

## **Repetitive Transcranial Magnetic Stimulation in Spasmodic Dysphonia**

**Funding Sponsor:** Minnesota's Discovery, Research, and InnoVation Economy (MnDRIVE) and Department of Rehabilitation Medicine, Division of Physical Therapy, University of Minnesota

**Study Product:** Magstim 2002 and Magstim Rapid2 Magnetic Stimulators

**Protocol Identifiers:** CTSI ID 25008

**IDE Number: Trial** None, non-significant risk

**Registration: Version /** IRB# 1609M94001

**Date:** 8/2/2017

**CTgov Number:** NCT02957942

**Principal Investigator:** Mo Chen

### **CONFIDENTIAL**

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## Statement of Compliance

This document is a protocol for a human research study. This study will be conducted according to US and International standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting this research prior to the enrollment of any subjects.

As Principal Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the IRB and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and to maintain study documentation for the period of time required.

\_\_\_\_\_  
Mo Chen, PhD

\_\_\_\_\_  
Date

As a Sub-Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the IRB and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and to maintain study documentation for the period of time required.

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Teresa Jacobson Kimberley, PT, PhD

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Date

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Rebekah Summers, BS

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Date

## Version History

Version #	Approval Date	Significant Changes from Previous Version
Version 1	12/13/2016	Original Protocol Version
Version 2	2/13/2017	Change in subject compensation
Version 3	8/2/2017	Change in enrollment number and change PI

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## Study Summary

<b>Title</b>	Repetitive Transcranial Magnetic Stimulation in Spasmodic Dysphonia
<b>Short Title</b>	rTMS in Spasmodic Dysphonia
<b>Protocol Numbers</b>	CTSI 25008
<b>Study Sponsor</b>	Minnesota's Discovery, Research and InnoVation Economy, Dept. Rehabilitation Medicine, Division of Physical Therapy
<b>Principal Investigator</b>	Mo Chen, PhD
<b>Study Design</b>	Pilot study: 2 groups, pre/post test design
<b>Study Duration</b>	24 months
<b>Study Center(s)</b>	CTSI
<b>Objectives</b>	The overall purpose of this study is to test whether brain excitability can be modulated in people with spasmodic dysphonia (a neurological disorder affecting the vocal folds) using repetitive transcranial magnetic stimulation (rTMS). More specifically, the study objectives include: (1) Determine safety and feasibility of the proposed protocol; (2): Determine amount of intracortical inhibition in the laryngeal motor cortex as measured in the thyroarytenoid muscle both within and between groups, before and after rTMS; (3) Explore changes in voice quality following rTMS.
<b>Number of Subjects</b>	Fifty participants will be enrolled.
<b>Main Inclusion / Exclusion Criteria</b>	<p><i>Primary inclusion for spasmodic dysphonia:</i></p> <ul style="list-style-type: none"> <li>(1) 21-75 years of age</li> <li>(2) Diagnosis of adductor spasmodic dysphonia</li> <li>(3) Symptoms at worst severity if receiving regular botulinum injections</li> </ul> <p><i>Primary exclusion for participants with spasmodic dysphonia:</i></p> <ul style="list-style-type: none"> <li>(1) Other forms of dystonia</li> <li>(2) Vocal fold pathology or paralysis</li> <li>(3) Diagnosis of voice tremor</li> <li>(4) Laryngeal surgery</li> <li>(5) Laryngeal cancer or neurological condition other than dystonia</li> <li>(6) Contraindication to TMS</li> <li>(7) Medications with effect on CNS</li> <li>(8) Inability to complete tasks associated with study</li> <li>(9) Adult lacking ability to consent</li> </ul> <p><i>Primary inclusion for healthy participants (controls):</i></p> <ul style="list-style-type: none"> <li>(1) 21-75 years of age</li> <li>(2) Absence of vocal fold pathology</li> </ul> <p><i>Primary exclusion for healthy participants (controls):</i></p> <ul style="list-style-type: none"> <li>(1) Any health condition or disability that would interfere with participation</li> </ul>

	(2) Contraindications to TMS (3) Medications with effect on CNS (4) Adult lacking ability to consent
<b>Study Device</b>	Device: Magstim 200 <sup>2</sup> and Rapid <sup>2</sup> Magnetic Stimulators and Magstim BiStim Module Manufacturer: Magstim Company LTD, Spring Gardens Carmarthenshire, Wales, UK SA34OHR  US Distributor: Jali Medical, Inc. 500 West Cummings Park, Suite 4950 Woburn, MA 01801
<b>Duration of Device Exposure</b>	Each subject will receive a 20 minute session of low-frequency rTMS (1Hz, 1200 pulses). Single pulse TMS testing also will be applied for approximately 30 min before and after rTMS.
<b>Reference Therapy</b>	None
<b>Endpoints</b>	Corticospinal excitability and voice quality will be measured before and after rTMS application. Self-reported voice disability also will be assessed.
<b>Statistical Methods</b>	Corticospinal excitability and voice quality will be examined for effects of rTMS and group.

## **List of Abbreviations**

AdSD	Adductor spasmodic dysphonia
AE	Adverse Event
BTX	Botulinum Toxin
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
EMG	Electromyography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
IRB	Institutional Review Board
PHI	Protected Health Information
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
TMS	Transcranial Magnetic Stimulation
UADE	Unanticipated Adverse Device Effect
UPIRTSO	Unanticipated Problems Involving Risk To Subjects or Others



## **1.0 Study Contact Information**

### **1.1 Principal Investigator Contact Information**

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### **1.3 Key Study Personnel**

NA

## 2.0 Introduction

### 2.1 Background and Rationale

Focal dystonia is a neurological movement disorder characterized by excessive involuntary muscle contractions of any body part, severely impairing a person's ability to function in their daily life. Often patients are misdiagnosed and receive years of unnecessary treatment. Adductor spasmodic dysphonia (AdSD) is the primary form of laryngeal dystonia and is characterized by excessive contraction of intrinsic muscles in the larynx, leading to intermittent hyper-adduction of the true vocal folds ('vocal cords') during speech (Aminoff *et al.*, 1978). This results in severe difficulty in speaking, hindering effective communication and severely reducing quality of life.

The cause of AdSD is unknown and there are no treatments that produce long-term benefits. Neuroimaging and neurophysiology studies have suggested that AdSD and other focal dystonias are associated with decreased inhibition and excessive plasticity in sensorimotor areas in the brain (Kimberley *et al.*, 2009; Kimberley and Pickett, 2012; Kimberley *et al.*, 2013; Kimberley *et al.*, 2015a; Samargia *et al.*, 2016). However, to our knowledge, no studies have investigated the effects of modulating excitability of the laryngeal motor cortex in healthy individuals or AdSD. This gap in the field is likely due to challenges in recording corticospinal excitability of intrinsic laryngeal muscles.

Dr. Kimberley's team has developed a transcranial magnetic stimulation (TMS) method to assess the cortical representation and excitability of the thyroarytenoid, a muscle affected in AdSD. Using this method, TMS data indicate differences in inhibition in people with AdSD vs. healthy controls. For this pilot project, we propose to further explore this excitability difference by investigating the effects of low-frequency inhibitory repetitive TMS (rTMS) applied to the laryngeal motor cortex of individuals with AdSD and healthy controls. Considering that rTMS at low frequencies ( $\leq 1$  Hz) produces lasting inhibition in a process analogous to long-term depression, and that AdSD is associated with decreased cortical inhibition, the purpose of this pilot study is to determine safety, feasibility and response to 1Hz rTMS to the laryngeal motor cortex in individuals with AdSD and healthy people.

### 2.2 Device Description

We will utilize two Magstim 2002 devices (US FDA #K060847) with a Bistim 70-mm figure-eight coil. rTMS will be delivered with air-film coils (real) and a Magstim Rapid2 device (US FDA #K051864). For data acquisition, the electrode wires will be connected to a bipolar electromyography (EMG) pre-amplifier (Y03, Motion Lab Systems, Inc., LA, USA) with the gain of x300. The EMG signal will be passed through a band-pass filter with the cutoff frequencies of 15Hz and 2000Hz and then digitized by an analog-to-digital convertor (NI 9234, National Instruments Corporation, Austin, TX, USA) with a resolution of 24-bits at a sampling rate of 6400Hz.

Both TMS devices are used for investigational purposes and labeled with the following statement: **CAUTION – Investigational Device. Limited by Federal law to investigational use.**

### **2.3 Device Accountability**

The device is not supplied to the subject, and will not be in the subject's possession at any time.

## **3.0 Study Objectives**

### **3.1 Primary Objective**

The purpose of this project is to determine safety, feasibility and response to 1Hz rTMS to the laryngeal motor cortex in individuals with AdSD and healthy people. The following Aims will be tested:

Aim 1: Determine safety and feasibility for the application of 1 Hz rTMS to the laryngeal motor cortex.

Hypothesis: rTMS to laryngeal motor cortex will be safe and feasible as measured by no serious adverse events and 100% study completion by participants.

Aim 2: Determine amount of intracortical inhibition in the laryngeal motor cortex as measured in the thyroarytenoid both within and between groups before and after rTMS.

Hypotheses:

- The AdSD group will demonstrate less inhibition in the laryngeal motor cortex at baseline.
- rTMS will increase intracortical inhibition for the laryngeal motor cortex in both groups, but AdSD individuals will show greater changes.
- There will be no difference between groups at posttest suggesting a normalizing of intracortical inhibition.

Aim 3: Explore changes in voice quality following rTMS with a blinded assessment by a voice expert.

Hypothesis: Clinical scores will show a trend toward improved voice quality in people with AdSD.

## **4.0 Study Design**

### **4.1 Overview of Study Design**

This experiment is a pilot study involving within and between group comparisons: AdSD compared to healthy controls, before and after rTMS delivery. Participants will be asked to come to the University of Minnesota for 1 session.

### **4.2 Anticipated Duration of the Clinical Investigation**

The study's duration is anticipated to require 24 months from enrollment to the final report to the IRB.

If for any reason the study is terminated prior to the completion of subject participation, subjects would be withdrawn in accordance with Section 5.10.

## **4.3 Evaluation Criteria/Effectiveness**

### **4.3.1 Primary Endpoint**

The primary clinical endpoint will be corticospinal excitability measured with TMS testing before and after application of low-frequency rTMS.

### **4.3.2 Secondary Endpoints**

Secondary endpoints will include clinical voice measures collected before and after rTMS procedures with a blinded assessment by a voice expert (Cara Donohue, SLP, and Sharyl Samargia, CCC-SLP, PhD) (Zraick *et al.*, 2011; Samargia *et al.*, 2016). In addition, self-reported voice disability will be assessed prior to rTMS delivery.

## **4.4 Study Population**

### **4.4.1 Sample Size**

This is the first pilot study of this kind and, therefore, no data are available for sample size calculation. Data from this pilot study will be used for effect size calculations for future investigations.

We plan to enroll 40 subjects (20 people with AdSD and 20 healthy controls). Due to the voluntary nature of our recruitment efforts, we expect a small number to dropout or fail screening qualifications. To ensure the needed number of enrollees, 50 subjects have been requested to be recruited in our IRB application.

Due to no direct benefit from participation, children will be excluded from this study.

### **4.4.2 Subject Recruitment**

Healthy participants: Subjects will be recruited from the general public. University and local community advertisement will be made. Subjects will then self-identify if interested to learn more about the study.

Spasmodic dysphonia participants: Subjects will be recruited from several sources:

1. People with AdSD who have directly contacted Dr. Teresa Kimberley about research opportunities and patients that have participated in other studies from our team will be inquired if they are interested in this new pilot project. Study staff will contact only those who have given permission to be contacted about future studies.
2. Dr. George Goding will ask his patient's that have AdSD if they are interested in hearing more about a study they may qualify for and if so will give him/her a flyer or direct him/her to talk to other study staff to learn more.
3. University and local community advertisement will be made. Postings also will be made on support group websites and organizations for dystonia. Subjects will then self-identify if interested to learn more about the study.

#### **4.4.3 Subject Screening**

Subjects will be screened by co-investigators using a list of exclusion criteria in person, by email or by phone. Screening questions include all inclusion and exclusion criteria. The maximum allowable time between screening and participation will be limited to the duration of the study. Prior to the start of the session, an on-site screening form will also be completed to ensure appropriate qualification. Females who could potentially be pregnant will be offered a pregnancy test at the CTSI and, if positive, they will not be allowed to participate. If they refuse testing as they are certain there is no risk they are pregnant, they will sign a waiver to clarify and be allowed to participate.

#### **4.4.4 Prior and Concomitant Therapy**

The risk of seizures is acknowledged but we emphasize that because of standards set for rTMS (Rossi *et al.*, 2009; Rossini *et al.*, 2015) this risk has been very well contained. Particularly due to our low rate stimulation and exclusion criteria we have minimized risk to participants. Our rTMS parameters are well within these safety guidelines (Rossi *et al.*, 2009; Rossini *et al.*, 2015). However, we still recognize that this remote risk requires a rigorous safety plan. We will ask subjects if they have any other medical conditions and if they are taking any medications. Important medication information such as any pro-epileptic medications and any history of seizure will be collected to screen those at risk for a TMS-induced seizure. Subjects will also be screened for previous surgeries that might include metal, indwelling medical devices, etc. In the event of a seizure during rTMS, subjects may be given oxygen by nasal cannula and, if the seizure does not abate in the expected time frame, the on-call physician may administer lorazepam or a related medication to interrupt the seizure. In the event of a headache from rTMS treatment, subjects may be given acetaminophen. See Brain Plasticity Lab white paper on TMS safety (attached).

Patients with AdSD who are currently receiving botulinum toxin injections will be asked about the duration between shots and scheduled to participate when their symptoms are reported to be the worst. This will typically be within 1 week of their regularly scheduled injections.

#### **4.4.5 Inclusion Criteria**

Subjects will be eligible to participate in the study if all of the following conditions exist:

*Primary inclusion for spasmodic dysphonia:*

- (1) 21-75 years of age
- (2) Diagnosis of adductor spasmodic dysphonia (AdSD)
- (3) Symptoms at worst severity if receiving regular botulinum injections

*Primary inclusion for healthy participants (controls):*

- (1) 21-75 years of age
- (2) Absence of vocal fold pathology

#### 4.4.6 Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

*Primary exclusion for participants with spasmodic dysphonia:*

- (1) Other forms of dystonia
- (2) Vocal fold pathology or paralysis
- (3) Diagnosis of voice tremor
- (4) Laryngeal surgery
- (5) Laryngeal cancer or neurological condition other than dystonia
- (6) Contraindication to TMS\*
- (7) Medications with effect on CNS
- (8) Inability to complete tasks associated with study
- (9) Adult lacking ability to consent

*Primary exclusion for healthy participants (controls):*

- (1) Any health condition or disability that would interfere with participation
- (2) Contraindications to TMS\*
- (3) Medications with effect on CNS
- (4) Adult lacking ability to consent

*\*TMS contraindications:*

- (1) The only absolute contraindication to TMS/rTMS is the presence of metallic hardware in close contact to the discharging coil (such as cochlear implants, deep brain stimulator, or medication pumps). In such instances there is a risk of inducing malfunctioning of the implanted devices.
- (2) Conditions classified as of increased or uncertain risk are listed below (Rossi et al., 2009; Rossini et al., 2015). Persons under those circumstances will be excluded from the study.
  - a. Pregnancy
  - b. Bipolar disorder
  - c. Epilepsy or history of seizure episodes in the past two years
  - d. Vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain, even without history of seizure, and without anticonvulsant medication
  - e. Use of medications that potentially lower seizure threshold
  - f. Severe or recent heart disease
- (3) There is a small risk of fainting and hearing impairment with TMS/rTMS. For these reasons, the following precautions will be taken:
  - a. Fainting: To avoid fainting, we will ask subjects to eat a full meal and drink extra decaffeinated fluids before study visits. We will also apply TMS and rTMS in a reclining chair.
  - b. Hearing impairment: Participants will wear earplugs during the experiment to avoid hearing damage.

Additional information about risks and precautions for TMS/rTMS are included in the IRB protocol (Section 3).

#### **4.4.7 Exit/Discontinuation Criteria**

Subjects will exit the study if any of the following conditions exist:

1. Subject voluntarily withdraws from the study.
2. Subject death.
3. Subject acquires any of the listed exclusion criteria.
4. Subject completes the protocol.
5. Subject's wellbeing, in the opinion of the Investigator would be compromised by study continuation.
6. Subject experiences an adverse event such as seizure.
7. DSMB and/or IRB recommendation

## **5.0 Study Procedures**

### **5.1 Informed Consent**

#### **5.1.1 Informed Consent**

All potential participants will receive a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in the study. Please see consent form for specific wording that is tailored for each participant category: spasmodic dysphonia or healthy participant.

The consent form will be submitted with the protocol for review and will only be used once approval by the IRB for the study is given. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form will be signed by the subject and the investigator-designated research professional obtaining the consent. A copy of the IRB-approved consent form will be kept on-site and by the sponsor-investigator.

#### **5.1.2 Vulnerable Populations**

No vulnerable populations are included.

### **5.2 Allocation Scheme**

Individuals will be assigned to each group based on their diagnosis and symptoms. All subjects will be assigned to the same procedures.

### **5.3 Clinical Procedures**

Clinical assessment: Voice measures consisting of standard and published clinical scales will be collected for all participants to explore changes in voice quality (Zraick *et al.*, 2011; Samargia *et al.*, 2016). Voice quality will be measured by asking subjects to repeat 10 sentences with a high number of initial adductor phonemes, which often elicit symptoms in those with AdSD. These voice samples will be acquired digitally using a microphone. The frequency of voice breaks in the

recorded 10 sentences will be counted. These voice breaks will be the measure of disease severity. Other voice characteristics will be assessed using the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) and the Voice Handicap Index (VHI). The CAPE-V is a reliable, valid clinical measure used by voice experts to assess voice quality. During a video recording, participants will be asked to repeat 6 sentences and then describe their voice problems. Voice experts will use the recording to rate voice quality based on several criteria (loudness, pitch, strain, breathiness, roughness, overall severity and others). In the current study, the total score in this scale will be used to rate the voice quality of participants before and after rTMS. The VHI is a self-administered questionnaire with questions about how often a given voice-related problem affects the life of participants. It reliably measures the influence of the subjects' voice disorder on their quality of life across three dimensions including: physical, functional and social. The total score for each participant will be measured before rTMS to assess how the voice disorder affects quality of life.

TMS testing: TMS testing will be performed to measure the corticospinal excitability before and after rTMS. TMS testing will be completed according to established methods (Kimberley and Di Fabio, 2010; Samargia *et al.*, 2014; Kimberley *et al.*, 2015a; Kimberley *et al.*, 2015b). Single and paired-pulse TMS testing will be delivered with a 70-mm figure-of-eight coil connected to a Magstim 200 stimulator (Magstim Company, Dyfed, UK), positioned on the scalp area over the left primary motor cortex. The laryngeal motor cortex will be identified by measuring the motor evoked potentials (MEP) of the thyroarytenoid muscle. Cortical stimulation will be spatially tracked with a neuronavigation system (BrainSight, Rogue Research Inc. Quebec, Canada) to decrease variability of stimulus delivery.

The TMS variables that will be measured in the study include single pulses that evoke a response in the muscle. The variable of interest is the amplitude of motor evoked potential (MEP) in response to different stimulation intensities and duration of silent period after the evoked response. Testing will include no more than 200 pulses (rTMS delivery will involve 1200 pulses — see below). Overall, the testing procedures will take approximately 60 minutes (30 minutes before and 30 after rTMS).

Fine-wire electrodes: All participants will undergo vocal muscle testing using fine-wire EMG. With the subject seated in a supportive chair, fine-wire EMG electrodes will be inserted in the thyroarytenoid muscles (the “vocal cords”) by a trained physician, Dr. Goding. The skin on the throat will be numbed using a lidocaine cream and also an injection of a lidocaine (numbing) agent. Once the skin has been numbed, the electrode will be placed into the muscle. To place the electrode, two fine wires will be inserted using a small gauge needle (30MM, 27 guage) with the edges of the wire electrode hooked around the tip of the needle and connected to an EMG machine. The needle will be passed through the skin and into the larynx. When the vocal cord is entered, an increased EMG signal associated with speech is detected. The needle will then be removed, leaving only the flexible wires in place.



Once the needle is removed, participants will not feel the presence of the electrode. Participants will be able to breath, talk and move their head with the electrode in place. At the end of the testing for vocal muscles, the electrodes will be gently pulled out. This process is nearly unnoticeable due to the very small diameter of the wires. Procedures will be the same as previous study (IRB # 0608M91226. Study Title “Pathophysiology of Spasmodic dysphonia: a TMS study”).

rTMS application: rTMS will be delivered to the left laryngeal motor cortex with a hand-held figure-of-eight coil positioned over the scalp and connected to a Rapid<sup>2</sup> magnetic stimulator (Magstim Company, Dyfed, UK). The protocol described below is FDA approved and has been used extensively by our lab without incident. The risk of seizure is minimized by using a low rate of stimulation and a sub-threshold level of intensity.

All participants will receive low-frequency rTMS pulses. rTMS at a low frequency is known to be inhibitory to the neurons receiving the stimulation. rTMS will be delivered at 90% of the threshold which elicits MEPs in the thyroarytenoid muscle, as determined during TMS testing. Pulses will be delivered at a frequency of 1 Hz without interruption (total = 1200 pulses) which has been shown to alter cortical excitability and behavior (Gerschlagler *et al.*, 2001). rTMS delivery will take 20-30 minutes. During the stimulation, the subject will only feel a slight tapping sensation on the head due to the repetitive discharging of the cutaneous nerves in the scalp. After stimulation, corticospinal excitability and voice quality will be measured.

Because the purpose of this study is to collect preliminary data for feasibility and safety, sham rTMS will not be tested.

#### **5.4 Follow-Up Procedures and Therapy Transitions**

There are no follow-up procedures or therapy transitions. Subjects receiving botulinum toxin will be allowed to continue with injections as they desire.

#### **5.5 Study Timetable / Schedule of Events**

Pre-screening of all participants will be completed by phone, email or in person. Onsite testing will include answering to study questionnaires, voice quality assessments, completing TMS tests, and the rTMS protocol. Testing will occur prior to botulinum toxin injection for those patients with AdSD currently being treated with the toxin. Data will be collect when symptoms are at their worst according to the patient’s self-report. However, due to the demanding time commitment placed on participants, flexibility will be allowed to modify the schedule if needed. Botulinum toxin injections will be administered by each participant’s physician and the costs associated with injection will not be covered by the study.

<i><b>Experiment schedule</b></i>	
<i>Pre-screening</i>	<i>Study visit</i>
Review consent form Medical history Eligibility	Consent and HIPAA On-site screening Report of symptoms Clinical assessment, voice quality and disability Corticospinal excitability (TMS pre-tests) 20 min of rTMS Voice quality assessment Corticospinal excitability (TMS post-tests) Report of symptoms

## **5.6 Study Protocol Compliance / Treatment Adherence**

Subjects will be notified of the voluntary nature of participation. In the consent forms, subjects are made aware of the resources for those who wish to withdraw from the study. Criteria and procedures for withdrawing subjects are noncompliance and disqualification by previously outlined criteria, such as a developed neurological disease, implanted device, or pregnancy. See section 5.8 for more detail. Refer to section 5.8 for subject withdrawal and replacement.

## **5.7 Deviations from the Clinical Protocol**

When a deviation from the protocol is necessary for an individual subject, the investigator will complete a description of the deviation from the protocol and justification on the Protocol Deviation Form.

## **5.8 Subject Withdrawal**

### **5.8.1 How to Withdraw Subjects**

Subjects may be withdrawn from the study for the following reasons:

- occurrence of intolerable pain or discomfort during testing
- failure to attend scheduled testing or treatment sessions
- subject consent withdrawal

In the event of subject withdrawal, all collected data and personal information will be documented and kept private. If a subject is withdrawn from the study, they will keep their identifier code and an additional subject will be recruited to account for the needed subject sample. Withdrawn subjects will be documented and future participants will start at the beginning of the study. Additional subjects will be drawn from the same pool of candidates who expressed interest in the study. The same recruitment procedures and experimental procedures will be followed for all subjects.

### **5.8.2 Data Collection and Follow Up for Withdrawn Subjects**

For withdrawn subjects, documentation will be made. If a subject withdraws before consenting to the study, screening information will be documented and reported.

Withdrawal will be determined from a volunteer's personal decline on-site in which case no calls or letters will need to be used.

## **5.9 Subject Compensation**

Subjects will receive a \$100 gift card to compensate for their participation in the study.

## **6.0 Data Collection and Analysis**

### **6.1 Subject Population(s) for Analysis**

All subjects will have corticospinal excitability and voice quality measurements taken before and after rTMS. All subject data will be processed and analyzed to explore for the effects of rTMS. Self-reported voice disability will be measured before TMS testing in participants with AdSD.

### **6.2 Statistical Methods**

For both groups, changes from baseline will be explored for effects of rTMS in corticospinal excitability and voice quality. Since this is a pilot study and the sample size will likely not be adequate for differential statistics, data will be analyzed with descriptive statistics (measures of central tendency and variability) to look for trends related to rTMS effects and group.

## **7.0 Safety and Adverse Events**

### **7.1 Definitions**

#### *Adverse Event (AE)*

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of laboratory or diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal
- Is associated with a serious adverse event
- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the Investigator to be of clinical significance.

#### *Serious Adverse Event (SAE)*

A serious adverse event (SAE) is any adverse event that is:

- Fatal
- Life-threatening
- Requires or prolongs a hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect

Important medical events are events that may not be immediately life-threatening, but are clearly of major clinical significance and may be SAEs.

They may jeopardize the subject, and may require intervention to prevent one or the other serious outcomes noted above.

#### *Hospitalization*

Hospitalization shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

#### *Unanticipated Adverse Device Effect (UADE)*

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

#### *Unanticipated Problems Involving Risk To Subjects or Others (UPIRTSO)*

An adverse event that in the opinion of the Principal Investigator is unexpected, related to the device, and serious.

## **7.2 Safety Monitoring Plan**

Plans to minimize risks to study participants:

- All investigators and study staff have completed required training re: human subject protections. Study staff will comply with all related regulations and laws, included, but not limited to 45CFR parts 60 and 64, and HIPAA Privacy Regulations.
- Subjects will be rigorously screened against inclusion/exclusion criteria to ensure that their participation is safe.
- Research staff conducting clinical research procedures will be appropriately trained, licensed, credentialed and supervised
- PI and study staff will monitor incidence of adverse events, feedback from subjects, observations from nurses, study staff, investigators and other safety indicators on a continuous basis.
- To monitor symptoms or changes in health status due to TMS testing and rTMS delivery, participants will be asked to complete the form “Subject Report of Symptoms” before TMS testing, right after rTMS application, and at the end of the experiment so that the required actions are taken.
- Study visits will be conducted at the CTSI Masonic Clinical Research Unit (MCRU) or Delaware Clinical Research Unit (DCRU) which are staffed with back-up personnel and have immediate access to Fairview’s emergency response personnel if needed.

- PI will ensure accuracy, completeness, clarity and timeliness of all study records.
- Study data & information will be kept confidential and managed in accordance with requirements of HIPAA. All data will be stored in locked offices and not released without subject permission.
- Subjects may discontinue participation at any time, for any reason. Any subject observed to have unacceptable responses to research procedures, or to be unable to safely tolerate participation in the study will be withdrawn.

### **7.2.1 Anticipated Risks / Risk Mitigation**

1. Personal information: There is a small risk of loss of confidentiality. Subjects will be asked if they have any medical conditions and if they are taking any medications. This is important to know so that only those subjects who meet the inclusion and exclusion criteria are accepted into the study. A number of procedures are in place to protect participant confidentiality. Every participant enrolled in the study will receive a unique code number. All records and results will be labeled with this code number and the code will be shared only with the study investigators. Any information that is included in published manuscripts (e.g. demographic information) will not be linked to any other information that would identify who the subject was.

2. TMS: Risks associated with TMS are rare but should be recognized and prevented with appropriate precautions. Serious adverse risks include the induction of a seizure. There have been reports of a seizure and induced mania from rTMS but none of these side effects have been reported with the type of rTMS that we are doing in this study. Mild adverse effects include fainting, headache, dental pain, and other changes in memory, mood, and hearing. The overall occurrence of a mild adverse event is 5% in sham and real TMS sessions combined (Maizey *et al.*, 2013). Participants will be asked to complete the form “Subject Report of Symptoms” before TMS testing and at the end of the experiment so that the required actions are taken in case there are any changes to their health status. Participants will be instructed to contact study staff if they noticed any of the symptoms listed above after participation in the study. In addition, study staff may contact participants (via email or phone call) to follow-up on any issues or symptoms that occur during the experiment. People with a history of seizure within the last two years or a history of bipolar disorder will not be allowed to participate in this study. The tests may be discontinued without the participant’s consent if the study team observes any abnormal responses. TMS delivery may also interfere with implanted devices and, thus, TMS is not appropriate for persons with medical devices such as deep brain stimulators, pace makers and medication pumps. Currently, the effects of TMS on hormonal cycles and the unborn fetus are unknown.

3. Needle (fine-wire) electrodes: Risks associated with the electrode placement are very rare and include vocal cord hemorrhage, hoarseness of voice, infection, or dysphagia (difficulty swallowing). Participants should not be on any blood thinner medication to avoid vocal cord hemorrhage. We will clean and prepare the skin

appropriately prior to using needle EMG to avoid infections. Subjects may experience localized minor discomfort in the area during the procedure and for 1-2 days afterwards.

### **7.2.2 Medical Monitoring for Participant Safety**

The Principal Investigator will oversee the safety of the study, including careful assessment and appropriate reporting of adverse events as outlined in Section 7.4. Dr. Goding, a University of Minnesota physician and ear nose and throat specialist, will be on-site during needle electrode placement and present for any necessary medical assistance. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

### **7.2.3 Study Stopping Rules**

If during a session, the subject should show any signs of disorientation or the presence of EMG activity that cannot be stopped by the subject, the session will be stopped for that subject.

## **7.3 Anticipated Adverse Events**

Risks associated with TMS are rare but should be recognized and prevented with appropriate precautions. Serious adverse risks include the induction of a seizure. Mild adverse effects include fainting, headache, dental pain, and other changes in memory, mood, and hearing. TMS delivery may also interfere with implanted devices.

## **7.4 Adverse Event Reporting**

All Adverse Events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that study treatment or participation is not the cause.

We will promptly review documented adverse effects and abnormal test findings to determine

- 1) if the abnormal test finding should be classified as an adverse effect;
- 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and
- 3) if the adverse effect meets the criteria for a serious adverse effect.

If our final determination of causality is “unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)”, the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If our final determination of causality is “unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)”, this determination and the rationale for the determination will be documented in the respective subject’s case history.

#### **7.4.1 Adverse Events:**

All observed or volunteered adverse effects and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit:

- 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and;
- 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

Adverse Events that do not qualify as Serious Adverse Events, or as Unanticipated Adverse Device Effects will be reported the IRB with the continuing review progress report. These events will be reported to FDA with the IDE Annual Report.

#### **7.4.2 Serious Adverse Events**

Principal investigation contact information for Serious Adverse Event Notification:

Mo Chen, PhD  
612/624-5220 (Telephone)

At the time of the initial report, the following information will be provided:

- |                    |   |
|--------------------|---|
| - Study Identifier | - Whether study treatment was discontinued  |
| - Study Center     | - Reason the event is classified as serious |
| - Subject Number   | - Event Description                         |
| - Date of Onset    | - Investigator assessment of association    |
| - Current Status   | between event and study device              |

Serious Adverse Events that are at least possibly related must be reported to the IRB within 10 working days, and to FDA within 15 calendar days.

#### **7.4.3 Unanticipated Adverse Device Effects**

We will submit a completed Form FDA 3500 A to the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed Form FDA 3500 A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of our follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; we will submit a completed Form FDA 3500 A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted Form FDA 3500 A, we will identify all previously submitted reports that that addressed a similar adverse effect experience and we will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

We will report to the IRB any observed or volunteered adverse effect that is determined to meet all of the following criteria:

- 1) associated with the investigational device or, if applicable, other study treatment or diagnostic product(s);
- 2) a serious adverse effect; and
- 3) an unexpected adverse effect.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the Sponsor-Investigator's receipt of the respective information.

Adverse effects which are

- 1) associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s);
- 2) fatal or life-threatening; and
- 3) unexpected

will be reported to the IRB within 24 hours of receipt of the respective information.

If the Adverse Event is Serious, Unanticipated, Device Related, and determined by the Sponsor to present an unreasonable risk to subjects, the Sponsor must terminate the study within 5 working days of that determination.

#### **7.4.4 UPIRTSO Events**

We will submit a report of UPIRTSO events to the IRB within 10 working days of first learning of the event.

### **7.5 Data Safety Monitoring Board**

The study involves no greater than minimal risk which does not require a safety monitoring board. The CTSI will monitor data integrity.

## **8.0 Data Handling and Record Keeping**

### **8.1 Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). This study does not include the collection of PHI and hence will not



require subjects to sign any release of PHI. Subjects will be asked to give demographic information, the medications they are taking, and any other health related problems.

## **8.2 Source Documents**

*Source Data* are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

## **8.3 Case Report Forms**

A Case Report Form will be completed for each subject enrolled into the clinical study. The investigator will review and approve each completed CRF; the investigator's signature serving as attestation of the investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Subjects will be asked to give demographic information, the medications they are taking, and any other health related problems. This information will be protected by limiting the number of persons involved in data collection and analysis as well as maintaining identifiers within a locked cabinet in a secure lab. No information from this study will be documented in the subject's medical record.

## **8.4 Clinical Reports**

An annual progress report will be submitted to the IRB. The PI will submit a final report of the clinical study to the sponsor and reviewing IRB within 3 months of termination or completion of the clinical study or the Investigator's part of the clinical study. This study does not involve other funding sources.

## **8.5 Records Retention**

We will retain the specified records and reports for 6 years.

## **9.0 Study Monitoring, Auditing, and Inspecting**

This study will be monitored according to FDA/GCP guidelines. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

### **9.1 Study Monitoring Plan**

Independent monitoring of the clinical study for clinical protocol will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the University of

Minnesota's Clinical and Translational Science Institute (CTSI). CTSI staff will monitor the data integrity of this study.

## **9.2 Auditing and Inspection**

We will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

We will accept inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

## **10.0 Ethical Considerations**

This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

## **11.0 Study Finances**

### **11.1 Funding Source**

This study is funded by departmental funds: Minnesota's Discovery, Research and InnoVation Economy (MnDRIVE) and Department of Rehabilitation Medicine, Division of Physical Therapy, at University of Minnesota.

Participant payment will be provided by the National Spasmodic Dysphonia Association (NSDA).

### **11.2 Conflicts of Interest**

The PI and study staff do not have any conflicts of interest. Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols

to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

## 12.0 Publications Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

## 13.0 References

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#### **14.0 Appendices and Attachments**

- Consent Form
  - Healthy: ConsentForm\_Healthy
  - Spasmodic dysphonia: ConsentForm\_SD
- HIPAA form
  - HIPAA\_0409\_rTMS in SD
- Recruitment and screening materials
  - Healthy: Recruitment flyer\_Healthy; Phone Script\_Healthy; Email Script\_Healthy
  - Spasmodic dysphonia: Recruitment flyer\_SD; Phone Script\_SD; Email Script\_SD
  - All: Initial Screening.doc, On site TMS screening, CAPE\_V, VHI
- Experiment procedures:
  - Experiment checklist
- Symptoms report
  - Subject Report of Symptoms
- TMS guidelines
  - UMN Brain Plasticity Laboratory NIBS\_White Paper
  - FDA guidelines\_rTMS