *versus* off stimulation, baseline *versus* on stimulation, and on stimulation *versus* off stimulation) and a Bonferroni-corrected p values will be completed.

We will also compare the effect of randomisation sequence on the difference in USDRS scores between the on-stimulation and off-stimulation periods in the blinded phase of the trial using an unpaired *t* test.

**Organization**

At the Surgical Centre for Movement Disorders at Vancouver General Hospital, we have a 15-year experience with DBS surgery and programming for movement disorders. Patients eligible for this study will be all patients who have already underwent or who will be undergoing thalamic DBS surgery to ameliorate their essential tremor. Patients will be tracked through Dr. Honey’s clinic and given a research identification number. After enrollment, they will be followed-up by Dr. Honey and programming will begin one-month after surgery. Data will be burned onto a CD using only their research identification number. This data will then be analyzed to determine if there is an improvement in the patient’s spasmodic dysphonia symptoms and quality of life. The results will be published in a peer-reviewed journal with no reference to individual patients.

## Figures

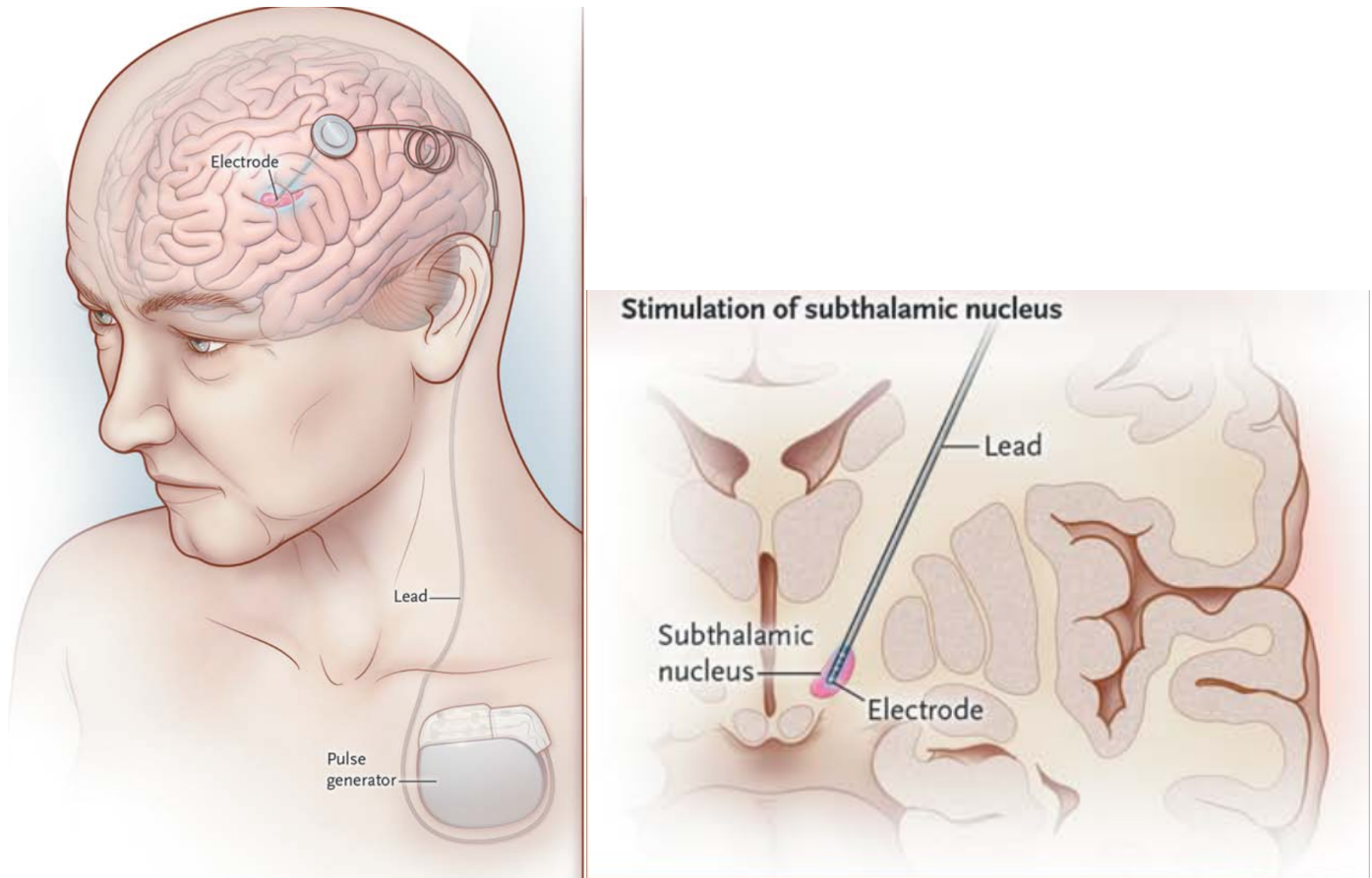


Fig. 1. illustrates how electrodes are implanted deep within the brain and are powered by a pulse generator implanted under the clavicle (collar bone).

Source: Okun, Michael. "Deep-brain stimulation for Parkinson's disease." *The New England Journal of Medicine* 367.16 (2012): 1529-38. Print.

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