THE NEUROSURGICAL TREATMENT OF SPASMODIC DYSPHONIA:
THINKING OUTSIDE THE VOICE BOX

by

Anujan Poologaindran

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Abstract

Spasmodic Dysphonia (SD) is a neurological speech disorder characterized by sudden and involuntary contractions in the laryngeal musculature during speech production. In adductor SD (80-90% of cases), the vocal cords slam together and stiffen making it difficult to produce speech. As a result, an individual’s quality of life is impacted due to significant social embarrassment and the inability to work. Since the 1980s, the standard of care for SD has been to inject botulinum toxin A (BTX) into the affected laryngeal muscles thereby diminishing the spasms. Unfortunately, this therapy is limited by the delayed-onset of benefits, wearing-off effects, and repeated injections required every 3 months. To make a quantum leap in treating SD and providing patients with long-term therapy, the central neurological problem needs to be addressed and not the resultant peripheral spasms. Deep Brain Stimulation (DBS) is a neurosurgical therapy that repairs malfunctioning neural circuits giving rise to pathological behavior; DBS is the standard of care for movement disorders such as Parkinson’s disease and essential tremor (ET). In this thesis, we set out to investigate 1) which motor thalamic neural circuit required neuromodulation for SD, 2) if thalamic laryngeal control was lateralized, and for the first time, 3) if chronic subcortical electrical stimulation can provide long-term relief in SD. First, we systematically interrogated the pallidal and cerebellar inputs into the thalamus of an ET patient with coincident SD. Next, we studied n=6 with ET and coincident voice tremor to assessed if left, right, or both thalamic electrodes were crucial for vocal fold control. Finally, we launched a Phase 1 trial (DEBUSSY) on unilateral thalamic DBS for SD. Overall, we determined that unilateral left thalamic Vim DBS can safely and instantaneously abort laryngeal spasms in
n=4 SD. There were no serious complications or adverse events to report. If voltage increased above the therapeutic range, dysarthria and contralateral dysmetria was induced but resolved with stimulation adjustment. Finally, the dentato-rubro-thalamic tract appears to be preferentially affected during DBS treatment for SD. Future work will characterize the long-term benefit of DBS in SD and further elucidate the mechanism by which DBS mediates improvement.
Spasmodic Dysphonia (SD) is a neurological speech disorder characterized by involuntary vocal cord spasms during speech production. With an average age of onset at 45, SD significantly affects an individual’s quality of life due to social embarrassment and inability to work. Since the 1980s, SD has been treated as a muscular problem. To make a quantum leap in treating SD, we must think outside the voice box and repair the brain region involved in generating these spasms. Deep Brain Stimulation (DBS) is a surgical therapy that involves implanting an electrode deep in the brain to repair abnormal electrical circuits. For the first time ever, we applied DBS for SD and found that a single electrode in the left motor thalamus safely and instantaneously aborts laryngeal spasms in SD without complications. This work represents the first neurological treatment for SD and represents a viable long-term solution for patients with severe SD.
Preface

This thesis is ultimately based on a collection of works aimed at elucidating the neurophysiology of laryngeal control and repairing malfunctioning neural circuits in spasmodic dysphonia.

Chapter 2. A version of this material has been submitted for publication as “Poologaindran A, Cheng J, Sulistyanto A, Morrison MD, Rammage LA, Sankar T, Allegretto M, Morzaria S, Appel-Cresswell S, Sossi V, Honey CR. Landmark Papers in Spasmodic Dysphonia: Trends in Clinical Care and Research”. I was involved in the investigation and design of this bibliometrics study and wrote the first draft of this article under the supervision of Christopher Honey and intellectual input from my co-authors.

Chapter 3. A version of this material has been published as “Poologaindran A, Ivanishvili Z, Morrison MD, Rammage LA, Sandhu M, Polyhronopoulos N, Honey CR. The Effect of Unilateral Thalamic Deep Brain Stimulation on the Vocal Dysfunction in a Patient with Spasmodic Dysphonia: Interrogating Cerebellar and Pallidal Neural Circuits. J Neurosurg. 2017. Mar 17:1-8”. Christopher Honey performed the surgical operation and Mini Sandhu and Nancy Polyhronopoulos performed DBS programming as related to Figures 3.1, 3.2, 3.3, and 3.4. I collected/analyzed data and wrote the entire manuscript with intellectual and editorial discussions with Christopher Honey. This article has been reprinted with permission from Journal of Neurosurgery.

Chapter 4. A version of this material is being submitted for publication “Sulistyanto A, Poologaindran A, Avecilias-Chasin J, Morrison MD, Rammage LA, Honey CR. Hemispheric
Analysis of Thalamic Deep Brain Stimulation for Voice Tremor: Is it Left, Right, or Both?” Dr. Honey and I conceived this experiment in order to study the lateralization of thalamic laryngeal vocal fold control for our study on DBS for Spasmodic Dysphonia. Adi Sulistyanto and myself collected data and analyzed data. Adi Sulistyanto wrote the first draft of the manuscript and I provided intellectual input into subsequent drafts.

Chapter 5. In the next 12 months, a version of this material will be submitted for publication as results of a clinical trial. Christopher Honey, along with Adi Sulistyanto, performed the DBS operations on n=4 patients for SD. Patient selection was completed by Murray Morrison and Linda Rammage. I helped in justifying this clinical trial with preliminary experiments, assisting with trial design, data collection, choice of primary endpoints, and represented the primary point of contact for all patients in the trial.

The University of British Columbia Clinical Research Ethics Board approved the study contents of Chapter 3 (H14-03192), Chapter 4 (H16-01694), and Chapter 5 (H15-02535). The patients provided informed consent for participation in this study. The study in Chapter 4 and Chapter 5 were also registered on clinicaltrials.gov (NCT02960243 and NCT02558634 respectively).
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Finally, I would like to thank my family and my friends for providing their continued support throughout my time at UBC.
Dedication

This work is dedicated to my Mother, Yogam.
Chapter 1: The Neuroscience of Speech Production and Pathophysiology of Spasmodic Dysphonia

Speech production is arguably the most complex motor skill routinely performed by humans — it is a defining characteristic of our species. The ability for our vocal cords to generate even non-meaningful syllabic utterances requires precise spatiotemporal interactions between several cortical and subcortical regions\(^1\). When component(s) of this complex neural network deviates from synchrony, neurological speech disorders may arise. For example, Spasmodic Dysphonia (SD), a neurological speech disorder characterized by sudden, involuntary spasms in the laryngeal musculature during speech production\(^2\).

This chapter will begin with outlining our current understanding of the anatomy and physiology of central voice production with a focus on the thalamic and cerebellar laryngeal control. A discussion on the clinical features/pathophysiology of SD and research questions in this thesis will conclude this introductory chapter.

1.1 Three Levels the CNS Controls Vocalization

The central nervous system (CNS) has three levels of increasing complexity that controls vocalization\(^2\): the lowest level of control is from the brain stem and spinal cord, the next level of control is from the periaqueductal gray area and cingulate cortex, and finally, the highest level of control is by the laryngeal motor cortex (LMC)\(^2,3\). Innate forms of vocalizations, such as a child crying or pain shrieking, rely on the lower two levels of control, while learned vocalizations, such as producing syllables, relies on the highest level of control\(^1\text{-}^4\). The following three sections will briefly discuss these three levels of control in health and disease.
The Brainstem and The Nucleus Ambiguus

Out of the three levels of CNS hierarchy for voice production, the brainstem houses the reticular formation and phonatory nuclei\(^2\). This level of voice control has two different neural circuitry inputs\(^2,5\). The first input is from the periaqueductal gray (PAG) and cingulate cortex (CC) through the nucleus retroambiguus –this circuit serves as a gating function for innate and emotion-related vocalizations\(^5\). The second input is from the pyramidal and extrapyramidal neural network, namely the motor cortex and basal ganglia –this circuit serves execute the motor commands for learned vocalization\(^2,5\).

The nucleus ambiguus is the motoneuron that contains cell bodies that innervates the ipsilateral muscles in the larynx and is the nucleus strongly associated with speech and swallowing processes\(^6\). The nucleus ambiguus directly connects to the intrinsic laryngeal musculature via the recurrent laryngeal nerve. Given it’s role in speech and breathing function, the nucleus ambiguus establishes also communicates with other brainstem nuclei involved in coughing and gagging\(^5,6\). When newborn cries, this first level of CNS vocalization is responsible for this effect, specifically because nonverbal emotional vocalization is not learned and not under higher cortical control. Perhaps the most striking example of the brainstem’s primitive role in vocalization is anencephalic infants ability to produce vocal utterances\(^7\). Lesions in the nucleus ambiguus results in paralysis and atrophy of the innervated muscles thereby leading to dysphagia and dysphonia\(^8\).

The Periaqueductal Gray and Cingulate Cortex

Moving one level above the brainstem control of vocalization, the next level involves
control from the periaqueductal gray (PAG) and cingulate cortex (CC). These two areas are actively involved in the voluntary initiation and suppression of vocal utterances, for example suppressing laughter\textsuperscript{1,4,5}. When controlling voice initiation and modulating voice intensity, the CC and PAG are critically involved in these two behaviours. The overall consensus in the field is that the PAG-CC neural circuitry is responsible for executing the “affective” component of vocalization\textsuperscript{1-5}. Despite CC destruction, the PAG is still involved during voice production\textsuperscript{2}, but with the loss of the emotional aspect. However, when the PAG is destroyed, all vocalizations from the CC are abolished resulting in mutism\textsuperscript{9,10}. Hunsperger demonstrated that PAG electrical stimulation in cats leads to hissing or meowing\textsuperscript{12}, while Juergens and colleagues demonstrated that PAG is responsible for yapping or trilling in the squirrel monkey\textsuperscript{13}. Thus, this second, more complex level of CNS vocalization, is critical for emotional modulation of voice production and operates independently from the neural circuit responsible for learned vocalizations.

\textit{The Laryngeal and Orofacial Motor Cortex}

The laryngeal and orofacial motor cortex represent the highest level in CNS voice production\textsuperscript{2-4}. Unlike the two lower levels of CNS vocalization, the brain stem circuitry and PAG-CC circuitry, the laryngeal and orofacial motor cortex are responsible for the development of learned voice production. This cortical area is located in the most ventral aspect of the motor cortex and adjacent to the sylvian fissure\textsuperscript{4} and commands the intricate motor execution of nearly 100 muscles involved in speaking, swallowing, and breathing. The voluntary control of voice production is carried out by the motor cortex via the corticobulbar tract and extrapyramidal system\textsuperscript{5}. To appropriately function during voice production, the motor cortex
receives several inputs from various brain regions. It receives input from the cerebellum via the ventral intermediate nucleus of the thalamus in order to achieve smooth and coordinated transitions between consecutive voiced sequences. It obtains sensory input from larynx via the ventrocaudalis nucleus of the thalamus and the somatosensory cortex. Finally, and arguably the most complex of neural computations, the laryngeal and orofacial motor cortex receives input from the premotor cortex, including Broca area, and from the supplementary and pre-supplementary motor areas to give rise to motor commands. Evidence for non-human primates (NHP) having reciprocal transcallosal inhibitory connections between the right and left laryngeal motor cortex (LMC) exists\textsuperscript{13,14}, however, in humans, this anatomical connection has yet to be demonstrated.

With regards to the muscles in the larynx, they all receive bilateral innervation from the left and right laryngeal motor cortex (LMC)\textsuperscript{2-5}. Thus, when one side is damaged due to a stroke or tumour, the individual can still maintain voluntary voice control\textsuperscript{5}. Interestingly, unlike humans, NHPs have indirect connections to the brainstem laryngeal motoneurons –this might explain their diminished capacity for learned vocalization\textsuperscript{5}. This difference in direct (humans) versus indirect (NHPs) connections to the laryngeal motoneurons likely represents an evolutionary advancement for humans to execute faster and more complicated laryngeal movements\textsuperscript{2,5}. When the LMC is damaged, very mild vocalization deficits occur in NHPs. In contrast, bilateral LMC lesions resulted in pseudomotor palsy and speech loss, preserving only PAG-CC dependent vocalizations such as laughing and crying\textsuperscript{1,2,5}. When subjects undergoing functional MRI scans were instructed speak and sing, the left facial motor cortex showed
stronger activated for the former, while the right facial motor cortex as more activated for the latter\textsuperscript{15,16}. This functional difference is supported by lesion data as left-sided lesions affect the linguistic component of speech\textsuperscript{17-19} while right-sided lesions affect the prosodical component of speech\textsuperscript{19-21}.

Given that voluntary control of breathing requires the use of similar neural networks for phonation\textsuperscript{4,22}, an fMRI study was used to study blood-oxygen level dependent (BOLD) changes when speaking and expiring. The authors found that when comparing the two conditions, there was a significant left-hemispheric activation in the premotor, motor, and auditory compared to the right, during speaking\textsuperscript{22}. A more recent study comparing breathing vs speech production also found a left-hemisphere bias on fMRI during speech, but not breathing\textsuperscript{23}. Together, these studies all point to a critical role for the left LMC in voice production and that future neuromodulation treatments for voice disorders should be aware of this bias during treatment\textsuperscript{24}.

1.2 Cerebellar and Thalamic Contributions to Speech Motor Production

The Cerebellum and Speech Motor Control

The cerebellum is intimately involved with regulating the exquisite temporal organization of motor plans required to produce smooth and coordinated speech\textsuperscript{1}. This viewpoint is strongly supported from studies reporting on cerebellar damage and/or lesions. For example, in the event of a cerebellar stroke to the superior cerebellar artery, ataxic dysarthria ensues\textsuperscript{24}. Dysarthria is characterized by inaccurate articulation, slower speech tempo, and prosodic\textsuperscript{25}. These stroke studies are supported by more recent Vim (cerebellar
input into thalamus) Deep Brain Stimulation (DBS) and Vim thalamotomy surgeries as a large electrical field or lesion size is known to cause ataxic dysarthria\textsuperscript{26}. Pathological adaptive timing mechanisms in the superior cerebellar cortex (SCC) is thought to give rise to dysarthria; the SCC is a critical area in motor learning and feedforward control during speech production\textsuperscript{4}.

The cerebellum is also involved in non-motor processing such as auditory and sensory information. The cerebellum’s lobule VII has been implicated sensory feedback control\textsuperscript{1,3,5}. This activity may be related to the cerebellum’s role in verbal working memory, which is impaired after cerebellar stroke\textsuperscript{27,28}. Furthermore, during covert or inner speech, the cerebellum plays a role in sequencing a pre-articulatory verbal code\textsuperscript{29,30}.

**The Thalamus and Speech Motor Control**

The thalamus can be thought of as the grand central station in the brain and plays an integrative role in three processes of voice production\textsuperscript{1,5}. The thalamus 1) processes laryngeal proprioceptive and tactile sensory information (via ventrocaudal nucleus) and 2) directs motor commands to larynx (via ventrolateral nucleus), and 3) processes incoming and outgoing auditory information (via medial geniculate nucleus).

Electrical stimulation of the left ventrolateral thalamus (VL) during functional neurosurgery revealed its prominent role in speech motor control. For example, neurosurgeon Georges Schaltenbrand reported that stimulation of the left VL thalamus during tremor cases can give rise to compulsory speech, such as single syllable exclamations\textsuperscript{31}. He also noted intraoperatively that stimulation can increase or decrease loudness or rate of speech. Lesions in the VL thalamus have resulted in breathy and monotonous voice production; in regards to
articulation, VL lesions have resulted in the loss of distinction between voice and unvoiced phonemes\textsuperscript{32-35}. Interestingly, deleterious effects of electrical stimulation or lesioning has a left-hemispheric bias, and is relatively inconsequential in the right. This finding may be related to the fact that the left ventrolateral thalamus not only projects to the primary motor cortex, but also to Broca’s Area and the supplementary motor area\textsuperscript{36,37}.

1.3 Spasmodic Dysphonia: Clinical Features and Pathophysiology

When one or more levels of the CNS hierarchy for voice control becomes dysfunctional, voice disorders such as Spasmodic Dysphonia (SD) may arise.

\textit{Clinical Features of Spasmodic Dysphonia}

SD is a task-specific focal dystonia characterized by sudden, involuntary spasms in the intrinsic laryngeal muscles during speech production\textsuperscript{1,2}. These spasms are not present during laughter or crying—suggesting the cingulate-PAG circuitry is not involved in the generation of these spasms. SD prevalence is approximately 1-2/100,000 with average age of onset of 45\textsuperscript{2}. Nearly 70\% of SD patients with SD are female and have have a gradual increase in spasms over their life\textsuperscript{38}. There are two main types of SD: adductor (affecting \textasciitilde 80-90\% of patients) and abductor (affecting \textasciitilde 10-20\% of patients)\textsuperscript{3}. Adductor SD is characterized by spasms, usually in the thyroarytenoid muscle (TA), that force the vocal folds together in adduction (or closes) during vowel sound\textsuperscript{3}. In nearly 25\% of adductor SD patients, the dystonic spasms are also accompanied with a tremor component defined as a rhythmic oscillation in intrinsic muscles of the larynx\textsuperscript{39}. In contrast, abductor SD results from spasms when the posterior cricoarytenoid muscles (PCA) abducts (or opens) the vocal folds\textsuperscript{3}. This results in the production of “voiceless”
speech which sounds ‘airy’ or breathy’. For an accurate diagnosis of SD, the NIH recommends nasolaryngoscopy examination during speech and other movement tasks\(^2\). The main treatment options for SD will be discussed in Chapter 2.

**Overview of Pathophysiology in Spasmodic Dysphonia**

As of only recently, insights into the neuroscience of SD has been increasing through anatomical and functional neuroimaging. Recently, Frank Guenther’s speech neuroscience laboratory used fMRI to compare adductor SD patients to healthy controls during a speech production task; the group found that SD patients had a hyperactivated laryngeal sensorimotor cortex compared to controls\(^{40}\). This finding is consistent with the findings of earlier studies\(^3,38\). Interestingly, abnormal activation patterns on fMRI were only found during symptomatic speech and not during asymptomatic laryngeal tasks\(^{38}\). In another imaging study, patients with SD had lower striatal dopamine D2/D3 receptors and levels of dopamine during symptomatic speech compared to controls\(^{41}\). Moreover, a combined post-mortem neuropathological and structural imaging study found reduction in axonal density and myelin along the pyramidal tracts\(^{42}\). Research in computational neuroscience have suggested an increase in the hyperactive feedforward command system leading to excessive articulatory movements during in speech production in SD\(^{40}\). This hyperactivity of the movement circuitry may be accompanied by a hyperactive somatosensory system which may lead to SD\(^4\). These viewpoints will be further discussed in Chapter 5 of this thesis.

### 1.4 Main Research Questions of the Thesis

In this thesis, we set out to investigate the following questions:
1. What are the most highly cited articles in the field of spasmodic dysphonia with regards to clinical care and research?
   ▪ We hypothesize that minimally-invasive peripheral options such as botulinum toxin A are the main treatment options for SD and dominate the most highly cited works in the field

2. Which neural circuit(s) governing articulatory movement requires neuromodulation for improvement of SD?
   ▪ Keeping consistent with the pathophysiology of other dystonias, we hypothesize that the pallidothalamic circuitry requires neuromodulation for SD. However, a growing body of evidence suggests the involvement of the cerebellothalamic tract in dystonia pathophysiology

3. Does the dominant or non-dominant motor thalamus or both play an important role in laryngeal vocal fold control?
   ▪ Keeping consistent with other movements, we hypothesize both motor thalamic Vim, not one alone, plays an important role in laryngeal vocal fold control and voice tremor

4. Based on our findings from Question 2 and 3, can chronic DBS in SD be safe and effective for SD?
   ▪ We hypothesize that DBS of the appropriate neural circuitry will lead to sustained and long-term improvement in SD, keeping consistent with our experience and literature on DBS for other dystonias.
To conclude, our ability to produce purposeful vocalizations and speak fluently is regulated by a complex neural network. SD is a disorder of the CNS and an example of when this complex neural network becomes dysfunctional. Based on the present literature, experts and our team believe that the single major area of further research required is developing a CNS-based treatment to treat the malfunctioning neural circuitry giving rise to SD.
Chapter 2: Landmark Papers in Spasmodic Dysphonia: Trends in Clinical Care & Research

In the 1980s, New York otolaryngologist Andrew Blitzer and colleagues first introduced and popularized the concept of botulinum toxin (BTX) injections for SD. In the 1990s, Gerald Berke and colleagues introduced Selective Laryngeal-Denervation- Reinnervation (SLAD-R) surgery as a surgical option for SD. Then in the early 2000s, Japanese surgeon Nobuhiko Isshiki developed thyroplasty for SD.

In this chapter, I sought to review the evolution in clinical care and research in SD using a formalized bibliometric approach. The number of citations a scientific article receives can be used as an objective marker to determine its relative influence on the discipline. An analysis of highly cited works in SD has yet to be carried out and can be valuable for several reasons. First, determining the characteristics of such works can serve as an indicator of the evolution of a field and future directions. Second, non-profit and governmental agencies can use this information for resource allocation purposes across projects, scientists, and centres. Third, a list of highly cited works is of significant educational value for both young trainees and experienced researchers/clinicians.

The primary objective of this review was to identify and characterize SD publications that have the greatest number of citations and provide a 2017 “snapshot” of the field. Normally, research in the evolution of a field identifies “citation classics” - that is, articles cited more than 400 times. However, given the relatively low incidence of SD, we aimed to identify the 50 most cited articles in the field rather than “citation classics”.
2.1 Methodology of Bibliometrics Study

To determine the 50 most cited papers in SD, we employed freely available software that calculates citation metrics: Harzing’s Publish or Perish. This software uses Google Scholar as its primary database. We searched titles and abstracts of indexed journal articles containing the following MeSH terms: spasmodic dysphonia, spastic dysphonia, functional dysphonia, laryngeal dystonia, and/or botulinum toxin, without date or other restrictions. We then reviewed the top 50 results containing the highest number of citations manually. Inclusion criteria consisted of articles, including systematic reviews, that were published in a peer-reviewed journal and focused on the characterization, diagnosis and/or treatment of SD. We excluded those articles that: i) dealt with a condition that was not SD; ii) utilized the term “dysphonia” in an unrelated context; or iii) were books, manuals, non-peer reviewed articles, guidelines, or other non-biomedical publications.

For content analysis, we subdivided each article into one of six categories: botulinum toxin (BTX) treatment studies, classification studies, surgical management, non-surgical management, laboratory studies and review articles. Botox studies included studies on the clinical treatment of SD. Classification studies included papers that dealt with definitions, incidence/prevalence over time, and clinical scale development. Surgical management articles were primarily focused on surgical technique description and outcomes while non-surgical management included articles covering speech-therapy and medication treatment. Laboratory studies included papers that investigated mechanisms and translational research, including, but not limited to genetics and biochemical features related to the development of SD. Finally,
reviews included articles discussing the state of SD care and management. A critical review of the highly cited articles by category was also conducted, commenting on for example, success rate of therapy or main complications.

Lastly, in a separate analysis, in order to determine the areas of on-going research in SD, we analyzed clinical trial registries (i.e-clinicaltrials.gov) using the same search terms listed above.

2.2 50 Most Highly Cited Articles in Spasmodic Dysphonia

A table of the top 50 highly cited articles in SD can be found in the Appendix.

Overview of Analysis

Using the methods described above, we analyzed the 50 most cited articles in SD (Appendix-A). Publication date ranged from 1959 to 2009, with The Laryngoscope as the journal publishing the most number of articles (15/50) and Mitchell F. Brin as the author with most publications (9/50) (Table 2.1-2.2). The most frequently cited article (471 citations) was published by Brin and colleagues in 1987 (“Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm”)49.

Table 2.1 Most Frequent Authors of Top 50 Cited Articles (at least 2) in SD

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of articles*</th>
</tr>
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<tbody>
<tr>
<td>Mitchell F. Brin</td>
<td>9</td>
</tr>
<tr>
<td>Andrew Blitzer</td>
<td>8</td>
</tr>
<tr>
<td>Stanley Fahn</td>
<td>7</td>
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<tr>
<td>RE Lovelace</td>
<td>5</td>
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<tr>
<td>Gayle E. Woodson</td>
<td>4</td>
</tr>
</tbody>
</table>

*total number of article contributions in top 50 most cited

Table 2.2- Most Frequent Journals of Top 50 Cited Articles

<table>
<thead>
<tr>
<th>Journal</th>
<th>Number of papers in top 50</th>
</tr>
</thead>
</table>
Botulinum toxin treatment remains the most well-studied treatment method for SD and it was the category with the most cited studies (17) followed by disease classification (14), laboratory studies (6), surgical management (6), review articles (4) and lastly non-surgical management (3) (Figure 2.1). The two decades with the most cited SD articles occurred were the 1980s and 1990s when 15 of the top 50 most cited articles were published (Figure 2.1). This was likely due to the introduction and popularization of the two current treatment methods for SD: botulinum toxin injection by Blitzer et al in the 1980s, and SLAD-R surgery by Gerald Berke et al in 1999.

**Figure 2.1 Heat Map Representation of Number of SD Articles Based on Year of Publication and Article Type** (BoTox: botulinum toxin treatment; Class: classification; Non-surg: non-surgical management; Surg: surgical management; Lab: laboratory studies; Review: review articles.)

<table>
<thead>
<tr>
<th>Journal</th>
<th>Number of papers in top 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Laryngoscope</td>
<td>15</td>
</tr>
<tr>
<td>Annals of Otology, Rhinology &amp; Laryngology</td>
<td>7</td>
</tr>
<tr>
<td>Journal of Voice</td>
<td>5</td>
</tr>
<tr>
<td>Otolaryngology - Head and Neck Surgery</td>
<td>4</td>
</tr>
<tr>
<td>Archives of Otolaryngology–Head &amp; Neck Surgery</td>
<td>4</td>
</tr>
</tbody>
</table>

Several authors have multiple publications in the top 50 cited works (e.g., Andrew
Blitzer, Mitchel Brin). This is evidence that the field of SD has been significantly influenced by only a handful of researchers.

**Botulinum Toxin Treatment Studies**

There were 17 studies on the technique, effectiveness and prognosis of botulinum toxin treatment for the various SD types (adductor, abductor, mixed, respiratory). This category contained the highest number of top 50 cited papers, reflecting the use of BTX as the most widely used therapy for SD.

**Treatment Outcomes with BTX**

Two were qualitative studies on treatment outcome as measured by patients’ perception of functioning and quality of life (QoL) with the Voice-Related Quality of Life (VR-QoL)\textsuperscript{51} and Voice Handicap Index (VHI)\textsuperscript{11}. Both studies demonstrated significant improvement in patient outcomes post botulinum toxin treatment, justifying the continued use of this treatment method for SD. Zwirner published two articles in the early 90s which focused on the quantification of acoustic changes in botulinum toxin treated adductor SD and noted a significant voice improvement with reduction of voice breaking and fundamental frequency\textsuperscript{52,53}. Specifically, he found that unilateral BTX injections were safe and effective in reducing intrinsic laryngeal hyperfunction in all eleven of his patients. These findings were supported by another study that also noted decreased fundamental voice frequency range and perturbation\textsuperscript{54}. The main complications for BTX treatment for SD these authors state were possibility of short-term swallowing or aphonia problems.
**Injection type (unilateral vs bilateral) for BTX**

Most studies employed a unilateral percutaneous thyroarytenoid muscle injection with botulinum toxin type A (Oculinum). Bilateral injection with dose titration had a positive effect on SD\(^{55,56}\) however unilateral injections has been shown to be sufficient in significantly decreasing spasmodic muscle activity in both the injected and non-injected muscles, indicating a local toxin diffusion effect and a potential CNS effect of BTX in improving SD.

**Injection procedure/location for BTX**

Most articles used electromyographic (EMG) guided injection which remains the gold standard for adductor SD treatment. Five articles detailed various approaches to the EMG guided thyroarytenoid injection method. Ford and colleagues demonstrated the effective usage of indirect laryngoscopy for toxin injection with no major complications\(^{55}\). Murry & Woodson found that patients undergoing a combined-modality treatment program for adductor SD with botulinum toxin injection and voice therapy maintained significantly higher mean airflow rates for longer periods\(^{56}\).

**Disease Classification Studies**

Fourteen of the top 50 highly cited articles were included in “classification” studies category. Articles focusing on the natural history and outcomes of SD, disease trends, epidemiology, and comparisons as well as new classifications, descriptions and measurements were included in this category. Three articles described clinical observation studies with/without treatment\(^{57,58,59}\). Two studies utilized EMG to examine laryngeal muscle activity\(^{57,60}\). Three studies focused on distinguishing essential voice tremor and dysphonia, while two focused on
diagnostic criteria/clinical features for dysphonia. One study was on quality of life impact of dysphonia while another was on life events preceding onset of functional dysphonia. One article examined SD risk factors and demographics.

**Surgical Management Studies**

Six articles in the top 50 most cited articles dealt with the surgical management of SD. These articles discussed three procedures: thyroplasty, recurrent laryngeal nerve section (RLN-S), and selective laryngeal denervation-reinnervation (SLAD-R). Herbert Dedo of San Francisco is credited for introducing RLN-S in the 1970s, where a portion of the recurrent laryngeal nerve was cut causing one-sided laryngeal nerve weakness. To enhance the RLN-S procedure, Berke et al. introduced the Selective Laryngeal-Denervation-Reinnervation (SLAD-R) surgery in 1999. He reported on 21 patients who were perceptually judged to have an overall severity of dysphonia that was “absent to mild” following the procedure. Only 1 patient underwent further botox post-operatively. The complications were mainly that a weak voice was present in the post-operative phase which lasted up to 3 months. Isshiki et al. developed midline lateralization thyroplasty for adductor SD in 2000 which involves physical separation of the vocal folds. He performed this procedure on 16 patients and found that the voice was “satisfactory” in all cases, except one cause of traumatic vocal cord paralysis.

**Non-Surgical Management Studies**

Three of the top 50 most cited articles strictly focused on the non-surgical management of SD. In particular, Roy, Ford & Bless (1996) utilized a manual massage of laryngeal muscle tension reduction to improve laryngeal elevation, focal tenderness and voice sustainment. Fex
and colleagues studied before and after effects of voice therapy on functional dysphonia and found that pitch perturbation quotient, amplitude perturbation quotient, and normalized noise energy for 1-4 kHz, and fundamental frequency all showed significant improvement. Meanwhile MacKenzie and colleagues conducted a randomized controlled trial to determine the effectiveness of voice therapy on dysphonia and found that voice quality as assessed by patient and observer ratings significantly improved by 4.1 points on relevant speech language pathology scales. The only aspect that did not improve in this RCT was amplitude perturbation, which showed improvement at six weeks, but not on the completion of the study. Moreover, the authors found that voice therapy had no significant impact on psychological distress or lower quality of life than controls. Ultimately, both studies demonstrated that voice therapy significantly improves voice quality on perceptual measures but not for long term improvement for qualify of life and decreasing psychological distress.

**Laboratory or Basic Science Studies**

Studies investigating the pathophysiology or imaging of SD were included as part of this category. There were six laboratory articles in the top 50 cited articles in SD: two neuropathological studies, two spectral analysis studies, one laryngeal imaging study, and one genetics study. The two neuropathological studies identified an association of SD with lesions in the brainstem and corticobulbar/corticospinal tract. Particularly, Schaefer determined significant correlates between degree of brainstem pathology and vocal tremor while Simonyan and colleagues found focal axonal degeneration and demyelination in the genu of the internal capsule, and clusters of mineral accumulations contacting calcium, phosphorous, and
iron, in the internal capsule, lentiform nucleus, and cerebellum. Robe and colleagues provided evidence for EEG abnormalities in SD and represents one of the major studies in the early 1960s that characterized this disorder of neurological rather than psychogenic origin. Awan and colleagues performed spectral analysis on acoustic data for different voice types and found that this automated analysis can accurately classify voice type 80% of the time. Genetic screening associated two mutations in the THAP1 (DYT6) gene with early-onset SD and other focal dystonias (Djarmati et al, 2009), suggesting that laryngeal dysfunction may be one of the early signs of generalized dystonia.

**Review Articles in Spasmodic Dysphonia**

There were four review articles in the top 50 most cited articles in the field of SD. These articles included a research priorities article, a systematic review, a clinical practice guideline, and an expert-review article. In 2008, a multi-disciplinary team led by Christy Ludlow aimed at identifying research priorities in SD. They concluded that the highest priority research was the characterization of SD versus other forms of focal dystonia, risk factor identification, and development of animal models for pathophysiologic studies and clinical trials. Ruotsalainen and colleagues conducted a systematic review on the treatment of functional dysphonia and prevention of voice disorders and found that voice therapy was effective for improving but not preventing voice disorders. In 2009, the American Academy of Otolaryngology- Head and Neck Surgery Foundation selected a multi-disciplinary panel to create a clinical practice guideline on hoarseness/dysphonia. Schwartz and colleagues strongly recommended clinicians not prescribe antibiotics to treat hoarseness and advocate for voice that reduces VR-QoL.
secondary to hoarseness. Finally, Nelson Roy wrote an expert-review in 2003 on the management and basis of functional dysphonia. Together, these articles have provided timely reviews and updates on the state of SD; highly cited reviews in the future will likely include the central neurological dysfunction involved in SD.

2.3 Publishing Trends over Time

An analysis of the top 50 works indicated that the late 1980s and early 1990s were the most productive time for the field of SD. While it typically takes time for publications to accumulate citations, the field’s most explosive time period came nearly 30 years ago. This coincided with the work of Brin, Blitzer and colleagues on using BTX for this dystonia and the development of BTX to relieve other focal dystonias (i.e. cervical dystonia). Most of the papers from this productive time period deal with BTX management and results.

In general, it is important to focus only on the absolute number of citations of an article, but also the rate of citations over time. For example, two papers with 200 citations may differ in relative impact if one was published 20 years ago (10 citations/year) and the other one was published 5 years ago (40 citations/year). The rate at which a paper is cited can be an indicator of its relative impact and how valuable it is for others in the field within a specified time frame. It is clear that the research into the neuroscience of spasmodic dysphonia and speech control science led by Simonyoan and Ludlow is of the highest relative impact over the last decade.
2.4 Citation Trends in Spasmodic Dysphonia versus Other Fields

In general, the number of highly cited papers is an indication of a field’s size and breadth, as well as the number of active researchers in that area. Such figures may reflect disease prevalence as well as research fund allocation. For example, approximately 107 articles in the field of Parkinson’s disease are considered “Citation Classics”, having been cited at least 400 times. With SD, there is only one article that reached the 400 mark. Comparing the prevalence of SD with Parkinson’s Disease, SD has an estimated prevalence of 1 case per 100,000 (National Spasmodic Dysphonia Association website) while PD has an estimated prevalence of about 300 per 100,000\(^7\). Therefore, given that there are 107 citation classics on Parkinson’s disease (Ponce & Lozano, 2011), the field of SD research only has one citation classic\(^{49}\) --indicating the small size of the SD research field.

2.5 Limitations of Bibliometrics Study

There are a few limitations of our work worth discussing. Our chosen approach and methodology may not have fully captured all the top citations in the field of SD research. We chose to employ Harzing’s Publish or Perish software with Google Scholar as the primary database as it widely encompasses various publication sources and is not biased in limiting the search to select journals. While we acknowledge that a different search engine may have yielded slightly different results, we believe our results are accurate based on similar findings through sample searches in PubMed and Web of Science.

We also set several exclusion criteria that may have impacted our findings. Our study does not include early manuscripts of spasmodic dysphonia from the late 1800s, namely papers...
outlining SD as a psychogenic disorder. We have also chosen not to include articles on certain voice disability scales in our analysis, such as the Voice Handicap Index (VHI) and Voice-Related Quality of Life (V-RQOL), as these tend to include general articles covering a wide range of voice disorders and do not focus on SD.\textsuperscript{76, 77}

Lastly, we acknowledge that the findings outlined in this study are limited to the current timeframe and that future results would be subject to constant changes and updates. We believe our results present a valuable and accurate insight into the past trends in SD research and point to area of research that may be active in the future.

**2.6 Implications for Practice**

This study identified the 50 most cited articles in spasmodic dysphonia. There are a few key implications for clinical practice. First, BTX remains the therapy of choice for SD but a common theme in the highly cited articles suggest problems with BTX and the need for a CNS-based therapy. Second, otolaryngologists, speech language pathologists (SLPs), and those involved in the care and research of SD patients should be familiar with most of these articles as they are a collection of the most impactful work in this field of medicine. Third, laryngology fellowship and SLP training programs could consider including these works in their curriculum to cover not only the historical aspects of SD care, but also pinpoint its scientific foundations, the growth of the field, and future directions. Lastly, young investigators and journal editors can gain insight into the attributes of these highly influential works to determine what work will have a major impact on the field. This collection of articles will likely undergo dynamic change.
over the next decade given the emergence of CNS-based treatments of SD and potential increased involvement of neurologists and neurosurgeons in the care of SD\textsuperscript{15}.

**Future Directions: Targeting the Source of Spasmodic Dysphonia**

Our group is developing Deep Brain Stimulation (DBS) for patients who have inadequate response to BTX and/or have failed SLAD-R surgery (DEBUSSY- clinicaltrials.gov identifier NCT02558634). At the the 3\textsuperscript{rd} International Congress on Treatment of Dystonia in Hannover, Germany, Dr. Andrew Blitzer, the pioneer of BTX for SD, was questioned informally by our team “Why has a CNS-based therapy not been developed for severe SD?” His response was “At the moment, we do not know where to go in the brain.” Our group’s recent report attempted to shed light on this scientific question and determine a suitable neurosurgical target\textsuperscript{15}. We believe that the cerebello-thalamo-cortical neural circuitry needs to be treated in SD. Ultimately, based on existing scientific and clinical evidence, we believe that the left (dominant) cerebellar neural circuitry needs to be principally repaired in SD and not the basal ganglia-pallidal neural circuitry (see article for detailed rational and discussion). While it is very unlikely DBS will replace BTX therapy for SD, it will likely be an option for abductor, respiratory, and severe adductor forms of SD.

In addition to our list of the 50 most cited works discussed above, we also searched clinicaltrials.gov using the same search terms to identify areas under investigation. We found that investigators from the University of Minnesota are researching the use of transcranial magnetic stimulation (TMS) for SD (clinicaltrials.gov identifier NCT02957942). Kristina Simonyan
at Mount Sinai is investigating sodium oxybate, a short-acting GABA-agonist recently demonstrated to provide benefit in SD.

Ultimately, due to the relatively low incidence of SD, larger, multi-centre studies are needed to more rapidly advance the field. Moreover, understanding the neuroscience behind—and developing CNS-based treatments for—SD requires greater funding from philanthropic and governmental organizations. Our work suggests that pre-eminent researchers in the SD field recognize that novel therapies are required for patients who have inadequate response to BTX or fail SLAD-R. Indeed, the next era of SD research may indeed be one of neuro-laryngolog
Chapter 3: Rational for Deep Brain Stimulation and Justifying Target Selection for Spasmodic Dysphonia

Spasmodic Dysphonia (SD), also known as laryngeal dystonia, is a central nervous system disorder where an individual’s ability to speak is limited due dystonic contractions in the intrinsic laryngeal. After cervical dystonia and blepharospasm, SD is the third most common focal dystonia, which significantly impairs communication. For the past 30 years, botulinum toxin A (BTX) injections into the laryngeal muscles has been the standard treatment. This therapy results in a temporary chemical denervation of the impaired muscles thereby diminishing the intensity of the spasms. Despite BTX’s popular and widespread use, it has multiple limitations rendering its use for severe SD patients substandard. Firstly, the therapeutic effect is temporary and repeated injections are necessary every three to four months. Secondly, with BTX therapy, there is a delay in the onset and a fading of the benefits—this results in best symptom control for only a portion of the treatment. Moreover, with repeated long-term injections, some SD patients may develop neutralizing antibodies to BTX. Another, more drastic, approach for SD has been peripheral laryngeal nerve surgery, formally called Selective-Laryngeal Dennervation Renervation (SLAD-R). Both BTX and SLAD-R mimic the early treatments for cervical dystonia, that is, they ignore the central neurological problem and focus on diminishing the resultant muscle spasms.

In adductor SD, which represents 80-90% of SD cases, the vocal cords hyper-adduct and stiffen making it difficult to produce speech. The resulting voice is commonly described as strained, choppy, and full of effort leading to a significant impact an affected
individual's quality of life. Very seldom, an essential tremor (ET) patient requiring DBS may present with coincident adductor SD. To study the underlying motor thalamic circuitry and SD, in one such patient with ET and coincident adductor SD, we studied the effects of thalamic Deep Brain Stimulation (DBS) on vocal function.

3.1 Methodology to Simultaneously Interrogate Cerebellar and Pallidal Neural Circuitry in SD

Patient Characteristics and Study Design

A right-handed 79-year-old female with ET was sent to our team for left thalamic DBS to improve dominant right upper limb tremor. Coincidentally, the patient also had a concurrent diagnosis of adductor SD. The SD was being treated with BTX for the previous two years at the Pacific Voice Clinic by Professor Emeritus Murray Morrison. A DBS electrode was placed into her left thalamic Ventral intermediate (Vim) nucleus via a trajectory selected to place the more proximal contacts in her Ventral oralis anterior (Voa) nucleus. Post-operatively, a mild change in the patient’s speech was noted by the attending neurosurgeon. Six months after optimizing the stimulation to reduce her right upper limb tremor, she entered the study. First, we compared measures of voice, and quality of life following 14 days of Vim DBS or 14 days of sham-stimulation in a prospective, randomized, evaluator-blinded manner. Second, we prospectively evaluated her vocal characteristics after five days of randomized, double-blinded focal stimulation of the following nuclei: Vim, Voa, and Vim + Voa. Based on the fusion note, low voltages (2.0 V) in bipolar configuration were used in an attempt to focus the stimulation within the desired nuclei. Bipolar electrode settings were purposely chosen in order to narrow the
electrical field and because the maximal current density is presumed to be near the cathodal (-) electrode contact.

**Surgery**

Standard frame-based stereotactic neurosurgical planning for Vim tremor surgery was conducted. We selected her left Vim target relative to the midcommissural point (MCP) to be anterior -5.5 mm, lateral -12.6 mm, and vertical 0.0 mm with an approaching ring angle of 60° (arc angle of 18°). We deliberately selected this anterior approach such that the proximal contacts of the electrode would be in the Voa nucleus. We chose this in the mistaken belief that the proximal electrode contacts would benefit her SD, while her more distal electrode contacts in the Vim nucleus would benefit her tremor. Microelectrode recording of thalamic bursting phase locked with arm tremor and macrostimulation to block tremor was used to confirm electrophysiological placement of the DBS lead (Medtronic 3387).

**DBS Stimulation Parameters**

DBS stimulation parameters were initially programmed to maximally alleviate her contralateral upper limb tremor, the original reason why this patient was referred to our team. We then evaluated her voice with the stimulation turned OFF for 14 days and ON for 14 days. The left electrode’s final stimulation parameters were Case +, contacts: 0 off, 1-, 2 off, 3 off; pulse width 90 μs, frequency 185 Hz, and voltage 3.0V.

Since we had deliberately taken an anterior trajectory through the motor thalamus to experimentally assess the cerebellar and pallidal circuit’s influence on voice, we were able to use low voltage stimulation confined to each nuclei. Low voltage focal Vim (cerebellar outflow)
stimulation parameters were: contacts 0-, 1+, 2.0 V, 185 Hz, and 60 μs. Low voltage focal Voa (pallidal outflow) stimulation parameters were: contacts 2-, 3+, 2.0 V, 185 Hz, and 60 μs. For multi-target stimulation, the stimulation parameters were: contacts 0-, 3+, 2.0 V, 185 Hz, and 60 μs.

**Voice Assessment**

The Unified Spasmodic Dysphonia Rating Scale (USDRS)\(^81\), a standardized voice scale to assess adductor SD severity, was completed independently by two raters. The raters, an experienced laryngologist (MDM) and a speech language pathologist (LR), obtained a 95% inter-rater reliability on sample recordings prior to evaluating study recordings. This evaluation was completed with raters and patient blinded to the DBS settings. The patient, blinded to settings, also completed a Voice-Related Quality of Life (VR-QoL) questionnaire\(^82\), a widely-accepted and standard questionnaire used in laryngology and speech-language pathology to assess QoL in dysphonic patients.

**Statistics**

The patient in this study completed the USDRS and VR-QoL assessments with DBS ON (optimized for tremor control), OFF, and at the end of each experimental focal thalamic stimulation (Vim, Voa, and both) for a total of five trials. Statistical analysis of the resulting data was completed in two stages. Stage 1 involved comparing the USDRS and Vr-QoL subsections with DBS OFF vs. ON using a Wilcoxon-signed rank test. Stage 2 involved comparing different combinations of focal thalamic stimulation with each other as measured by the USDRS and Vr-QoL subsections using a Wilcoxon-signed rank test. Since calculating total USDRS and VR-QoL
would be statistically inappropriate for a single patient, we analyzed each of the USDRS’s subsections after taking an average score between the raters for each of the 5 conditions. The subsections of the self-administered Vr-QoL was also analyzed in each of the five conditions. SPSS Version 22 was the statistical software used for inter-rater reliability and voice data analysis.

3.2 Findings from Low Voltage Experimental Thalamic DBS in a Case of SD

Unilateral left thalamic Vim stimulation (DBS ON) significantly improved SD vocal dysfunction compared to no stimulation (DBS OFF) as measured by the USDRS (p<0.01) and Vr-QoL (p<0.01). Figure 3.1 and Figure 3.2 depicts this improvement in vocal dysfunction as captured by the subsections of the USDRS and Vr-QoL. Figure 3.3 is a post-operative CT with the Schaltenbrand and Wahren Atlas overlay illustrating the location of each lead contact with respect to the individual thalamic nuclei. Contact 0 is in the ventral Vim (z=0) and Contact 2 is in the Voa (z=3). The Voa contact falls within Voa-thalamotomy target of 1-5mm above the AC-PC plane83,84. Pre-operatively, right limb tremor was 38 as measured by the tremor rating scale. During DBS ON and DBS OFF, tremor scored 3 and 41 respectively.

In our experimental motor thalamic investigation, both low voltage Vim (p<0.01) and multi-target Vim + Voa (p<0.01) was significantly superior to low voltage Voa stimulation as measured by the the USDRS. There was no significant difference (p>0.01) between low voltage Vim and multi-target stimulation. Low voltage Voa was ineffective as Voa stimulation was worse than sham stimulation (p<0.01). Figure 3.4 illustrates a box-plot comparison of voice during Vim, Voa, and multi-target thalamic stimulation as measured by the USDRS. A Wilcoxon-
signed rank test was performed on SPSS to compare each of the settings and p-values are provided in Figure 3.4.

Qualitatively, a clinician not involved in the USDRS evaluation noted instantaneous improvement in dysphonia during the DBS ON/OFF evaluations but also a 24-hour time period before full deterioration. This time course was interesting to us given the known DBS kinetics in ET (instantaneous) versus primary dystonia (weeks to months).

**Figure 3.1 DBS Effect on Unified Spasmodic Dysphonia Rating Scale in Index Case**

DBS ON (unilateral left Vim stimulation) compared to DBS OFF on the vocal dysfunction of SD as measured by the USDRS during reading (r) and speaking (s) conditions. DBS ON was significantly superior to DBS OFF ($p=1.11 \times 10^{-5}$) on the Wilcoxon-Signed Rank test. Only Burst Loudness did not improve during the speaking state. Note- an increase in speech rate on the USDRS represents an improvement. (Reprinted with permission).
Figure 2.2 DBS Effect on Voice-Related Quality of Life in Index Case

DBS ON (unilateral left Vim stimulation) compared to DBS OFF on patient quality of life as measured by the Vr-QoL. DBS improved all aspects of quality of life and was significantly superior to DBS OFF ($p=3.99 \times 10^{-3}$) on the Wilcoxon-Signed Rank Test. Note- Professional Duties was not applicable for this patient. (Reprinted with permission).
Figure 3.3 Fusion of Pre-Operative MRI and Post-Operative CT for Electrode Position

Fusion of pre-operative MRI and post-operative CT with Schaltenbrandt-Wahren atlas overlay illustrating the anterior DBS trajectory taken to place the left electrode. Contact 3 is in the antero-superior border of Voa, Contact 2 is in the ventral oralis anterior (Voa), Contact 1 is in the ventralis oralis posterior (Vop), and Contact 0, the most distal, is in the ventral intermediate nucleus (Vim). (Reprinted with permission).
Box-and-Whisker Plot Comparing Varying Thalamic Nuclei Stimulation on SD

Box-and-Whisker Plot comparing the effect of focal Vim, Voa, and Vim + Voa DBS stimulation on the vocal dysfunction of SD as measured by the USDRS (y-axis). The Wilcoxon-Signed Ranked test was used with SPSS to compare each group. The following statistical comparisons were made: Voa focal stimulation was significantly worse than DBS off (p=0.0028), Vim focal stimulation was significantly better than DBS off (p=0.0016), Vim + Voa focal stimulation was significantly better than DBS off (p=0.0011), Vim focal stimulation was significantly better than Voa focal stimulation (p= 2.69 x 10^{-5}), Vim + Voa focal stimulation was significantly better than Voa focal stimulation (p=2.05 x 10^{-5}), No significant difference between Vim and Vim + Voa stimulation (p=0.2003). (Reprinted with permission).
3.3 Treating Cerebellar Dysfunction may Mediate Improvement in SD

The production of spoken language is a complex process that relies on multiple interacting brain regions including the sensorimotor cortex, basal ganglia, thalamus, and cerebellum\textsuperscript{1-4}. When this neural network deviates from synchrony, speech disorders can occur inducing voice tremor\textsuperscript{85} and spasmodic dysphonia. Due to its network-wide effects\textsuperscript{86}, Deep Brain Stimulation (DBS) represents an attractive therapeutic option to repair abnormal circuit dynamics in neurological speech disorders.

In this report, the effect of unilateral left thalamic DBS on the vocal dysfunction of SD has been quantified for the first time. While only a single case, scattered reports exist on the benefits of thalamic DBS on the vocal dysfunction of SD\textsuperscript{87-90}. Marrying evidence from our work with these other studies, we hypothesize that the cerebello-thalamic circuit may have an abnormal rhythm in patients with SD and that DBS may ameliorate this.

Most dystonias are currently treated with pallidal (GPi) DBS\textsuperscript{91,92}. A significant portion of the pallidal outflow is directed to the Voa thalamic nucleus\textsuperscript{93}. Some focal dystonias have been treated with thalamic lesions\textsuperscript{44} and neuromodulation of that portion of the motor thalamus\textsuperscript{94}. Since SD (also known as laryngeal dystonia) is a focal dystonia, we were surprised that Voa (pallidal outflow) thalamic stimulation produced no benefit in vocal dysfunction. It was clear that the best clinical effects for our patient’s SD occurred with neuromodulation of the Vim (cerebellar outflow) thalamus.

Several recent lines of evidence point to cerebellar involvement in dystonia. Using the classic eye-blink conditioning paradigm, Teo and colleagues found physiological evidence for
cerebellar dysfunction in patients with cervical and hand dystonia\textsuperscript{95}. The area of lobules V and VI of the cerebellar cortex have been shown to be structurally abnormal in patients with focal hand dystonia (writer’s cramp)\textsuperscript{96} and cervical dystonia\textsuperscript{97}. Le ber et al. described eight dystonia-plus syndrome patients with predominant SD and cerebellar atrophy\textsuperscript{98}. Using PET imaging, Ali and colleagues demonstrated that therapeutic BTX injections decrease cerebellar hyperactivity in SD patients\textsuperscript{99}. Our recent study on a patient with hemi-dystonia demonstrated optimal clinical benefits when cerebellar circuits were included in neuromodulation\textsuperscript{100}. In a rodent study, Raike et al. used lentiviral-mediated conditional genetics to regionally limit cerebellar function\textsuperscript{101}. The authors found that abnormalities restricted to only 10-15\% of Purkinje cells was sufficient to induce focal dystonia. Koch et al. published a small study reporting cerebellar stimulation improved cervical dystonia\textsuperscript{102}. Together, these studies provide evidence that cerebellar dysfunction is implicated in the genesis of focal dystonia and the production of speech.

Alcohol consumption is widely known to improve ET symptoms. PET studies in alcohol-responsive ET patients have demonstrated that alcohol reduces cerebellar hyperactivity\textsuperscript{103}. Recently, Simonyoan and colleagues determined that nearly 60\% of SD patients also improve their symptoms with alcohol consumption\textsuperscript{104}. Perhaps alcohol-induced suppression of SD works in a similar manner as tremor suppression in ET, providing additional support to treat the cerebellar dysfunction in SD.

Finally, the clinical evidence following thalamic DBS for essential tremor and coincident SD is encouraging\textsuperscript{87-90}. Lyons et al. was the first to report that SD may respond to thalamic
We have not yet tested the effect of GPi DBS on SD. Our data, together with other studies, hints that it may not be as effective as Vim DBS. Dystonia is increasingly being characterized as a multi-nodal network disorder where dysfunction at any single node can give rise to dystonia\textsuperscript{105}. Our initial impression is that SD requires targeting the Vim to maximally improve vocal dysfunction.

The coordination of speech production is facilitated by the cerebellar motor input to the laryngeal motor cortex via the motor thalamus\textsuperscript{3-5}. This neural circuit controls the timing between single components of a movement, scales the size of muscular action, and coordinates the sequence of agonists and antagonists in normal speech production\textsuperscript{106}. While the basal ganglia undoubtedly plays an important role in limb, axial, and facial dystonia (including tongue), it appears that treating cerebellar dysfunction is required to correct abnormal speech coordination in SD.

3.4 Conflicting Evidence for Pallidal (GPi) Neuromodulation for SD

Contradictory reports exist on the value of GPi DBS in improving vocal dysfunction in SD and concurrent primary dystonia. Recently, Risch et al. reported a single patient having an “impressive” benefit in SD following GPi DBS for primary dystonia\textsuperscript{107}. Mure and colleagues report a SD and concurrent DYT6 dystonia patient who did not respond to GPi DBS, but interestingly responded to thalamic ventral lateral anterior (VLa) DBS\textsuperscript{108} – a pallidal receiving area of the thalamus. However, in a 2009 long-term outcomes report of GPi DBS for primary dystonia, the authors note that out of 10 patients with concurrent SD, two showed no benefit and two worsened after GPi DBS\textsuperscript{109} (unfortunately no information was provided on the
remaining 6 patients). The authors note that speech and swallowing was the only body site that did not improve at every time endpoint in their long-term pallidal DBS outcomes study. In another long-term follow-up study of 22 patients over 3 years, Vidailhet et al. also report speech and swallowing the only body site to not significantly improve following GPi DBS\(^{110}\). In a cohort Meige syndrome (n=7)\(^{111}\) and cranio-facial/cervical dystonia (n=6)\(^{112}\), pallidal DBS had no significant benefit on speech and swallowing. Thus, based on the available clinical evidence, pallidal neuromodulation has limited benefit on laryngeal dysfunction whereas evidence for cerebellar neuromodulation have all been positive, especially in SD.

### 3.5 Unilateral or Bilateral DBS Targeting for Spasmodic Dysphonia

Patel et al. reported subjective improvement in voice following unilateral left Vim DBS in a patient with ET who developed SD years after receiving DBS\(^{90}\). Our patient also improved objectively following unilateral Vim DBS. Ali et al. suggested that the left hemisphere may play a cardinal role in adductor SD after determining asymmetric hemispheric changes on PET following BTX injections\(^{99}\). Moreover, a recent transcranial magnetic stimulation (TMS) study found abnormal left motor cortex excitability during a ‘reading-aloud’ task in adductor SD patients compared to healthy controls; no significant changes in excitability were found in the right motor cortex\(^{113}\). A recent resting-state fMRI study found significant abnormal connectivity in the left inferior parietal cortex (together with the left sensorimotor cortex) in SD compared to healthy controls\(^{114}\). This likely contributes to abnormal sensorimotor integration, loss of proprioceptive and tactile feedback, and inappropriate modulation of learned speech production present in SD. Finally, cerebellar stroke studies have implicated the right, not left,
posterolateral cerebellum critical for motor and cognitive aspects of speech\textsuperscript{115,16}. Together, these studies point toward a unifying theme: SD is a task-specific dystonia with neurophysiological speech motor control defects primarily in the left cerebral hemisphere while relatively sparing the right hemisphere.

Ultimately, additional studies are needed to determine if unilateral or bilateral thalamic neuromodulation is required for optimal voice improvement in SD. Unilateral surgery has the obvious advantage of fewer brain penetrations with a resultant reduction in complications. Our patient improved from unintelligible to easily understandable speech following a single DBS lead. Further clinically insignificant improvements in voice following contralateral surgery (if true) may not warrant the additional risks.

3.6 Limitations of Sentinel DBS Case for SD

An inherent limitation in the USDRS (and other adductor SD severity scales) is that the test is conducted under non-stressful conditions. Patients are asked to read standardized sentences in a quiet, isolated environment and assessed on numerous vocal characteristics\textsuperscript{81}. In reality, our patient and others with SD report that their symptoms are far worse under real life stressful conditions such as the workplace environment, public speaking, and socializing. The USDRS thus underestimates the SD symptom severity. In these real life stressful conditions, our patient reported (subjectively) that the beneficial effects of DBS were even more profound.

The DBS settings were programmed to maximally alleviate limb tremor. If patients with pure SD (no tremor) were to benefit from neuromodulation, programming parameters may be even better optimized to provide better voice benefits. Lastly, a small portion of the patient’s
vocal dysfunction was attributable to essential voice tremor. The improvement of her overall vocal quality of life (as measured by Vr-QoL) was therefore due to a reduction in both her SD and vocal tremor. Nevertheless, co-incidence of SD and voice tremor is around 50%\textsuperscript{117,118}, hence treating two disorders with one electrode is an exciting prospect which requires further research.

This report quantifies the beneficial effects of DBS on adductor SD while assessing the underlying thalamic circuitry for the first time. Unilateral neuromodulation of the left thalamus in the region of cerebellar input appears to be sufficient for clinically significant vocal improvement. Surprisingly, stimulating the pallidal receiving area of the thalamus (Vo\textsubscript{a}) was ineffective and worse than sham stimulation. While only a single case, other reports exist on the positive effects of thalamic Vim DBS on dysphonia. Neuroimaging evidence also exists on cerebellar dysfunction in SD. Leaders in SD research have identified the need for a Phase 1 exploratory trial of DBS in patients with severe SD who are not adequately treated by BTX\textsuperscript{71}. A Phase 1 pilot trial (DEBUSSY, NCT02558634) is underway at our centre to evaluate the safety and preliminary efficacy of DBS in SD.
Chapter 4: Probing the Lateralization of Thalamic Laryngeal Control: Insights from Deep Brain Stimulation for Voice Tremor

4.1 An Opportunity to Investigate Lateralization of Thalamic Laryngeal Control before DBS for Spasmodic Dysphonia

Voice tremor (VT) is a neurological speech disorder characterized by involuntary rhythmic oscillations in the muscles of phonation thereby producing a quavering voice\textsuperscript{117}. Approximately 25\% of SD patients also present with coincident VT\textsuperscript{117}. Along with dystonic laryngeal spasms and muscle tension dysphonia, VT is one of the three classical features of the SD syndrome. Previous studies have reported on the beneficial effects of bilateral or Vim stimulation on voice tremor, but, none have to date systematically studied if the left, right, or bilateral thalamic stimulation was responsible for the greatest clinical effect. For the first time, in this study, we sought to characterize the lateralization of thalamic laryngeal control in a series of VT patients with bilateral Ventral intermediate nucleus (Vim) Deep Brain Stimulation (DBS) electrodes in a prospective, randomized, double-blinded manner. The study will add to our understanding on if a single electrode in the left (or dominant) hemisphere, not right (or non-dominant), is sufficient to treat SD’s dystonic laryngeal spasms and vocal tremor.

4.2 Methodology of Hemispheric Analysis of Vim DBS for Voice Tremor

Patient Population

Vancouver Functional Neurosurgery (VFN) has a 20-year history of implanting thalamic DBS electrodes for essential tremor (ET). All patients already successfully being treated for
essential tremor, but with a pre-operative VT, were recruited to participate in this study. Eight patients were identified and six consented to the enroll in the study. Baseline data collection included age, sex, handedness, duration of DBS therapy, unilateral or bilateral Vim surgery, and DBS stimulation parameters. (Table 4.1).

**Table 4.1 Patients Characteristics in EVT Study**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Handedness</th>
<th>Duration of DBS Prior to Study Entry (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVT #1</td>
<td>67</td>
<td>M</td>
<td>R</td>
<td>8</td>
</tr>
<tr>
<td>EVT #2</td>
<td>80</td>
<td>M</td>
<td>R</td>
<td>3</td>
</tr>
<tr>
<td>EVT #3</td>
<td>65</td>
<td>F</td>
<td>R</td>
<td>8</td>
</tr>
<tr>
<td>EVT #4*</td>
<td>59</td>
<td>M</td>
<td>L*</td>
<td>8</td>
</tr>
<tr>
<td>EVT #5</td>
<td>63</td>
<td>M</td>
<td>R</td>
<td>5</td>
</tr>
<tr>
<td>EVT #6</td>
<td>71</td>
<td>M</td>
<td>R</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Surgery & DBS Stimulation Parameters**

Standard frame-based stereotactic neurosurgical planning for Vim tremor surgery was conducted in all patients. Microelectrode recording of thalamic bursting phase locked with arm tremor and macrostimulation to block tremor was used to confirm electrophysiological placement of the DBS lead (Medtronic 3387). DBS devices were programmed to maximally alleviate limb tremor. Table 4.2 delineates the Left and Right electrode stimulation parameters prior to study entry.

**Table 4.2 Patient Characteristics in EVT Study**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Voltage</th>
<th>Frequency</th>
<th>Pulse Width</th>
<th>Contacts Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1-</td>
<td>L: 2.4</td>
<td>L: 180</td>
<td>L: 60</td>
<td>L: 0- 1+ R: 8+ 9-</td>
</tr>
<tr>
<td></td>
<td>R: 3.4</td>
<td>R: 180</td>
<td>R: 60</td>
<td></td>
</tr>
<tr>
<td>Patient 2-</td>
<td>L: 3.0</td>
<td>L: 185</td>
<td>L: 90</td>
<td>L: C+ 1- R: n/a</td>
</tr>
<tr>
<td></td>
<td>R:</td>
<td>R:</td>
<td>R:</td>
<td></td>
</tr>
</tbody>
</table>
### Study Design & Voice Assessment

After several sessions of optimizing DBS parameters for limb tremor, patients with bilateral implants (n=4) were randomized to receive: none, left-only, right-only, or bilateral Vim stimulation for 15 minutes each to assess voice tremor. Patients with unilateral Vim stimulation (n=2) were only randomized to receive: none or side of unilateral Vim stimulation. A 30 minute wash-out period was used prior to randomization into one of the conditions and a five-minute washout period was used in between settings.

With their limbs at rest, subjects read the ‘Rainbow Passage’, sustained vowels ‘a’ and ‘e’, and produced one minute of spontaneous speech. Audio recordings were acquired from an Olympus Digital Voice Recorder (DM-620). A speech-language pathologist (SLP) blinded to these settings then evaluated voice recordings using the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) scale, a standard scale used in speech-language pathology and otolaryngology. The SLP specifically evaluated for characteristics of voice tremor, such as rate, regularity, and amplitude of the tremor. In addition, fluctuation of frequency and intensity, as well as the steadiness of the voice were also be analyzed.
**Statistical Analysis**

Statistical analysis was performed on R and RStudio. It involved comparing different combinations of DBS left ON only, right ON only, both ON, or both OFF on Cape-V scores using a Wilcoxon-signed rank test.

4.3 **Findings from Left, Right, and Bilateral Vim DBS for Voice Tremor**

The hemispheric analysis of Vim DBS on voice tremor revealed interesting results. The following were three unique findings: 1) no significant difference between right Vim DBS compared to DBS OFF for voice tremor (p=0.26), 2) no significant difference between left Vim DBS compared to DBS ON for voice tremor (p=0.19), and 3) left Vim DBS significantly improved voice tremor compared to DBS OFF (p=0.006). Figure 4.1 illustrates this hemispheric analysis of DBS for voice tremor while Figure 4.2 illustrates a rare right-brain dominant patient.

**Figure 4.1 Hemispheric Analysis of Left, Right, or Bilateral Vim DBS for Voice Tremor**

No significant difference between right Vim DBS compared to DBS OFF (p=0.26), no significant difference between left Vim and DBS Both ON (p=0.19), and left Vim DBS significant improved voice tremor compared to DBS OFF (p=0.006). Cape-V is on the y-axis where increase in score represents increase in severity.
4.4 Neurophysiological Explanation for Dominant Thalamic Control over the Larynx

In this chapter, it was found that the left thalamic Vim (or dominant) plays a crucial role in mediating improvement in voice tremor and that the right thalamic Vim (or non-dominant) plays a relatively insignificant role. Given that Vim DBS has been demonstrated to affect the cerebrocerebellar motor circuit, this circuit in acoustic communication is presumed to be human-specific. This is based on the evidence that cerebellar dysfunction in humans causes speech and voice disorders (i.e. ataxic dysarthria), but cerebellar lesions do not impair vocalization in non-human primates or songbirds.

Neuroanatomically, there is no controversy that the vocal cords are bilaterally innervated. The larynx is a midline structure and the two vocal folds operate as a coordinated pair to produce symmetrical and synchronous movements; asymmetrical...
movements of the vocal folds are indicative of pathology. This symmetry is most likely supported by the bilateral innervation of the nucleus ambiguus by the LMC.

When studying the neurophysiology of speech production, one must take into account the confounding effects of language. Speech inherently attempts to convey meaning as communication with words and sentences involve language processing which is very well-known since Broca’s time to be left-lateralized. Is speech motor control left-lateralized as well, similar to language? A recent combined functional MRI and tractography study investigated the differences between syllable production and controlled breathing—both processes relying on the same structural neural network but potentially different functional neural networks. By choosing syllable production with minimal semantic values and controlling for breathing production, the authors were able to study the functional connectivity of simple laryngeal motor behaviours. The authors found a left-hemispheric lateralization of functional networks during voice production but not breathing despite the presence of similar structural neural connectivity. Specifically, during syllable production, a left-lateralization in the cortical connectivity to the left LMC was found. Our findings that the left thalamic Vim plays a crucial role in laryngeal control is consistent with this study on functional left-lateralization during simple syllable production. Additionally, during rapid modulation of consonant-vowel transitions, Simonyan and colleagues found a larger functional connectivity between the left laryngeal motor cortex and the left auditory cortex, indicating a preferential during this complex spatio-temporal process. Finally, cerebellar stroke studies have implicated the right, not left, posterolateral cerebellum critical for motor and cognitive aspects of
speech. Moreover, consonant-vowel syllable productions have been demonstrated to activate discrete regions of the cerebellum. Together, it is possible that the right cerebellar/left frontal projections need to be repaired in spasmodic dysphonia patients.

To conclude, recent neuroimaging studies all have demonstrated a bilateral structural neural network for intrinsic laryngeal movement, however, this network is uniquely left-lateralized during voice production. This may be a reason why left Vim DBS improves shows a dramatic improvement in voice tremor and vocal fold movement compared to no DBS or right-only Vim DBS.

4.5 Limitations of DBS Study on Lateralization of Thalamic Laryngeal Control

One of the limitations in this study is that patients with thalamic DBS electrodes were studied several years after chronic stimulation. Thus, it is difficult to quantify the long-term effects that chronic thalamic DBS might have had on the DBS voice tremor score. Despite this, we believe that baseline DBS OFF tremor scores might actually be higher had there been no chronic stimulation. Second, patients’ stimulation parameters were not adjusted to minimize dysarthria. To minimize this confounder, the SLP was specifically asked to score for the tremulous component of voice, rather than other components of such as dysarthria, breathiness, and etc. Extrapolating from our knowledge of Vim DBS for limb tremor, it is unlikely that had dysarthria had been minimized, voice tremor would have improve. Finally, the speech task employed in this chapter only involved holding a vowel during connected speech. It would have been interesting to also have acquired a speech task requiring modulation of prosody to determine if the right thalamic Vim plays a more crucial role than the left.
Chapter 5: Thalamic Deep Brain Stimulation for Spasmodic Dysphonia: Interim Results of a Prospective, Randomized, Double-Blinded Trial (DEBUSSY)

5.1 Setting the Stage for DBS for Spasmodic Dysphonia

The aim of this thesis was to ultimately develop a CNS-based treatment for SD, a significant gap in the field highlighted by clinicians, scientists, and the public. In Chapter 2, a formalized bibliometrics approach was used to demonstrate that since the 1980s, the main treatment option for SD has been BTX injections and an alternative approach was peripheral laryngeal nerve surgery. Both these approaches mimic the early treatments of cervical dystonia—ignore the cerebral neurological problem but focus on weakening the resultant muscle spasms. In Chapter 3, we aimed to determine which component of the motor thalamic circuitry likely required repair to improve the symptomatology of SD. We determined that the cerebellothalamic circuitry, not pallidothalamic circuitry, required treatment despite SD’s classification as a dystonia and speech disorder. Finally, in Chapter 4, we aimed to determine if there was a lateralization in thalamic laryngeal control in a group of patients with voice tremor, a key feature in nearly 25% of SD patients. We found that the left (or dominant) thalamic Vim (cerebellar input into thalamus), not right (or non-dominant), had a unique role in controlling and treating laryngeal tremor. Together, these studies provided us the platform to launch a Phase 1 prospective, randomized, controlled, trial called DEBUSSY (DEep Brain StimUlation for Spasmodic DYsphonia)

In this chapter, interim results of the clinical trial for this new DBS indication will be discussed.
5.2 Clinical Trial Design and Detailed Methodology

**Patient Population and Trial Inclusion/Exclusion Criteria**

n=6 adductor SD patients were recruited for DEBUSSY. All patients were recruited based on the NIH-defined nasolaryngoscopic diagnosis of SD by an experienced otolaryngologist, Professor Emeritus Murray Morrison. A sample size of six was chosen given that it is standard for Phase 1 DBS pilot trials.

**Table 3.1 Inclusion/Exclusion Criteria for DEBUSSY**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Diagnosis of isolated adductor SD as per NIH-defined criteria</td>
<td>1) Diagnosis of other movement disorders such as essential tremor or dystonia affecting other body parts other than the larynx</td>
</tr>
<tr>
<td>2) Inadequate or suboptimal response to Botox injections for DS</td>
<td>2) History of selective-laryngeal denervation renervation surgery for adductor SD</td>
</tr>
<tr>
<td></td>
<td>3) Previous history of brain surgery</td>
</tr>
<tr>
<td></td>
<td>4) Diagnosis of neurodegenerative disorder such as Parkinson’s disease or Alzheimer’s disease</td>
</tr>
<tr>
<td></td>
<td>5) History of intracranial pathology such as brain tumour, multiple sclerosis, or stroke</td>
</tr>
</tbody>
</table>

**Clinical Trial Design**

Once patients were screened for the inclusion/exclusion criteria, they were asked to sign study consent forms as per our university protocol. All patients then ceased BTX injections for six months prior to DBS surgery. The rational for this is that BTX injections into the thyroartenoid muscles have been demonstrated to be present for at least 3-4 months—we chose an upper estimate of six months prior to patients having DBS surgery. The figure below illustrates the design of DEBUSSY.
Patients will be randomized to either active stimulation (treatment arm) or no stimulation (control arm) for 3 months, crossed-over for another 3 months, and conclude with un-blinded stimulation for 6 months. The purpose of the cross-over design is to evaluate the patients in a double-blinded manner and monitor the time course of wash-out and improvement. Moreover, this design allows us to determine potential study designs for future trials, especially if they involve comparing GPi vs Vim, or left vs. right DBS, or DBS + Botox (or DBS alone). The speech-language pathologist and patient will be blinded for the first six months after surgery.

**Primary and Secondary Endpoints of Clinical Trial**

The primary endpoints will be the Unified Spasmodic Dysphonia Rating Scale (USDRS) and the Voice-Related Quality of Life (VR-QoL), two widely-used scales by Otolaryngologists and Speech-Language Pathologists (SLPs) to assess the severity of SD. Secondary endpoints will be the Voice Handicap Index-10 (VHI-10) and Beck’s Depression Inventory (BDI), and Montreal Cognitive Assessment (MoCA). Both primary and secondary endpoints will be collected pre-operatively and at 4, 7, and 13 months post-operatively in a double-blinded fashion. The
success of the trial will be determined by noting safety/adverse effects of DBS in SD patients and comparing DBS 3-months ON versus 3-months OFF with blinded primary end-point evaluations. R and RStudio statistical Package will be used for statistical analysis.

**Surgical Targeting of Left Medial Vim Nucleus**

Given that the Vim is somatotopically arranged, with the lateral aspect containing neuronal cell bodies for appendicular body regions while the medial aspect contain neuronal cell bodies for the head and axial body regions, we elected to target the left medial Vim using standard functional neurosurgical techniques for DBS surgery. The target was selected on T1 images to be \( \frac{1}{4} \) of the distance from ACPC, \( \sim 10-11 \) mm lateral from the edge of the 3\textsuperscript{rd} ventricle. A trajectory was selected such that it avoided the sulci and entry into the ventricles.

Intraoperatively testing involved testing for laryngeal spasm reducting during the “Rainbow Passage”. Electrophysiological macrostimulation was combined with acceptable thresholds for capsular and Vc side effects. If expected benefits did not occur or low threshold for side effects were encountered, the electrode was repositioned as deemed appropriate by the attending surgeon.

**DBS Programming Strategy for DEBUSSY**

Post-operatively, programming for DEBUSSY will follow the standard guidelines for Vim programming for tremor. A pre-operative MRI will be fused to the post-operative CT to delineate exact electrode positioning and guide the determination of the best electrode contact. After 1 month of turning on the stimulator, patients will then enter the blinded phase.
of the study after testing their DBS setting in a variety of acoustic environments (i.e. home, work, outside.

**Risks of Neurosurgical Intervention for SD**

The reported risk for DBS surgery varies in the literature but most centres quote a 1% chance of a stroke that can be potentially devastating or lethal and a 5% chance of infection or technical malfunction. At our centre, the last 500 DBS operations resulted in 2 (0.4%) strokes and a 3.5% infection rate, the latter can be treated with antibiotics. All patients were informed of this risk.

**White Matter Tractography and Volume of Tissue Activated Analysis**

The white matter tracts (WMT) around the motor thalamus have yet to be investigated as having implications in speech motor control. Clinically, our group and others have shown that motor thalamic DBS ameliorates vocal dysfunction in SD. Using Diffusion Tensor Imaging (DTI), we hypothesize that the Dentato-Rubro-Thalamic tract (DRT) is the WMT that will most likely be modulated by the DBS electrode’s stimulation field. This analysis will be achieved by fusing a pre-operative DTI scan (showing the WMTs) to a postoperative CT (showing electrode location) using our neuronavigational software (StealthViz 1.3) and using FSL DTI tools. We plan to determine exactly which WMTs are in the vicinity of the clinically effective DBS electrical field using a patient-specific volume of tissue activated algorithm. This imaging component of our work will allow us to better understand the neuroanatomy mediating clinical (or lack of) improvement.
5.3 Intra-operative Findings of DBS for SD

To date, for the first time ever, n=4 SD patients have completed unilateral left medial Vim DBS surgery while n=2 are currently scheduled for surgery. Table 5.2 lists the recruited patients’ characteristics.

Table 5.2 Recruited Patient Demographics for DEBUSSY

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Handedness</th>
<th>Age at Time of Surgery</th>
<th>Age of Onset</th>
<th>Years of Botox Treatment</th>
<th>Relevant Medications</th>
<th>Alcohol-Responsive SD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBUSSY #1</td>
<td>F</td>
<td>Right</td>
<td>59</td>
<td>36</td>
<td>11</td>
<td>None</td>
<td>Unsure</td>
</tr>
<tr>
<td>DEBUSSY #2</td>
<td>F</td>
<td>Right</td>
<td>59</td>
<td>49</td>
<td>10</td>
<td>Propranolol</td>
<td>Yes</td>
</tr>
<tr>
<td>DEBUSSY #3</td>
<td>F</td>
<td>Right</td>
<td>76</td>
<td>54</td>
<td>22</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>DEBUSSY #4</td>
<td>F</td>
<td>Right</td>
<td>53</td>
<td>43</td>
<td>2</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>DEBUSSY #5</td>
<td>F</td>
<td>Right</td>
<td>60</td>
<td>51</td>
<td>2</td>
<td>Trazodone</td>
<td>Yes</td>
</tr>
<tr>
<td>DEBUSSY #6</td>
<td>F</td>
<td>Right</td>
<td>69</td>
<td>39</td>
<td>43</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>

All four patients reported instantaneous cessation of laryngeal spasms during macroelectrode stimulation prior to permanent electrode placement. Qualitatively, all patients reported significant “ease” and no spasms present when reading the “Rainbow Passage” intraoperatively. There are no incidence of stroke or complications to report. Three patients exhibited capsular and sensory thresholds at acceptable voltages when confirming electrode placement. One patient had significant paresthesia at an extremely low voltage with minimal benefit to voice. This suggested our electrode trajectory was a few millimetres too posterior and close to the ventrocaudal (VC) nucleus and stimulating the medial lemniscus pathway. A new trajectory 2 mm anterior was selected and resulted in instantaneous cessation of laryngeal spasms with acceptable capsular and sensory thresholds.

5.4 Post-Operative Findings of DBS for SD

Immediate Post-Operative Phase: Microlesion Effect
Immediately post-surgery, all patients exhibited a striking microlesion effect resulting in a clinical improvement in the SD. Naturally this resulted in feelings of elation for all patients, but patients were reminded that this microlesion effect will subside within a few weeks. All patients were discharged one or two days after surgery without any complications. DEBUSSY #2, a very interesting patient given that she had failed peripheral laryngeal nerve surgery, had a microlesion effect. The microlesion effect is likely caused by simply placing a DBS electrode in the Vim, essentially mimicking a “micro”-thalamotomy.

**Post-Operative Phase: DBS Programming Effects**

Table 5.3 lists all the patients’ best electrode contact with stimulation parameters after having tested them in a variety of acoustic environments.

**Table 5.3 Final DBS Programming Settings before Blinded Phase in DEBUSSY**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Final DBS Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEBUSSY #1</td>
<td>C+, 1-, 2.5V, 60 μs, 185 Hz</td>
</tr>
<tr>
<td>DEBUSSY #2</td>
<td>C+, 1-, 4V 60 μs, 185 Hz</td>
</tr>
<tr>
<td>DEBUSSY #3</td>
<td>C+, 0-, 2V, 60 μs, 185 Hz</td>
</tr>
<tr>
<td>DEBUSSY #4</td>
<td>C+, 1-, 4.4V, 60 μs, 185 Hz</td>
</tr>
</tbody>
</table>

Group-wise, all patients benefited most from monopolar settings, bipolar settings did not seem to elicit most optimal benefit. This parallels the electric field for ET programming, where monopolar stimulation likely results in the best clinical setting because of a larger influence on Vim neurons and associated afferent and efferent fibers. Dysarthria and/or dysmetria was
elicited in all patients when voltage was increased by 0.5V from Table 7. Contralateral facial contracture was elicited when voltage was increased by 1V from Table 5.3.

5.5 Neurophysiology Mechanism of Action of Thalamic DBS Surgery for SD

This section will describe the potential neurophysiological mechanism underpinning DBS clinical benefit and side effects in SD.

Without DBS: Aberrant Feedforward and Feedback Control System in SD

Before considering how DBS may improve SD, it is important to discuss the present viewpoints of SD in speech motor control literature. At the moment, an active topic of discussion in SD research is whether or not the basal ganglia are the locus of the primary deficit in these disorders. Given that SD is characterized by spasms of the intrinsic laryngeal musculature during speech, botulinum toxin (BTX) injections into the afflicted muscles reduces the spasms and provides temporary symptomatic relief. Interestingly, the effects of BTX extend beyond local muscle paralysis—Bielamowicz and Ludlow (2000) identified reduced spasmodic bursting in non-injected muscles as well as injected muscles. The authors hypothesized that such changes are indicative of modification to the somatosensory feedback control system after botulinum toxin injection.

One leading theory regarding the neural impairment underlying SD is an overactivation in the feedforward control system for laryngeal control and/or a overactivation of somatosensory feedback system which may be responsible for SD.
Abnormal somatosensory activity has also been noted during speech in spasmodic dysphonia participants. Simulation studies from computational neuroscience also indicate that hyperfunction of the somatosensory feedback control for the laryngeal muscles can produce SD symptoms such as voice breaks. As previously mentioned in Chapter 1, the Guenther laboratory demonstrated that individuals with SD have excessive brain activity in the left laryngeal sensorimotor cortex during speech production compared to healthy controls. Finally, hyperactivity in the left posterior superior temporal gyrus has also reported in SD. The left-sided bias may reflect the fact that left-hemisphere’s auditory cortex is thought to be heavily involved in processing rapidly changing acoustic stimuli (20-50 Hz). It is possible that DBS of the left Vim downregulates and treats this sensory and motor hyperactivity observed when compared to control.

**How Vim DBS may Improve SD: Correcting Excessive Feedforward Commands through Increased GABA Levels**

The dentato-rubro-thalamic tract (DRT) is the main output of the lateral cerebellum and projects to the motor cortex via the ventrolateral thalamus (including Vop/Vim). The DRT is mainly involved in the control of voluntary movements such as a single-joint and multi-joint goal-directed movements. At the level of the thalamus, the Vim has a somatotopic arrangement where the medial cell bodies have been demonstrated to be preferentially involved in control of axial movements. Medial Vim DBS likely acts to disrupt or desynchronize thalamic neurons from their preferred frequency that is generating the pathological laryngeal spasms. Moreover, Vim DBS may serve to decrease the critical state of thalamocortical neurons.
able to generate laryngeal spasm expression by introducing a new clinically beneficial frequency.

Using DTI tractography, when modelling the volume of tissue activation (VTA) around the best and worst electrode contact in our most severe SD patient, we found that VTA preferentially modulated the fibers travelling from right dentate, left ventrolateral thalamus, to the left laryngeal motor cortex (see below). This may lead to correcting the hyperactivity of the feedforward commands in the left laryngeal motor cortex. High-frequency left Vim DBS likely causes an inhibitory effect of the Vim neuronal cell body, and thereby activating the axons.

Figure 5.2 Best and Worst DBS Contacts for DEBUSSY #3, with Overlay of Electrical Field and White Matter Tract
From a molecular point of view, it has been suggested that GABAergic deficiencies in SD may contribute to the loss of inhibition, excessive feedforward commands, and thus generate dystonic laryngeal movements. Interestingly, Rumbach and colleagues demonstrated that sodium-oxybate, a short-acting GABA-agonist, can provide temporary benefit in the majority of SD patients. Alcohol, which has been shown to modulate CNS levels of GABA, is also capable of providing temporary relief in the majority of SD patients. Thus, taken together with the recent PET findings of reduced GABAergic neurotransmission in SD compared to healthy controls, it is likely that increasing GABA levels may stabilize the balance between excitation and inhibition within the dystonic neural network, leading to reduction of laryngeal spasms. Synaptically, GABA would inhibit neuronal activity by allowing chloride ions to enter the post-synaptic neuron thereby making it less excitable.

Naturally, one may wonder if Vim DBS in SD achieves clinical benefit through inhibition of the hyperactive dentate-thalamo neural circuit ending in the laryngeal motor cortex through increased GABA levels. Insight for this perspective can be gleaned from the 25-years of research of Vim DBS and thalamotomy for essential tremor. Andres Lozano and colleagues determined that microinjections of muscimol (a GABA-agonist) into the Vim of ET patients led to selective inhibition of thalamic neuronal cell bodies leading to benefit in limb tremor. This study provided credibility that direct GABA-mediated inhibition of Vim thalamocortical relay neurons, which project to the primary, premotor, and supplementary motor cortical areas, can reduce tremor and in our case, dysphonia.
Recently, Samargia and colleagues demonstrated a shortened cortical silent period (CSP) in the left motor cortex in adductor SD patients compared to healthy controls\textsuperscript{135}. CSP is a measure of cortical excitability and a physiological marker for investigating intracortical inhibition; A shortened CSP indicates a dysfunction in inhibitory mechanisms, in essence “too little” inhibition\textsuperscript{135}. Moreover, a recent transcranial magnetic stimulation study found abnormal left motor cortex excitability during a “reading-aloud” task in adductor SD patients compared with healthy controls; no significant changes in excitability were found in the right motor cortex\textsuperscript{136}. Left thalamic Vim DBS is a potential long-term therapeutic that may potentiate endogeneous GABA neurotransmitters, similar to alcohol and sodium oxybate, and restore equilibrium and govern symptomatic improvement in SD.

Modulating Vocal Cord Movements: An Evolutionary Perspective

Chapter 3 of this thesis discussed the clinical evidence from the literature on the merits of Vim DBS over GPi DBS for Our vocal folds move at a frequency several orders of magnitude higher than our limbs or appendicular body parts. For rapid modulation of such a system, the cerebellum is likely selectively involved more than the basal ganglia. Moreover, the involuntary laryngeal spasms in SD are only specific at vowels. Functional MRI studies have implicated a discrete region in the cerebellum to be implicated during vowel production. Thus, we fundamentally believe that SD is a movement coordination problem requiring principal treatment of the cerebellar input into the thalamus, rather than a basal ganglia dysfunction.

DBS Side Effects for SD Explained by Local Neuroanatomy
One of the side-effects encountered in this study was stimulation-induced dysarthria (SID) which was reversible when the voltage or pulsewidth is decreased or settings switched to bipolar configuration. This clinical effect can be explained by the electric field spreading too far laterally into the internal capsule and affecting the corticobulbar fibers—a well-reported finding in Vim DBS for essential tremor patients. Contralateral dysmetria was also reported as a stimulation-induced side-effect, presumably also caused by capsular spread of the electrical field. Interestingly, of the n=4 patients operated on with Vim DBS for SD, patients who encountered dysarthria or dysmetria at relatively lower voltages also had their electrode leads placed relatively more laterally than the intended target. Transient paresthesia was also reported in all patients, both intraoperatively and post-operatively during DBS programming. This finding can be explained by the electrical field spreading too far posteriorly into the Vc sensory thalamic nucleus and affecting the medial lemniscal pathway. In summary, side-effects of Vim DBS for ET can be extrapolated to SD as well and be minimized through well-established DBS programming methods.

In an important 2008 consensus paper by leaders in SD research titled “Research Priorities in Spasmodic Dysphonia”, the authors state “caution should be used, however, given the reduced benefit of DBS for voice and speech deficits in some cases”\(^71\). This is a misconception that is worthy of discussion from a practical point of view. SID is a side-effect caused by increasing the DBS electrode’s voltage above the optimum therapeutic range during Vim thalamic DBS. SID can be minimized or completely alleviated by adjusting stimulation parameters. In practice, the patient can always choose to eliminate SID by reducing the
stimulation intensity (possibly, but not always, at the expense of incomplete reduction of symptoms) – the choice will be theirs.

In a recent meta-analysis by Alomar et al., the authors found that left-sided neurosurgical thalamic procedures caused 2-3 times more speech impairment\(^2\). It is critical note, that this calculation lumped thalamotomies (destroying the part of the thalamus) AND thalamic Deep Brain Stimulation (DBS) together. In the sub-group analysis, the authors found unilateral left-sided thalamotomy caused 40.7% speech impairments whereas unilateral DBS caused SID in 11% of patients. Finally, in 2017, this figure of 11% SID can likely be further reduced given the introduction of directional electrodes (d-leads) and high-definition pre-operative targeting. Unlike traditional omni-directional leads, d-leads allow post-operative programming to be even more sophisticated as clinicians can “steer” the current away from side-effects such as SID. Furthermore, an additional reason for SID is due to misplacing the electrode a few millimetres from the ideal target. This surgical problem has significantly decreased with the use of 3 Tesla pre-operative MR-imaging. Thus, we believe the figure of 11% for SID following unilateral left thalamic DBS is actually lower today given that some of the studies included in the meta-analysis employed 1.5 Tesla MR-imaging and relatively older techniques.

5.6 Limitations of Clinical Trial on DBS for SD

There are a few important limitations to discuss in this clinical trial and DBS for SD. First, as previously stated in Chapter 3, the primary endpoint is the Unified Spasmodic Dysphonia Rating Scale (USDRS). This scale is administered in a quiet environment in a clinician’s office and
thus, would not capture the severity of SD (and DBS effect) during stressful or loud conditions. Nevertheless, any benefit (or lack of) due to DBS would be captured in the voice-related quality of life as this scale more appropriately captures realistic conditions and the effect of therapy. Second, all patients had been receiving BTX injections for several years prior to joining this study. A recent report suggests that after several years of BTX spasms, majority of patients do not return to full baseline prior to BTX injections. Thus, the baseline scores of SD on the USDRS is likely lower than what is reported and the effect of DBS could be even greater had patients enrolled into DEBUSSY without trialing BTX. This would be an unlikely clinical scenario given that BTX is the first-line option for SD and proceeding to DBS would be inappropriate. Moreover, given that the DBS effects are quite dramatically powerful, there is a strong possibility that the patients and evaluators in the study will become unblinded –however, this study design is the gold-standard in the field and if the treatment effect is incredibly profound to result unblinding of participants, it only strengthens the case for treatment. Lastly, DBS is ultimately an invasive procedure and will likely be reserved for the most severe SD patients receiving more inadequate response to less minimally invasive therapies.
Chapter 6: Future Directions and Concluding Remarks on Neuromodulation for SD

This thesis aimed to develop the first ever CNS solution for spasmodic dysphonia. Prior to this, Botox injections and peripheral nerve surgery were the main treatment options for SD\textsuperscript{71}. Moreover, anecdotal and subjective reports in the literature existed on developing a long-term CNS treatment strategy for severe SD. For the first time, we set out to formally investigate if we can apply DBS, a neural circuitry targeting therapy, to SD and provide patients who have inadequate response to Botox or peripheral nerve surgery a treatment to target the source of the disorder.

Three unique and significant contributions of knowledge to functional neurosurgery and speech neuroscience have been made through this thesis:

(1) In n=4 SD patients, unilateral left thalamic ventral intermediate nucleus (Vim) instantaneously and continuously aborts laryngeal spasms in the intra-operative and post-operative DBS setting. When voltage is increased above the therapeutic range, transient side effects of dysarthria and dysmetria are encountered. Despite one patient with a failed peripheral laryngeal nerve surgery operation, thalamic DBS is able to block thyroartenoïd laryngeal spasms in SD suggesting that these patients too will benefit from an intracranial procedure.

(2) The white matter tract connecting the contralateral dentate nucleus, ipsilateral Vim, and ipsilateral laryngeal motor cortex is significantly affected by the volume of tissue
activation (VTA) around the most effective electrode contact compared to the least effective contact in SD.

(3) The left (or dominant) Vim plays a crucial role in laryngeal vocal fold control compared to the relatively insignificant role of the right (or non-dominant) Vim. Specifically, unilateral left Vim DBS improves voice tremor and connected speech production compared to right (non-dominant) Vim DBS.

The immediate strengths and limitations of the individual components of this thesis are outlined in the aforementioned chapters. Overall, low sample size, but acceptable by functional neurosurgery standard, is a general limitation of this thesis. When testing a new DBS indication, the goal is to demonstrate safety and hence, an n=6 is the standard size for a Phase 1 trial. In this thesis, there are no events of stroke or infection to report. Results to date suggest strong preliminary efficacy of SD and suggest potential applications to more severe forms of SD, such as abductor spasmodic dysphonia and/or adductor laryngeal breathing dystonia (see section 6.2 for further discussion).

Moving forward, the immediate next steps involve Vancouver Functional Neurosurgery (VFN) completing the DEBUSSY clinical trial and performing group-wise DTI tractography and PET analysis. From here, the field of neuro-laryngology can take one of several directions. The obvious next-step would be to conduct a multi-centre trial with a larger sample size. While our initial results suggest that unilateral Vim DBS is sufficient to clinically treat SD, we have not proved that bilateral Vim DBS or GPi DBS is inferior to unilateral Vim. At the moment, whether or not the field decides to make these direct comparisons is uncertain. In my view, it is unlikely
such trials will occur given the disease prevalence of SD and that the vast majority of patients will benefit from Botox injections. More likely to occur is determining if Vim DBS + Botox injections is better than either alone—this can be easily studied in the initial DEBUSSY cohort.

The remainder of this chapter will discuss long-term future directions such as developing closed-loop DBS for SD and DBS for SD subtypes.

### 6.1 Closed-Loop DBS for Spasmodic Dysphonia

At present, Deep Brain Stimulation (DBS) for movement disorders all involve introducing an artificial stimulation paradigm set by a DBS programming clinician. The holy grail of neuromodulation for movement disorders is sensing the brain’s physiological signals during movement and automatically applying a stimulation paradigm in a physiologically optimal manner. For example, given that SD is a task-specific movement disorder, electrical stimulation from the DBS lead should only be present during speech, but not during rest or emotional vocalizations. The obvious benefit in closed-loop DBS is a significant increase in battery life and decreased DBS programming time. Furthermore, early results for closed-loop DBS for Parkinson’s disease and essential tremor have all demonstrated improved clinical outcomes compared to open-loop stimulation. Future DBS studies in SD should acquire intraoperative electrophysiology to characterize cortical and subcortical local field potential activity around the target nucleus during speech and rest.

### 6.2 DBS for Rare Subtypes of Spasmodic Dysphonia

In this thesis, adductor SD (which represents 80-90% of cases) was the main focus. Adductor SD is characterized by involuntary spasms that force the vocal folds together—this results in a voice that is often described as strained, choppy, and full of effort. This thesis
demonstrated the safety and preliminary efficacy of unilateral Vim DBS stimulation for adductor SD.

Two more uncommon subtypes of SD are abductor SD (~10-15% of cases) and mixed adductor/abductor SD (~1% of cases)\textsuperscript{71}. Abductor SD is characterized by involuntary opening of the vocal folds which produces a breathy and whispery voice – this subtype does not respond to Botox injections as well as adductor SD\textsuperscript{4}. Mixed adductor/abductor SD involves a combination of hyperadduction and hyperabduction of the vocal folds and produces a mixed phenotype\textsuperscript{139}. Both of these two subtypes are rooted in central neurological dysfunction, similar to adductor SD, and would likely respond favorably to thalamic DBS and merit investigation.

Finally, adductor laryngeal breathing dystonia (ALBD) has also been described in the literature\textsuperscript{140}. ALBD is characterized by sudden involuntary spasms of the vocal folds during inspiration\textsuperscript{140} -- this severe form of dystonia likely has a neural circuit dysfunction during breathing and likely different in CNS pathophysiology compared to spasmodic dysphonia. Nevertheless, globus pallidus interna (GPI) DBS is a potential option for ALBD given the basal ganglia’s crucial role during breathing\textsuperscript{141}. 

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# Appendices

## Appendix A - List of Top 50 Highly Cited Articles in the Field of Spasmodic Dysphonia

(as of Feb 1 2017) categorized by article type

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<td>Schaefer SD. Neuropathology of spasmodic dysphonia. The Laryngoscope. 1983 Sep 1;93(9):1183-204.</td>
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