PROTOCOL TITLE:

Effect of Short-term Laryngeal Vibration on Voice Quality Grant title: Feasibility of laryngeal vibration as a treatment for spasmodic dysphonia

PRINCIPAL INVESTIGATOR or FACULTY ADVISOR:

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VERSION NUMBER/DATE:

2 – 14 October 2020

PROTOCOL TITLE: Effect of Short-term Laryngeal Vibration on Voice Quality. Grant title: Feasibility of laryngeal vibration as a treatment for spasmodic dysphonia
VERSION DATE: 01/31/2021

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.2	31 January 2020	Amended the title to include "Short-term"	No
2	14 August 2020	1- Substituted the original stationary, wired laryngeal vibration device with a wearable, wireless device. 2- Shortened the procedure. Instead of 3x17 min vibration, participants will only receive 2x20 min vibro-tactile stimulation. 3- An option for remote testing was added to the protocol.	Yes
3	24 August 2020	Responded	
4	14 October 2020	Responded	Remote testing consent added.
5	31 January 2021	1- Added usability testing questionnaire to the protocol	Yes

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ABBREVIATIONS/DEFINITIONS

- EEG: Electroencephalogram
- FD Focal dystonia
- SD: Spasmodic dysphonia
- VTS: Vibro-tactile stimulation

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STUDY SUMMARY

Study Title	Effect of Laryngeal Vibration on Voice Quality
Study Design	Single-intervention, pre- posttest design. Subjects perform voice production tasks before, during and after vibration.
Primary Objective	The purpose of this research is to examine the effects of laryngeal vibration on objective markers of speech quality in healthy human volunteers and people with spasmodic dysphonia, a voice disorder affecting the laryngeal muscles.
Secondary Objective(s)	Obtain preliminary data in a limited sample of SD patients that show the potential effectiveness of the approach after a single application of vibro-tactile stimulation (VTS) of the larynx.
Research Intervention(s)/Investigational Agents	Vibro-tactile stimulation of the superficial skin surface above the larynx (human voice box)
Scientific Assessment	Nationally based non-federal funding organizations-National Spasmodic Dysphonia Association
IND/IDE # (if applicable)	NSR IDE
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Study Population	People diagnosed with spasmodic dysphonia and healthy adult volunteers without a voice disorder
Local Sample Size (number of participants recruited locally)	We have recruited 17 – 9 females, 6 males (as of 6/5/2018)

1.0 Objectives

1.1 Purpose:

The general aim of the research is to provide scientific evidence that VTS represents a non-invasive form of neuromodulation that can induce measurable improvements in the speech of SD patients. This research addresses a clinical need to develop alternative or auxiliary treatments for a rare voice disorder with limited treatment options. A successful completion of the proposed work will be an important step in advancing laryngeal VTS as a therapeutic intervention for improving the voice symptoms in SD. Specifically, the scientific yield by achieving the specific aims is threefold: First, it will elucidate the unknown neurophysiological mechanism behind laryngeal VTS by documenting the neural changes associated with VTS. Second, it will establish that VTS can improve voice quality in SD. Third, by documenting that laryngeal VTS yields long-term benefits on voice quality in SD patients, it would provide a solid basis for a clinical trial that needs to address open questions on optimal dosage and duration of VTS-based voice therapy, the magnitude of the therapeutic effect across adductor and abductor SD and its long term efficacy.

2.0 Background

2.1 Significance of Research Question/Purpose:

The general aim of the study is to provide preliminary scientific evidence that VTS represents a non-invasive form of neuromodulation that can induce measurable improvements in the speech of SD patients. This work addresses a clinical need to develop alternative or auxiliary treatments for a rare voice disorder with very limited treatment options. A successful completion of the proposed work will be an important step in advancing laryngeal VTS as a therapeutic intervention for improving the voice symptoms in SD.

2.2 Preliminary Data:

We conducted a series of preliminary investigations to assess the feasibility of applying VTS to the human larynx. First, we searched for suitable vibrators that could be applied to the skin above the voice box and provide the necessary amplitude to penetrate sufficiently the thyroid cartilage and to stimulate the underlying mucosal mechanoreceptors and/or proprioceptors of extrinsic laryngeal muscles. Second, we recorded the acoustic signals during vocalization with and without VTS to determine its effect on voice production. Third, we measured the EEG responses to laryngeal vibration to understand the cortical responses to laryngeal VTS.

Selecting and piloting appropriate vibrators. We systematically tested a range of commercially available, small precision vibrators that delivered

amplitudes between 1.7-14.3 G (based on 100g inertial load testing). Vibrators were attached to the skin above the larynx of healthy volunteers and tested under varying voltage inputs. During testing subjects repeatedly vocalized vowel tones for 6-second intervals that were recorded for later acoustic frequency analysis. It became clear that vibrators with amplitudes above 6G are unsuitable (e.g. induced a gag reflex at higher voltage; uncomfortable to wear for prolonged periods of time (> 10 min). We systematically narrowed the selection to a encapsulated cylinder vibrator (Fig. 1) that has a maximum amplitude < 6G and produced clearly detectable periodic signals in the acoustic data at frequencies that were within the frequency range known to stimulate laryngeal mechanoreceptors [1].

Existing Literature:

SD is a characterized by involuntary, random movement of laryngeal muscles causing disruption of fluent speech with strained-strangled voice quality. SD is more prevalent in women [2, 3]. Onset is typically in midlife. There are two types of SD: (a) adductor (AD) typified by uncontrolled vocal fold closure, and (b) abductor (AB) characterized by uncontrolled vocal fold opening. The AD form is more common and typically occurs during the voiced components of speech. SD symptoms are task specific, occurring during speech but not during other phonatory (e.g., prolonging vowels) or non-phonatory tasks (e.g., breathing). SD shares several abnormal neurologic signs with FD of the head, neck and hand. For example, abnormal blink reflexes were observed in SD, torticollis, and blepharospasm [4-7] and abnormal long-latency responses to peripheral nerve stimulation have been observed in SD [8], in blepharospasm and oromandibular dystonia [9]. Recent evidence from our group and the work of others strongly indicate that basal ganglia-related diseases such as Parkinson's disease or certain forms of dystonia are associated with somatosensory and specifically proprioceptive abnormalities that are closely linked to the observed motor deficits [10-21] (for reviews see: [22, 23]). Finally, our own work confirmed that SD as a voice disorder is associated with a deficit in arm kinaesthesia [24] – a finding consistent with results from patients with FD of the head and neck [21].

Neurophysiology behind VTS. It has long been established that VTS can stimulate muscle spindles [25-27] and mechanoreceptors [28] affecting motor behavior and inducing changes in kinaesthesia [29-31]. In general, vibrating the skin at amplitudes of ≤ 15 μm is sufficient to activate Ia muscle spindle afferents of superficial muscles, which evokes a contractile response called the Tonic Vibration Reflex [26, 27]. To elicit kinaesthetic illusions, vibration must typically range between 40-100 Hz [32, 33]. Brief vibration to a relaxed muscle typically leads to an increase in muscle tone that can easily be overcome by voluntary phasic innervation [34], while

excitatory input to spinal α-motor neurons is depressed when vibration is applied for prolonged periods [35]. At the cortical level it has been shown that prolonged muscle tendon vibration of wrist flexors (30 min) induced an increase in corticospinal excitability of the antagonistic wrist extensors lasting up to 60 min after vibration indicating that VTS can induce measurable changes in short-term cortical plasticity [36, 37].

Somatosensory deficits and VTS in FD. Numerous research reports documented somatosensory deficits in FD (for review see [38]). For example, proprioceptive-based finger position sense thresholds and the perception of arm motion are abnormal in patients with cervical dystonia or blepharospasm [21, 39]. The abnormalities in tactile and proprioceptive processing are not restricted to the affected dystonic musculature, but were also documented in non-affected body regions [21, 40, 41] indicating a generalized somatosensory deficit in FD. Recording of somatosensory evoked potentials (SEPs) and TMS data document that abnormal processing of somatosensory information in FD is associated with abnormally enhanced cortical excitability and decreased intracortical inhibition [42, 43], which also has been confirmed for SD [44]. The susceptibility of FD to somatosensory stimulation has long been known, because patients with task-specific dystonia may use sensory tricks (*geste antagoniste*) to temporarily alleviate dystonic symptoms by touching or pressing areas of or near the dystonic musculature [45, 46]. Research on cervical dystonia documented that effective sensory tricks are associated with pallidal and motor cortical desynchronization at low frequencies (6-8Hz) [47]. It has further been shown that FD responds to VTS. Vibrating dystonic neck muscles of patients with torticollis, who exhibit abnormally tilted head postures, induced head righting and nearly restored normal head posture [48]. Vibrating non-dystonic arm muscles in patients with cervical dystonia and blepharospasm skewed arm position sense to a greater extent than healthy controls [39]. In summary, there is overwhelming evidence that somatosensory processing is affected in many forms of FD (for reviews see [22, 38]). VTS has been shown to influence somatosensory perception and may reduce the severity of dystonic postures [13, 39, 45, 48].

One challenge in applying VTS to the speech motor system is that intrinsic laryngeal muscles and the mucosa of the epiglottis are shielded by thyroid cartilage. While proprioceptors of limb muscles can be stimulated by placing vibrators on the skin above them, this is not possible for laryngeal muscles. That is, non-invasive vibrators are needed that can be easily attached to the skin above the larynx and vibrate with sufficient amplitude to induce responses in laryngeal mechanoreceptors. Many of the vibrators that have been used in the past to investigate vibration responses in limb muscles are not suitable due to size, weight and voltage requirements. Fortunately, recent advancements in vibrator technology (largely driven by cell phone

engineering) have produced small, low voltage, yet powerful vibrators that, for the first time, make it feasible to wear and operate vibrators at the neck for *a prolonged time without restricting a person's movement.*

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

If successful, the work under this protocol would lay the scientific foundation for a clinical trial to examine the usefulness of the approach in a larger patent sample. It would document the sensorimotor cortical activation patterns associated with SD and the cortical responses to VTS. It would promote development of wearable, user-programmable medical devices that could apply VTS while monitoring its effect on voice production in real-time. Ultimately, VTS would enlarge the available therapeutic arsenal by either augmenting existing Botox therapy or becoming an alternative intervention option for patients who do not tolerate Botox injections.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

The participants will wear a light-weight, wearable collar (See figure 1) that can be removed as easy as a bracelet. The complete system consists of two components: 1) a flexible enclosure that houses the electronics, 2) a collar made of soft, wear-resistive, and washable textile materials. The collar has a pouch, in which the electronics enclosure can be inserted. The enclosure can be removed from the textile collar for separate cleaning of the collar after prolonged wear, which is every single testing session.

The output of the microphone or accelerometer embedded in the device will be stored locally in the wearable device for automatic internal processing in the wearable device to activate the vibrators or calculate the threshold using the developed algorithms. The stored data will be automatically removed every 60 s and data will be never transferred out of the wearable device. In the control mode, either the voice or the accelerometer data will be used by the device to activate the vibrators when the user vocalizes or speaks. We have implemented a detection algorithm that uses either the accelerometer signal or the acoustic signal from the microphone to turn the vibrators on and off.

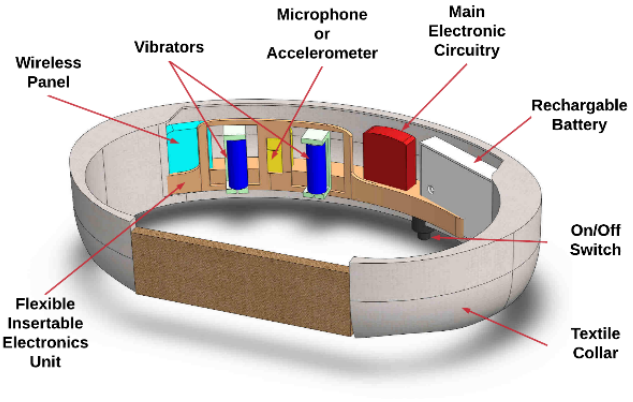

***Figure 1**: Schematic illustration of a laryngeal vibration device having vibrators carried by a collar.*

***Figure 2**. Vibratory motor used for this study (Precision Microdrives Ltd., London, UK, Model 307 – 100) Length: 25 mm. Diameter: 9 mm.*

The device applies vibration to the to the skin above the larynx using two vibratory motors. The vibratory motors (Precision MicrodrivesTM, Model 307 – 100) used are low-voltage (~1V) and non-invasive. For this protocol, they vibrate at frequencies between 30 - 100 Hz (i.e. 100 times per second). The small electric motors are encapsulated (see **Fig. 2**). There are no moving parts that can come in contact with the skin. At a stimulation frequency of 100Hz, the inertial load is approximately 2.7G, which translates to a vibration amplitude well below the threshold that may induce a swallowing reflex (> 6G). The vibrators embedded in the device are movable, thus we are able to position them around the larynx of every participant. The microphone embedded in the device is positioned in front of the larynx. Prior to testing, the microphone of the wearable device will record the audio signal for 1 minute. During this time the participant will be silent. The recorded audio signal used to determine a signal power threshold to adjust the signal-to-noise ratio of the voice signal. These recorded data will not be transferred from the wearable device, but are deleted from device memory as soon as the threshold calculation is

completed. The process of calculating threshold is automatic and does not require interaction by the user or the experimenter.
Using the calculated threshold, the speech detection algorithm will turn on the vibrators. To ensure consistency across all participants, the vibration frequency will be held constant at 100Hz for all participants.
The rotating mass of each vibrator in of the device is encapsulated. It does not come in direct contact with the skin. The position of vibrators relative to the voice box can be adjusted. The vibrators need to be placed around the larynx (Figure 3). For in-person testing, the study personnel will manually adjust the location of the device vibrators according to the width of the larynx of the participant. For remote session testing, the participant will measure the width of his/her larynx during the video call with study personnel. Next, the participant will be instructed to move the vibrators and place them apart to the value of measured larynx width from the previous step. Finally, the participant will wear the wearable device in front of the camera. The study personnel via video call will check and make sure the placement is consistent with the study protocol.

The device has a physical on/off switch that the user controls. No tablet or computer is necessary for operation. Participants will download an app to their smart phones. That app will allow users 1) to turn the vibratory motors on or off remotely (i.e. without the use of the physical switch), 2) to change to mode of operation to continuous vibration for a specified time between 1-20 min,), or 3) to turn on the voice detection mode, during which VTS will only be turned on during detected speech. The vibration frequency cannot be altered by the user. A resistor embedded in the electronics controls the output voltage to 1.1 V, which corresponds to a 100Hz vibration.

4.2 Drug/Device Handling:

The strength of the vibration is similar to the vibration experienced from vibrating cell phones or gaming joysticks. Vibro-tactile stimulation at the applied frequency and amplitude is not known to cause pain or tissue damage. The participant may feel a mild tingling or vibrating sensation. Preliminary testing on healthy human subjects showed that at the given vibration parameters (see 4.1) no adverse reactions occur.

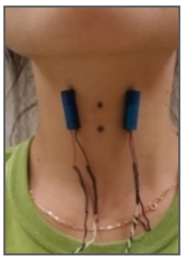

Figure 3. *Demonstrating the placement of vibratory motors on the larynx. During this study, the vibrators are embedded in the wearable collar.*

5.0 Procedures Involved

5.1 Study Design:

Subjects will perform voice production tasks before, during and after vibration. The subject will wear the collar around their neck. Two light-weight, low voltage, non-invasive surface electrical vibratory motors that are embedded in the wearable collar will be positioned on the skin of the anterior portion of the neck adjacent to the voice box to vibrate the larynx (see **Fig. 3** for demonstrating the location of vibrators). Voice production before, during, and after the vibration will be recorded via a microphone for subsequent acoustic analysis on voice quality by speech analysis experts. In addition, during voice production, electroencephalography (EEG) will be recorded with a 64-channel system (Active 2 BioSemi B.V., Amsterdam, The Netherlands or the mobile ANT Neuro EEGO EEG System, Hengelo, The Netherlands) at a sampling frequency of 512 Hz. Subjects will wear a regular head cap arranged in the standard 10-20 configuration (see **Figure 1**). Four additional external electrodes will be used. Two electrodes will be placed above and below the left eye to detect eye movements. Another two electrodes will be attached on bilateral mastoid processes to serve as reference electrodes. A water-based conductive gel is applied between the electrodes and the skin, which can be cleaned easily with water.

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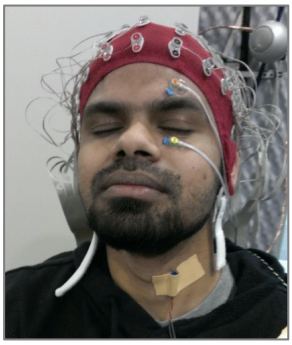

Figure 1 *EEG cap with 10-20 electrode configuration*

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5.2 Study Procedures:

Voice assessment. To assess voice quality, participants will perform two voice production tasks. First, they will vocalize the vowels 'ahh' and 'ee'. They will perform each task three times per assessment. Second, they read aloud twenty test sentences. They will repeat these assessments several times during testing (see **Fig. 4**). The sentence reading task consists of a set of test sentences based on a 20-sentence inventory described by Ludlow et al. as being sensitive to the voice symptoms experienced in SD [2]. Participants will read the sentences at their own comfortable pace and loudness. In addition, participants will rate their perceived effort level of vocalization on an ordinal scale of 0 to 10 (0 being with no effort and 10 being with maximal effort).

Application of laryngeal vibration. Each VTS trial begins with a 10-second rest period, followed by 4 seconds of vocalization. After 2 seconds of vocalization, vibration will set in while the subject continues to vocalize. Thus, each trial has a *rest*, a *vocalization only*, and a *vocalization + vibration* period. Each participant performs 50 trials per set.

The timeline of the complete protocol is illustrated in Figure 4. Testing will begin with a pretest voice assessment, followed by two sets comprising the *vibration only* and *vocalization + vibration* conditions. The order of the conditions will be counter-balanced between subjects to account for possible order effects. During the *vibration only* condition, subjects will be silent and are allowed to read for diversion. After each set a 5-min break will be given and fluids will be offered. Voice assessment batteries will be administered after each set. After completion of two sets and final voice assessments are immediately after treatment (Post 2 OFF), and 20 min and 60 min after VTS has stopped (Post 20, Post 60).

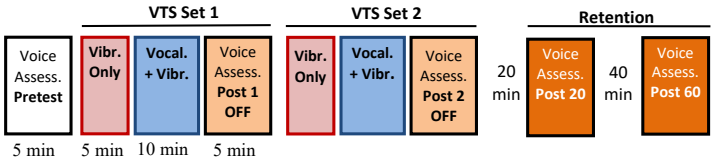

Figure 2 *Experimental design for in-person testing.*

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Usability questionnaire: The last section of study is to ask participants to fill out a questionnaire about the usability of the wearable collar.

Optional remote testing

In case a laboratory visits is not feasible, testing will be conducted remotely. Testing consists of a single session and will be conducted via a video call. A high-quality microphone, a voice recorder, the wearable collar, and study and device instruction will be provided to the participant prior to the video call. In addition, participants will download the smartphone application for controlling the device before the video call. The smartphone application is developed for main operating systems which are Android and iOS (for iPhone) and the phone only requires to have Android version 7 or higher, or iOS version 11 or higher for iPhone.

There is no EEG and eye movement recording during the remote testing, and only voice will be recorded using the microphone and the voice recorder that has been shipped to the participant.

At the beginning of the remote session the participant will be instructed to measure the width of their larynx during the video call with study personnel. The study personnel will make sure the measurement in done correctly. Next, the participant will be instructed to move the vibrators and place them apart to the value of measured larynx width from the previous step. Finally, the participant will wear the wearable device in front of the camera. The study personnel via video call will check and make sure the placement is consistent with the study protocol.

The remote testing session will only involve voice recording using the provided microphone and voice recorder. The instruction for using devices is in the package that the participant received before the video call. A study personnel who conducts the study will walk the participant through the instruction and assures that the devices are properly set up before starting the remote testing. The testing follows the following procedure (See Figure 6):

For the baseline assessment, participants will vocalize the vowels ‘ahh’ and ‘ee’ each five times and read aloud the 20 test sentences from Appendix A of Ludlow et al. [2]. Participants will read the sentences at their own comfortable pace and loudness. In addition, participants will rate their perceived effort level of vocalization on an ordinal scale of 0 to 10 (0 being

with no effort and 10 being with maximal effort). This concludes the pretest voice assessment (see Fig. 6). Subsequently, participants will apply the laryngeal vibration on themselves as instructed for a period of 10 minutes. A study personnel will instruct the participant for each step of the testing. The voice assessment will be repeated after each set of VTS and twice during the retention period (see Fig. 6) The procedure for remote testing is identical to the in-laboratory visit except it does not include EEG and eye movement recording.

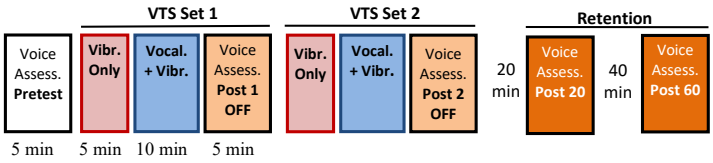

Figure 6. *Experimental design for remote testing.*

The recorded voice data will be stored on the voice recorder that was sent to the participant. The voice data are already deidentified. The audio file names do not contain any HIPPA incompliant information. The files names comprise only the subject ID and the session number (i.e prestest, set 1, etc.). Upon completion of the remote testing session, the participant will receive a prepaid shipping label via email. The participant will print the label and send the equipment back to the laboratory, thus there is no shipping cost for the participant
The stored deidentified voice data will be then removed from the voice recorder and will stored separately on a password protected University of Minnesota HIPAA compliant server where in-laboratory testing data is also located.
Usability questionnaire: The last section of study is to ask participants to fill out a questionnaire about the usability of the wearable collar.

5.3 Study Duration:

The study consists of a single session. Total exposure time to vibration will be approximately 30 minutes. Each VTS set will last 20 minutes. There will be 5 minutes breaks between sets. The interspersed, repeated voice assessment will allow to document time-dependent changes in voice quality and cortical activation due to laryngeal vibration up to 60 minutes past VTS application. Total duration of the study will be 115 minutes.

5.4 Individually Identifiable Health Information:

For SD participants, we collect health information concerning disease duration, and any possible treatment (Botox injection) that they receive and when the last Botox injection had occurred prior to testing. For healthy control participants we only collect initial contact information, but no PHI. The respective HIPAA Agreement Template Form has been uploaded to ETHOS. The PI and his study team have no direct access to any other medical records.

6.0 Data and Specimen Banking

N/A.

7.0 Sharing of Results with Participants

N/A

8.0 Study Population

8.1 Inclusion Criteria:

8.1.1 Patients:
Diagnosis of spasmodic dysphonia made through a voice disorder specialist.

8.1.2 Controls:

Healthy adults, aged 18-75 years with no known neurological or orthopedic deficits that may affect speech motor functions.

8.2 Exclusion Criteria:

8.2.1 Patients:
- Regular intake of benzodiazepines
- Cognitive impairment: score < 27 on Mini-mental state examination; score > 19 on Beck depression inventory
- Identifies with a neurological or musculoskeletal impairment affecting speech motor function. These impairments may include a form of: Dyskinesia, Dystonia, Essential Tremor, Huntington's Disease, Multiple System Atrophy, Muscle Tension Dysphonia, Parkinsonism, Progressive Supranuclear Palsy, Spasticity, Intracranial Neoplasm (brain tumor), Spinal Neoplasm, Cerebrovascular Accident (Stroke), Mild Traumatic Brain Injury, Intracranial Hemorrhage, Multiple Sclerosis

8.2.2 Controls:
- History of impairments affecting speech function.
- Regular intake of benzodiazepines.
- Cognitive impairment: score < 27 on Mini-mental state examination; score > 19 on Beck depression inventory.

8.3 Screening:

SD participants will be screened by Dr. George Goding at the Fairview Lion's Voice Clinic or Dr. Kari Urberg at the Park Nicollet Voice Clinic, St. Louis Park, MN. All SD subjects will be assessed by the clinicians using an established protocol [2]. The clinical assessment consists of a questionnaire (CAPE V) [49], clinical speech evaluation and a nasoendoscopic exam. These clinical assessments are part of the routine exam that patients receive for diagnostic purposes. They are not an explicit part of this study.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☒ None of the above

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

Number of patients with spasmodic dysphonia (SD) will be 20 and number of healthy control subjects (CTL) are 20.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

Voice-disordered subjects (SD) will be recruited through our own SD patient database, through Dr. George Goding at the Fairview Lion's Voice Clinic, or through Dr. Kari Urberg at the Park Nicollet Voice Clinic, St. Louis Park, MN. Control subjects will be recruited from the community via flyer and will be matched for gender and age to the SD participants.

11.2 Identification of Potential Participants:

SD patients are seen regularly by Drs. Goding and Urberg as part of their clinical routine. Dr. Goding sees approximately 30-40 patients a month and administers Botox injections as medically indicated. Both clinicians will identify potential participants and inform them about the study possibility. The initial contact to potential participants is made by either Dr. Goding or Dr. Urberg at their respective clinics. We will not access patient databases in either clinic to identify potential participants through the study coordinator. Note that potential participants are regularly seen by Drs. Goding/Urberg as part of the ongoing patient treatment (e.g. Botox injections). At these scheduled visits Drs. Goding/Urberg will share the study information flyer (see ETHOS section: Recruitment Materials) with potential participants and explain to them the scope of the study. If patients are interested in participating, the contact information of the study coordinator will be shared with the patient, who can then contact the study team. Once the study coordinator is contacted by a potential participant, he will explain the study procedure in detail and will invite participation. If agreeable, a date for obtaining informed consent and data collection is set. Prior to study begin, investigators will obtain and document informed consent from each participant according to21 CFR 50, Protection of Human Subjects (see also section 20.0).
Both Drs. Goding and Urberg have legitimate access to patient PHI as part of their clinical work. Relevant PHI (type of diagnosis, disease duration, frequency of Botox injections) will not be shared with the study team of the PI before consent has been obtained and the participant has signed the appropriate HIPAA form.

11.3 Recruitment Materials:

Healthy and SD participants will be invited to the study via flyers that summarize the study and its goals.

11.4 Payment:

Study participants will be reimbursed $100 for one time in-lab study visit. Study participants will be reimbursed $50 for remote study.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants may opt to take a break or withdraw at any time during the study, if they experience discomfort or become fatigued.

Although our preliminary investigation showed that the applied vibration frequency and amplitude is not sufficient to induce a swallowing or gag reflex, we will stop the procedure, if such incidence is observed. Elicitation of a swallowing reflex is not harmful, but its repeated non-volitional elicitation may cause discomfort.

12.2 Withdrawal Procedures:

If such event would occur, we would give the participant the option to adjust the vibration parameters or to completely withdraw from the study. Any data collected up to that point would be destroyed and not used in further analysis.

12.3 Termination Procedures:

Upon reaching the limit of the proposed study population, recruitment will stop and only data analysis will continue. Once the analysis is completed, the de-identified data sets will remain on UMN HIPAA compliant servers. They will form the basis for any scientific publication resulting from the study. We will then orderly terminate the study following the procedures required by IRB.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Vibration Risks. The risks in this study are minimal other than the possibility of skin redness over the skin or feelings mimicking numbness over the neck area during trials. These discomforts, if any occurs, usually disappear within minutes after vibration is removed.
EEG Risks. There is no particular risk associated with EEG recordings. The procedure is non-invasive and no energy is imposed by the system to the participant. Participants may opt to take a break or stop/withdraw at any time, if they experience any discomfort due the wearing of the EEG cap.
Wearable Collar Risks: This risk of using the collar with respect to irritation/rubbing is minimal. Because the textile is chosen from biocompatible material and the collar is not moving during the testing, there is minimal risk associated with it. In addition, because the electronics do not have any contact with the tissue and are enclosed in a housing, the risk of the electronics being affected by moisture/sweat is minimal.

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

There is no direct benefit to participating in this study. At this point, there are no known data that provide conclusive evidence for the effectiveness of laryngeal vibration in reducing voice disorder symptoms.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

Analysis of voice data. Acoustic analysis will follow the methodology described by [50]. Waveform and wide-band spectrograms will be used to identify and measure the duration of the variables. The acoustic signal will be examined for the presence of phonatory breaks and aperiodic breaks. Phonatory breaks are defined as any voiced phonemic segment without sound that is greater than 50ms; the duration of phonatory breaks will be measured. Aperiodic segments will be identified as any voiced phonemic segment that contains non-repetitive cycles that are greater than 50ms; and the duration of the break will be measured. To standardize the duration measures for both phonatory and aperiodic breaks, the sum of the duration of breaks will be divided by the sum of the duration of all voiced segments for each subject. Inter-rater reliability will be measured using Cohen's alpha and intra-rater reliability will use Pearson's r correlation (expected to range between r=.89 to r= .98 according to [50]). For both break types, the absence of phonation or the presence of aperiodicity at the boundary of a syllable or the beginning of a word will not be considered. We will perform a MANCOVA procedure employing all acoustic variables with pre-/posttests as independent factors. If the MANCOVA is significant, separate univariate ANOVAs will be performed on each acoustic variable (dependent) and assessment conditions as a repeated measure (independent) [50]. Appropriate Bonferroni adjustments will account for multiple testing.

Analysis of EEG data. EEG recordings during speech are known to be susceptible to noise from the multiple muscles in and near the head that are involved in speech production. We have been cognizant to this fact and a) designed a simple vocalization task that does not involve complex patterns of muscle activation and b) use modern noise removal techniques that have been successfully applied for the analysis of voice related EEG. Dr. Yang is an expert in the analysis of speech-related EEG and will lend his expertise for EEG data analysis, which is based on the widely utilized MATLAB EEGlab toolbox [51]. Space limitation does not permit to describe all processing steps in detail. However, here we outline its major approach. First, to remove motion and electromyographic artifacts, all channels will be filtered (0.5 Hz high-pass and 20 Hz low-pass FIR filter). Second, target events will be extracted and trials containing non-physiological signal amplitudes will be rejected (typically outside [-100 μv 100 μv]). Third, for further objective noise removal the ADJUST algorithm (Automatic EEG artifact Detector based on the Joint Use of Spatial and Temporal features)

will be utilized - algorithm also included in the NIH Neuroimaging Tools and Resources Platform. Finally, an Independent Component Analysis (ICA) will be applied [52]. The ICA statistically decomposes all 64 channels into 64 independent sources of information (components) whose weighted sum is assumed to result in the formation of the recorded data. After this step, the pruned components are combined, generating a cleaner data set. After the ICA weights have been computed, the ADJUST will be employed to detect those independent components, which based on the statistical criteria of the algorithm, were the potential sources of stereotyped artifacts (eye blinks, vertical eye movement, horizontal eye movement, generic discontinuity i.e. inappropriate signals due to noisy channels or muscle activation) [53]. The statistical criteria for removing noise components include temporal kurtosis and spatial average difference [SAD] (from eye blinking), the maximum epoch variance [MEV] and SAD (from vertical eye movements), the MEV and spatial eye difference [SED] (from horizontal eye movements), and MEV and the generic discontinuity spatial feature [GDSF] (from bad channels and muscle activation). After the removal of noise components, a time-frequency analysis will be carried out on all channels of the pruned dataset. The analysis will yield the mean event-related changes in the spectral power "ERSP" (from pre-stimulus baseline) for the different frequency ranges at each time instance of all epochs.

16.0 Confidentiality

16.1 Data Security:

All private information will be stored in a secured location and all recorded and derived data from either in-laboratory testing or remote testing will be de-identified and stored separately on a password protected University of Minnesota HIPAA compliant server. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. However, your record for the study may be reviewed by departments at the University with appropriate regulatory oversight.

17.0 Provisions to Monitor the Data to Ensure the Safety of Participants

17.1 Data Integrity Monitoring.

The PI and study coordinator oversee the progress of the study and to ensure that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, and applicable regulatory requirements. This study does not constitute a clinical trial at this point. Neither CITI, nor IRB have requested additional intramural or extramural monitors. Consequently, no independent monitoring reports. This study is currently not listed with clinicaltrails.gov.

17.2 Data Safety Monitoring.

Protection of subject confidentiality will be strictly monitored. All records will be kept confidential and without identifying the subjects in published materials. Only authorized personnel directly associated with the study will have access to digital files or paper data sheets with original data sets that may contain information about subject identity. The paper files will be kept in locked file cabinets in the laboratory of the PI, to which only authorized personnel has access. The files containing the subject identifying codes will be destroyed after 10 years. All digital data will be stored on a secure, HIPAA compliant server maintained by the University of Minnesota Office of Information Technology and/or using "Box" as the HIPAA compliant tool (*see https://it.umn.edu/center-excellence-hipaa-data*). All research personnel completed the required data and safety monitoring courses (e.g., responsible conduct of research, HIPAA, etc.).

18.0 Provisions to Protect the Privacy Interests of Participants

18.1 Protecting Privacy: As described in section 11, participants will only contact information as it is needed to interact with them prior or after testing. The collected PHI is very limited and will only be used in de-identified form during analysis and in any possible scientific publications. During the consent process, we explicitly tell the participant what PHI if any will be collected and how long we will store it. We also describe the study procedure in detail and emphasize that the procedure is not invasive and carries no known health risk.

18.2 Access to Participants*:*

Only the study coordinator has access to PHI or address information about the participants. The other members of the study team only have access to de-identfied data.

19.0 Compensation for Research-Related Injury

19.1 Compensation for Research-Related Injury:

In the unlikely event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to subjects or their insurance company.

20.0 Consent Process

20.1 Consent Process (when consent will be obtained):

- <u>For in-laboratory testing:</u>
  - Consent will take place either in the laboratory prior to testing by signing the consent document in person or digitally through REDCap via a tablet provided to the participant or a link to the eConsent that has been shared with the participant before the laboratory visit.

Investigators will obtain and document informed consent from each participant according to 21 CFR 50, Protection of Human Subjects.

- There are, at minimum, several days and often weeks between informing the prospective participants and obtaining the consent. This study requires that patients are seen towards the end of their Botox cycle. Once a potential study participant contacts the study coordinator, has received the relevant study information, and has agreed to participate, the coordinator and the participant agree on a date suggested by the participant. The patients know best when they become symptomatic and the effect of the Botox injection is wearing off.
- The referring clinician determines that a potential participant understands the information.
- Copy of the consent form for the in-laboratory testing has been uploaded to ETHOS.

- For remote testing:
  - Consent will take place prior to testing digitally through REDCap via a link to the eConsent that has been shared with the participant prior to the remote testing and video call. Investigators will obtain and document informed consent from each participant according to 21 CFR 50, Protection of Human Subjects.
  - There are, at minimum, several days and often weeks between informing the prospective participants and obtaining the consent. This study requires that patients are seen towards the end of their Botox cycle. Once a potential study participant contacts the study coordinator, has received the relevant study information, and has agreed to participate, the coordinator and the participant agree on a date suggested by the participant. The patients know best when they become symptomatic and the effect of the Botox injection is wearing off.
  - The referring clinician determines that a potential participant understands the information.
  - Copy of the consent form for the remote testing has been uploaded to ETHOS.

21.0 Setting

21.1 Research Sites:

Locations where participant will be recruited. Healthy participants will be invited to the study via flyers, and SD individuals will be invited through

Dr. George Goding at the Fairview Lion's Voice Clinic, or Dr. Kari Urberg at the Park Nicollet Voice Clinic, St. Louis Park, MN.
Locations where the research will be conducted: Multiple Sensory Perception Laboratory, Elliott Hall, University of Minnesota

22.0 Multi-Site Research

N/A

23.0 Resources Available

23.1 Resources Available:

- We have been collaborating with Drs. Goding and Urberg for several years. We are recruiting patients with voice disorders since 2012 and have not had difficulties meeting our recruitment goals.
- As of June 2018 this protocol has been in place for four years. We anticipate to finish work under this current protocol by the end of this year.
- The in-person testing will take place in the Multisensory Perception Laboratory (MSP Lab) in Elliott Hall, University of Minnesota campus. This is a core research facility of the Center for Translational Sensory Science (CATSS). The MSP Lab consists of two rooms, each with a large sound-attenuating chamber for participant testing, and many specialized pieces of equipment (see below). The MSP Lab is a shared research space and is available to groups throughout the University of Minnesota community, as well as industry groups associated with CATSS.
- The MSP Lab is not a clinical entity. No physicians or licensed psychologists are on staff. If participants require medical help because of an anticipated or unanticipated event during participation, investigators will have to notify emergency services through a 911 call.
- All study personnel has been trained to perform their respective function according to the protocol. They are aware of their duties for informing participants and for obtaining consent. They all have received the necessary human subject protection training as required by University policies.

24.0 References

1. Davis, P.J. and B.S. Nail, *Quantitative analysis of laryngeal mechanosensitivity in the cat and rabbit.* J Physiol, 1987. **388**: p. 467-85.
2. Ludlow, C.L., et al., *Research priorities in spasmodic dysphonia.* Otolaryngology - Head and Neck Surgery, 2008. **139**(4): p. 495-505.e1.
3. Soland, V.L., K.P. Bhatia, and C.D. Marsden, *Sex prevalence of focal dystonias.* J Neurol Neurosurg Psychiatry, 1996. **60**(2): p. 204-5.

4. Cohen, L.G., et al., *Blink reflex excitability recovery curves in patients with spasmodic dysphonia.* Neurology, 1989. **39**(4): p. 572.
5. Tolosa, E. and L. Montserrat, *Depressed blink reflex habituation in dystonic blepharospasam.* Neurology, 1985. **35**(supplement 1): p. 251-260.
6. Tolosa, E., L. Montserrat, and A. Bayes, *Blink reflex studies in focal dystonias: enhanced excitability of brainstem interneurons in cranial dystonia and spasmodic torticollis.* Movement Disorders: Official Journal of the Movement Disorder Society, 1988. **3**(1): p. 61-69.
7. Topka, H. and M. Hallett, *Perioral reflexes in orofacial dyskinesia and spasmodic dysphonia.* Muscle & Nerve, 1992. **15**(9): p. 1016-1022.
8. Ludlow, C.L., et al., *Abnormalities in long latency responses to superior laryngeal nerve stimulation in adductor spasmodic dysphonia.* The Annals of Otology, Rhinology, and Laryngology, 1995. **104**(12): p. 928-935.
9. Berardelli, A., et al., *Pathophysiology of blepharospasm and oromandibular dystonia.* Brain: A Journal of Neurology, 1985. **108 (Pt 3)**: p. 593-608.
10. Adamovich, S.V., et al., *The interaction of visual and proprioceptive inputs in pointing to actual and remembered targets in Parkinson's disease.* Neuroscience, 2001. **104**(4): p. 1027-1041.
11. Contreras-Vidal, J.L. and D.R. Gold, *Dynamic estimation of hand position is abnormal in Parkinson's disease.* Parkinsonism & Related Disorders, 2004. **10**(8): p. 501-506.
12. Demirci, M., et al., *A mismatch between kinesthetic and visual perception in Parkinson's disease.* Annals of Neurology, 1997. **41**(6): p. 781-788.
13. Konczak, J. and G. Abbruzzese, *Focal dystonia in musicians: linking motor symptoms to somatosensory dysfunction.* Front Hum Neurosci, 2013. **7**: p. 297.
14. Konczak, J., et al., *The perception of passive motion in Parkinson's disease.* Journal of Neurology, 2007. **254**(5): p. 655-663.
15. Konczak, J., et al., *Haptic perception of object curvature in Parkinson's Disease.* PLoS ONE, 2008. **3**(7): p. e2625.
16. Konczak, J., et al., *Parkinson's disease accelerates age-related decline in haptic perception by altering somatosensory integration.* Brain, 2012. **135**(Pt 11): p. 3371-9.
17. Maschke, M., et al., *Dysfunction of the basal ganglia, but not the cerebellum, impairs kinaesthesia.* Brain, 2003. **126**(Pt 10): p. 2312-22.
18. Maschke, M., et al., *Perception of heaviness in Parkinson's disease.* Movement Disorders: Official Journal of the Movement Disorder Society, 2006. **21**(7): p. 1013-1018.
19. Maschke, M., et al., *The effect of subthalamic nucleus stimulation on kinaesthesia in Parkinson's disease.* Journal of Neurology, Neurosurgery & Psychiatry, 2005. **76**(4): p. 569 -571.
20. O'Suilleabhain, P., J. Bullard, and R.B. Dewey, *Proprioception in Parkinson's disease is acutely depressed by dopaminergic medications.* Journal of Neurology, Neurosurgery & Psychiatry, 2001. **71**(5): p. 607 -610.

21. Putzki, N., et al., *Kinesthesia is impaired in focal dystonia.* Movement Disorders, 2006. **21**(6): p. 754-760.
22. Patel, N., J. Jankovic, and M. Hallett, *Sensory aspects of movement disorders.* Lancet Neurol, 2014. **13**(1): p. 100-12.
23. Konczak, J., et al., *Proprioception and motor control in Parkinson's disease.* J Mot Behav, 2009. **41**(6): p. 543-52.
24. Chen, Y.W., P. Watson, and J. Konczak, *Reduced arm kinaesthetic sensitivity in spasmodic dysphonia.* Society for Neuroscience Abstracts, 2013. **43**: p. 437.17.
25. Brown, M.C., I. Engberg, and P.B. Matthews, *The relative sensitivity to vibration of muscle receptors of the cat.* J Physiol, 1967. **192**(3): p. 773-800.
26. Brown, M.C., I. Enberg, and P.B. Matthews, *The use of vibration as a selective repetitive stimulus for Ia afferent fibres.* J Physiol, 1967. **191**(1): p. 31P-32P.
27. Bianconi, R. and J. van der Meulen, *The response to vibration of the end organs of mammalian muscle spindles.* J Neurophysiol, 1963. **26**: p. 177-90.
28. Vedel, J.P. and J.P. Roll, *Response to pressure and vibration of slowly adapting cutaneous mechanoreceptors in the human foot.* Neurosci Lett, 1982. **34**(3): p. 289-94.
29. Goodwin, G.M., D.I. McCloskey, and P.B. Matthews, *Proprioceptive illusions induced by muscle vibration: contribution by muscle spindles to perception?* Science, 1972. **175**(4028): p. 1382-4.
30. Goodwin, G.M., D.I. McCloskey, and P.B. Matthews, *The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents.* Brain, 1972. **95**(4): p. 705-48.
31. Roll, J.P. and J.P. Vedel, *Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography.* Exp Brain Res, 1982. **47**(2): p. 177-90.
32. Cordo, P., et al., *Proprioceptive consequences of tendon vibration during movement.* J Neurophysiol, 1995. **74**(4): p. 1675-88.
33. Cordo, P.J., et al., *Effect of slow, small movement on the vibration-evoked kinesthetic illusion.* Exp Brain Res, 2005. **167**(3): p. 324-34.
34. De Gail, P., J.W. Lance, and P.D. Neilson, *Differential effects on tonic and phasic reflex mechanisms produced by vibration of muscles in man.* J Neurol Neurosurg Psychiatry, 1966. **29**(1): p. 1-11.
35. Shinohara, M., *Effects of prolonged vibration on motor unit activity and motor performance.* Med Sci Sports Exerc, 2005. **37**(12): p. 2120-5.
36. Steyvers, M., et al., *Frequency-dependent effects of muscle tendon vibration on corticospinal excitability: a TMS study.* Exp Brain Res, 2003. **151**(1): p. 9-14.
37. Forner-Cordero, A., et al., *Changes in corticomotor excitability following prolonged muscle tendon vibration.* Behav Brain Res, 2008. **190**(1): p. 41-9.
38. Stamelou, M., et al., *The non-motor syndrome of primary dystonia: clinical and pathophysiological implications.* Brain, 2012. **135**(Pt 6): p. 1668-81.
39. Grünewald, R.A., et al., *Idiopathic focal dystonia: a disorder of muscle spindle afferent processing?* Brain, 1997. **120 (Pt 12)**: p. 2179-85.
40. Fiorio, M., et al., *Tactile temporal discrimination in patients with blepharospasm.* J Neurol Neurosurg Psychiatry, 2008. **79**(7): p. 796-8.

41. Molloy, F.M., et al., *Abnormalities of spatial discrimination in focal and generalized dystonia.* Brain, 2003. **126**(Pt 10): p. 2175-82.
42. Kanovsky, P., et al., *Abnormalities of cortical excitability and cortical inhibition in cervical dystonia Evidence from somatosensory evoked potentials and paired transcranial magnetic stimulation recordings.* J Neurol, 2003. **250**(1): p. 42-50.
43. Zeuner, K.E. and F.M. Molloy, *Abnormal reorganization in focal hand dystonia--sensory and motor training programs to retrain cortical function.* NeuroRehabilitation, 2008. **23**(1): p. 43-53.
44. Samargia, S., R. Schmidt, and T.J. Kimberley, *Shortened cortical silent period in adductor spasmodic dysphonia: Evidence for widespread cortical excitability.* Neurosci Lett, 2014. **560**: p. 12-5.
45. Kägi, G., et al., *Sensory tricks in primary cervical dystonia depend on visuotactile temporal discrimination.* Mov Disord, 2013. **28**(3): p. 356-361
46. Poisson, A., et al., *History of the 'geste antagoniste' sign in cervical dystonia.* J Neurol, 2012. **259**(8): p. 1580-4.
47. Tang, J.K., et al., *Changes in cortical and pallidal oscillatory activity during the execution of a sensory trick in patients with cervical dystonia.* Exp Neurol, 2007. **204**(2): p. 845-8.
48. Karnath, H., J. Konczak, and J. Dichgans, *Effect of prolonged neck muscle vibration on lateral head tilt in severe spasmodic torticollis.* Journal of Neurology, Neurosurgery & Psychiatry, 2000. **69**(5): p. 658-660.
49. Zraick, R.I., et al., *Establishing validity of the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V).* Am J Speech Lang Pathol, 2011. **20**(1): p. 14-22.
50. Sapienza, C.M., S. Walton, and T. Murry, *Adductor spasmodic dysphonia and muscular tension dysphonia: Acoustic analysis of sustained phonation and reading.* Journal of Voice, 2000. **14**(4): p. 502-520.
51. Delorme, A. and S. Makeig, *EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis.* J Neurosci Methods, 2004. **134**(1): p. 9-21.
52. Hyvarinen, A. and E. Oja, *Independent component analysis: algorithms and applications.* Neural Netw, 2000. **13**(4-5): p. 411-30.
53. Mognon, A., et al., *ADJUST: an automatic EEG artifact detector based on the joint use of spatial and temporal features.* Psychophysiology, 2010. **48**(229-240).