Vibro tactile stimulation as a treatment for the voice disorder spasmodic dysphonia

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Dedication

This thesis is dedicated to

My parents

and

My lovely wife Katayoon

For boundless love and affection,
For always inspiring me to push the boundaries of my capabilities, and
For making sure that I always get the best in my life.

Abstract

Spasmodic dysphonia (SD) is rare focal dystonia affecting the laryngeal musculature. Patients with SD typically experience a strained or choked speech and report that it takes an exhausting effort for them to speak. The disorder develops spontaneously during midlife. Its progression is gradual in the first year and then becomes chronic for life. At present, there is no cure for SD and it is unresponsive to behavioral speech therapy. It is treated primarily with Botulinum toxin (Botox) injections for temporary symptom relief. Proprioceptive deficits are an underlying feature of SD - a finding that opens an avenue for a missing behavioral treatment for the disease. Specifically, vibro-tactile stimulation (VTS) could be the suitable tool, given that it alters afferent signals from the mechanoreceptors in the vibrated muscles and skin.

This cumulative dissertation concerns a non-invasive neuromodulation approach using VTS for treating the voice symptoms in people with SD. It consists of three separate projects. The first project examined the short-term effect of vibro-tactile stimulation (VTS) on speech quality and cortical activity of 12 participants with adductor SD and one with abductor SD. The results showed that 9 participants (69%) exhibited a reduction of voice breaks and/or a meaningful increase in smoothed cepstral peak prominence, an acoustic measure of voice/speech quality. Symptom improvements persisted for 20 minutes past VTS. In addition, VTS induced a significant suppression of theta band power over the left somatosensory-motor cortex and a significant rise of gamma rhythm over the right somatosensory-motor cortex. Our results show convincingly that VTS represents a non-invasive form of neuromodulation that induces measurable short-term improvements in patients' speech with adductor SD.

The second project represents a logical step to expand on the previous work to improve VTS technology and make it wearable. To that effect, I have designed and developed a wearable non-invasive collar-like device that applies VTS to the laryngeal muscles. The device provides two operational modes, continuous VTS and real-time VTS, using a developed speech detection technology. The speech detection algorithm allows for individualized system calibration providing flexibility in adjusting the device for users with different anatomy and/or disease severity.

For the final project, I used the device that was developed in project 2 to examine the efficacy of VTS for treating voice symptoms in people with abductor SD. The results showed an improvement in at least one marker of voice quality for 3 out of 4 participants. The improvement lasted for 20 and 60 minutes after cessation of VTS for one participant. However, we require a larger sample to have a confident response rate to the laryngeal VTS in AB SD. The current analysis of electrocortical responses to VTS in people with AB SD did not closely mimic the event -elated cortical activity patterns seen in AD SD. More data are needed to delineate consistent patterns of cortical responses induced by laryngeal VTS in AB SD.

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List of Abbreviations

SD	Spasmodic dysphonia
FD	Focal dystonia
AB	Abductor
AD	Adductor
CD	Cervical dystonia
TA	Thyroarytenoid
PCA	Posterior cricoarytenoid
LCA	Lateral cricoarytenoid
Botox	Botulinum toxin
ERSP	Event related spectral perturbation
ERD	Event related desynchronization
ERS	Event related synchronization

Introduction

This dissertation concerns a non-invasive neuromodulation approach for treating the voice symptoms in people with spasmodic dysphonia (SD), a form of focal dystonia of the larynx. This is a cumulative doctoral dissertation. It consists of three separate projects. The first project investigated the short-term effect of vibro-tactile stimulation (VTS) in people with adductor SD. The second project represents a logical extension of the previous work by improving the previous wired VTS technology and making it wearable. To that effect, I have designed and developed a wearable non-invasive collar-like device that applies VTS to the laryngeal muscles. For the final project, I used the wearable device developed in project 2 to examine the efficacy of VTS for treating voice symptoms in people with the abductor SD.

Spasmodic dysphonia (SD) – a voice disorder

Spasmodic dysphonia is a rare speech disorder (1 per 100,000 cases) developing spontaneously during midlife. The progression is gradual in the first year and then becomes chronic for life (Ludlow, 2011; Ludlow et al., 2008). The average age of the disorder's onset is between 30-50 years old (Enver and Pitman, 2020). SD is the third most prevalent type of focal dystonia after cervical dystonia (CD) and blepharospasm (Castelon Konkiewitz et al., 2002). It is more prevalent in women than men (Ludlow et al., 2008; Soland et al., 1996).

Patients with SD typically have a strained or choked speech and report that it takes an exhausting effort for them to speak (Ludlow, 2011). The cause of SD is unknown, but it is considered a form of task-specific focal dystonia (FD), meaning that involuntary spasms of the laryngeal musculature occur during speech but not during other phonatory

(e.g., prolonging vowels) or non-phonatory tasks (e.g., breathing). (Ludlow, 2011; Ludlow et al., 2008; Pool et al., 1991).

Types of spasmodic dysphonia

There are two types of SD: adductor (AD), typified by uncontrolled vocal fold closure; and abductor (AB), characterized by uncontrolled vocal fold opening. AD type of SD is more predominant (at least 80%) and typically occurs during the voiced components of speech which are words starting with or containing vowels. Conversely, AB results in a breathy or prolonged speech during the unvoiced components of speech such as /h/, /s/, /p/, and /f/ (Ludlow, 2011; Van Pelt et al., 1994). AB patients struggle with the phonation onset after an unvoiced consonant (Van Pelt et al., 1994).

AD SD and AB SD affect different laryngeal muscles (Hoffman et al., 2009). AD is associated with hypertonia of the thyroarytenoid (TA) muscle (Van Pelt et al., 1994), yet abnormal activation of the thyroarytenoid can also be observed in AB SD (Watson et al., 1991). Symptoms in AB SD are thought to be associated with abnormal hyperactivity of posterior cricoarytenoid (PCA) or failure of the lateral cricoarytenoid (CT) or thyroarytenoid muscle contraction (Cyrus et al., 2001; Hoffman et al., 2009). In addition, Cyrus et al. found an asymmetrical activation between both sides of CT muscle in AB SD patients (Cyrus et al., 2001). However, Van Pelt investigated the laryngeal muscle activity during movement intervals between AB SD and AD SD and did not find any significant difference (Van Pelt et al., 1994). These studies suggest that although speech symptoms between AB and AD are different, the pathophysiological profiles of both forms of SD are overlapping and not distinct, which introduces challenges both in diagnosis and treatment of SD.

Current treatments

At present, there is no cure for SD. It does not respond to behavioral speech therapy. Current therapeutic options are limited and are mostly directly altering or obstructing laryngeal muscle action rather than blocking or altering abnormal cortical activity.

The gold standard treatment for SD is local Botulinum toxin (BOTOX) injection to the laryngeal muscles, where the primary injection muscle in AD SD is TA and in AB SD is PCA (Ludlow et al., 2008). The effectiveness of Botox is temporary, and patients need to have periodic injections for an average of every 3 to 6 months. The dosage has a wide range across patients (Blitzer et al., 1998; Ludlow et al., 2008). Although Botox provides average symptom relief of 90% of normal function for AD SD(Blitzer et al., 1998), it is not well tolerated by all SD patients (Watts et al., 2004) and has minor or no effects on some patients, especially AB SD (Ludlow et al., 2008).

Over the past decades, there have been several attempts for surgical treatment of spasmodic dysphonia, mostly focusing on AD SD (Enver and Pitman, 2020). One approach is selective laryngeal AD muscles denervation-reinnervation (SLAD-R) (G. S. Berke et al., 1999), where the result shows that 80% of patients with AD SD showed a decrease in symptoms leaving the rest of the patients with unsatisfactory results with a breathy voice. Another surgical approach is midline lateralization thyroplasty for AD SD to restrain the glottis overclosure during speech (Isshiki et al., 2000), although, the results of this surgical intervention is rather mixed. A novel surgical treatment is laser TA myoneurectomy that shows encouraging results (Schuering et al., 2020). However, after 12 months past surgery, 45% of the patients observed voice deterioration and underwent a second surgical procedure. Another alternative potential treatment of SD is

deep brain stimulation (DBS). A case study showed that bilateral deep stimulation of ventral intermediate nucleus (VIM) of the thalamus might be a viable target for treatment of severe SD (Lyons et al., 2010). At this point, DBS is not an established intervention to treat the voice symptoms of SD.

Neurophysiology behind spasmodic dysphonia

The underlying neural mechanism of SD is not entirely understood, but it is known to involve structural and functional alterations in the basal ganglia–thalamo-cortical circuitry, the brainstem, and the cerebellum (Ludlow et al., 1995b; Samargia et al., 2014; Simonyan et al., 2013; Simonyan and Ludlow, 2010; Simonyan et al., 2008). The pathophysiology of SD is characterized by an abnormally high synchronous activity within and across cortical neural networks involved in voice production that is mainly lateralized in the left hemisphere (Khosravani et al., 2019a). In addition, SD, like several other forms of focal dystonia (FD), including cervical dystonia (CD) and blepharospasm, present with somatosensory system abnormalities even in non-dystonic muscles (Ali et al., 2006; Konczak et al., 2015; Maschke et al., 2003; Patel et al., 2014a; Putzki et al., 2006). For example, abnormal blink reflexes were observed in SD, torticollis, and blepharospasm (Cohen et al., 1989; Tolosa et al., 1988; Topka and Hallett, 1992), and abnormal long-latency responses to peripheral nerve stimulation have been observed in SD (Ludlow et al., 1995a), in blepharospasm and oromandibular dystonia (Berardelli et al., 1985). Recent evidence from our group and the work of others strongly indicate that basal ganglia-related diseases such as Parkinson's disease and certain forms of dystonia are associated with somatosensory and specifically proprioceptive abnormalities that are closely linked to the observed motor deficits (Contreras-Vidal and

Gold, 2004; Demirci et al., 1997; Konczak et al., 2007; Maschke et al., 2003; Maschke et al., 2005; Patel et al., 2014b; Putzki et al., 2006).

Somatosensory deficits in FD

Numerous research reports documented somatosensory deficits in FD. For example, proprioceptive-based finger position sense thresholds and the perception of arm motion are abnormal in patients with cervical dystonia or blepharospasm (Grünewald et al., 1997; Putzki et al., 2006). The abnormalities in tactile and proprioceptive processing are not restricted to the affected dystonic musculature but were also documented in non-affected body regions (Fiorio et al., 2008; Molloy et al., 2003; Putzki et al., 2006), 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 (Kanovsky et al., 2003; Zeuner and Molloy, 2008), which also has been confirmed for SD (Samargia et al., 2014). In addition, there is convergent evidence that FD is associated with kinaesthetic deficits that are also manifest in non-dystonic musculature (Konczak and Abbruzzese, 2013; Putzki et al., 2006).

Majority of individuals with SD experience abnormalities related to their limb movements (Pool et al., 1991). Recent work from our group confirmed upper limb proprioceptive deficits in SD (Konczak et al., 2015), demonstrating that, like other forms of FD, SD is associated with a generalized somatosensory deficit.

Somatosensory stimulation – a potential treatment approach

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 (Kägi et al., 2013; Poisson et al., 2012). Research on cervical dystonia documented that effective sensory tricks can ease dystonic symptoms and are associated with pallidal and motor cortical desynchronization at low frequencies (6-8Hz) (Tang et al., 2007).

Moreover, studies on the effects of sensory stimulation of the larynx have indicated a reduced inhibition of laryngeal muscle responses to sensory stimulation, i.e., a reduced suppression of motor responses to laryngeal sensory stimulation (Ludlow et al., 1995a). Functional neuroimaging in SD during phonation has also shown increased central activation in the laryngeal somatosensory cortex in patients with SD (Simonyan and Ludlow, 2010). These studies highlight different forms of somatosensory abnormalities in SD, which may contribute to the pathomechanism of the disease. This notion opens an avenue for a potential behavioral treatment for SD that seeks to modulate the somatosensory information of the laryngeal musculature to improve the speech motor output.

In particular, the vibro-tactile stimulation (VTS) of laryngeal muscles might be a suitable tool for this purpose, given that it is shown to alter the afferent proprioceptive signals produced by the vibrated muscle mechanoreceptors and muscle spindles (Bianconi and Van Der Meulen, 1963; Brown et al., 1967c).

Effects of vibro-tactile stimulation (VTS)

It has long been established that VTS can stimulate muscle spindles (Bianconi and Van Der Meulen, 1963; Brown et al., 1967a, 1967b) and mechanoreceptors (Vedel and Roll, 1982) affecting motor behavior and inducing changes in kinaesthesia (Goodwin et al., 1972a, 1972b; Roll and Vedel, 1982). 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* (Bianconi and Van Der Meulen, 1963; Brown et al., 1967b). To elicit kinaesthetic illusions, vibration must typically range between 40-100 Hz (Cordo et al., 1995; Cordo et al., 2005). Brief vibration to a relaxed muscle typically leads to an increase in muscle tone that can easily be overcome by voluntary phasic innervation (De Gail et al., 1966), while excitatory input to spinal α-motor neurons is depressed when vibration is applied for prolonged periods (Shinohara, 2005). 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 (Forner-Cordero et al., 2008; Steyvers et al., 2003).

VTS can reduce the severity of dystonic postures in FD. Vibrating dystonic neck muscles of patients with torticollis, who exhibit abnormally tilted head postures, induced head righting, and nearly restored normal head posture (Karnath et al., 2000; Zhu, 2020). Vibrating non-dystonic arm muscles in patients with cervical dystonia and blepharospasm skewed arm position sense to a greater extent than healthy controls (Grünewald et al., 1997). VTS has been shown to influence somatosensory perception

and may reduce the severity of dystonic postures (Grünewald et al., 1997; Kägi et al., 2013; Karnath et al., 2000; Konczak and Abbruzzese, 2013).

Vibro-tactile stimulation as a potential treatment for SD

No studies exist that investigated the effects of VTS in SD. There are several physiological similarities between the speech and limb motor systems that make VTS use plausible, but anatomical differences make the application of VTS more challenging. The knowledge on the distribution and function of somatosensory receptors within the laryngeal musculature is still inconclusive. A series of neuroanatomical, histochemical, and electron microscopic studies supported the existence of muscle spindles in the larynx (Baken and Noback, 1971; Grim, 1967; Hirayama et al., 1987; Paulsen, 1958; Tellis et al., 2004), while others failed to provide support for the existence of intrafusal muscle fibers in cricothyroid and thyroarytenoid muscles (Brandon et al., 2003) or could not elicit stretch responses in these areas (Loucks et al., 2005).

Moreover, the mucosa of the epiglottis is known to have an array of mechanoreceptors responsive to mechanical stimulation between 10-70Hz with a depression amplitude of <100µm (Davis and Nail, 1987; Nagai, 1982). It was further demonstrated that the sensory basis for the laryngeal adductor response is dependent on the stimulation of mechanoreceptors in the laryngeal mucosa in the cat and humans (Andreatta et al., 2002; Loucks et al., 2005). Further, the finding of Krause-type sensory corpuscles at the free edge of the vocal cords underlines the notion that many of these mechanoreceptors provide proprioceptive feedback not only useful for swallowing but for voice control (Nagai, 1982). In addition, it needs to be considered that Botox treatment may impair

responses of laryngeal muscle spindles in SD because their innervating γ-motor neurons are cholinergic.

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. Thus, 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 to investigate vibration responses in limb muscles are not suitable due to size, weight, and voltage requirements. Recent advancements in vibrator technology 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.

Given that SD, like other FDs, is associated with abnormally increased cortical excitation and heightened levels of neuronal synchronization (Samargia et al., 2014; Zeuner and Molloy, 2008), this work proposes that VTS can reduce sensorimotor cortical excitation in SD by desynchronizing motor cortical neuron activity as has been shown in cervical dystonia (Tang et al., 2007).

Project rationale

SD is associated with similar proprioceptive deficits as other forms of FD, and altering or modulating proprioceptive signals may be a way to normalize motor output. No data exist on how SD patients respond to VTS. New advances in vibrator technology make the application of VTS to stimulate laryngeal proprioceptors in SD feasible. The

neurophysiological mechanism behind the VTS efficacy in SD is based on the stimulation of laryngeal mechanoreceptors.

The general aim of this dissertation 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 work seeks to address a clinical need to develop alternative or auxiliary treatments for a rare voice disorder with limited treatment options. In addition, this project introduces a novel new wearable vibrator technology that allows for the in-home and clinical application of VTS.

Project 1: The Effects of one-time laryngeal vibration on cortical activation patterns and markers of voice quality in people with spasmodic dysphonia

Recent work from our group confirmed upper limb proprioceptive deficits in SD (Konczak et al., 2015), confirming that a generalized somatosensory deficit is present in this disorder. This finding opens an avenue for a new and missing behavioral treatment for SD that seeks to alter or mask the faulty central processing of proprioceptive inputs to improve speech motor output. Laryngeal vibro-tactile stimulation (VTS) might be a suitable tool, given that it alters the afferent proprioceptive signals produced by the vibrated muscle spindles and mechanoreceptors (Bianconi and Van Der Meulen, 1963; Brown et al., 1967b). To further investigate the effect of VTS on patients with SD, a few questions need to be explored:

- Can VTS provide measurable symptomatic relief for patients with SD? If so, is there any objective changes in the voice quality after VTS?
- What are the changes in the cortical activity associated with VTS?

Accordingly, this project sought to systematically evaluate the effect of laryngeal VTS on people with SD. The findings of this study would set the basis for taking a step toward developing a novel, non-invasive neuromodulation treatment for SD.

Specific aims

Aim 1: Demonstrate the effects of one-time laryngeal vibration on markers of voice quality in people with spasmodic dysphonia.

Aim 2: Demonstrate the effects of one-time laryngeal vibration on cortical activation patterns in people with spasmodic dysphonia.

Methods

Participants

Thirteen people with SD (8 female, 5 male; mean age ± std: 58.6 ± 12.5 years) were recruited from the Fairview Clinic at the University of Minnesota and attended the study (See **Table 1** for clinical characteristics of study participants). The experimental protocol was approved by the Institutional Review Board of the University of Minnesota. All participants gave their informed consent prior to the experiment. Patients receiving botulinum toxin (Botox) treatment were tested toward the end of their injection cycle to ensure their voice was in the symptomatic stage.

***Table 1**. Clinical characteristics of study participants. F: female, m: Male, R: Right*

Subject ID	Gender	Age	Dominant Hand	SD type	Voice Tremor	Diagnosis Duration (mo.)	Botox cycle (mo.)	Last Botox Injection (mo.)
SD 01	F	71	R	ADD	Moderate	44	4	9
SD 02	F	48	R	ADD	No	48	4	3
SD 03	M	59	R	ADD	No	40	4.5	4.5
SD 04	M	60	R	ADD	No	50	>3	3
SD 05	M	73	R	ABD	No	180	NA	36
SD 06	F	57	R	ADD	Moderate	36	NA	NA
SD 07	F	62	R	ADD	Mild to moderate	411	5	2
SD 08	Male	26	R	ADD	No	93	2-5	2.5
SD 09	F	65	R	ADD	Mild to moderate	204	2	2
SD 10	F	56	R	ADD	Mild	324	6	6
SD11	F	57	R	ADD	No	15	3	3
SD12	M	74	R	ADD	No	396	4	4
SD13	F	54	R	ADD	No	288	3	3.5

Apparatus

As stimulators, we used a pair of light-weight encapsulated cylindrical vibrators (Pico Vibe, Precision Microdrives Ltd., London, UK) (See **Figure 1**). The vibration frequency for VTS was set to100Hz in this study. Preliminary work in our laboratory with healthy human volunteers showed that using these vibrators, a vibration frequency of 100Hz is capable of generating peaks in the power spectrum of the voice signal that is within the frequency range known to stimulate laryngeal mechanoreceptors in animals (Davis and Nail, 1987) or induce kinaesthetic illusions in humans, which are known to be based on muscle spindle input (Cordo et al., 1995; Cordo et al., 2005). Thus, we could reasonably assume that besides tactile receptors of the skin above the voice box, laryngeal mechanoreceptors were also stimulated.

Figure 1. *Final tested micro vibrators. Right: Coin vibrator (Ø 12mm; thickness: 3.4mm. Left: Encapsulated cylinder vibrator (length: 25mm; Ø 8.8mm). U.S. quarter coin for comparison.*

EEG data were recorded with the ActiveTwo data acquisition system (Biosemi B.V. Ltd, Amsterdam, Netherlands). The sampling rate was set at 512 Hz. Brain potentials were captured via Biosemi's 64-channel EEG cap with an equiradial system of electrode placement. Participants were guided throughout the experiment by a series of 250ms long auditory cues (1000Hz, 98dB) generated by RPvdsEx software (Tucker-Davis Technologies Ltd., Alachua, USA). The TDT system and RPvdsEx software were also

used to control the activation of the vibrators. The time-stamp of auditory cues and vibration onset/endpoint were captured simultaneously.

Experimental Procedure and Behavioral Task

The experiment took place in an electrically and acoustically shielded chamber at the Multiple Sensory Perception Laboratory at the University of Minnesota. Participants sat on a comfortable chair, asked to avoid extra movements and to focus their visual gaze at a fixation point on the front wall. The pair of vibrators was attached externally and bilaterally on the participant's neck over the laryngeal area (see Figure 2).

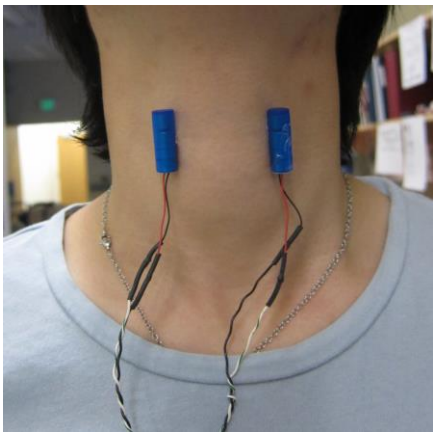

Figure 2. *Setup for the application of laryngeal VTS. The encapsulated cylindrical vibrators were attached to the laryngeal area of the neck, laterally to the thyroid cartilage.*

Prior to the experiment, the severity of speech symptoms was evaluated by (1) reading a series of standard sentences (Woodson, 2010) devised for the evaluation of voice quality in AB/AD spasmodic dysphonia (For the list of sentences, see Appendix I); and (2) pronouncing vowel /a/ three times, each lasting four seconds. All speech and voice signals were recorded for later offline analysis.

The experimental protocol comprised two blocks: (1) laryngeal vibration (*VTS Only*), and (2) vowel vocalization accompanied by laryngeal VTS (*Vocalization + VTS*). During the

VTS Only condition, the laryngeal vibrators were alternately turned on and off (3 seconds ON following 3 seconds OFF) for 50 repetitions and then stayed ON continuously for the final 3 minutes. During the *Vocalization + VTS* condition, participants received an auditory cue (1000Hz, 98dB) for 250ms and then vocalized the vowel /a/ continuously for 4 seconds. During the second half of the vocalization period, laryngeal VTS was applied. Participants stopped vocalization with the cessation of laryngeal VTS. This procedure was repeated 50 times with 4-second long resting intervals in between. Both conditions were applied in two sets, with each set lasting 17 minutes. Between sets, at the end of set 2, and 20 minutes after the cessation of VTS (Retention), voice/speech quality was evaluated using the same assessment tasks given at *Baseline* (see Figure 3).

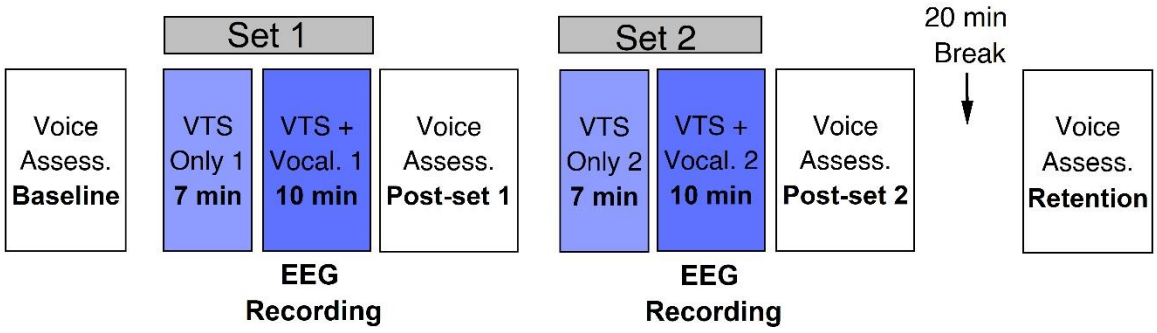

Figure 3. *The experimental protocol for the project I*

Speech Quality Measures

Participants read two sets of standard sentences (Woodson, 2010) for the speech evaluation of people with adductor and abductor SD in their normal conversational style (See Appendix I). Assessment of these recorded voice data was performed offline. Two voice measures were obtained: (1) the number of voice breaks and (2) the change in the *cepstral peak prominence* (CPP) of voice (Fraile and Godino-Llorente, 2014).

CPP is an acoustic measure of speech quality defined as the logarithm of the Fourier Transform of the signal's power spectrum and reveals the degree of regularity in the voice data. Three unit change in CPP in a positive direction is indicative of a meaningful improvement in voice/speech quality. CPP is considered one of the most reliable measures of dysphonia severity (Maryn et al., 2009). Here, we employed a smoothed cepstral peak prominence technique, referred to as CPPs, in which the individual cepstra are smoothed before extracting the peak and computing the peak prominence (Hillenbrand and Houde, 1996). At first, all speech signals were broken and labeled into 'voiced' and 'unvoiced' segments. Then, CPPs values were derived only for the 'voiced' periods. The PRAAT software was used for the acoustic analysis of the voice data.

EEG signal processing

The EEGLab toolbox of MATLAB (The MathWorks, Natick, MA) was used for exploring the EEG data (Delorme and Makeig, 2004). The EEG signal processing steps were as followed:

1. The averaged signal of the two external electrodes embedded over bilateral mastoid bones was used to reference all electrodes.
2. The data were high-passed filtered at the cut-off frequency of 1Hz to address possible baseline drifts using a zero-phase FIR filter. A zero-phase notch filter was used to remove power line noise.
3. In order to weaken the potential effect of non-cortical sources that might have been commonly captured by electrodes, each channel was re-referenced to the common average of all electrodes.

4. Segments of EEG recordings from 1000ms before audio cue to 4000ms after the onset of vocalization were extracted as data epochs. The 1000 ms period prior to the audio cue was used as the baseline (resting state) for the cortical activity.
5. We subsequently used the 'runica' algorithm to perform independent component analysis (ICA) on all data channels. ICA is a method to decompose independent sources that are linearly mixed.
6. An automated multiple artifact rejection algorithm, 'SASICA' (Chaumon et al., 2015) implemented on the resultant components to identify and remove the contaminated ICs. This algorithm recruits spatiotemporal criteria to distinguish the artifactual components. This is critically important for the identification and removal of muscle artifacts that may have contaminated the EEG data during vowel vocalization.
7. Finally, the remaining ICs were linearly summed up, and the output dataset was used for extracting the features.

Electrocortical measures

As a primary EEG measure, we obtained the event-related spectral perturbation (ERSP) of somatosensory-motor cortical electrodes in response to VTS. ERSP measures the average time course of relative changes in the spontaneous EEG amplitude spectrum induced by a set of similar experimental events, which in this project is Vocalization and VTS. ERSP presents the logarithm of the mean event-related alteration in spectral power relative to the resting state at each frequency bin (Makeig, 1993).

To calculate the ERSP, the average baseline spectral power was calculated for each trial. Then, the spectral power of each trial was divided to the average baseline to

normalize the response. Finally, the spectral power of all trials was averaged to compute the ERSP. In addition, a two-tailed permutation significance probability was be performed to measure the significant difference to the baseline power. In our assessment, the significance level was set as 0.05.

Band-specific features were separately extracted for the physiologically-relevant frequency ranges (i.e., <50Hz): theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz), and the low gamma (30-49Hz). ERSP was extracted for six sites: CP5, C5, FC5, CP6, C6, and FC6 (See **Figure 4**). CP5 and CP6 were nearby bilateral somatosensory cortical areas. C5 and C6 were nearby bilateral motor cortical areas. FC5 and FC6 were nearby bilateral premotor cortical regions. Indices' 5' and '6' reflect the cortical areas close to bilateral vocalization regions over somatosensory and motor homunculi (Caviness et al., 2006; Mor et al., 2018).

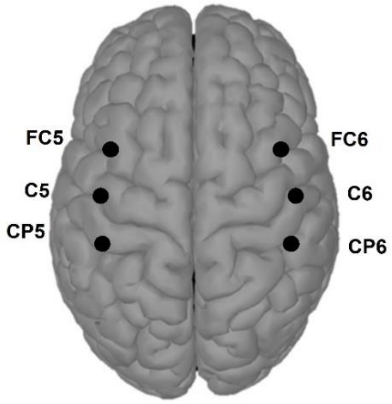

Figure 4. *Position of cortical electrodes of the EEG cap. Somatosensory (CP5 and CP6), motor (C5 and C6), and premotor (FC5 and FC6) for left and right hemispheres, respectively.*

As a secondary EEG measure, we obtained the event-related coherence (ERCOH) between pairs of somatosensory-motor cortical electrodes as an indicator of the level of synchrony between the two electrodes (Pfurtscheller and Andrew, 1999). ERCOH was

derived for CP5-FC5 and CP6-FC6 electrode pairs. Before the computation of ERCOH, EEG epochs were pre-whitened to exclude possible autocorrelations/trends that might interfere with the data.

EEG features were extracted from the Vocalization + VTS conditions of both sets (see **Figure 3**) to investigate the immediate cortical response to VTS. For each condition, the 4000ms long trials were divided into two segments:

1) ***VTS-off*** (before the onset of laryngeal vibration) – Only Vocalization.
2) ***VTS-on*** (after the onset of laryngeal vibration) – Vocalization and vibration.

For each participant, the ERSP measure of the average of the 50 recorded epochs was derived separately for the VTS-off and VTS-on segments. Because the first 500ms of the VTS-off period additionally contain cortical auditory evoked potentials (Alvarenga et al., 2013) or be influenced by the reaction time of the study participants (Santee and Kohfeld, 1977), the first 500ms of vocalization were excluded from further EEG analysis (i.e., the VTS-off interval was defined between 500-2000ms after the presentation of the auditory cue).

Statistical analysis

For SD1 to SD3, no EEG data were available. Statistical comparisons of the pre- versus post-VTS cortical potentials were performed on the available EEG data of 10 participants. The Kolmogorov-Smirnov test was implemented to examine the normality of the data. Since the distribution of the data was not normal, the non-parametric Wilcoxon sign rank test was used for statistical assessments. For each frequency band and the group of electrodes covering each hemisphere, p-values were adjusted for multiple comparisons using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

The significance level was set at p-value = 0.05. The effect size was calculated using Cohen's d.

Results

Changes in markers of speech quality

We recorded the voice of 13 SD participants as they read a list of sentences devised for the speech evaluation of SD (Woodson, 2010) at four different time stamps along with the experimental protocol (see **Figure 3**):

1) ***Pretest (Baseline):*** Prior to VTS;
2) ***Post-test 1:*** After 14.7 minutes of VTS;
3) ***Post-set 2:*** after 29.4 minutes of VTS;
4) ***Retention:*** 20 minutes past the cessation of VTS.

Subsequently, we derived the number of voice breaks and CPPs as measures of speech quality from the acoustic signal. The clinical and self-perceived markers of speech for the Pretest show that participants experienced different levels of voice symptom severity. (See **Table 2**)

Table 2. *Clinical and self-perceived markers of speech and voice symptom severity for study participants.*

Subject ID	Number of Voice Breaks	Self-Rated Effort Scale (ADD/ABD Sentences)	Self-Rated Effort Scale (Vowel /a/)
SD 01	5	4	7
SD 02	4	3	2
SD 03	0	2	3
SD 04	0	2	3
SD 05	12	3	2
SD 06	9	5	7
SD 07	0	4	5
SD 08	2	7	6
SD 09	4	9	8
SD 10	2	2	2
SD 11	0	2	3
SD 12	0	2	2
SD 13	0	3	3

Nine out of 13 participants (69%) responded to VTS and showed a reduction of the number of voice breaks and/or a rise of CPPS (> +1dB) at Post-set 1 and/or the Post-set 2 as compared to Pretest. The remaining four participants did not show a consistent response to VTS as quantified by a rise in CPPS. It is noteworthy that none of the non-responding patients exhibited voice breaks at Pretest (see **Figure 5**; bottom panels).

Improvements in both speech quality measures for the responders were preserved at the retention stage (see **Figure 5**; top panels). As a group, participants showed a significant rise of CPPS after 14.7 minutes of laryngeal VTS in comparison to their Pretest (*p = 0.02, d = 1.06*), which was retained at 20 minutes past the last application of VTS (*p = 0.006, d = 1.15;* see **Figure 5**). The corresponding effect sizes were large (Cohen's d > 0.8) at both time stamps. In addition, 6 out of 7 SD participants (86%) who exhibited voice breaks at Pretest showed a reduction of voice breaks in response to laryngeal VTS, with four patients having no voice breaks after 14.7 minutes of VTS (see **Figure 5** and **Table 3**).

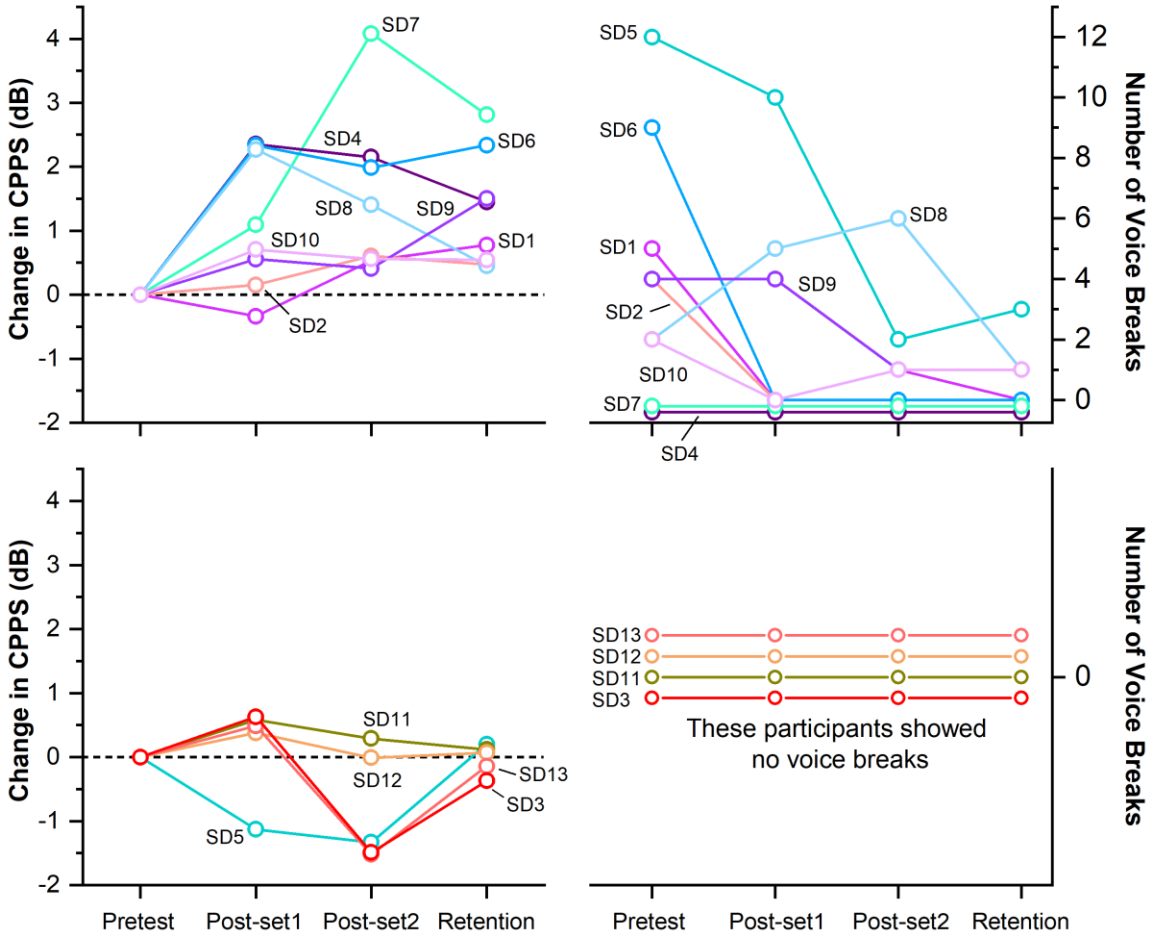

Figure 5. *Change in the number of voice breaks and CPPs as at different stages of VTS application (Pretest, Post-set1, Post-set2, and Retention). Responders to VTS are shown in the top graphs, non-responders in the bottom graphs). Note that all non-responders exhibited no voice breaks prior and during VTS. Typically, responders showed improvements in both markers of voice/speech quality. Note that SD 5 showed no effect in CPPs, but drastically reduced the number of voice breaks with VTS application (From Khosravani et al., 2019b).*

Table 3. *VTS induced change in smoothed cepstral peak prominence (ΔCPPS) and the number of voice breaks (ΔVB) relative to baseline (Pretest). Unit for ΔCPPS is dB.*

Subject ID	Post-Set 1 (ΔCPPS, ΔVB)	Post-Set 2 (ΔCPPS, ΔVB)	Retention (ΔCPPS, ΔVB)
SD1	(-0.34, -5)	(0.53, -4)	(0.78, -5)
SD2	(0.15, -4)	(0.60, -4)	(0.47, -4)
SD3	(0.63, 0)	(-1.50, 0)	(-0.37, 0)
SD4	(2.35, 0)	(2.15, 0)	(1.45, 0)
SD5	(-1.13, -2)	(-1.33, -10)	(0.2, -9)
SD6	(2.33, -9)	(1.98, -9)	(2.34, -9)
SD7	(1.10, 0)	(4.08, 0)	(2.81, 0)
SD8	(2.27, +3)	(1.40, +4)	(0.45, -1)
SD9	(0.56, 0)	(0.41, -3)	(1.50, -)
SD10	(0.71, -2)	(0.56, -1)	(0.55, -1)
SD11	(0.58, 0)	(0.29, 0)	(0.12, 0)
SD12	(0.38, 0)	(-0.01, 0)	(0.07, 0)
SD13	(0.49, 0)	(-1.52, 0)	(-0.13, 0)

Change in the cortical oscillatory behavior in response to laryngeal VTS

The effect of VTS on cortical oscillatory activity over somatosensory and premotor cortex resulted in an almost immediate suppression of low-frequency oscillations as illustrated in an exemplar time-frequency plot of one SD participant in **Figure 6**.

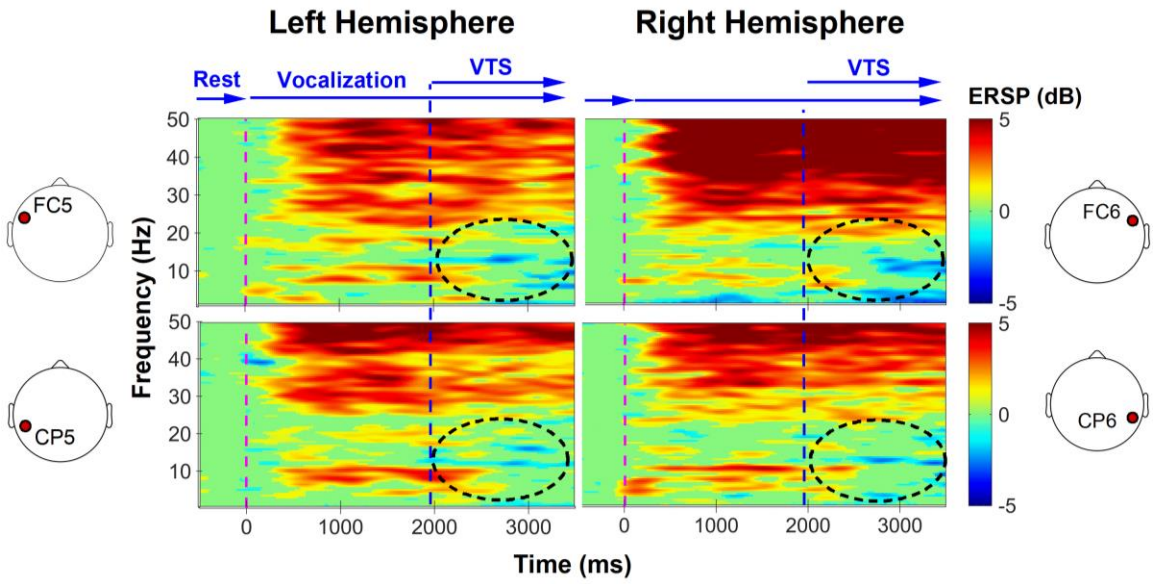

Figure 6. *Effect of laryngeal VTS on bilateral right somatosensory and premotor cortical ERSP for VTS-off (0-2000ms) versus VTS-on (2000-4000ms) in a single patient. Note that laryngeal VTS resulted in the event-related desynchronization of low-frequency oscillations over somatosensory-motor cortical areas in both hemispheres (see dashed ellipses) (From Khosravani et al., 2019b).*

For the complete patient sample, the application of VTS during the first 14.7 minutes (Set 1; see **Figure 3**) induced a significant event-related desynchronization of cortical theta-band oscillations over the left somatosensory, motor, and premotor cortex (C5: *p = 0.049, d = 0.82*; CP5: *p = 0.049, d = 0.47*; FC5: *p = 0.049, d = 0.65;* see **Figure 7**, top panels), and a significant immediate rise of the somatosensory and motor cortical gamma power over the right hemisphere: (*C6: p = 0.037, d = 0.48*; CP6: p = *0.037, d = 0.39*; FC6: *p = 0.029, d = 0.51,* see **Figure 7**, top panels). After participants had received VTS in Set 2, a similar pattern of cortical activity emerged. It again resulted in a

significant desynchronization of theta oscillations over the left motor cortical area (C5: *p = 0.012, d = 0.83*), and a significant rise of gamma oscillations over the right somatosensory-motor cortical regions: (*C6: p = 0.015, d = 0.38*; CP6: p = *0.027, d = 0.36*; FC6: *p = 0.015, d = 0.47*; see **Figure 7**, bottom panels).

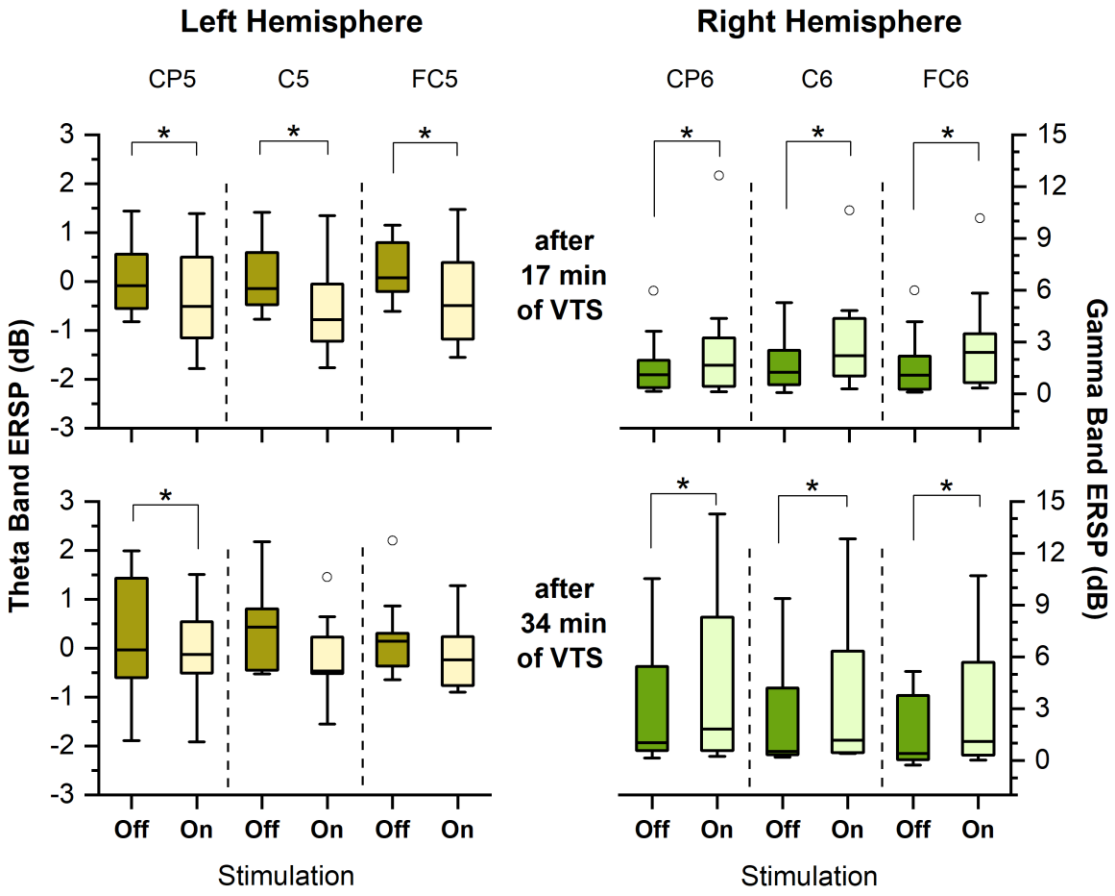

Figure 7. *Effect of VTS on ERSP over somatosensory and motor cortical areas for theta and gamma bands during Vocalization. Boxplots reflect the data for all subjects during the two sets of VTS (see Fig. 1B for the timing of the sets).* ***Left panels:*** *Theta band ERSP for left somatosensory (CP5), motor (C5), and premotor (FC5) cortical electrodes after the first and second set of VTS.* ***Right panels:*** *Gamma band ERSP over right somatosensory (CP6), motor (C6), and premotor (FC6) cortical electrodes after the first and second application of VTS. The boxplots represent the distribution of individual ERSP values within each group. The lower and upper boundaries of each box depict the 25% and 75% quartiles, respectively. The horizontal line within the box indicates the median. The upper and lower whiskers extend to +1.5 and -1.5 interquartile range, respectively. Outliers are shown as white circles. * indicates a p-value of < 0.05 (From Khosravani et al., 2019b).*

There were no significant changes of theta spectral power over the right hemisphere or of gamma-band power over the left hemisphere. Similarly, assessment of ERSP in other frequency bands (alpha and beta) did not reveal any significant changes pre- versus post-VTS for any of the electrodes over left/right hemispheres (all *p's> 0.05*).

We also performed a Pearson's correlation analysis between the change in behavioral markers of voice quality (CPPS or the number of voice breaks) and theta/gamma ERSP for all participants collectively (responders and non-responders). No significant correlational relationships were observed. We then repeated the same analysis only on the responder group for whom either a rise in the CPPS or a decline in the number of voice breaks was observed (SD1, SD2, SD4, SD5, SD6, SD7, SD8, SD9, SD10). Again, no significant relationships were found.

A subsequent coherence analysis examined potential differences in the spectral characteristics of somatosensory-motor cortical interactions in each hemisphere. This analysis found no evidence that laryngeal VTS significantly affected the inter-regional spectral coherence between somatosensory and motor cortical areas within each hemisphere (all *p's> 0.05*).

Discussion

The goal of this study was to explore whether laryngeal VTS can provide benefits for patients with SD by monitoring its short-term effects on voice quality and the associated activity over laryngeal somatosensory-motor cortical areas. The main findings of this research are as follows:

First, a one-time application of laryngeal VTS resulted in the significant improvement of two standard measures of voice/speech quality in 69% of the patients. The effect

persisted for at least 20 minutes after the cessation of VTS. What seemed to discriminate the "responders" from those participants, who received little to no benefits from VTS, was that "non-responders" were more mildly affected and had no voice breaks prior to receiving VTS (see **Figure 5**).

Second, the application of laryngeal VTS induced an immediate significant suppression of theta band synchronization over the left somatosensory-motor cortex and the immediate significant rise of gamma-band synchronization over the right somatosensory-motor cortical region.

Possible mechanisms behind the effectiveness of laryngeal VTS for improving speech in SD

An abnormal kinaesthetic function has been reported in non-dystonic limbs and muscle systems in SD (Konczak et al., 2015) and other forms of focal dystonia such as blepharospasm and cervical dystonia (Putzki et al., 2006). This implies that a more generalized somatosensory deficit underlies or is associated with the focal motor dysfunction in dystonia. Here, we explored if modulating somatosensory inputs could provide an avenue for a missing behavioral treatment for SD. Our approach of applying VTS constitutes a form of non-invasive neuromodulation that alters the output of afferent proprioceptive and tactile mechanoreceptors (Bianconi and Van Der Meulen, 1963; Brown et al., 1967c), which is then centrally processed. Among the prominent neuropathological features of dystonia are reduced neuronal discharge rates and altered discharge patterns within the basal ganglia-thalamo-cortical motor circuitry (Vitek, 2002). Invasive neuromodulation techniques, such as deep brain stimulation, attempt to normalize the irregular neuronal discharge patterns by applying high-frequency impulses

to targeted subcortical nuclei (Hendrix and Vitek, 2012; Johnson et al., 2008) with the aim to restore the activity of upstream motor cortical networks. Here we suggest that a non-invasive high-frequency peripheral stimulation via laryngeal VTS may similarly modulate the discharge patterns of neurons in the somatosensory-motor speech network (Ludlow, 2015), which can positively affect the speech motor output in SD.

Modulation of cortical oscillations in response to laryngeal VTS

We recorded EEG signals to understand how laryngeal VTS affects cortical activity in SD. We found that in our sample of SD participants applying laryngeal VTS was associated with a significant suppression of theta-band power oscillations over the left somatosensory-motor cortex and a significant rise of gamma rhythm over right somatosensory-motor cortex (see **Figure 7**). Theta oscillations are detectable in a number of brain nuclei, including the *striatum (J. D. Berke et al., 2004; Goto and O'Donnell, 2001).* Previous research identified abnormal theta oscillations at subcortical and cortical levels in other forms of focal dystonia, such as cervical dystonia (Liu et al., 2002; Liu et al., 2008). These abnormal theta oscillations in *globus pallidus internus* significantly correlate with the severity of symptoms in cervical dystonia (Neumann et al., 2017).

The susceptibility of focal dystonia to somatosensory stimulation has long been recognized as patients with task-specific dystonia may use sensory tricks (*geste antagoniste*) to alleviate dystonic symptoms temporarily by touching or pressing areas of or near the dystonic musculature. The neurophysiological correlate of an effective sensory trick is the suppression of abnormal cortical theta oscillations in CD (Tang et al., 2007). The similarity between our EEG finding of suppressed theta band power in SD

and the one reported for patients with CD (Tang et al., 2007) suggests that the improvement of abnormal speech motor output in SD via laryngeal VTS may activate the same neurophysiological mechanism underlying an effective sensory trick in CD.

Another identified feature of modulated sensorimotor cortical processing due to VTS was the rise of gamma rhythm over the right somatosensory-motor cortex. Gamma band oscillations are believed to form through the activation of excitatory pyramidal neurons and inhibitory interneurons regulated by the GABA-mediated synaptic current (Nowak et al., 2018). The synchronization of gamma oscillations underlies task-specific functions such as somatosensory processing (Bauer et al., 2006) and motor preparation (Engel et al., 2001; Nowak et al., 2018). Gamma activity in the 40Hz range has been detected during speech (Palva et al., 2002). Movement-induced changes in gamma amplitude seem to reflect of the processing of afferent proprioceptive feedback in motor cortex (Miller et al., 2010; Muthukumaraswamy, 2010). Moreover, a rise of subcortical gamma-band synchronization correlates with the amplitude and velocity of hand movements, highlighting its involvement in the neural control of movement (Brücke et al., 2012). Given the empirical evidence showing that cortical gamma-band activity underlies volitional motor control, our finding of a VTS-induced rise of gamma oscillations cortical areas involved in voice and speech motor control indicates that laryngeal VTS alters information processing within speech cortical networks, which positively influences the voice quality of people with SD.

Limitations of the study

This study yielded initial evidence that laryngeal VTS can improve voice symptoms in SD. The main limitation of this study is the lack of a control SD group that would allow for

the systematic examination of possible confounding placebo or practice effects. Although we cannot exclude the possibility that the observed improvements in voice symptoms constitute a placebo effect, we know from our pilot work that attaching the vibrators to the skin above the voice box (without being turned on) does not improve voice quality in SD. That is, it is unlikely that mere tactile stimulation would suffice in reducing voice symptoms. Moreover, there are no reports indicating that touching the neck constitutes a widely used and effective sensory trick in SD. In addition, the observed improvements in voice quality are not explained as a Hawthorne or special attention effect. On the contrary, as these patients were tested in their symptomatic stage when speech production is exhausting and effortful, one would expect that repeated vocalization and speech over more than 30 minutes results in a decline of speech, which we did not observe. Participants had not practiced the relevant test sentences prior to testing, nor is there evidence that voice symptoms in SD subside with repeated and prolonged speech. Finally, the effects on speech were observed when VTS was not applied. We recorded speech always after the end of each set of VTS (see **Figure 3**). In addition, the positive effects on markers of speech lasted for 20 minutes after the cessation of VTS.

Another limitation is that while this study provided an insight into the improvement of voice symptoms in SD, most participants (except SD05) were diagnosed with ADD SD. Although the participant with AB SD (SD05) showed improvement in voice quality (See **Table 3** and **Figure 23**), a more systematic effort to study the effect of VTS on patients with AB SD is needed. Project 3 of this dissertation addressed this knowledge gap and examined the effect of laryngeal VTS on the voice quality and cortical activation of patients with AB SD.

A different drawback concerns the lack of an objective established clinical scale to classify disease severity. Understanding why and how disease severity interacts with laryngeal VTS could be very useful in predicting who would respond well and would likely be a non-responder to VTS. We choose CPPS and the number of voice breaks as prominent predictors of SD severity (Peterson et al., 2013). The inclusion of other outcome measures such as the consensus auditory-perceptual evaluation of voice (CAPE-V) (Kempster et al., 2009) may provide additional markers for examining the effectiveness of laryngeal VTS. In summary, obtaining additional outcome measures to characterize disease severity in SD and then testing the effects of VTS in a larger sample of SD patients would be clinically meaningful in understanding who responds well to laryngeal VTS and who will likely not benefit from this treatment.

Conclusions

This is the first study that investigated the effect of laryngeal VTS on SD voice symptoms. Its results lay the scientific foundation for a randomized clinical trial to examine the usefulness of the approach in a larger patient sample and document the longitudinal changes in voice quality and the underlying cortical responses to laryngeal VTS in SD. Such clinical trials must address the shortcomings of this feasibility study. Its results should solidify our knowledge on the effectiveness of VTS for treating the voice symptoms in SD.

The current study showed that the application of laryngeal VTS could result in meaningful improvements of speech quality in SD. Laryngeal VTS induced a significant suppression of theta band power over the left somatosensory motor. Similar suppression

of theta oscillations is observable in cervical dystonia patients applying effective sensory tricks, suggesting that VTS in SD may activate a similar neurophysiological mechanism.

Disclaimer: The lead investigator of this project was Sanaz Khosravani, who is also the first author of the relevant publication. My role in this project was participant recruitment from Fairview Clinic at the University of Minnesota, assembling vibrators and preparing data collection procedures, EEG and auditory data collection, EEG data analysis and interpretation, and presenting the results in scientific conferences and meetings.

Deliverables

Peer-reviewed publications

1. Khosravani S., **Mahnan A.,** Yeh I-L., Aman J., Watson P.J., Zhang Y., Goding G., Konczak J., (2019), Laryngeal vibration as a non-invasive neuromodulation treatment to improve voice symptoms in spasmodic dysphonia, *Scientific Reports,* Vol: 9, 17955.
2. Khosravani S., **Mahnan A.,** Yeh I-L., Watson P.J., Zhang Y., Goding G., and Konczak J. (2019), Atypical somatosensory-motor cortical response during vowel vocalization in spasmodic dysphonia, *Clinical Neurophysiology,* Vol: 130, Issue: 6, Page: 1033-1040

Conference presentations

1. **Mahnan A.,** Khosravani S., Watson P.J., Zhang Y., Goding G., Konczak J., (2020), Vibro-tactile Stimulation as a Feasible Symptomatic Treatment for the Voice Disorder Spasmodic Dysphonia, *Voice Foundation Symposium*, May 27-31, 2020, Philadelphia, PA. (Oral presentation).
2. Konczak J., **Mahnan A.,** Khosravani S., Zhang Y., Watson P.J., A feasibility study on laryngeal vibro-tactile stimulation as a new treatment for the voice disorder spasmodic dysphonia, American Society for Neurorehabilitation, October 16-18, 2019 Chicago, IL.
3. **Mahnan A.**, Khosravani S., Watson P.J., Zhang Y., Goding G., Konczak J., First evidence that laryngeal vibration can improve voice symptoms in the voice disorder spasmodic dysphonia, *48th Annual meeting of society for neuroscience,* October 19-23, 2019, Chicago, IL.

4. Konczak J., Khosravani S., **Mahnan A.**, Zhang Y., Watson P.J., Abnormal electrocortical responses during vocalization as a neural correlate of the dystonic voice symptoms in spasmodic dysphonia, *48th Annual meeting of society for neuroscience,* October 19-23, 2019, Chicago, IL.
5. **Mahnan A.,** Khosravani S., Yeh I-L., Aman J., Watson P.J., Zhang Y., Goding G., Konczak J., Non-invasive neuromodulation treatment to improve voice symptoms in spasmodic dysphonia using laryngeal vibration, *7th Minnesota Neuromodulation Symposium*, April 18-19, 2019, Minneapolis, MN.
6. Khosravani S., **Mahnan A.,** Yeh I-L., Watson P.J., Zhang Y., Goding G., Konczak J., Behavioral and neural correlates of laryngeal tactile stimulation in spasmodic dysphonia, *48th Annual meeting of society for neuroscience,* November 3-7, 2018, San Diego, Ca.
7. Khosravani S., **Mahnan A.,** Yeh I-L., Watson P.J., Zhang Y., Goding G., Konczak J., Laryngeal vibro-tactile stimulation for spasmodic dysphonia: Effects on voice quality and its neural correlate over somatosensory-motor cortex*, Progress in Clinical Motor Control I: Neurorehabilitation*, July 23 - 25, 2018, Pennsylvania State University, PA.
8. Khosravani, S., **Mahnan A.**, Yeh, I., Zhang, Y., Goding, G., Watson, P., Konczak, J., Effects of cutaneous Vibro-tactile stimulation of the laryngeal area on voice quality and somatosensory – motor cortical neural activity in Spasmodic Dysphonia, *47th Annual meeting of society for neuroscience*, November 11-15, 2017, Washington DC.
9. Konczak, J., **Mahnan A.**, Yeh, I., Watson, P., Khosravani S., Effect of Laryngeal Vibro-Tactile Stimulation on Voice Quality and Sensorimotor Cortical Activation in Spasmodic Dysphonia, *27th Annual Meeting of the Neural Control of Movement*, May 2-5, 2017, Dublin, Ireland.

Acknowledgment

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Project 2: Design and development of a wearable non-invasive device for treatment of SD

The results of project I showed convincingly that VTS represents a non-invasive form of neuromodulation that induces measurable improvements in the speech of SD patients. The limitation of the vibration technology that was implemented in the project I was that the participant was tethered to a device via cables that provided the power to control the vibrators. This limits the application of the VTS to only stationary settings. Accordingly, the next logical step to expand on the previous work was to improve on the VTS technology and to make it wearable. To that effect, I have designed and developed a wearable non-invasive collar-like device that applies VTS to the laryngeal muscles.

Today, powerful vibrators are so small that they can be securely attached to bodily surfaces like the skin above the thyroid cartilage. In addition, voltage requirements to operate these vibrators are low, making battery-operated vibrators a reality in every cell phone. This project exploited this new vibrator technology to develop a non-invasive wearable device using lightweight, low-voltage, and low-cost vibrators to apply laryngeal VTS.

Developing a wearable device with an ergonomic and anatomically correct enclosure for the electronics poses several challenges, for example:

- The materials cannot be rigid.
- The enclosure needs to be flexible to accommodate a user's anatomical variability of the neck. It must align closely to the larynx (voice box) of each individual user because the vibrators need to be in constant contact with the skin.

- The device should be light-weight, battery-operated, and controllable via a wireless connection with either a computer or smartphone-based app.
- Users should be able to wear it freely during the day. It can be removed as easy as a bracelet.
- The device needs to employ robust speech detection technology to provide a targeted VTS only during the speaking task as a symptomatic stage in people with SD.
- The computational cost of the speech detection algorithm must be minimal.

Accordingly, this project aims to develop an innovative technology that allows for both in-home and clinical application of VTS beyond a controlled laboratory environment.

Specific aims

Aim 1: Design and develop a wearable non-invasive device for applying VTS to the laryngeal musculature behind the thyroid cartilage as a symptomatic treatment for the voice disorder spasmodic dysphonia.

Aim 2: Incorporate speech detection technology as a function of the device to activate the vibration only during the speaking task, which is the specific symptom of people with spasmodic dysphonia.

Aim 3: Conduct a prototype bench testing to evaluate both the functionality and usability of the device on a subgroup of people with spasmodic dysphonia.

Device description

The complete system consists of three components:

1) A flexible printed circuit board (PCB) that embeds the electronics,

2) A collar made of soft, wear-resistive, and washable textile materials, and
3) Operating software to control the sensors, vibrators, and power.

Electronic circuitry

To address the ergonomic and individual anatomical characteristics of the neck of each user, we employed a flexible printed circuit board (PCB) technology. This thin PCB enclosure contained all the microcontrollers and sensors that are required for the VTS application (See **Figure 8**). The electronic hardware of the device consists of the following:

- A Bluetooth module (model HC-05) enclosed in the PCB for sending real-time data to an external control unit which is a computer or a smartphone.
- The circuitry has two sensors for recording real-time data as an input to the speech detection algorithm; A) a high sensitivity electret condenser microphone (model B4012AP422-003) is embedded in the PCB, and Ban accelerometer (model BU-23842-000) is connected to the PCB via a socket. The accelerometer needs to be attached to the user's neck to record the neck surface vibrations as a mean for detecting speech in real-time.
- Two rechargeable lithium batteries (3.7V, 290 mAh) serve as a power supply obviating the need for a wired power supply. The batteries are connected to the PCB via a power socket.
- An ARM microcontroller (model STM32F405RGT6) manages power consumption, controls the vibrators, and communicates with the control unit via Bluetooth module. The microcontroller tunes the vibration frequency and magnitude by changing the duty cycle of the PWM pulse.

- Two encapsulated micro-vibration DC electric motors (Precision Microdrives Type 307–100) are connected to the PCB board via a socket. Each vibrator can be moved 4 cm horizontally to accommodate variable neck anthropometry.
- A Micro-USB B port is connected to the PCB for charging the batteries and providing power to the microcontroller.
- A sliding single pole single throw switch is attached to the PCB to turn on/off the device manually.

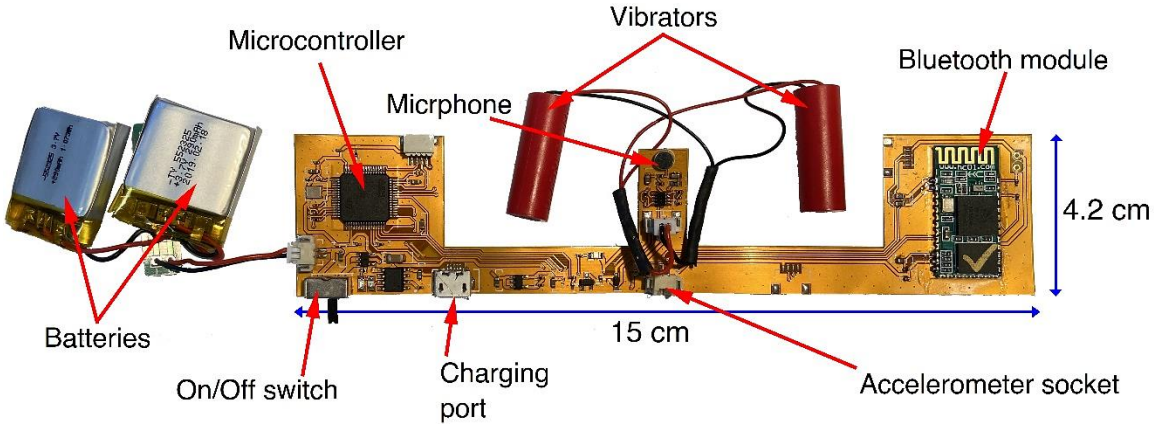

Figure 8. *The developed flexible PCB. The dimension of the PCB board is w x h 4.2 x 15 cm. Vibrators and batteries are connected to the board via specific sockets. Accelerometers are not shown in this figure.*

Cloth Collar

The electronic circuitry is inserted in a pouch of a soft and wear-resistive textile collar (See **Figure 9**B). The electronic enclosure can be removed from the textile collar so that the collar can be cleaned separately. The collar consists of the following:

- **Cover:** soft, wear-resistive spandex fabric (82% Nylon, 18% Spandex) (See **Figure 9**A)

- **Spacer:** Neoprene scuba fabric (90% polyester and 10% spandex). The spacer stiffens the cover shell so that it can hold the batteries and vibratos in place. The PCB sits between the spacer and the inner side of the cover shell (See **Figure 9**B).
- **Elastic Strap**: The inner side of the strap is coated with a Silicone layer that provides friction and will function as a gripper to hold the vibrators, PCB board, and batteries in place (See **Figure 9**B).
- **Invisible Zippers:** Opens the pouch of the collar to insert the electric circuitry.
- **Two Velcro straps:** attached to the outside shell of the spandex cover to strap the collar around the neck.
- **Microphone location mark:** A red thread was sewed on the inside of the cover to indicate the microphone's location. The users must align this mark to the center of their larynx before wearing the collar around the neck.

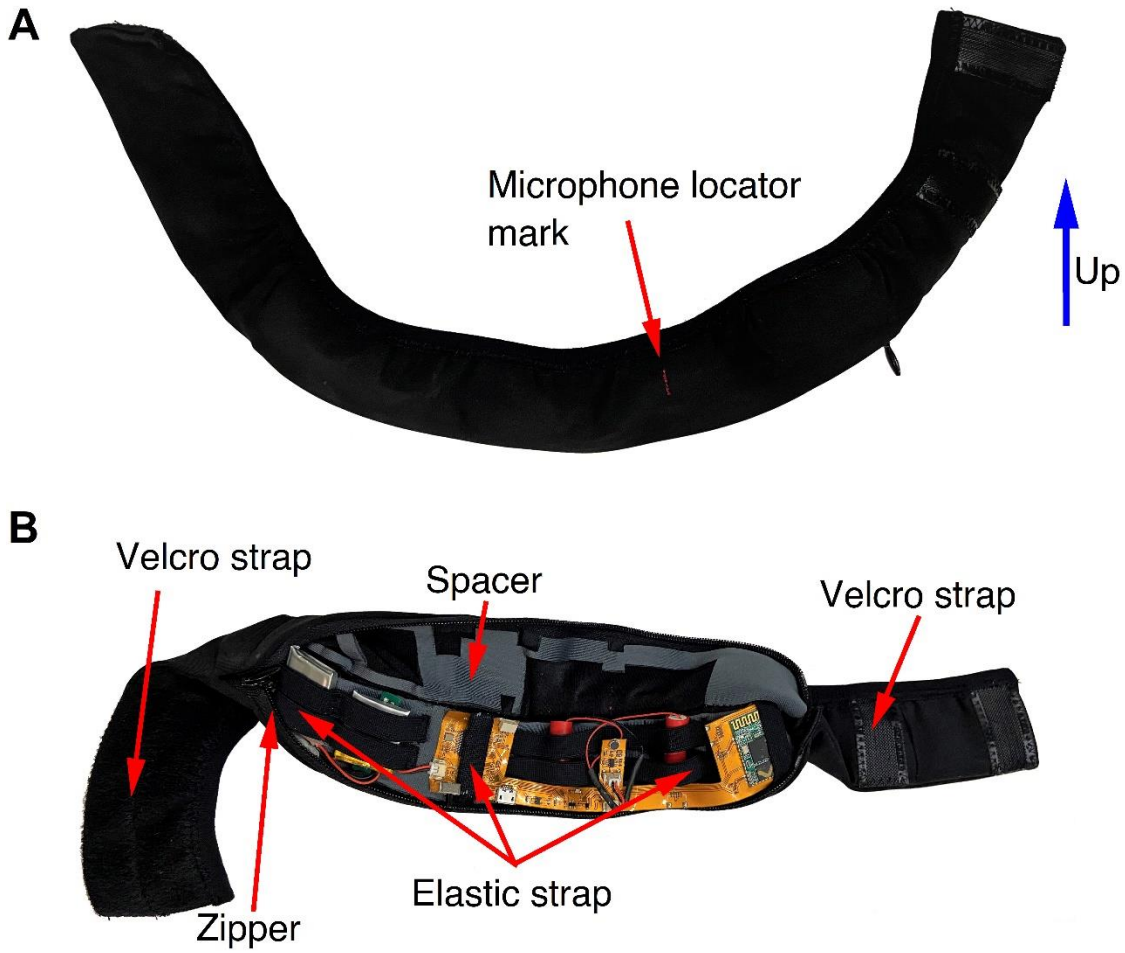

Figure 9. *Textile collar (Dimension W x H 4.5 x50 cm). A) Cover of the collar. The collar will be worn around the neck of the user, while the microphone locator mark needs to be located in the center of the larynx. B) Inside of the collar pouch. PCB, vibrators, and batteries are held in place using elastic grips. Vibrators can move up to 4 cm horizontally to accommodate different neck anatomies.*

Operating software

The device is developed to accommodate different scenarios that a user might need to employ laryngeal VTS. One scenario is the application of VTS for a limited duration (e.g., before attending an important meeting). Another scenario is applying VTS in real-time during speech (e.g., when giving a verbal presentation). As such, the device has two operational modes (See **Figure 10**):

1) **Continuous VTS.** User can turn on the device to receive VTS for a limited duration of their choice (e.g., 10 min) at a specified frequency. The device will automatically turn off the vibrators at the end of the chosen period.
2) **Real-time VTS.** The device only activates the vibrators during the user's speech. Using built-in sensors, Microphone, or an accelerometer, the device records the voice data and processes them in real-time. Once the speech detection algorithm identifies the real-time data as a voiced segment, vibrators will be automatically turned on. The frequency of the VTS can be specified via the user's input. The default vibration is set to 100 Hz.

Switching between two operational modes can be executed by the control unit via sending an order using the wireless module embedded in the device.

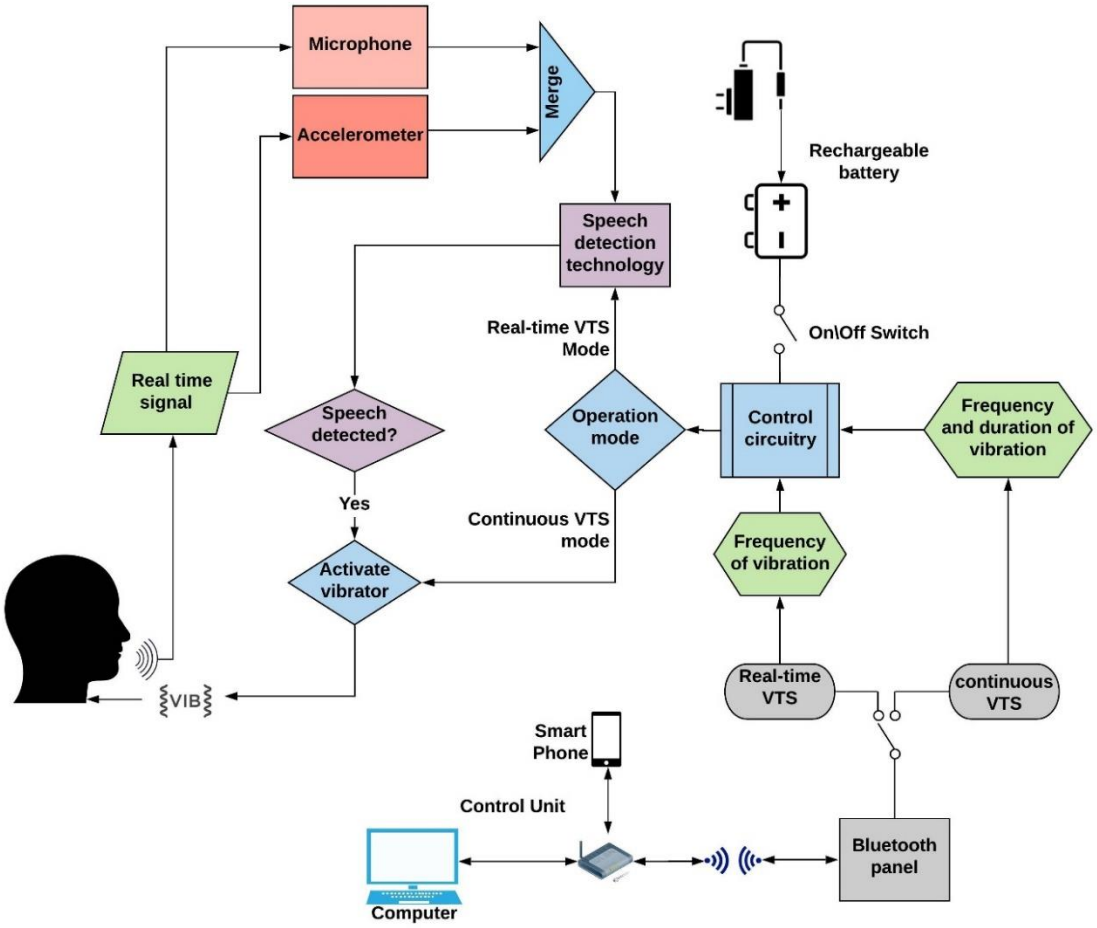

Figure 10: *Schematic device function. The system has two operational modes: Continuous VTS and Real-time VTS. The control unit sends an order to the device to switch between the two operational modes.*

Speech detection procedure

Most speech analysis research focuses on populations with healthy speech production. However, challenges with voice detection are exacerbated in dysphonic patients due to the strained speech produced, often at a much lower volume than is normal for the healthy population. As dysphonia severity increases, the effectiveness of microphone-based measures decreases (Hillman et al., 2006). Some devices, like the Ambulatory Phonation Monitor (Cheyne et al., 2003), have been tested in SD population and

resulted in satisfactory outcomes. However, while existing devices are able to utilize either amplitude or frequency based algorithms for speech detection, none have done so with concurrent VTS in the vicinity of the microphone and accelerometer, as this study proposes. The introduction of VTS adds noise to the recording, which could interfere with the existing speech detection techniques. The second aim of project II is to develop a signal processing algorithm for real-time speech detection and implementation of VTS during the speech task.

One basic, computationally efficient measure to characterize a signal for speech detection is signal power in the time domain. Power, *P*, of a discrete-time signal is defined as the absolute squares of its time-domain samples (*x(n)*)divided by the signal length (*N*):

$$P = \frac{1}{N}\sum_{n=0}^{N-1}|x(n)|^2 \qquad (1)$$

To differentiate speech signals from no activity using the signal power requires setting a threshold value. In case the signal power is above the threshold, the voice interval will be assigned as a speech frame.

Threshold calculation

There are two methods for assigning the threshold that have been implemented in the device: A) *Manual input*, where the user sends the threshold value to the device using the control unit, and B) *Automatic threshold calculation.*

The steps for automatic threshold calculation are as follows (see **Figure 11**):

1) A 30 seconds audio signal in which the user will be asked to remain silent will be recorded using the embedded sensors in the device. The recording will be temporary stored in the device.
2) The 30-second interval will be divided into 50-millisecond subintervals.
3) Each subinterval signal will be filtered using a zero-phase bandwidth FIR filter (80 – 600 Hz, Order =20).
4) The signal power will be calculated for each subinterval.
5) The average signal power of all subintervals will be computed, which is then defined as the threshold for speech activity (see **Figure 11**).

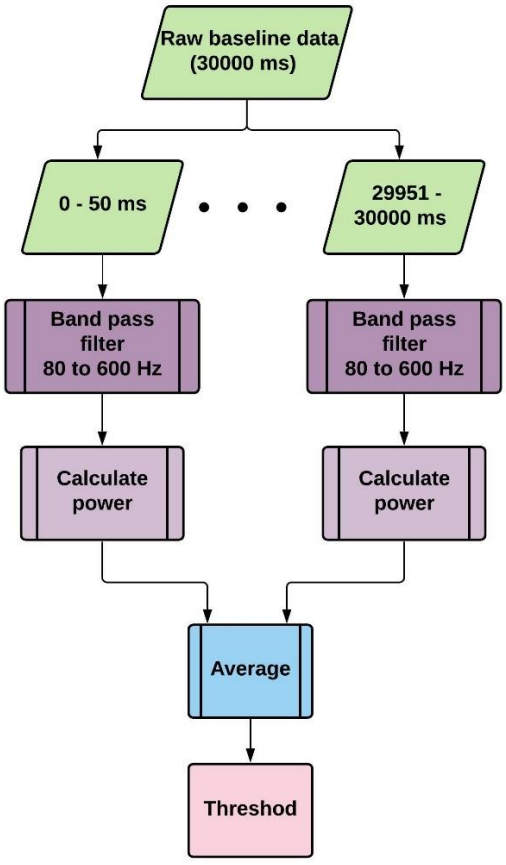

Figure 11. *Threshold calculation flowchart. A 30000-ms interval of the baseline trial will be divided into 50-ms subintervals. The subintervals will be filtered, and their signal power values for each of these subintervals will be calculated. The power values will be then averaged together to calculate the threshold for speech activity.*

Speech detection algorithm

The speech detection algorithm is required for targeted real-time VTS during the speech. The developed algorithm introduces a 200-millisecond interval as a delay before the onset of VTS. The signal of the implemented delay period will be processed in the speech detection algorithm to determine whether it is a *voiced* or *not voiced* interval. The determination procedure is as follows (See **Figure 12**):

1) The 200-millisecond interval will be divided into four 50 millisecond subintervals.
2) Each subinterval will be filtered using a zero-phase bandwidth FIR filter (80 – 600 Hz, Order =20).
3) The power of each subinterval will be calculated.
4) Signal power will be compared to the threshold to determine if it is above the threshold value.
5) If any two contiguous subintervals have greater signal power than the threshold, the entire 200-millisecond interval will be considered voiced.
6) The device will turn on the vibrators for the interval duration (200 milliseconds).
7) Whether the interval is classified as a voice on not voiced, the next interval will enter the algorithm for classification.

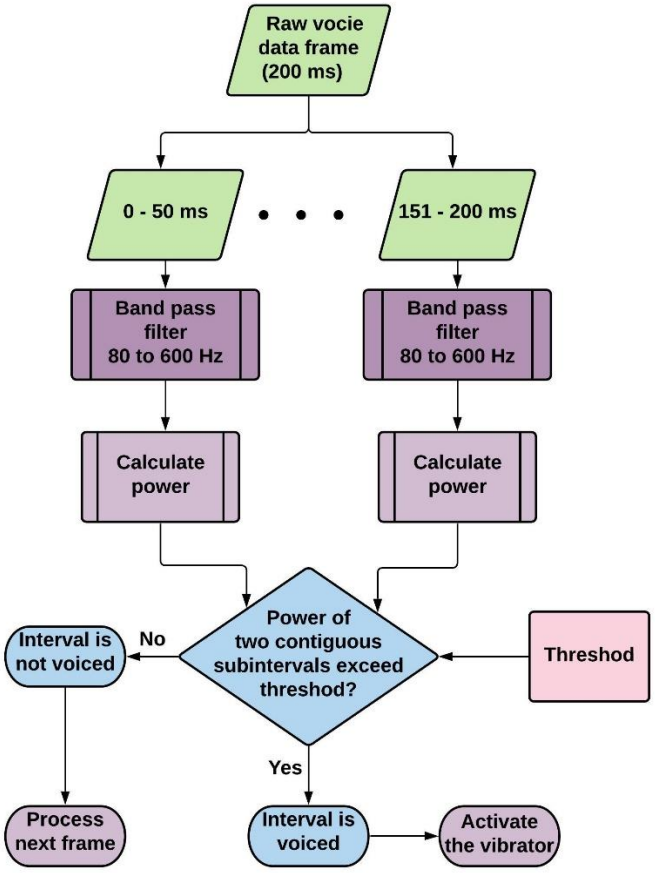

Figure 12. *Speech detection Algorithm: The 200-millisecond interval will be divided into four subintervals of 50 milliseconds. If two contiguous subintervals have a signal power greater than the threshold, the entire interval will be considered as voiced.*

Collar usability assessment

In order to check the functionality and usability of the device, we have developed a survey (see Appendix II) and recruited a subset of individuals with SD to wear the device and provide feedback by responding to the survey.

Methods

Participants

Five people with SD (5 female; mean age ± std: 53 ± 13.2 years) were recruited to participate in the study (See **Table 4** for clinical characteristics of study participants).

The experimental protocol was approved by the Institutional Review Board of the University of Minnesota. All participants gave informed consent prior to the experiment. None of the participants were receiving Botox treatment or undergoing any other treatment during the course of the study, and their voice was at the symptomatic stage.

Table 4. *Clinical characteristics of study participants. (F: female)*

Subject ID	Gender	Age	SD type	Voice Tremor	Self severity assessment	Diagnosis Duration (mo.)	Botox cycle (mo.)	Last Botox Injection (mo.)
ABSD 1	F	34	ABD	No	Severe	144	NA	141
ABSD 2	F	70	ABD	Severe	Extremely severe	192	NA	192
ABSD 3	F	52	ABD	No	Mild	9	NA	NA
ABSD 4	F	50	ABD	No	Severe	120	NA	96
ABSD 5	F	59	ABD	No	Very severe	144	NA	48

Apparatus

We used the developed device as the apparatus for this study (See **Figure 9**). The vibration frequency for VTS was set to100Hz in this study.

Experimental Procedure and Behavioral Task

The experiment took place at the Multiple Sensory Perception Laboratory at the University of Minnesota. Before asking the participant to wear the collar, the participant's width of the thyroid cartilage was measured. Accordingly, the vibrators were moved horizontally to be positioned laterally to the thyroid cartilage. Then, the participants sat

on a comfortable chair and instructed to wear the device without any help from the investigators (see **Figure 13**).

We activated the VTS for two sets of 5-minute periods using the continuous VTS operational mode of the device. After the second VTS set, participants filled out the developed usability questionnaire (see Appendix II) to provide their feedback.

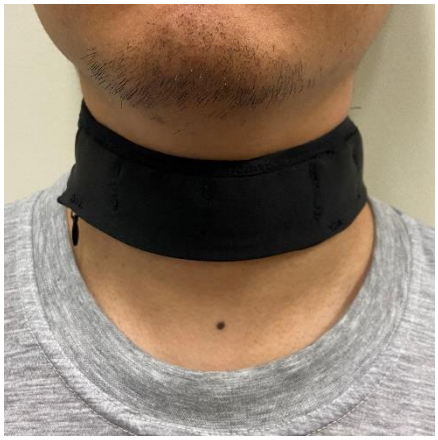

Figure 13. *Setup for the wearable device around the neck.*

Results

The task of wearing the device with no assistance was *neutral* for 1 (ABSD 4), *easy* for 1 (ABSD3), and *very easy* for 3 (ABSD1, ABSD2, ABSD5) of the participants. Only one participant (ABSD4) required assistance to put on the collar. However, wearing the device was *uncomfortable* for 1 (ABSD4), *neutral* for 1 (ABSD3), *comfortable* for 1 (ABSD1), and *strongly comfortable* for 2 (ABSD2, ABSD5) of the individuals.

When asked about the restriction of the collar around the neck, two responded *tight* (ABSD3, ABSD5), one *neutral* (ABSD4), one *unrestricted* (ABSD 1), and one *very unrestricted* (ABSD2). In addition, except for one (ABSD4), none of the participants

indicated that their neck movement was restricted. None of the participants had any difficulty swallowing, and the collar fabric was felt neutral or pleasant on their skin.

During the VTS, the vibration frequency was comfortable for all participants. It had no side effects and did not irritate their skin. For two of the participants (ABSD1, ABSD4), it was difficult to talk while wearing the device when the VTS was off. However, after VTS was on, it became easier for one participant (ABSD 1) to speak.

The immediate participants' subjective change in the voice quality after the onset of VTS was *unnoticeable* for 1 (ABSD 4) and *neutral* for 2 (ABSD 2, ABSD 3) individuals, but it was *noticeable* for 2 of them (ABSD 2, ABSD 5). However, the prolonged perceived subjective change in the voice quality was *noticeable* in 2 (ABSD 1, ABSD 5) and v*ery noticeable* in 1 (ABSD 2) participant. ABSD 1 reported, "*spasms felt noticeably lighter, less tight*". ABSD 5 stated, "*I felt less hesitancy speaking*". Finally, ABSD 2 noted, "*I didn't feel the need to breathe and prep before speaking; the sounds just came out naturally*".

Discussion

The goal of this usability study was to explore the utility and functionality of the wearable VTS device. Participants wore the wearable device around their necks and experienced VTS on their larynx. The main findings of this qualitative research are as follows:

First, participants reported being comfortable wearing the device around their necks. It did not cause any side effects. However, not all participants were comfortable wearing the device in public. They were concerned about the noise that the device generates because of the activation of the vibratos. Future generations of the device need to provide a proper enclosure that can reduce the noise.

Second, the application of laryngeal VTS resulted in a subjective improvement of the voice quality in two out of 5 participants. Project 3 of this dissertation systematically sought to evaluate quantitative effects of laryngeal VTS provided by this project's developed device.

Conclusion

This project concerned the design and development of a non-invasive neuromodulation wearable device that provides laryngeal VTS. The device provides two operational modes, continuous VTS and real-time VTS during speech using newly developed speech-detection technology. The speech-detection algorithm allows for individualized system calibration providing flexibility in adjusting the device for users with different anatomy or disease severity. This study was conducted as part of our effort for developing a new treatment for SD. Our device can be an important step in advancing laryngeal VTS as a therapeutic intervention for improving the voice symptoms in SD. If successful, our laryngeal vibration technology could become a low-cost, wearable, non-invasive treatment for SD, which can enhance the available therapeutic arsenal by either augmenting existing Botox therapy or becoming an alternative intervention option for patients who do not tolerate Botox injections.

Deliverables

Published conference proceedings

1. Dubey S., **Mahnan A.,** Konczak J., Real-time voice activity detection using neck-mounted accelerometers for controlling a wearable vibration device to treat speech impairment, 2020 Design of Medical Device Conference, April 6-9, 2020, Minneapolis, MN. *Frontiers in Biomedical Devices* 83549, V001T09A007
2. **Mahnan A.**, Faraji S.A., Konczak J., Wearable non-invasive neuromodulation device for the symptomatic treatment of the voice disorder spasmodic dysphonia, *Proceedings of the*

2019 Design of Medical Devices Conference, 2019 Design of Medical Devices Conference. Minneapolis, Minnesota, USA. April 15–18, 2019. V001T02A001. ASME.

US Patent

1. Konczak J., **Mahnan A.**, Wearable Devices and Methods for Treatment of Focal Dystonia of the Neck, Head, and Voice (US Patent Application US20190159953A1).

Acknowledgment

This project was supported by the Clinical and Translational Science Award (CTSA), and National Spasmodic Dysphonia Association grant (PI J Konczak), and the University of Minnesota's MnDRIVE (Minnesota's Discovery, Research, and Innovation Economy) discoveries through industry partnerships fellowship in neuromodulation.

PROJECT 3: Obtaining clinical efficacy data of the wearable neuromodulation device in a sample of patients with AB SD

People with the abductor type of SD have even more limited treatment options than those with AD SD. Most of the AB SD patients do not respond to Botox injection. This project specifically targeted people with AB SD to investigate if and how they respond to the laryngeal VTS. It used the third-generation prototype of the device described in Project 2. This project explored the following questions:

- Can VTS provide measurable symptomatic relief for patients with AB SD?
- Do the results of voice quality markers correlate with the improvements observed in AD SD patients that were tested in project 1?
- What are the changes in the cortical activity associated with VTS in AB SD patients?
- Can we observe the same electrocortical responses from project 1 in people with AB SD?

At the time of the submission of this dissertation, the recruitment of patients was not completed. I here present all data currently available. This work is funded by the National Association of Spasmodic Dysphonia (PI Konczak).

Specific aims

Aim 1: Demonstrate the effects of the on-time application of laryngeal vibration using the wearable device. Obtain objective markers of voice quality in people with AB SD before, during, and after the application of VTS.

Aim 2: Monitor the changes in cortical activation patterns associated with laryngeal VTS in people with AB SD. Following the approach from project 1, electrocortical response to VTS will be measured and compared to people with AD SD.

Methods

Participants

Four people diagnosed with AB SD (4 female; mean age ± std: 51.5 ± 14.7 years) were recruited and attended the study (See **Table 5** for clinical characteristics of study participants). The experimental protocol was approved by the Institutional Review Board of the University of Minnesota. All participants gave their informed consent prior to the experiment.

None of the patients were receiving Botox treatment or undergoing any other treatment in the course of the study, and their voice was in the symptomatic stage.

Table 5. *Clinical characteristics of study participants. (F: female)*

Subject ID	Gender	Age	SD type	Voice Tremor	Diagnosis Duration (mo.)	Botox cycle (mo.)	Last Botox Injection (mo.)
ABSD1	F	34	ABD	No	144	NA	141
ABSD2	F	70	ABD	Severe	192	NA	192
ABSD3	F	52	ABD	No	9	NA	NA
ABSD4	F	50	ABD	No	120	NA	96

Apparatus

We used the wearable VTS device described in detail in Project 2 as the apparatus for this study (See **Figure 9**). EEG data were recorded with the ActiveTwo data acquisition system (Biosemi B.V. Ltd, Amsterdam, Netherlands). The sampling rate was set at 4096 Hz. Brain potentials were captured via Biosemi's 64-channel EEG cap with an equiradial system of electrode placement. Participants were guided throughout the experiment by a series of two 300-ms long auditory cues (2000 Hz and 900Hz) generated by RPvdsEx software (Tucker-Davis Technologies Ltd., Alachua, USA). The developed wearable device was used to control the activation of the vibrators. The time-stamp of auditory cues was recorded.

All speech and voice signals were recorded for later offline analysis. An external microphone (electret condenser microphone, Sony ECM-88B) was located close to the participant's mouth. The microphone was connected to an audio recorder (MixPre-3 II, Sounds Devices, LLC.) which transferred the audio data for recording to Audacity software via a USB connector. Thus, we were able to monitor the voice activity and device function during the trial.

Experimental Procedure and Behavioral Task

The experiment took place in an electrically and acoustically shielded chamber at the Multiple Sensory Perception Laboratory at the University of Minnesota. Participants sat on a comfortable chair, asked to avoid extra movements and to focus their visual gaze at a fixation point on the front wall. Before asking the participant to wear the collar, the width of the thyroid cartilage of the participant was measured. Accordingly, the vibrators moved horizontally to be positioned laterally to the thyroid cartilage. Using a marker on

the collar cover (See **Figure 9**A), we ensured that the microphone was located on the center of the larynx. Subsequently, the vibrators were positioned externally and bilaterally on the participant's neck over the laryngeal area (see **Figure 13**).

Prior to the experiment, the severity of speech symptoms was evaluated in a voice assessment task (Baseline) by (1) reading a series of standard sentences (Woodson, 2010) devised for the evaluation of voice quality in AB/AD SD (For the list of sentences, see Appendix I); and (2) pronouncing vowels /i/ and /ɑ/ five times, each lasting four seconds. Participants read the sentences at their own comfortable pace and loudness. In addition, participants rated their perceived effort level of vocalization immediately after the voice assessment task on an ordinal scale of 0 to 10 (0 being with no effort and 10 being with maximal effort) (See Appendix III)

The experimental protocol comprised two blocks:

1) **Laryngeal vibration (*VTS Only*):** the laryngeal vibrators were turned on using the continuous mode of the device (See **Figure 10**) for 5 minutes.
2) **Vowel vocalization accompanied by laryngeal VTS (*Vocalization + VTS*).**
   During this condition, participants received two auditory cues. They were instructed to start vocalizing vowel /ɑ/ after hearing the first auditory cue (1500Hz, duration: 250ms). The participants were asked to cease the vocalization after hearing the second auditory cue (900Hz, duration: 250ms). The period between two auditory cues was set to 4.5 seconds.
   For this condition, we have modified the speech detection mode of the device and developed a new operational mode for speech detection during the experiment (see **Figure 14**). In this setting, the device will detect the onset of

speech within 200ms and then turns on stimulation with a 2000ms delay (i.e., at 2200ms after voice onset). Subsequently, laryngeal VTS will be applied during the second half of the vocalization period for 2 seconds (i.e., from 22000-42000ms). This procedure was repeated 50 times with 4-second long resting intervals in between.

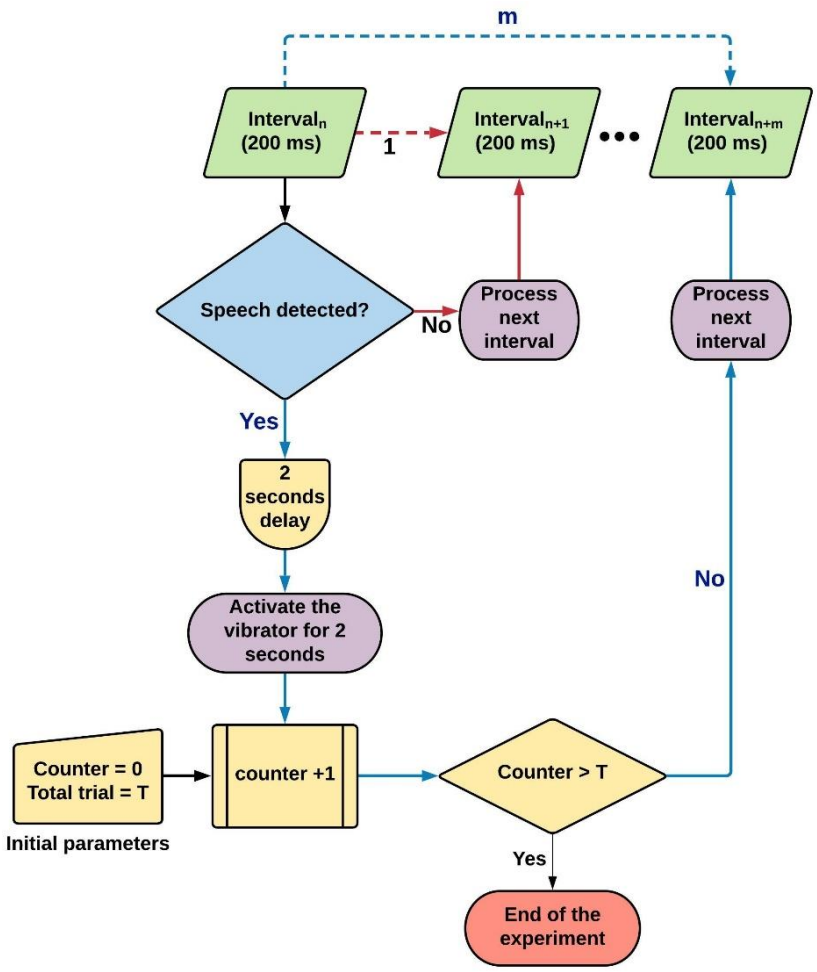

Figure 14. *Flow chart for the speech detection algorithm during the experiment. A 200-millisecond signal interval will be evaluated for speech activity. If the interval is classified as voiced, a 2 s delay will be introduced to the system. This will allow the participant to vocalize for 2 s. After the delay, the device will activate the vibrators for 2 s, resulting in Vocalization + VTS condition. If the interval is classified as unvoiced, the next 200-millisecond interval will be evaluated. The total number of trials (T=50 in project III) and threshold will be assigned manually before starting this operational mode. The device will exit this operation mode after activating the VTS for assigned total trials (50). m=4500 milliseconds.*

Both conditions were applied in two sets, with each set lasting 12 minutes. Between sets, at the end of set 2, and 20 and 60 minutes after the cessation of VTS (Retention), voice/speech quality was evaluated using the same assessment tasks given at *Baseline* (see **Figure 15**).

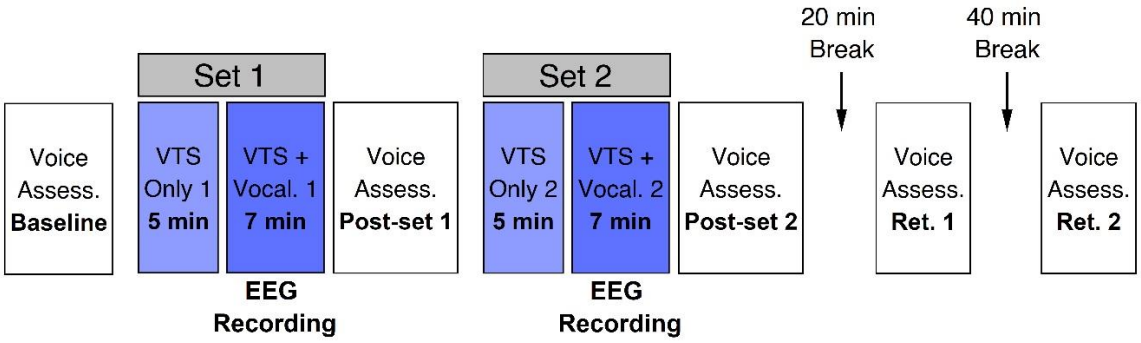

Figure 15. *The experimental protocol for project III*

Objective Measures of Speech Quality

Three acoustic signatures characterize the voice symptoms of people with AB SD (Edgar et al., 2001): (1) prolonged word and sentence duration, (2) number of phonatory breaks, and (3) delayed voice onset time. People with AB SD experience atypical voicing gaps that increase word duration, mistimed onset of voicing, and atypical breaks in voicing.

In our study, participants read two sets of standard sentences (Woodson, 2010) for the speech evaluation of people with adductor and abductor SD in their normal conversational style (See Appendix I). Assessment of these recorded voice data was performed offline. Two voice measures were obtained: (1) the duration of speech, and (2) the change in the smoothed cepstral peak prominence (CPPs) of voice (See Project I for details on CPP).

At first, all speech signals were broken and labeled into three categories: 1) 'voiced sentences', 2) 'unvoiced sentences', and 3) 'unvoiced words': which made up the unvoiced sentences and were comprised of a number of unvoiced phonemes. (See Appendix I for the list of each category). Then, CPPs values and speech duration were derived. The Audacity software was used to record the audio signals, and PRAAT software was used for the acoustic analysis of the voice data. Acoustic analysis was performed by individuals blind to experimental conditions.

EEG signal processing

The EEGLab toolbox of MATLAB (The MathWorks, Natick, MA) was used for exploring the EEG data (Delorme and Makeig, 2004). The EEG signal processing steps were as followed:

1. The data were high-passed filtered at the cut-off frequency of 0.1Hz to address possible baseline drifts, and low-pass filtered at 50 Hz. Both filters used a zero-phase FIR filter. A zero-phase Slepian window filter was used to remove power line noise.
2. Because we used the speech detection technology, the vocalization + VTS task did not start at the same time after the first auditory cue for all the trials. Using the recorded audio signal, we manually measured the time to vocalization onset after the first cue and vocalization duration. We then corrected the EEG signal time log of each trial to accommodate these variabilities.
3. Segments of EEG recordings from 1000ms before vocalization to 4000ms after the onset of vocalization were extracted as data epochs using the corrected time

logs. The 1000 ms period prior to the vocalization was used as the baseline (resting state) for the cortical activity.

4. In order to weaken the potential effect of non-cortical sources that might have been commonly captured by electrodes, each channel was re-referenced to the common average of all electrodes.
5. EEG data were resampled to 500 Hz to decrease the processing time and cost of the next steps.
6. We subsequently used the 'runica' algorithm to perform independent component analysis (ICA) on all data channels. ICA is a method to decompose independent sources that are linearly mixed.
7. An automated multiple artifact rejection algorithm, 'SASICA' (Chaumon et al., 2015) implemented on the resultant components to identify and remove the contaminated ICs. This algorithm recruits spatiotemporal criteria to distinguish the artifactual components. This is critically important for the identification and removal of muscle artifacts that may have contaminated the EEG data during vowel vocalization.
8. Finally, the remaining ICs were linearly summed up, and the output dataset was used for extracting the features.

Electrocortical measures

As a primary EEG measure, we obtained the event-related spectral perturbation (ERSP) of somatosensory-motor cortical electrodes in response to VTS (For details on ERSP, see Project I). Band-specific features were separately extracted for the physiologically relevant frequency ranges (i.e., <50Hz): theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz),

and the low gamma (30-49Hz). ERSP was extracted for six sites: CP5, C5, FC5, CP6, C6, and FC6 (See **Figure 4** and Project I for more details).

EEG features were extracted from the Vocalization + VTS conditions of both sets (see **Figure 15**) to investigate the immediate cortical response to VTS. For each condition, the 4000ms long trials were divided into two segments:

1) ***VTS-off*** (before the onset of laryngeal vibration) – Only Vocalization.
2) ***VTS-on*** (after the onset of laryngeal vibration) – Vocalization and vibration.

For each participant, the ERSP measure of the average of the 50 recorded epochs was derived separately for the VTS-off and VTS-on segments. Because the period for vocalization onset is variable for each participant and each trial, in some instances, the voice activity period might exceed the 4.5 seconds duration between two auditory cues. As such, because the second auditory cure additionally contain cortical auditory evoked potentials (Alvarenga et al., 2013) or the EEG signal might be influenced by the reaction time of the study participants (Santee and Kohfeld, 1977), the period that exceeds the onset of the second auditory cue were excluded from further EEG analysis (i.e. the 4.5 second interval, might be shorter is some trials). For ERSP computation, the outcome value is time-normalized; thus, the difference in time duration for analysis does not affect the results.

In order to quantify the changes in the electrocortical activity of participants in response to laryngeal VTS, two variables were calculated:

1) **Absolute ERSP change:** measured from the subtraction of computed ERSP in VTS-on (Vocalization and vibration) from VTS-off (Vocalization):

$$\text{Absolute ERSP change} = \text{ERSP}_{\text{VTS-on}} - \text{ERSP}_{\text{VTS-off}} \quad (2)$$

The unit of absolute ERSP change is in dB. The negative value of the absolute ERSP change indicates an event related desynchronization (ERD) in cortical electrodes induced by VTS. Conversely, a positive value for Absolute ERSP is defined as event related synchronization (ERS) as a result of VTS application.

2) **Relative ERSP change:** measured from dividing absolute ERSP change to the ERSP in VTS-off (Vocalization).

$$\text{Relative ERSP change} = \frac{\text{ERSP}_{\text{VTS-on}} - \text{ERSP}_{\text{VTS-off}}}{\text{ERSP}_{\text{VTS-off}}} \quad (3)$$

Relative ERSP change is unit-less and indicates the magnitude of ERD or ERS compared to the ERSP in VTS-off.

Results

Participants underwent two sets of vowel vocalization. This study only investigated AB SD participants. Vocalizing the vowel /ɑ/ requires an extensive effort for individuals with AB SD. During the data collection procedure, we observed that participants experienced fatigue at the end of the second vowel vocalization set and their voice quality declined (See **Figure 24** and **Figure 25** in Appendix IV). Because fatigue might have confounded the auditory and electrocortical data, we here report only data of set 1, but included the data set 2 in the supplement of this dissertation (See Appendix IV).

Changes in markers of speech quality

We recorded the voice of 4 AB SD participants as they read a list of sentences devised for the speech evaluation of SD (Woodson, 2010) at five different time stamps along with the experimental protocol (see **Figure 15**):

1) ***Pretest (Baseline):*** Prior to VTS;
2) ***Post-test 1:*** After 8.8 minutes of VTS;
3) ***Post-set 2:*** after 17.6 minutes of VTS;
4) ***Retention 1:*** 20 minutes past the cessation of VTS.
5) ***Retention 2:*** 60 minutes past the cessation of VTS.

Subsequently, we derived the duration and CPPs for each of the three following segments, Unvoiced and voiced sentences and unvoiced words (See Appendix I), as measures of speech quality from the acoustic signal.

The clinical and self-perceived markers of speech for the pre-test (baseline) show that participants experienced different levels of voice symptom severity (See **Table 6**).

Table 6. *Clinical and self-perceived markers of speech and voice symptom severity for study participants (UVS: unvoiced sentences, VS: voiced sentences, UVW: unvoiced words).*

Subject ID	Self-Rated Effort Scale				Duration (s)		
	UVS	VS	Vowel /e/	Vowel /a/	UVS	VS	UVW
ABSD1	5	4	1	3	42.42	23.78	34.39
ABSD2	7	7	10	9	42.5	26.25	33.4
ABSD3	3	2	2	3	39.03	25.77	29.28
ABSD4	8	5	4	3	NA	NA	NA

The speech analysis was completed for 3 participants. Two of the three participants (ABSD1 and ABSD3) responded to VTS and showed a reduction in the duration of all three voice segments, unvoiced and voiced sentences, and unvoiced words at Post-set 1 as compared to Pretest. ABSD1 showed the greatest change in the duration variables and also a rise of CPPs (> +1dB) for unvoiced and voiced sentences (See **Figure 16**A). The participant ABSD2, who was diagnosed with AB SD and severe voice tremor, did not show any improvements (See **Figure 16**B). Improvements in all six speech quality measures for the ABSD1 were preserved at both 20 and 60-minute retention stages (see **Figure 17**A and **Figure 18**A). For ABSD3, the effect of VTS declined after 20 minutes (see **Figure 17**C) and dissipated after 60 minutes post VTS (see **Figure 18**C).

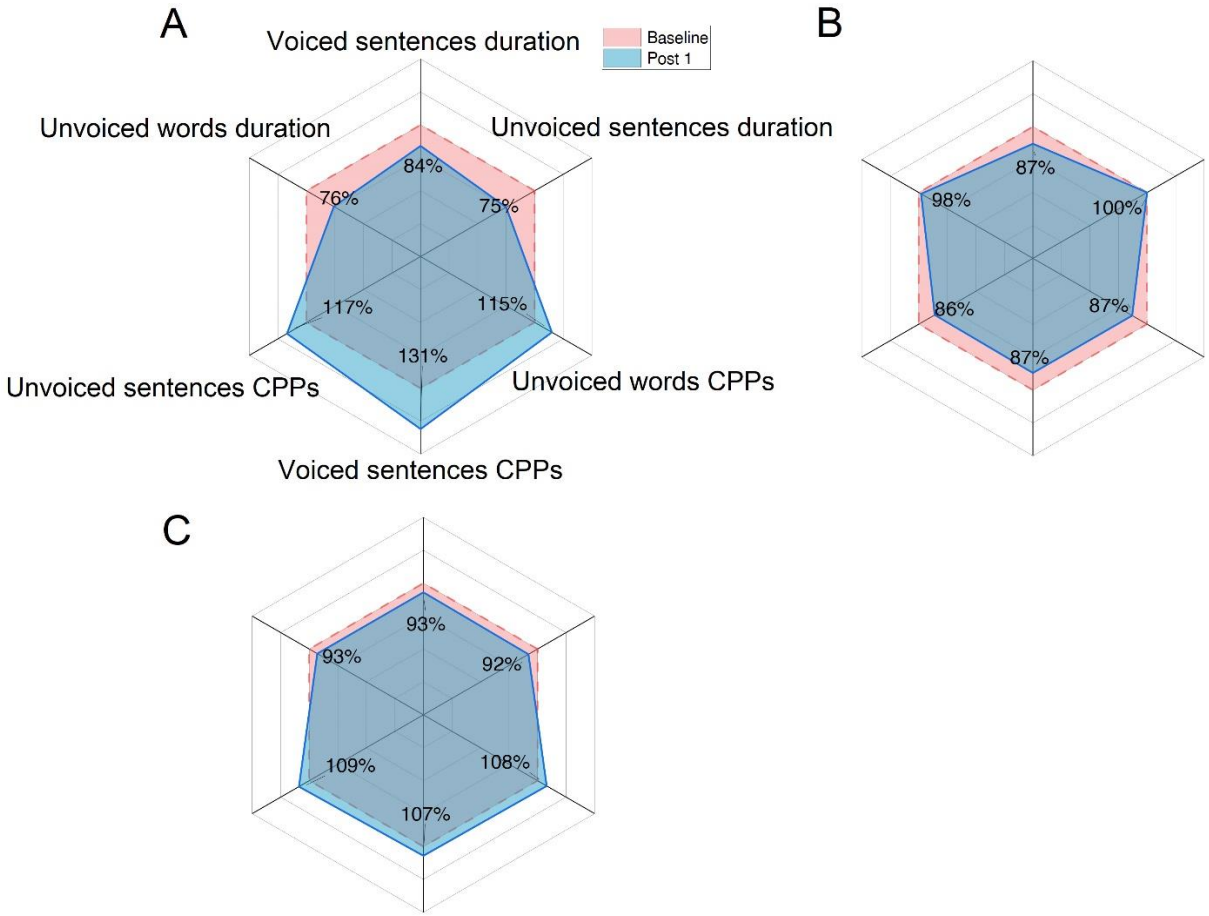

Figure 16. *Change in the duration and CPPS at Post-set1 in comparison to Baseline (Pretest). An improvement in voice quality will be achieved by a decrease in duration and increase in CPPs. The numbers on the graph represent the percentage of change in comparison to baseline (100%). A) ABSD1 showed an improvement in both duration and CPPs changes. B) ABSD2 did not experience any improvement. C) ABSD3 showed only minor improvements in both duration and CPPs.*

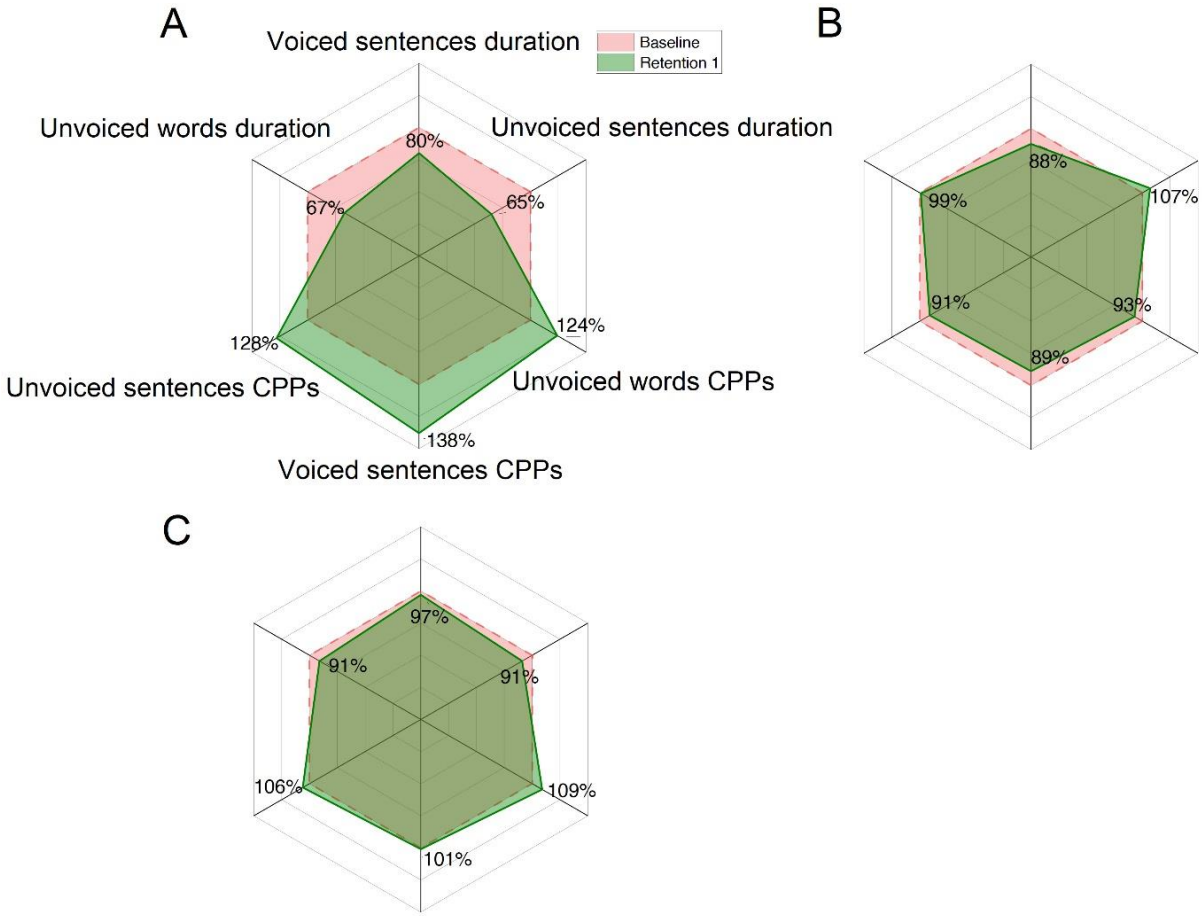

Figure 17. *Change in the duration and CPPS at Retention 1 (20 minutes after VTS) in comparison to Baseline (Pretest). The numbers on the graph represent the percentage of change in comparison to baseline (100%). A) ABSD1 showed an improvement in both duration and CPPs changes. B) ABSD2 did not experience any improvements, except a decrease in voice sentences duration. C) ABSD3 showed only minor improvements in both duration and CPPs.*

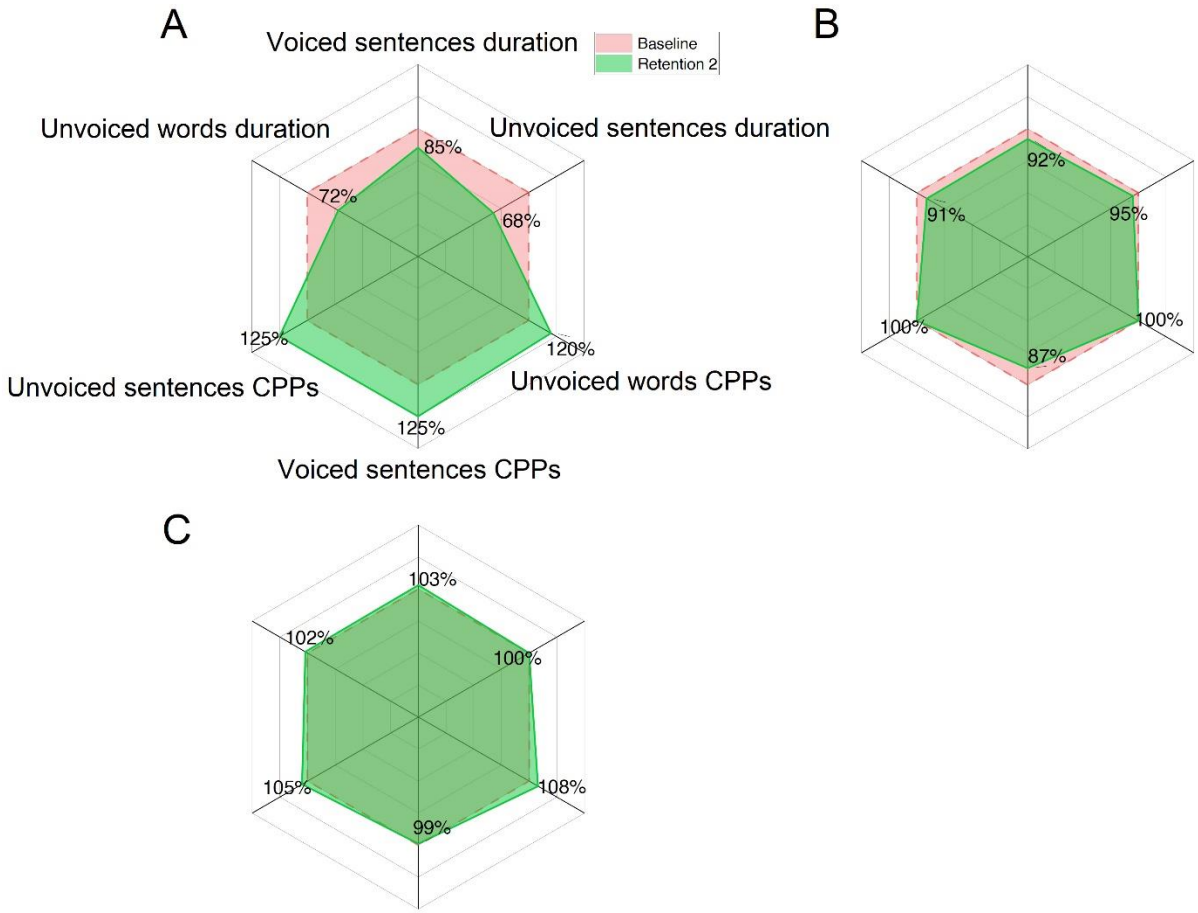

Figure 18. *Change in the duration and CPPS at Retention 2 (60 minutes after VTS) in comparison to Baseline (Pretest). The numbers on the graph represent the percentage of change in comparison to baseline (100%). A) ABSD1, the improvements in both duration and CPPs changes were still present. B) ABSD2 experienced minor improvements in the duration but did not experience any improvements in CPPs. C) ABSD3, returned to the baseline status.*

Table 7. *VTS induced change in smoothed cepstral peak prominence (∆CPPS) relative to baseline (Pretest). Unit for ∆CPPS is dB.*

Subject ID	Post-Set 1 ∆CPPS (dB)			Post-Set 2 ∆CPPS (dB)			Retention 1 ∆CPPS (dB)			Retention 2 ∆CPPS (dB)		
	UVS	VS	UVW	UVS	VS	UVW	UVS	VS	UVW	UVS	VS	UVW
ABSD1	1	2.2	0.9	0.9	1.8	0.8	1.6	2.7	1.4	1.4	1.8	1.2
ABSD2	-1.1	-1.3	-1	0	-0.3	0.4	-0.7	-1.1	-0.6	0	-1.3	0
ABSD3	0.7	0.8	0.7	1.6	1.2	2.1	0.5	0.1	0.8	0.4	-0.1	0.7
ABSD4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 8. *VTS induced change in the duration (∆duration) of unvoiced sentences (UVS), voiced sentences (VS), unvoiced words (UVW) relative to baseline (Pretest). Unit for ∆duration is in second.*

Subject ID	Post-Set 1 ∆duration (s)			Post-Set 2 ∆duration (s)			Retention 1 ∆duration (s)			Retention 2 ∆duration (s)		
	UVS	VS	UVW	UVS	VS	UVW	UVS	VS	UVW	UVS	VS	UVW
ABSD1	-10.8	-3.9	-8.1	-8.3	-1.8	-5.8	-14.8	-4.9	-11.3	-13.6	-3.5	-9.7
ABSD2	0.2	-3.6	-0.7	15.5	-0.3	3	3	-3.1	-0.2	-2.3	-2	-3
ABSD3	-2.9	-1.8	-2.1	-4.1	-2	-3.2	-3.5	-0.9	-2.5	0	0.7	0.6
ABSD4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Change in the cortical oscillatory behavior in response to laryngeal VTS

The effect of the first 8.8 minutes of VTS (set 1 in **Figure 15**) on cortical oscillatory activity over the premotor, motor, and somatosensory cortex showed variable electrocortical responses in the four participants. For cortical theta-band oscillations (4-8 Hz), ABSD1 and ABSD2 showed event related synchronization (ERS) for both right and left cortical electrodes (FC6, C6, CP6, FC5, C5, and CP5). However, ABSD 3 observed event related desynchronization (ERD) in right cortical electrodes. Conversely, ABSD4 showed ERD for all the left hemisphere cortical electrodes (See **Figure 19**). The result of ABSD4 is aligned with what was recorded in project 1.

The first set of VTS in ABSD1 induced ERD of the cortical alpha frequency band (8-13Hz) in left somatosensory and motor cortical electrodes (CP5 and C5). The result in ABSD3 was in contrast, showing ERS in CPS and C5. ABSD2 and ABSD4 showed ERS in all the electrodes, except CP5 in ABSD4, for the alpha oscillation band (See **Figure 20**). The VTS induced activity in cortical frequency band of Beta (13-30 Hz) in ABSD2, ABSD3, and ABSD4 resulted in ERS in all cortical electrodes, except FC6 in ABSD2. However, ABSD1 observed ERS only in C6, CP6, and FC5 (See **Figure 21**). Finally, the cortical activity in the lower gamma frequency band (30-50 Hz) showed ERD in all cortical electrodes for ABSD2 and ABSD3 (except FC6 in ABSD3). ABSD1 observed ERS only in C5, CP5, and CP6. However, ABSD4 showed ERS in all the cortical electrodes (See **Figure 22**).

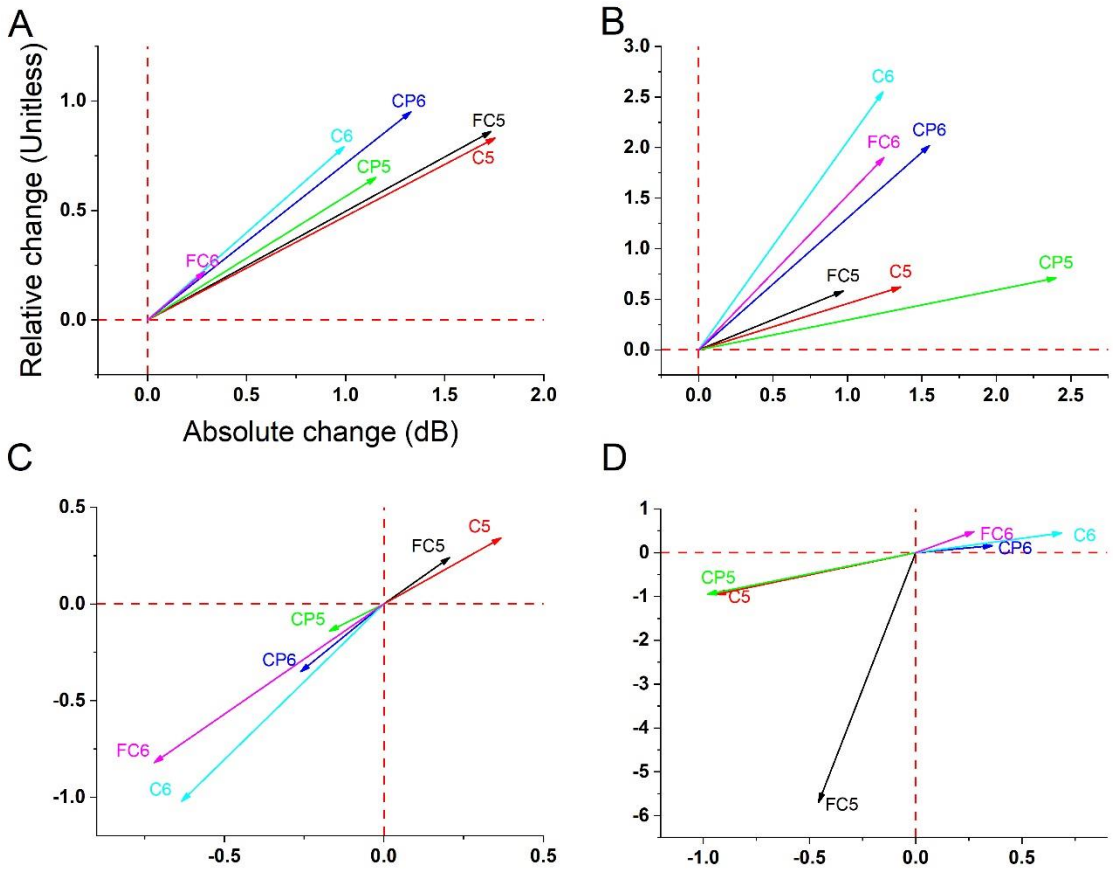

Figure 19. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for <u>thet-band</u> (4 to 8 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 1*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 did not observe any desynchronization.* ***B)*** *ABSD2 did not experience any desynchronization.* ***C)*** *ABSD3 experienced desynchronization in right cortical electrodes (FC6, C6, and CP6) and left motor electrode (C5).* ***D)*** *ABSD4 showed suppression of all left cortical electrodes. The result that was observed in project 1. Unit for the absolute change is in dB.*

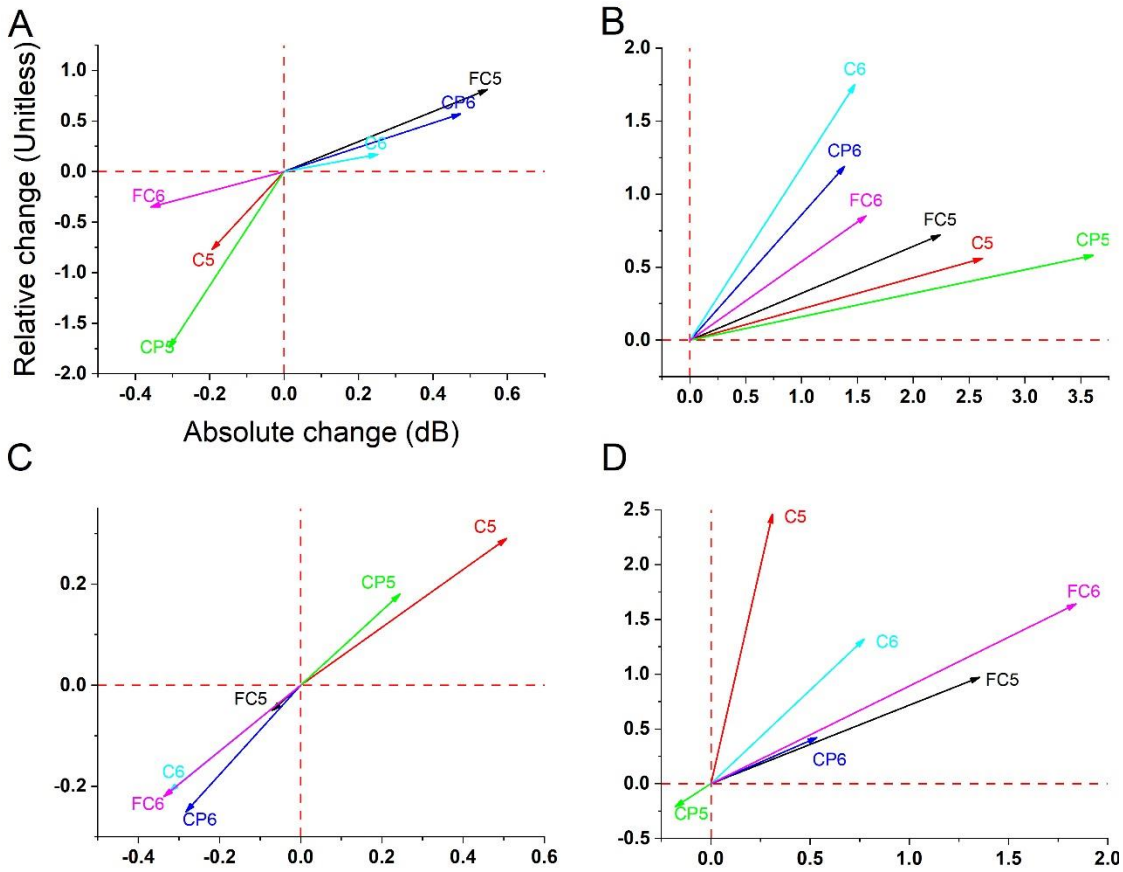

Figure 20. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for alpha-band (8 to 13 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 1*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 observed desynchronization only in C5, CP5, and FC6.* ***B)*** *ABSD2 experienced synchronization in all the electrodes.* ***C)*** *ABSD3 experienced synchronization in two of the left cortical electrodes (CP5 and C5).* ***D)*** *ABSD4 had synchronization in all the electrodes except CP5. Unit for the absolute change is in dB.*

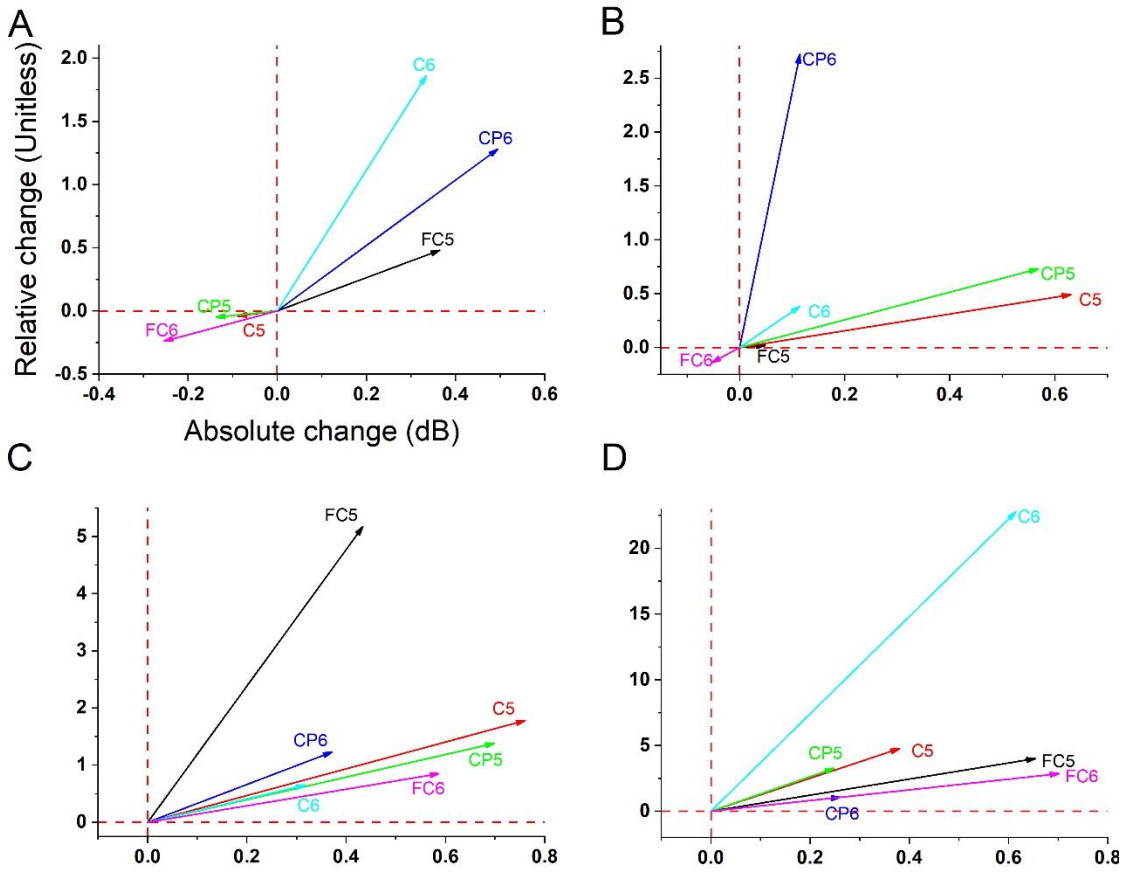

Figure 21. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for beta-band (13 to 30 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 1*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 observed desynchronization only in C5, CP5, and FC6.* ***B)*** *ABSD2 experienced synchronization in all the electrodes, except FC6.* ***C)*** *ABSD3 experienced synchronization in all the cortical electrodes.* ***D)*** *ABSD4 had synchronization in all the electrodes. Unit for the absolute change is in dB.*

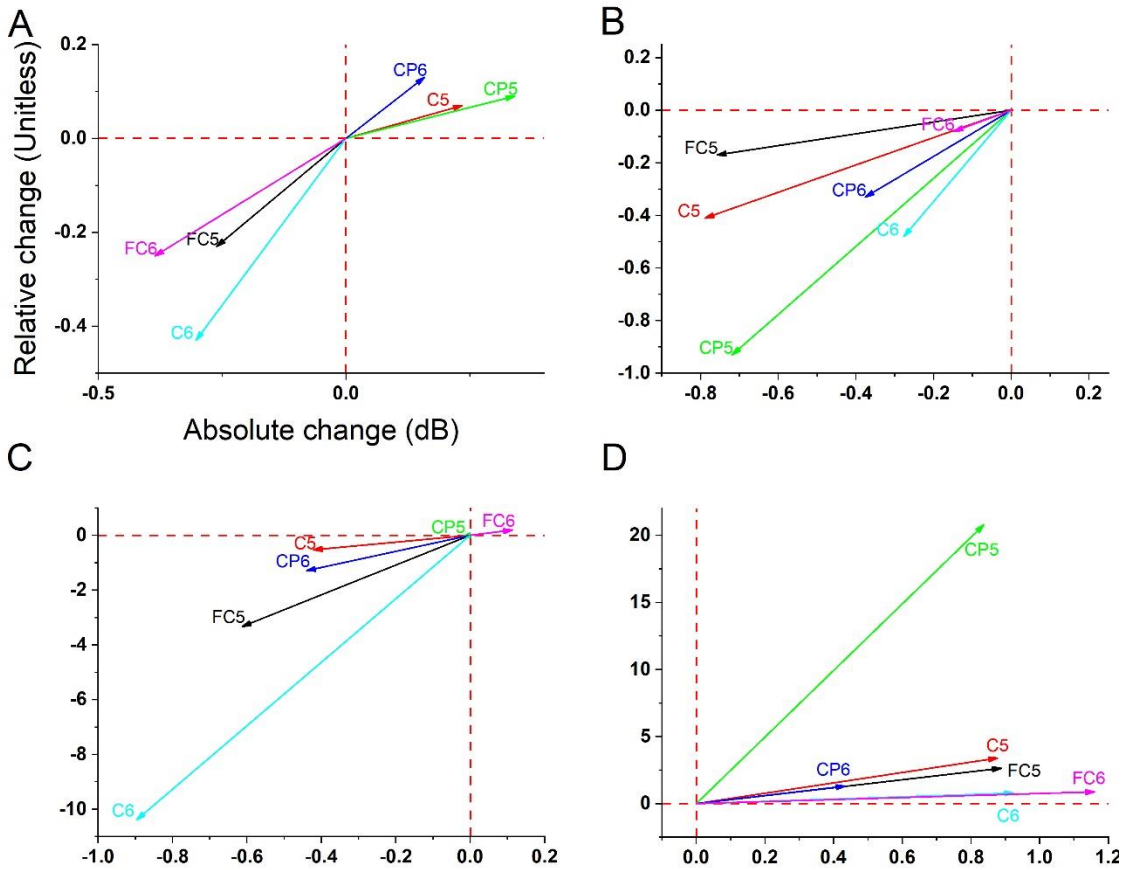

Figure 22. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for lower gamma band (30 to 50 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 1*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 observed synchronization only in C5, CP5, and CP6.* ***B)*** *ABSD2 experienced desynchronization in all the electrodes.* ***C)*** *ABSD3 experienced desynchronization in all the cortical electrodes except FC6.* ***D)*** *ABSD4 had synchronization in all the electrodes. Unit for the absolute change is in dB.*

Table 9. *ERSP values over the somatosensory, motor, and premotor cortical areas for theta band (4 to 8 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	1	-2.01	-0.28	-2.12	-0.37	-1.77	-0.61	-1.31	-1.02	-1.26	-0.27	-1.40	-0.07
ABSD2	1	-1.66	-0.69	-2.20	-0.84	-3.40	-1.00	-0.65	0.59	-0.49	0.75	-0.77	0.78
ABSD3	1	-0.85	-0.64	-1.07	-0.71	-1.26	-1.43	-0.88	-1.60	-0.62	-1.25	-0.74	-1.00
ABSD4	1	-0.08	-0.54	0.99	0.05	1.04	0.06	-0.57	-0.30	-1.53	-0.85	-2.28	-1.92

Table 10. *ERSP values over the somatosensory, motor, and premotor cortical areas for alpha band (8 to 13 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	1	-0.67	-0.13	-0.25	-0.44	-0.18	-0.49	-1.03	-1.39	-1.51	-1.26	-0.83	-0.36
ABSD2	1	-3.12	-0.88	-4.65	-2.03	-6.19	-2.58	-1.86	-0.28	-0.85	0.63	-1.16	0.22
ABSD3	1	-1.29	-1.36	-1.76	-1.25	-1.35	-1.11	-1.56	-1.90	-1.52	-1.84	-1.13	-1.41
ABSD4	1	-1.39	-0.04	-0.13	0.18	0.88	0.70	-1.12	0.72	-0.59	0.19	-1.28	-0.74

Table 11. *ERSP values over the somatosensory, motor, and premotor cortical areas for beta band (13 to 30 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	1	0.75	1.12	2.23	2.14	2.88	2.75	1.04	0.79	0.18	0.51	0.39	0.88
ABSD2	1	-2.67	-2.63	-1.29	-0.66	-0.78	-0.21	-0.39	-0.44	-0.31	-0.19	0.04	0.16
ABSD3	1	-0.08	0.35	-0.43	0.33	-0.51	0.19	-0.69	-0.11	-0.49	-0.17	-0.30	0.07
ABSD4	1	-0.16	0.49	0.08	0.46	0.08	0.32	0.25	0.95	-0.03	0.59	-0.25	0.02

Table 12. *ERSP values over the somatosensory, motor, and premotor cortical areas for lower gamma band (30 to 50 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	1	1.15	0.89	3.17	3.41	3.65	3.99	1.53	1.14	0.70	0.40	1.25	1.40
ABSD2	1	-4.42	-5.17	-1.92	-2.71	-0.77	-1.49	-1.89	-2.04	-0.58	-0.85	1.14	0.76
ABSD3	1	-0.18	-0.80	-0.80	-1.22	-0.45	-0.47	0.59	0.70	-0.09	-0.98	-0.34	-0.78
ABSD4	1	0.34	1.22	-0.26	0.62	0.04	0.88	1.31	2.47	1.17	2.09	0.33	0.76

Discussion

This is the first study (albeit a “pilot: study) that investigated the effects of laryngeal vibration on voice symptoms in people with AB SD. At the time of submission of this dissertation, the recruitment was not completed, and only data of four participants is reported. Because of this limited data set, it was not opportune to perform any inferential statistics on possible treatment effects. Thus, the main focus reports the individual data of the four participants with AB SD and contrast their voice and EEG data to the results of project 1, which applied the same VTS to people with AD SD. One participant, SD05, from project 1 was diagnosed with AB SD. He showed improvement in voice quality after VTS (See **Figure 5**). We have included this participant in this project’s discussion. The main findings of this research are as follows:

First, a one-time application of VTS on people with AB SD in three out of four participants (ABSD1, ABSD3, and SD05) showed an improvement in one of the markers of speech production. The effect persisted in two of them (ABSD1 and SD05) after 20 minutes and one, ABSD1, after 60 minutes after cessation of VTS. The results imply that VTS has a potential positive effect in at least a subsection of patients with AB SD. This initial data set confirmed that VTS can potentially have a beneficial effect on the voice symptoms in people with abductor-type SD. This finding extends on the previous research of project 1, showing that laryngeal VTS can ameliorate the voice symptoms in AD SD. As with the AD SD group of project 1, there are subgroups of “responders” and “non-responders” to the laryngeal VTS. However, at this point, more data on AB SD are required to determine a more firm rate of effectiveness in this group.

Second, we expected that the application of laryngeal VTS in AB SD to induce similar electrocortical responses as seen project 1. However, we did not observe the same consistent results. For instance, although ABSD1 observed improvement in voice quality markers but did not show an immediate significant suppression of theta band synchronization over the left somatosensory-motor cortex. However, we observed alpha-band synchronization in ABSD1 (See **Figure 20**). The same response was also observed in SD05, who participated in project 1 (See **Figure 23** in Appendix IV). Furthermore, the immediate significant rise of gamma-band was observed over the right somatosensory-motor cortical region of SD05 but was only present in motor cortical region of ABSD1. The data suggest that we might notice ERD/ERS in other oscillatory cortical bands or regions in AB SD that were not significant in project 1. In addition, there might be some similarities within or across two types of SD. Unfortunately, we do have sufficient data at this stage to substantiate the results and provide a cortical activity pattern in AB SD.

Limitations of the study

The repetitive vocalization of vowel /a/ required substantial efforts from the AB SD participants. This resulted in exhaustion at the end of the second set of VTS (see **Figure 15**) and a decline in the voice quality. However, the voice quality improved after the 20-minute break for retention (see **Figure 15**). We did not face this challenge in project 1, as most of the participants were diagnosed with AD SD. Modification in the experimental protocol by providing a 20 minutes break between two sets of VTS might alleviate the induced fatigue.

Another major challenge was incorporating a speech detection algorithm for providing periodic laryngeal VTS during vowel vocalization and EEG data collection. In the current study, we provided two auditory cues to control the timing of the vocalization. However, because people with AB SD experience delayed in the time for the onset of voice (Edgar et al., 2001), the participants did not start vocalization immediately after the first auditory cue. In some instances, the delay was more than one second. This delay in onset might result in an overlap between the second auditory cue and the Vocalization and VTS task. In this study, to avoid the interference of cortical activity of the second auditory cue and VTS, we only analyzed the period up to the second auditory cue. Future studies need to modify the experiment protocol and remove the second auditory cue. Because the vibrators will automatically turn off after two seconds (see **Figure 14**), the participant can end vocalization after VTS is ceased in each trial.

Like already discussed in project 1, the lack of an established clinical rating scale to assess disease severity limits the interpretation of the voice as well as the EEG-based data. From a clinical and therapeutic point of view, it would be highly desirable to be able to correlate improvements in voice quality due to laryngeal VTS and the associated EEG responses to markers of disease severity in order to understand what patient profile would predict the effectiveness of laryngeal VTS.

Conclusions

This study provided initial foray into the effectiveness of laryngeal VTS on voice quality and cortical activity of people AB SD. The results suggested that, in principle, laryngeal VTS can induce improvements in voice quality in people with AB SD. This preliminary finding aligns with the results observed in project 1 that showed that laryngeal VTS

alleviated voice symptoms in approximately 70% of people with AD SD. However, we require a larger sample to have a confident response rate to the laryngeal VTS in AB SD. The current analysis of electrocortical responses to VTS in people with AB SD did not closely mimic the event -elated cortical activity patterns seen in AD SD. More data are needed to delineate consistent patterns of cortical responses induced by laryngeal VTS in AB SD, but the project shows that a promising outcome may result.

Acknowledgment

This project was supported by a grant from the National Spasmodic Dysphonia Association (NSDA) (PI J Konczak) and the doctoral dissertation fellowship from the University of Minnesota.

Future work

This dissertation describes the evolution of an idea for an intervention to an advanced prototype of a medical device that may deliver such intervention. I have completed the necessary stages of both the development and commercialization of a wearable medical device as a non-invasive neuromodulation treatment. The following are recommendations for future work that are required for translating the current prototype into a commercially available medical device:

1. A smart-phone based application needs to be developed to control the device, removing the burden of the presence of an expert to operate the device.
2. The developed device needs to be tested on a large patient population both for short and long durations. The user's usability responses will guide the development of future generations of the device.
3. SD is a rare disorder, and patient recruitment remains the main challenge for conducting research on SD. A multi-center longitudinal clinical trial with a large patient sample will provide insights into the long term effects of laryngeal VTS on voice quality and electrocortical activity in SD. This developed wearable device has the potential to be a suitable approach to provide VTS. It increases accessibility and eliminates the purchasing equipment that are necessary for controlling the stimulation. In addition, the device provides the opportunity to set up a portable testing site.
4. Another approach for overcoming the recruitment challenge using the developed device is to conduct remote testing. The device can be shipped to the patients, and an investigator will be able to conduct remote control of the device to conduct the study.

5. The device can be sent to the patient for in-home testing for a limited period (e.g., one month). The patient can use the technology during activities of daily living. Such a study can provide a clearer understanding of the effectiveness of laryngeal VTS beyond the laboratory environment.
6. Further studies are required to investigate the effect of VTS on other neurological disorders such as cervical dystonia, focal hand dystonia, and chronic cough.
7. Finally, with some modifications, the developed wearable device can be adapted for the treatment of other disorders such as chronic cough or cervical dystonia.

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Appendix I

Voiced sentences

1) Tom wants to be in the army.
2) We eat eels every day.
3) He was angry about it all year
4) I hurt my arm on the iron bar.
5) Are the olives large?
6) John argued ardently about honesty.
7) We mow our lawn all year.
8) Jane got an apple for Ollie.
9) A dog dug a new bone
10) Everyone wants to be in the army.

Unvoiced sentences

1) He is hiding behind the house.
2) Patty helped Kathy carve the turkey.
3) Harry is happy because he has a new horse.
4) During babyhood he had only half a head of hair
5) Who says a mahogany highboy isn't heavy?
6) Boys were singing songs outside of our house.
7) The puppy bit the tape
8) See, there's a horse across the street.
9) Sally fell asleep in the soft chair.
10) The policy was suggested in an essay on peace.

Unvoiced words: The words are underlined. (47 words)

1) He is hiding behind the house.
W01 W02 W03 W04

2) Patty helped Kathy carve the turkey.
W05 W06 W07 W08 W09

3) Harry is happy because he has a new horse.
W10 W11 W12 W13 W14 W15

4) During baby hood, he had only half a head of hair.
W16 W17 W18 W19 W20 W21

5) Who says a mahogany high boy isn't heavy?
W22 W23 W24 W25 W26

6) Boys were singing songs outside of our house.
W27 W28 W29 W30

7) The puppy bit the tape.
W31 W32 W33

8) See, there's a horse across the street.
W34 W35 W36 W37 W38

9) Sally fell asleep in the soft chair.
W39 W40 W41 W42 W43

10) The policy was suggested in an essay on peace.
W44 W45 W46 W47

Appendix II

1. **What is the type of your voice disorder?**

    - Adductor spasmodic dysphonia (ADD SD)
    - Abductor spasmodic dysphonia (ABD SD)
    - Mixed (both ABD and ADD SD)
    - Muscle tension dysphonia

2. **Do you have voice tremor?** Yes/No.

3. **How often do you find yourself repeating your sentences because your peers have difficulty understanding you?**

Very frequently	Frequently	Infrequently	Very infrequently	Never

4. **What do you think is the severity of your voice disorder?**

Very Mild	Mild	Severe	Very severe	Extremely severe

5. **Are you taking Botulium toxin injection?** Yes/No
    a. If yes, what is the frequency of your Botox injection?

6. **Are you undergoing any other treatment besides Botox injection?** Yes/No
    a. If yes, please elaborate?

7. **How difficult was it to put on the device by yourself?**

Very difficult	Difficult	Neutral	Easy	Very easy

8. **Did you require assistance to put on the collar?** Yes/No.
    a. If yes, how could we make it easier for you?

9. **How comfortable was it for you to wear the collar?**

Strongly uncomfortable	Uncomfortable	Neutral	Comfortable	Strongly comfortable

10. **Assuming that you could choose the fabric color and/or design, would you feel comfortable wearing this collar in public?**

Strongly uncomfortable	Uncomfortable	Neutral	Comfortable	Strongly comfortable

    a. If you chose below neutral, what is the reason?

    b. In what way could we redesign the device to increase your comfort level?

11. **How restricted was the collar around your neck?**

Very tight	Tight	Neutral	Unrestricted	Very unrestricted

12. **How restricted was your neck movement while you wore the collar?**

Very restricted	Restricted	Neutral	Unrestricted	Very unrestricted

13. **How difficult was it to swallow while you had the collar around your neck and the vibrators were on?**

Very difficult	Difficult	Neutral	Easy	Very easy

14. How did the fabric of the collar feel on your skin?

Very irritating	Irritating	Neutral	Pleasant	Very pleasant

15. When in operation (vibrators are "on"), did the device irritate your skin? Yes/No

16. Did you feel the level of vibrator level is uncomfortable? Yes/No

a. If you chose yes, did you have any side effects (e.g., soreness, continuous tingling after vibration had ended, skin irritation, etc.)? Yes/No

b. If you had any side effects, please describe them briefly?

17. How difficult was it to talk while wearing the collar, and it was NOT vibrating?

Very difficult	Difficult	Neutral	Easy	Very easy

18. How difficult was it to talk while wearing the collar, and it was vibrating?

Very difficult	Difficult	Neutral	Easy	Very easy

19. How do you feel your voice changed while wearing the collar and the vibrators were OFF?

Very unnoticeable	Unnoticeable	Neutral	Noticeable	Very unnoticeable

20. How do you feel your voice or voice quality changed while wearing the collar and immediately after the vibrators were ON?

Very unnoticeable	Unnoticeable	Neutral	Noticeable	Very unnoticeable

21. Did you feel that your voice or voice quality changed over time during or after vibration?

Very unnoticeable	Unnoticeable	Neutral	Noticeable	Very unnoticeable

22. If you responded above "Neutral" to the previous question, please explain the noticeable changes.

23. What was the voice production effort while wearing the collar when compared to not wearing it?

Very demanding	Demanding	Neutral	Undemanding	Very undemanding

Appendix III

LEVEL	DESCRIPTION
10	Maximum vocal effort
9	Very very severe vocal effort (almost maximum)
8	
7	Very severe vocal effort
6	
5	Severe vocal effort
4	Somewhat severe vocal effort
3	Moderate vocal effort
2	Slight vocal effort
1	Very slight vocal effort
0.5	Very very slight vocal effort (just noticeable)
0	No vocal effort at all

Appendix IV

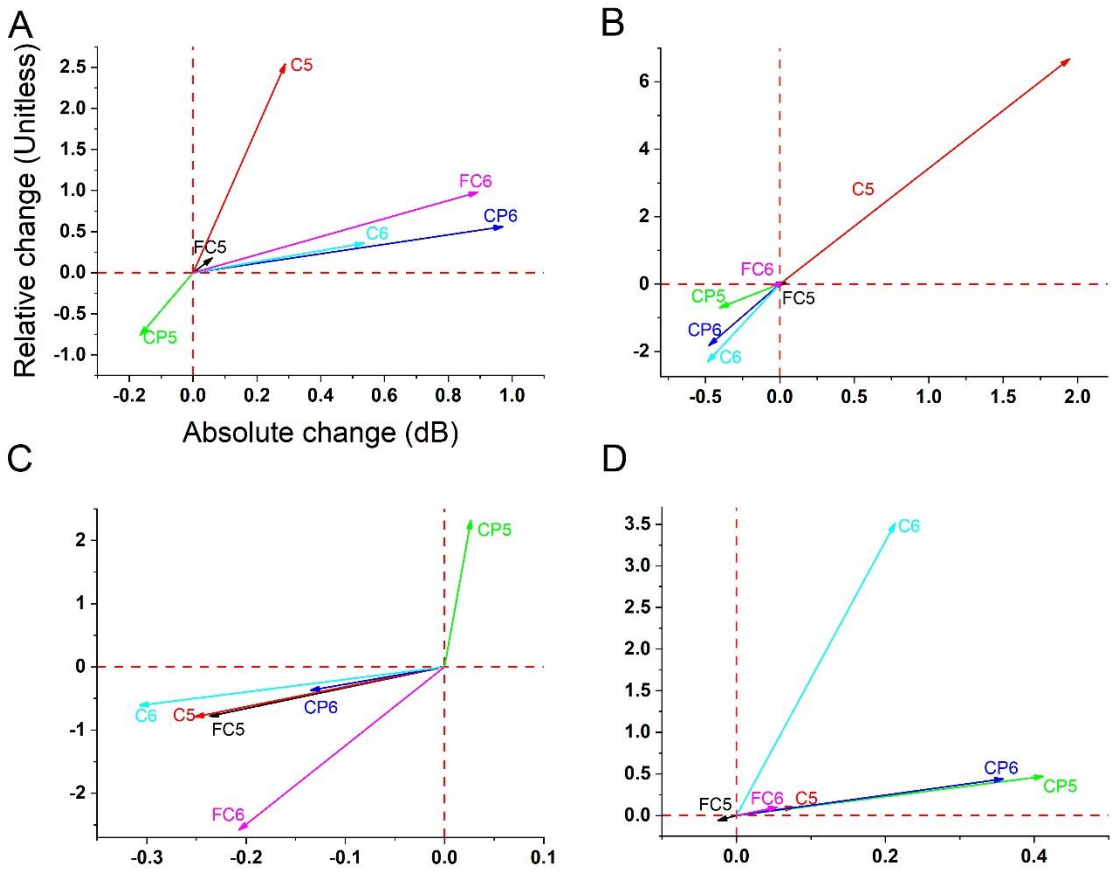

Figure 23*. Change in ERSP over the somatosensory, motor, and premotor cortical areas for SD05 in project 1 during Vocalization+VTS compared to Vocalization in* ***Set 1*** *(See* ***Figure 3****). SD05 was diagnosed with AB SD (See* ***Table 1****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *Theta band (4 to 8 Hz). All electrodes showed synchronization except CP5.* ***B)*** *Alpha band (8 to 13 Hz). SD05 observed desynchronization in C6, CP6, and CP5. The change in GC5 and FC6 was minor.* ***C)*** *Beta band (13 to 30 Hz). All cortical electrodes resulted in desynchronization except CP5.* ***D)*** *Lower gamma band (30 to 50 Hz). All the electrodes, except FC5, resulted in synchronization in the lower gamma band. Unit for the absolute change is in dB and relative change is unitless.*

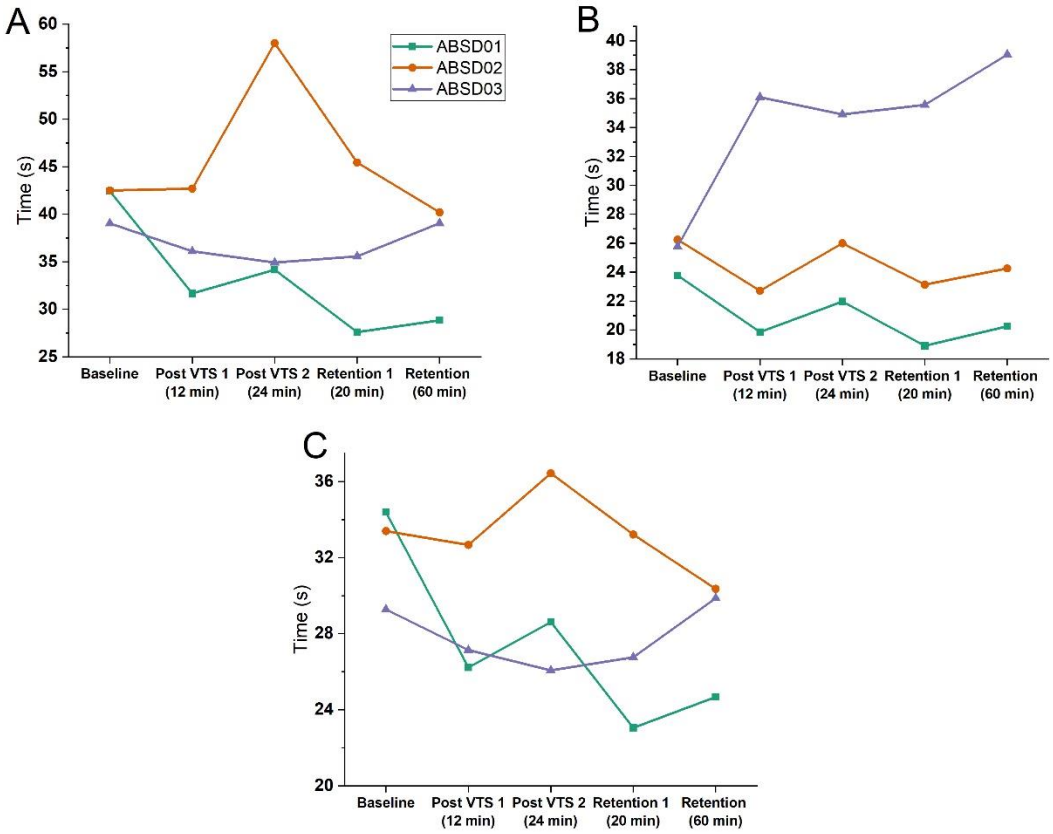

Figure 24*. The duration of the reading of the voice tasks during the experiment (see* ***Figure 15****). The data from Post-VTS 2 shows that the voice quality decreases. The participants were fatigued from the set 2 vocalization. A) Unvoiced sentences, B) Voiced sentences, and C) Unvoiced works.*

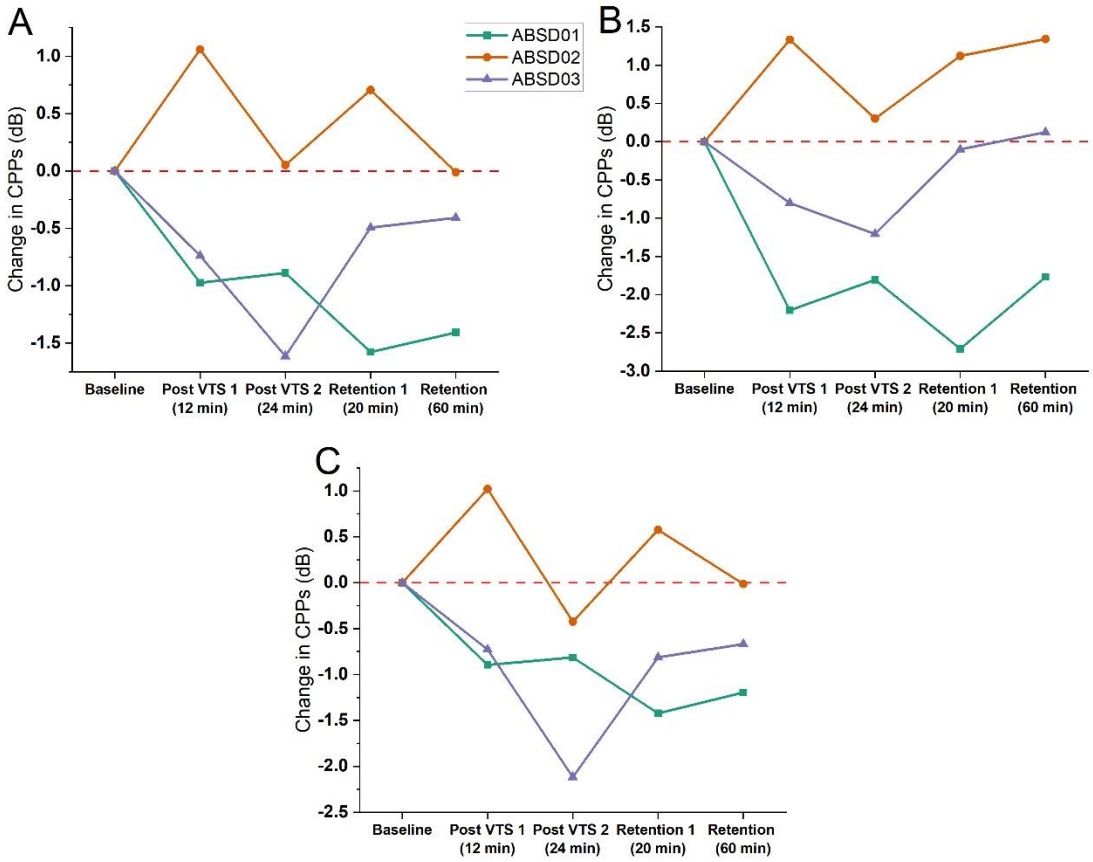

Figure 25. *The change in CPPs value compared to the baseline for voice assessment sections tasks of the experiment protocol (See* ***Figure 15****). The data from Post-VTS 2 shows that the voice quality decreases. The participants were fatigued from the set 2 vocalization. A) Unvoiced sentences, B) Voiced sentences, and C) Unvoiced works.*

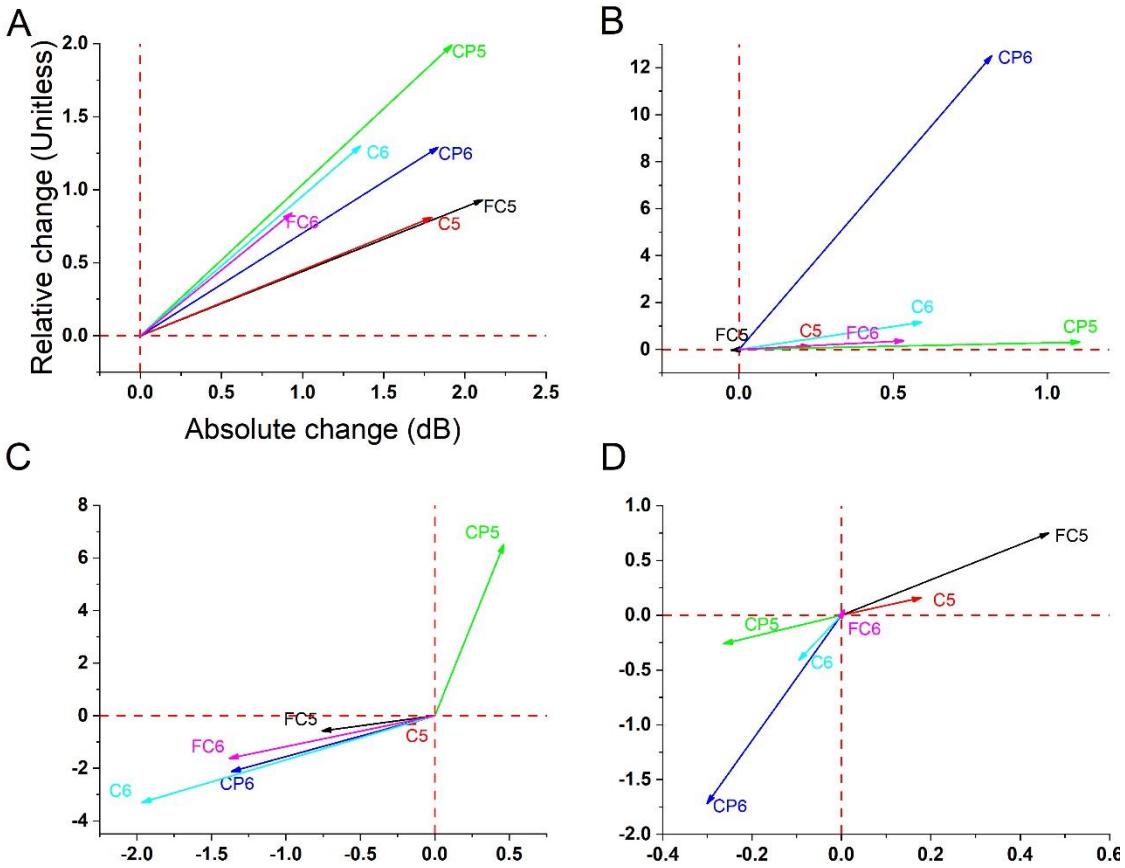

Figure 26. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for theta band (4 to 8 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 2*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 did not observe any desynchronization.* ***B)*** *ABSD2 did not experience any desynchronization.* ***C)*** *ABSD3 experienced desynchronization in right cortical electrodes (FC6, C6, and CP6) and left motor (C5) and premotor (FC5) cortical electrodes.* ***D)*** *ABSD4 showed suppression of left somatosensory (CP5) and right motor and somatosensory electrodes. Unit for the absolute change is in dB.*

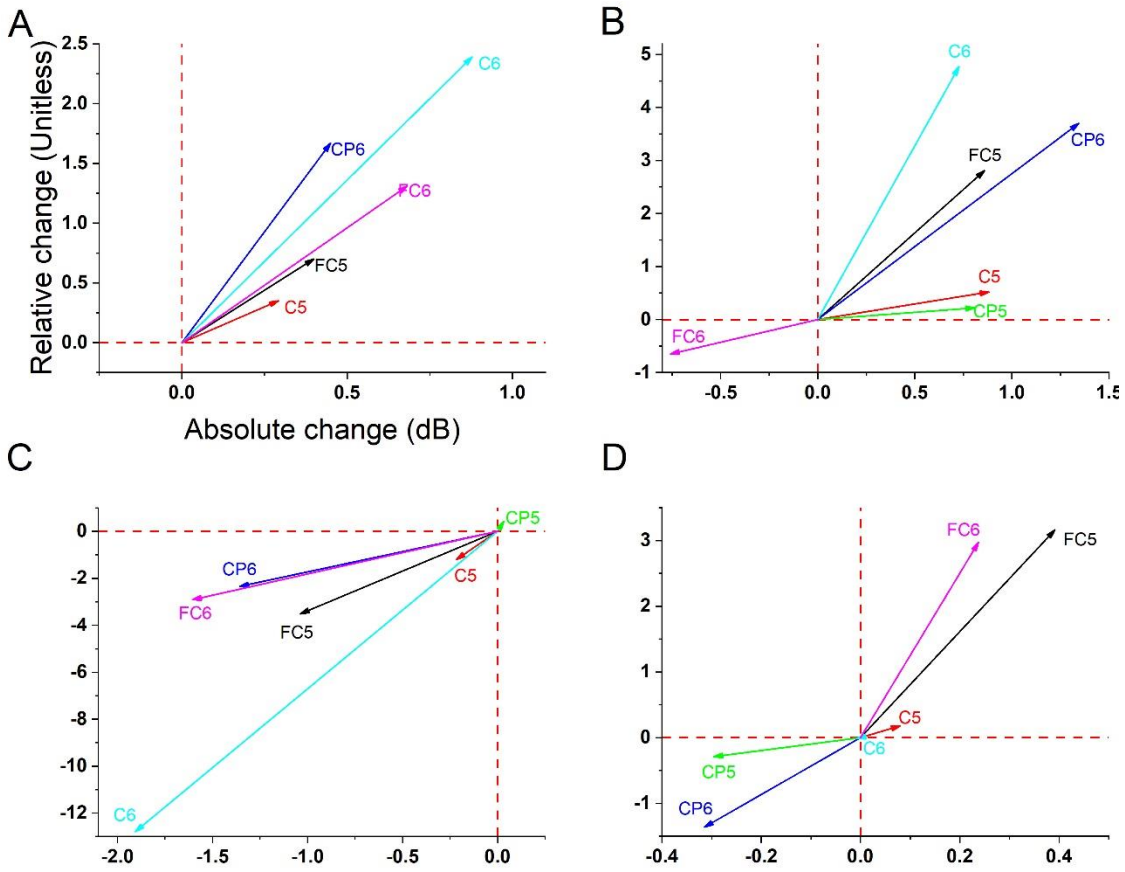

Figure 27. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for Alpha band (8 to 13 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 2*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 observed synchronization in all electrodes.* ***B)*** *ABSD2 experienced synchronization in all electrodes except FC6.* ***C)*** *ABSD3 experienced desynchronization in all electrodes except CP5.* ***D)*** *ABSD4 had desynchronization in CP5 and CP6. Unit for the absolute change is in dB.*

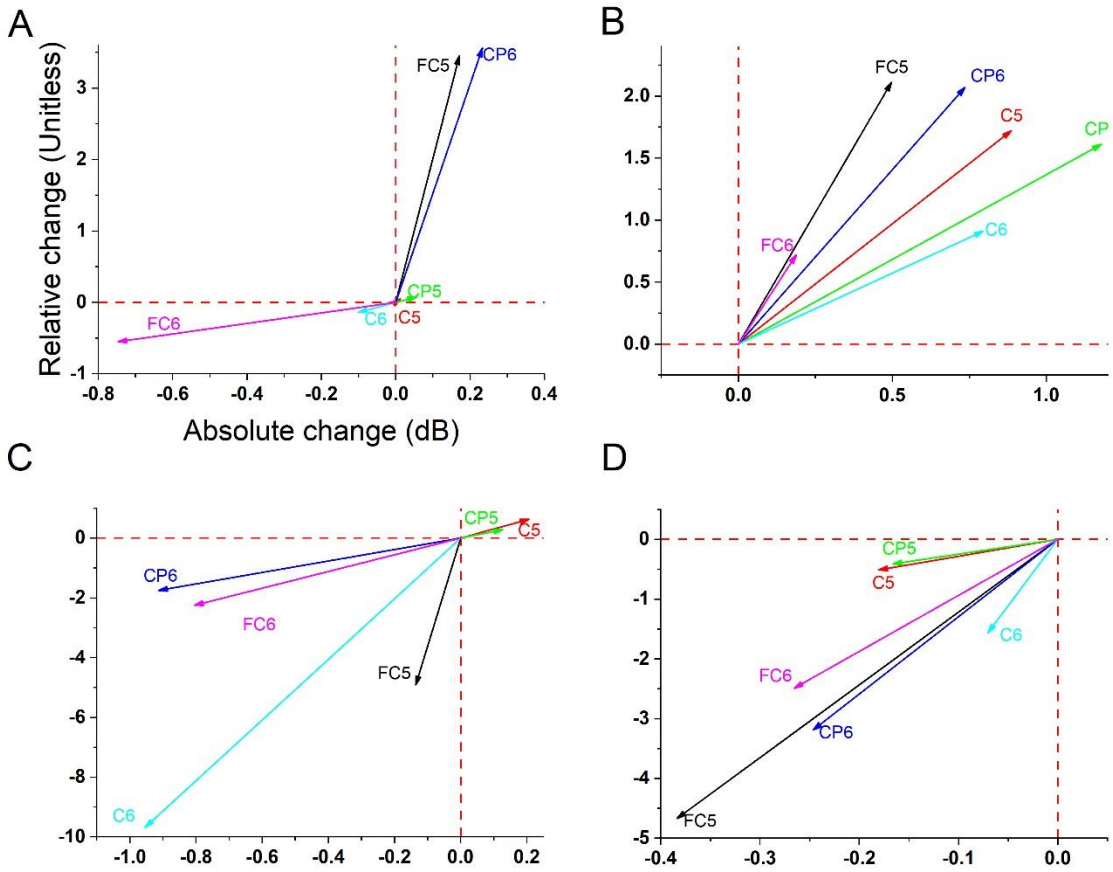

Figure 28. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for <u>Beta band</u> (13 to 30 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 2*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 observed desynchronization only in C6 and FC6.* ***B)*** *ABSD2 experienced synchronization in all the electrodes.* ***C)*** *ABSD3 experienced desynchronization in all the cortical electrodes except C5 and CP5.* ***D)*** *ABSD4 had desynchronization in all the electrodes. Unit for the absolute change is in dB.*

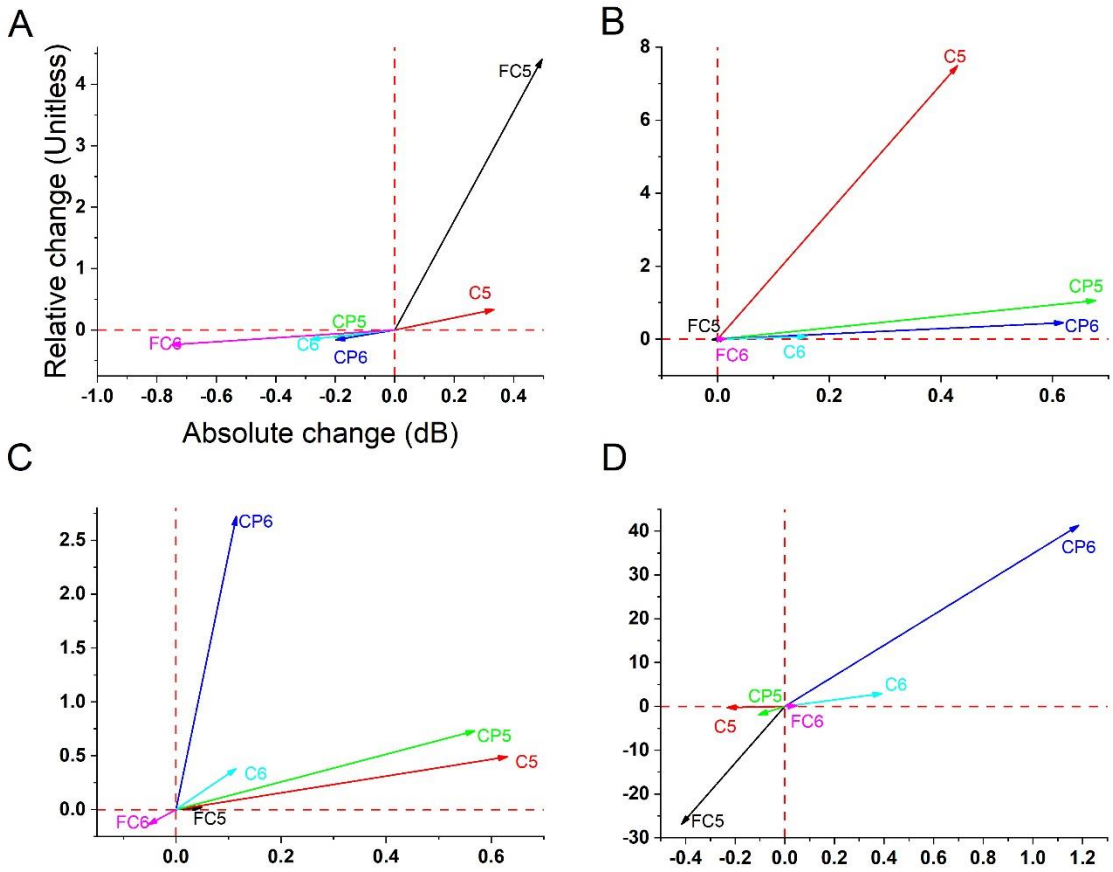

Figure 29. *Change in ERSP over the somatosensory, motor, and premotor cortical areas for lower gamma band (30 to 50 Hz) during Vocalization+VTS compared to Vocalization in* ***Set 2*** *(See* ***Figure 15****). Arrows reflect the data for all six electrodes (See* ***Figure 4****).* ***A)*** *ABSD1 observed synchronization only in C5 and FC5.* ***B)*** *ABSD2 experienced synchronization in all the electrodes.* ***C)*** *ABSD3 experienced synchronization in all the cortical electrodes except FC6.* ***D)*** *ABSD4 had synchronization in only FC6, C6, and CP6. Unit for the absolute change is in dB.*

Table 13. *ERSP values over the somatosensory, motor, and premotor cortical areas for theta band (4 to 8 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	2	-2.28	-0.17	-2.21	-0.41	-0.97	0.95	-1.11	-0.18	-1.04	0.31	-1.42	0.42
ABSD2	2	-0.64	-0.67	-1.66	-1.43	-3.56	-2.45	-1.46	-0.93	-0.51	0.08	0.07	0.89
ABSD3	2	1.31	0.55	0.58	0.39	0.07	0.53	0.85	-0.53	0.60	-1.37	0.64	-0.72
ABSD4	2	0.62	1.08	1.11	1.28	1.02	0.76	-0.13	-0.12	0.23	0.13	0.18	-0.13

Table 14. *ERSP values over the somatosensory, motor, and premotor cortical areas for alpha band (8 to 13 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	2	-0.57	-0.17	-0.84	-0.55	0.01	0.57	-0.52	0.16	-0.37	0.51	-0.27	0.18
ABSD2	2	-0.31	0.55	-1.69	-0.81	-3.69	-2.88	-1.17	-1.93	-0.15	0.58	0.36	1.71
ABSD3	2	0.30	-0.74	-0.18	-0.40	-0.08	-0.04	0.55	-1.05	0.15	-1.76	-0.58	-1.94
ABSD4	2	-0.12	0.27	0.45	0.53	1.04	0.74	0.08	0.32	0.90	0.90	0.23	-0.08

Table 15. *ERSP values over the somatosensory, motor, and premotor cortical areas for Beta band (13 to 30 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	2	0.05	0.22	0.27	0.28	0.79	0.85	1.35	0.60	0.72	0.62	0.07	0.30
ABSD2	2	-0.23	0.26	-0.52	0.37	-0.73	0.45	0.26	0.45	-0.87	-0.08	-0.36	0.38
ABSD3	2	-0.03	-0.16	-0.33	-0.12	-0.45	-0.32	0.36	-0.45	0.10	-0.86	-0.52	-1.44
ABSD4	2	-0.08	-0.47	0.35	0.17	0.40	0.24	-0.11	-0.37	-0.04	-0.12	0.08	-0.17

Table 16. *ERSP values over the somatosensory, motor, and premotor cortical areas for lower gamma band (30 to 50 Hz) for Vocalization and Vocalization+VTS tasks (See* ***Figure 15****) for all participants. Unit for ERSP is dB.*

Subject ID	Set	FC5		C5		CP5		FC6		C6		CP6	
		Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS	Voc	Voc+VTS
ABSD1	2	0.11	0.61	1.01	1.35	1.66	1.46	3.16	2.41	1.85	1.56	1.22	1.02
ABSD2	2	-1.19	-1.20	-0.06	0.37	0.64	1.31	-2.28	-2.27	-2.17	-2.01	-1.37	-0.75
ABSD3	2	-1.15	-1.95	-1.13	-1.17	0.07	-0.04	-0.15	-0.44	-0.99	-1.40	-0.98	-1.38
ABSD4	2	0.02	-0.40	0.84	0.61	0.06	-0.05	-0.30	-0.26	-0.13	0.26	-0.03	1.16