

Non-Invasive Mechanosensory Perturbation to Test Voice-Related Motor and Somatosensory Cortical Responses in Spasmodic Dysphonia

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Director, Center for Clinical Speech, Voice, and Swallow Physiology

University of Wisconsin – Whitewater

**Supported by NIH Grants DC014519, DC010900, RR025012
and the Dystonia Coalition**



Background

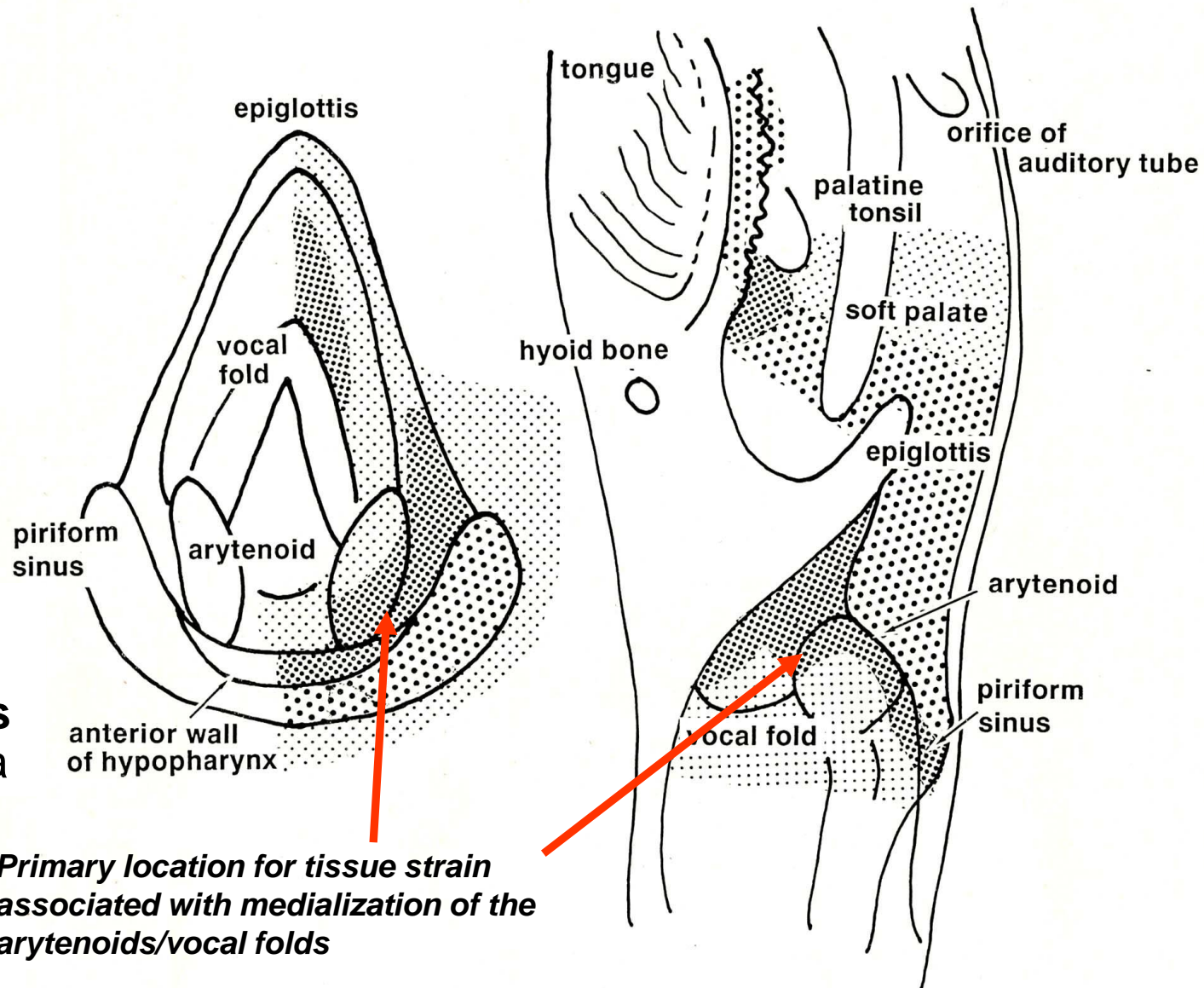
- Mechanosensation (sense of touch) in the larynx has often been associated with ballistic or defensive gestures including those for airway protection.
- The laryngeal mechanosensorium may also be directly involved in the regulation of fine motor control of the larynx for voice.

Laryngeal Mechanosensory Mechanisms

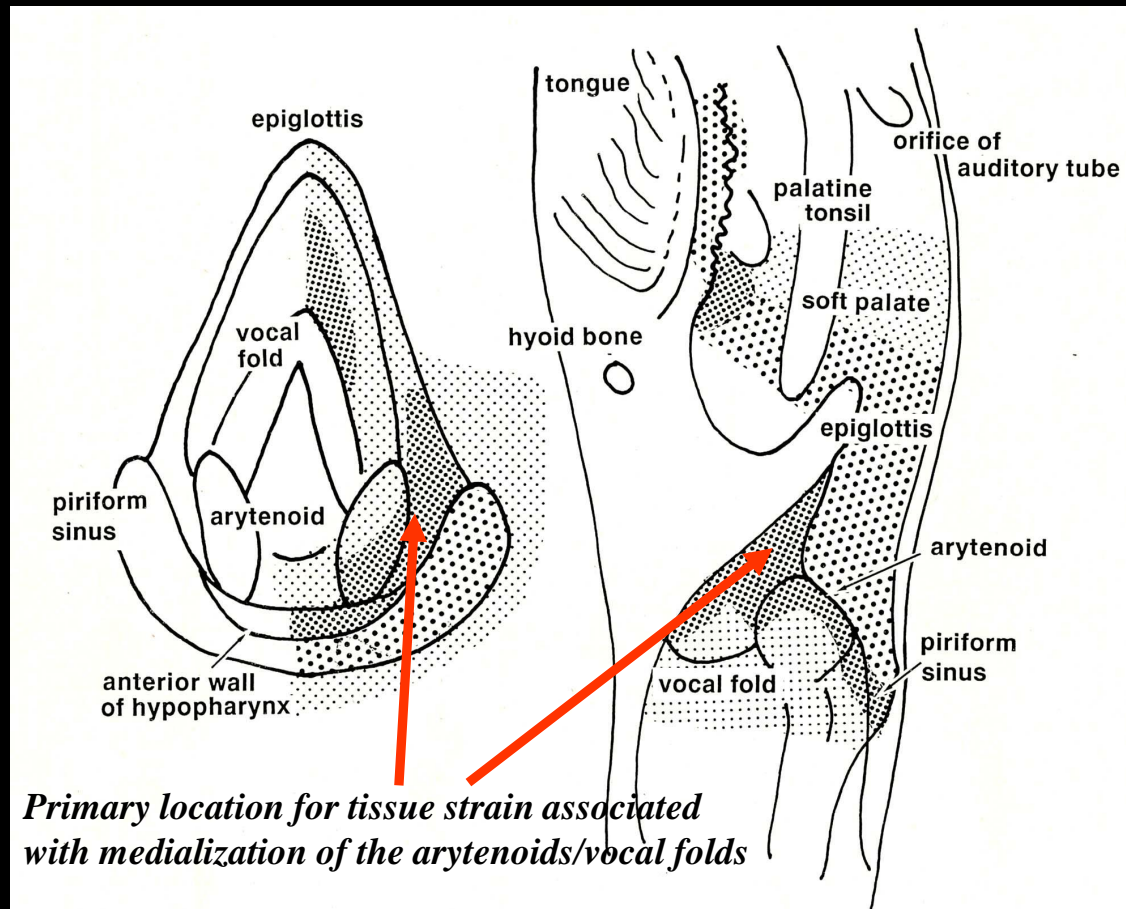
Internal branch
of superior
laryngeal nerve
(CN X)

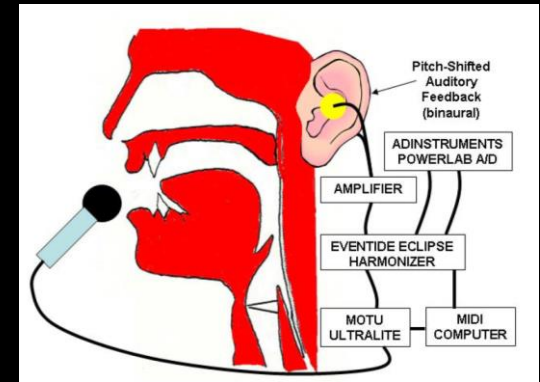
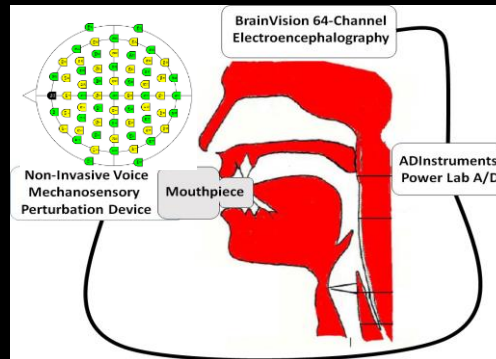
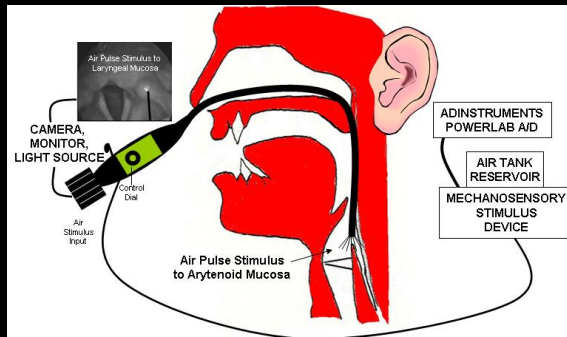
Dependent upon
**rapidly adapting
mechanoreceptors**
in laryngeal mucosa

*Primary location for tissue strain
associated with medialization of the
arytenoids/vocal folds*



The trouble is – of course – the sensory receptors in the larynx are a challenge to access.





Our Approaches to Study Somatosensory and Auditory Mechanisms of Voice Control

Left: Direct Somatosensory Stimulation of the Laryngeal Mucosa (developed in our laboratory)

Center: Non-Invasive Mechanosensory Perturbation During Breathing and Voice (developed in our laboratory)

Right: Pitch-Shifted Auditory Feedback (developed with collaborator Dr. Charles Larson)

> IEEE Trans Biomed Eng. 2009 Apr;56(4):1154-9. doi: 10.1109/TBME.2008.2007968. Epub 2008 Oct 31.

Design of a new somatosensory stimulus delivery device for measuring laryngeal mechanosensory detection thresholds in humans

Michael J Hammer¹

> Exp Brain Res. 2014 Jan;232(1):13-20. doi: 10.1007/s00221-013-3703-1. Epub 2013 Nov 12.

Voice-related modulation of mechanosensory detection thresholds in the human larynx

Michael J Hammer¹, Mallory A Krueger

> Exp Brain Res. 2010 Mar;201(3):401-9. doi: 10.1007/s00221-009-2048-2. Epub 2009 Dec 15.

Laryngeal somatosensory deficits in Parkinson's disease: implications for speech respiratory and phonatory control

Michael J Hammer¹, Steven M Barlow

Project Number: 7R01DC014519-04

Title: SENSORY INTERACTION IN VOICE AND VOICE DISORDERS

Contact PI / Project Leader: HAMMER, MICHAEL J

Awardee Organization: UNIVERSITY OF WISCONSIN WHITEWATER



Dear Dr. Hammer,

Thank you for submitting your application entitled *Non-Invasive Mechanosensory Perturbation Technique to Test Voice-Related Motor and Somatosensory Cortical Responses in Spasmodic Dysphonia: A New Clinical Approach* for the Dystonia Coalition Pilot Project Program. Your application has been carefully evaluated by our review committee and we are delighted to tell you that it was very well received. We are delighted to fund it in full. Congratulations!

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Email: jhsmith@dystonia.edu

RARE DISEASES
CLINICAL RESEARCH NETWORK

Hammer MJ, *Korzyukov OA, *Frodel TR, *Sake HC, *Smazinski MJ. Voice-Related Motor and Somatosensory Cortical Responses to Rapid Perturbations in Airway Resistance.

Hammer MJ, *Palm SA. Task-Specific Laryngeal Mechanosensory Modulation is Altered in Individuals with Adductor Spasmodic Dysphonia: Direct Evidence of Increased Somatosensory Excitability.

Brain Research 1732 (2008) 146703

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Research report

Auditory-vocal control system is object for predictive processing within seconds time range

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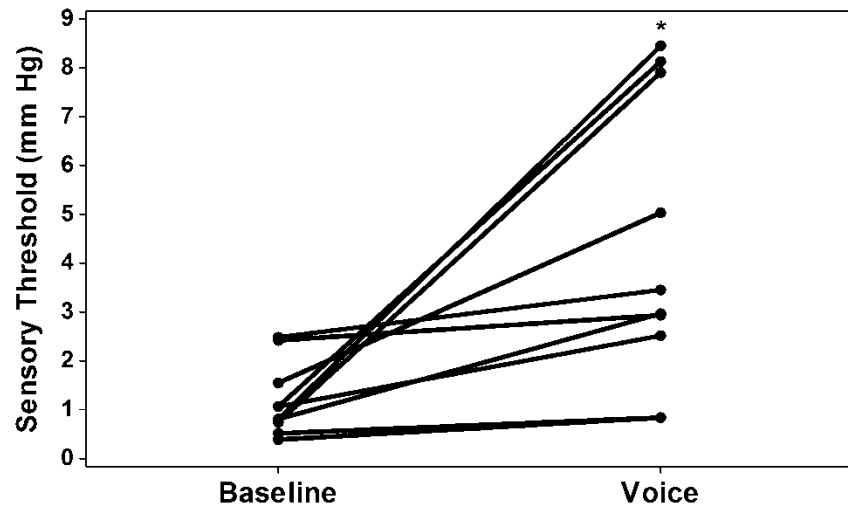
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Subthalamic nucleus deep brain stimulation changes speech respiratory and laryngeal control in Parkinson's disease

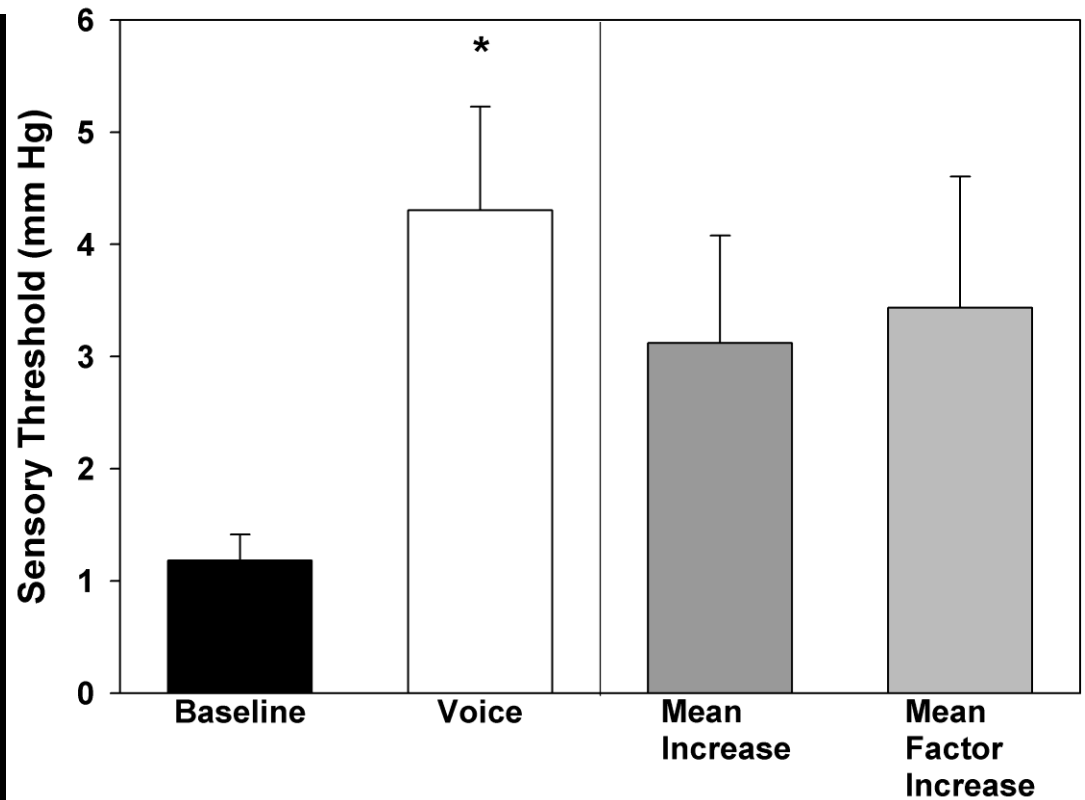
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Voice-Related Modulation of Mechanosensory Detection Healthy Mechanisms

Hammer MJ, Krueger MA. (2014).
Experimental Brain Research. 232, 13-20.



NIH Extramural Nexus

Thursday - October 2, 2014 7:04 PM

Subject Line: “NIH Update: Look at science funding across agencies, Considering sex as a biological research variable, Peer review webinars, Subaccounting for NIH awards”



Janine A. Clayton is director of the US National Institutes of Health Office of Research on Women's Health, and associate director for research on women's health, Bethesda, Maryland, USA. Francis S. Collins is director of the US National Institutes of Health, Bethesda, Maryland, USA.

NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

Voice-related modulation of mechanosensory detection thresholds in the human larynx

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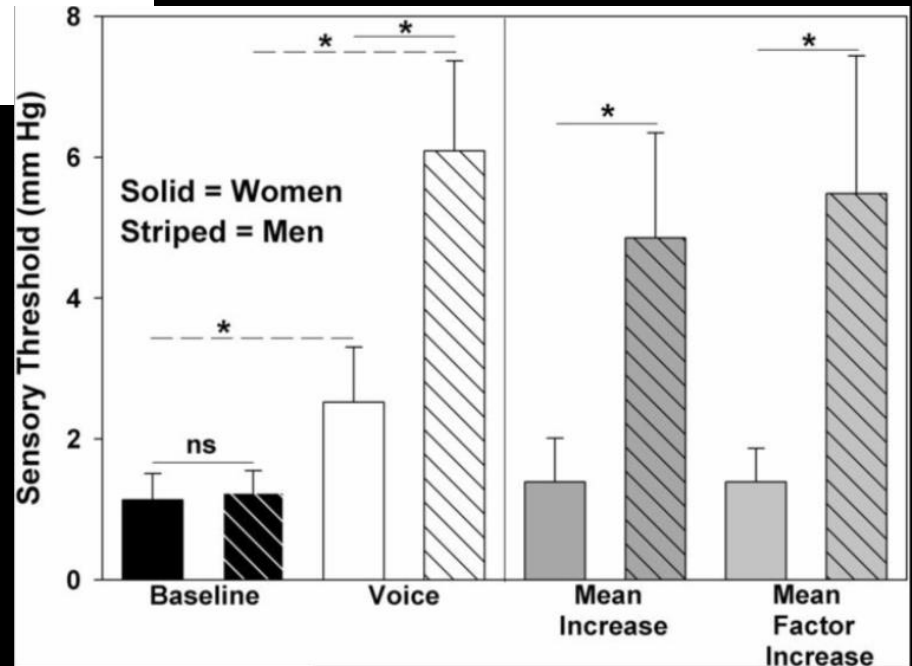
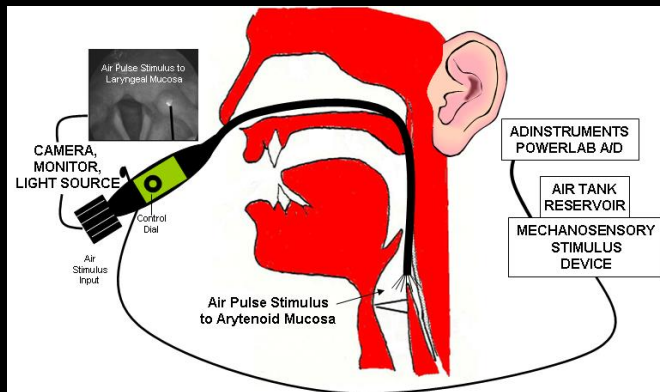


Figure 3 Laryngeal mechanosensory detection thresholds for baseline tidal breathing and voice conditions for women (solid) and men (striped). (* $p < 0.05$) On the left, bar height represents mean (standard error) detection threshold for baseline and voice conditions. On the right, bar height represents mean increase and mean factor increase in detection threshold compared with baseline. (1 mm Hg = 133.32 Pa)

Adductor Spasmodic Dysphonia (ADSD)

Adductor Spasmodic Dysphonia (ADSD) is a chronic, speech-specific focal laryngeal dystonia characterized by intermittent hyperadduction of the vocal folds, voice breaks, strained-strangled voice, and increased effort to speak.

Sensory Mechanisms in Laryngeal Dystonia

Abnormal sensory mechanisms have been proposed as a potential contributor to focal dystonias, including the laryngeal dystonia of ADSD. However, the potential sensorineural mechanisms underlying the laryngeal dystonias remain largely unexplored.

JANUARY 16, 2017

TIME

Depression.
Heart trouble.
Migraines.
Erectile dysfunction.
Back pain.
Sweaty palms.
Drooling.
And 793 other problems.

How Botox Became the Drug That's Treating Everything.

By Alexandra Sifferlin



time.com

Somatosensory Changes with Botulinum Toxin

Task-Specific Laryngeal Mechanosensory Modulation is Altered in Individuals with Adductor Spasmodic Dysphonia: Direct Evidence of Increased Somatosensory Excitability

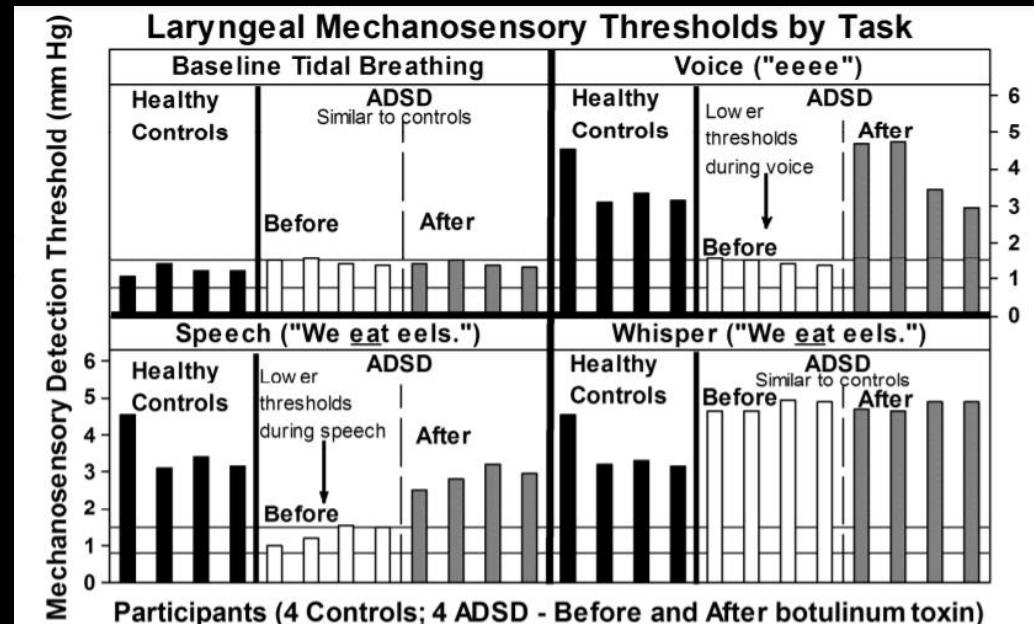
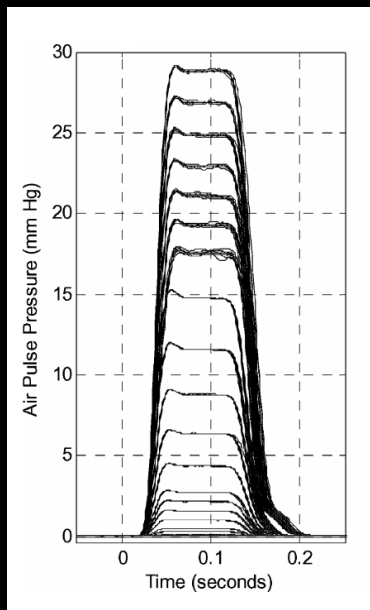
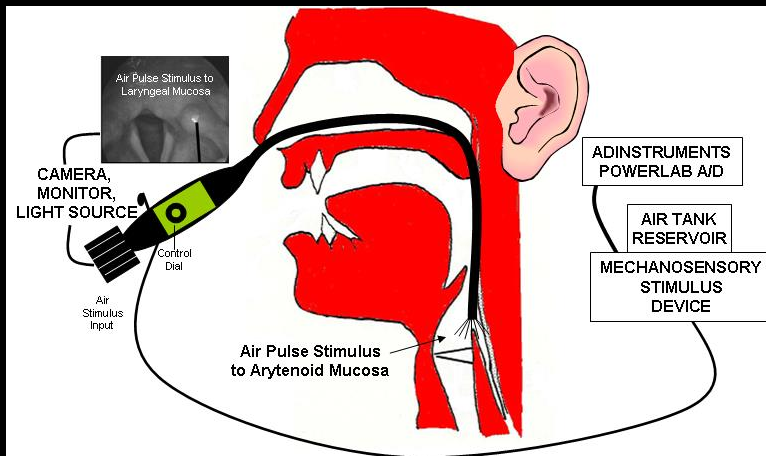
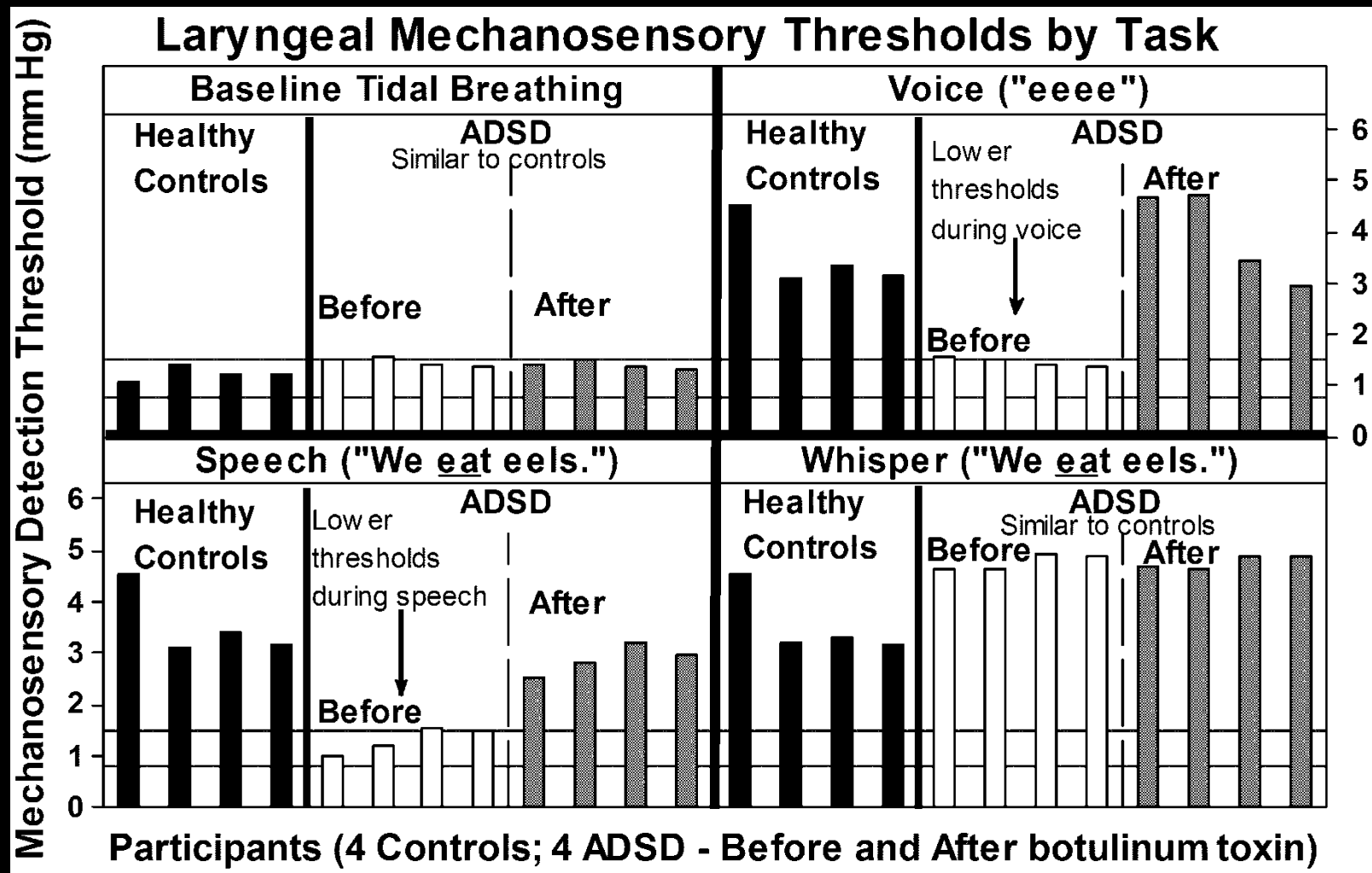
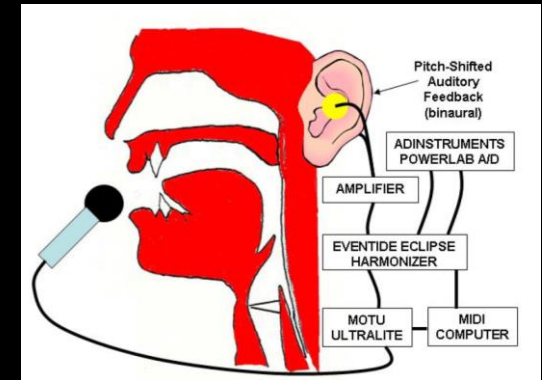
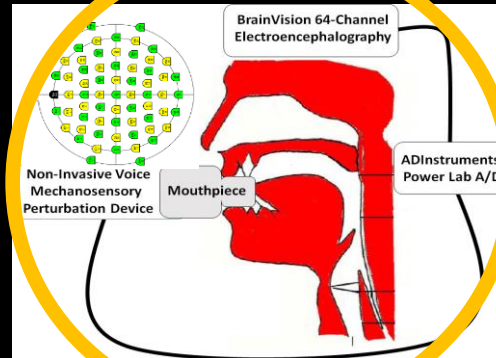
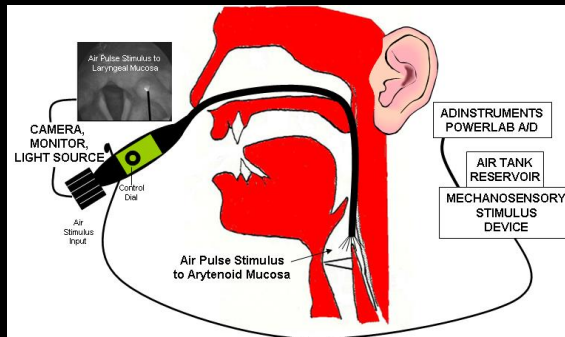


Figure 9. Preliminary data from 4 participants with ADSD immediately before (white bars) and 2 weeks after (gray bars) bilateral injection of botulinum toxin into the thyroarytenoid muscles, and 4 healthy controls (black bars). Horizontal lines denote 'normal' detection threshold range for tidal breathing. Healthy controls exhibited consistent, increased detection thresholds during voice, speech, and whisper. Before injection, ADSD participants exhibited task-specific abnormal detection thresholds (increased laryngeal mechanosensory sensitivity) during voice and speech tasks, but relatively 'normal' thresholds during baseline tidal breathing and whisper. Two weeks after injection, ADSD participants exhibited similar detection thresholds to controls for each task.

Exaggerated Laryngeal Sensitivity in Dystonia (Spasmodic Dysphonia)



Non-Invasive Approach



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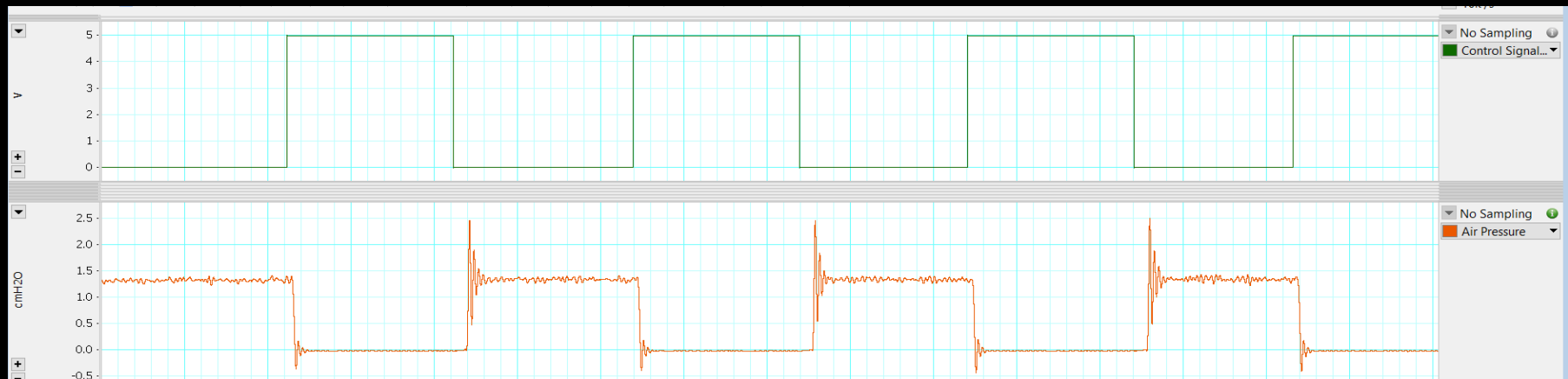
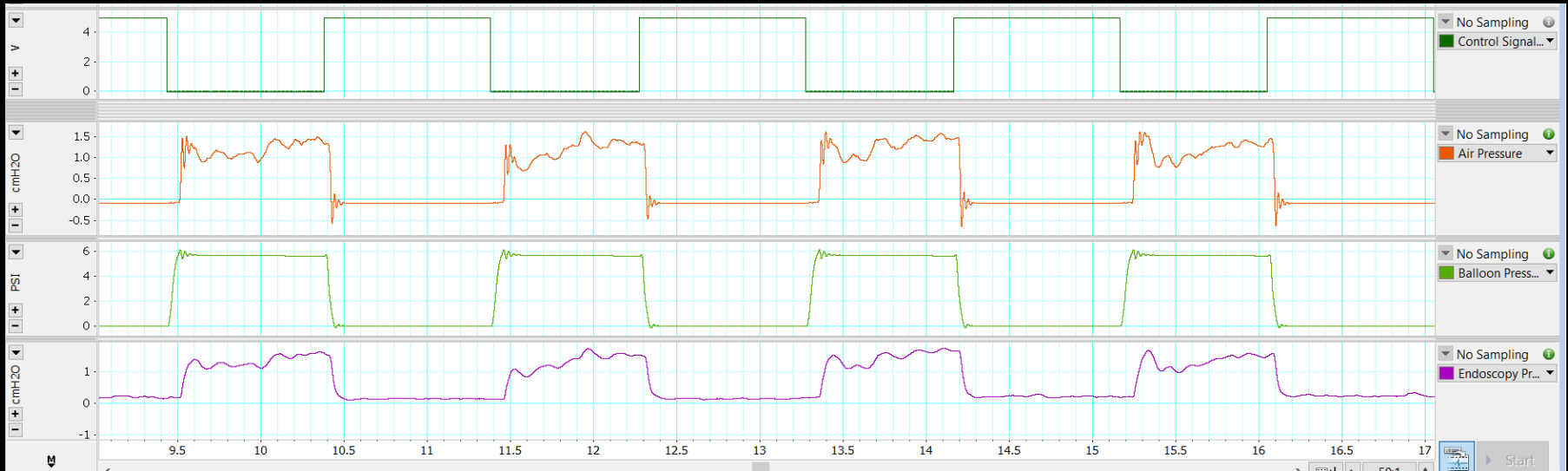
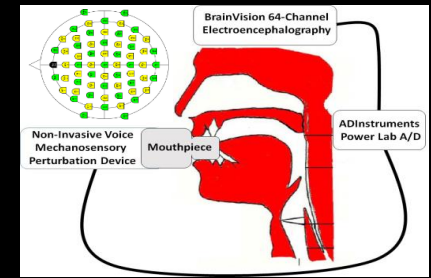
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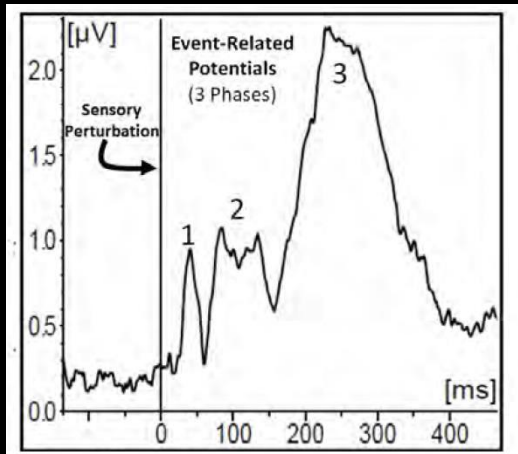
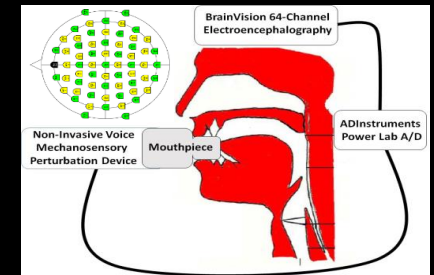


Figure 2. Grand average of event-related potentials (global field power) from 12 healthy participants. Mechanosensory perturbation (rapid shift in resistance from high resistance to low resistance) occurs at $t = 0$ indicated by the solid vertical line. Three discrete phases are seen in the event-related response. Detailed localization and spectral analysis suggests the following localization.

Phase 1 (~40ms) = primary motor cortex

Phase 2 (~100ms) = primary somatosensory cortex

Phase 3 (~250ms) = frontal lobe region indicating surprise

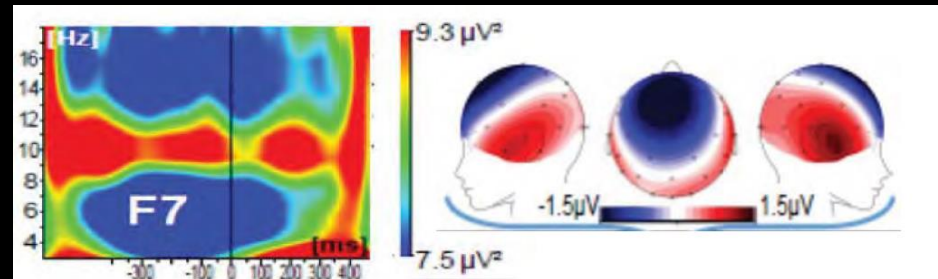


Figure 3. Sensory Input to Laryngeal Primary Motor Cortex.

Left: Grand average spectral power from frontal electrode F7. Mechanosensory perturbation occurs at $t = 0$ indicated by the solid vertical line. Mu spectral power centered at 10Hz (horizontal red band) decreases with a latency of ~40ms after the sensory perturbation, consistent with sensory input arriving to the laryngeal motor cortex.

Right: Topographic map averaged over the time interval 32-52ms after sensory perturbation suggesting inferior frontal lobe, and consistent with sensory input to the laryngeal motor cortex.

N = 12 Healthy Adults

Participants

- **Adductor Spasmodic Dysphonia**
 - **N = 10 Women with ADSD**
 - **No history of other neurological or psychiatric disease**
 - **No history of pulmonary disease**
- **Healthy Controls**
 - **N = 10 Age-Matched Women (for direct comparison)**
 - **N = 10 Age-Matched Men (to examine potential sex effects)**
 - **No history of neurological or psychiatric disease**
 - **No history of pulmonary disease**
 - **Normal speech, swallow and voice**

Test Sessions

ADSD – Two Test Sessions

“Baseline” - After a return to baseline symptoms (minimum of 3-4 months after most recent injection)

“Post-Injection” – After botulinum toxin injection (scheduled ~2-4 weeks after injection) when each has experienced symptom relief based on a detailed diary and clinical/instrumental voice assessment).

Age-Matched Healthy Controls – Two Test Sessions

Two Separate Test Sessions – Separated by 2-3 weeks.

Tasks

1. “Baseline” Tidal Breathing

During tidal breathing, the mechanosensory perturbation device will be TTL triggered by the initiation of the expiratory phase of respiration as transduced using a standard air flow transducer.

2. Sustained vowel “ahhh” at a comfortable habitual pitch and loudness

3. Whispering the vowel “ahhh”

4. Sustaining vowel “ahhh” in ‘falsetto’.

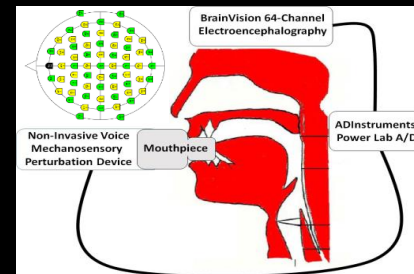
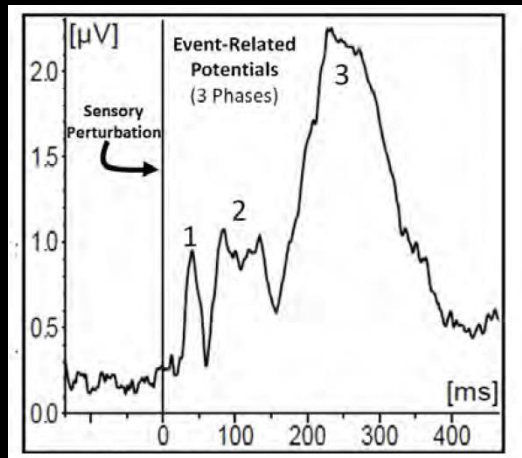
During voice tasks, stimulus presentation is similarly triggered by TTL 2-2.5 seconds after the onset of vocalization.

Tasks

We will use the TTL signal to time-align and signal average the EEG trials.

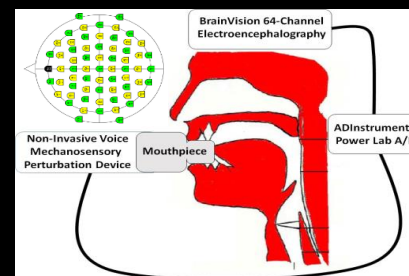
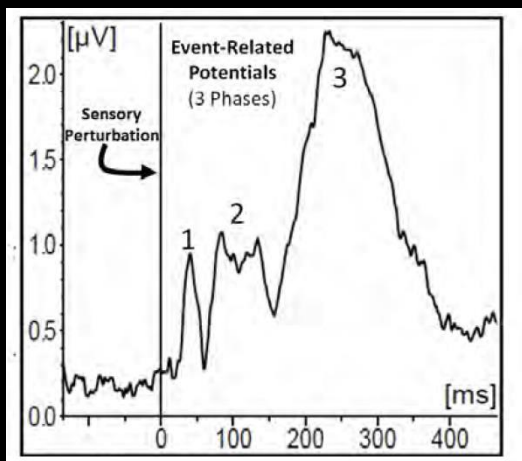
Based on previous feasibility trials, we plan to use an alternating block design to reduce potential response habituation.

For each task, each participant will undergo 120 trials (12 blocks x 10 trials per task). We will counterbalance the order of tasks tested across participants



Hypotheses

1. We hypothesize that individuals with ASD will exhibit larger amplitude evoked cortical responses during voiced phonation tasks compared with healthy controls. (But similar during respiratory, whisper, and falsetto tasks.)
2. We also hypothesize that the magnitude of sensory-evoked cortical responses during the voiced phonation task will strongly correlate with clinical/instrumental measures of laryngeal, speech, and voice severity.
3. We hypothesize that sensory and speech/voice measures will “improve” with botulinum toxin treatment.



Next Steps

- Continue data collection and analysis.
- Prepare Application for R01 Grant

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