

Bimodal Neuromodulation for Tinnitus Treatment

Hubert H. Lim, Ph.D.

Endowed Lions Professor

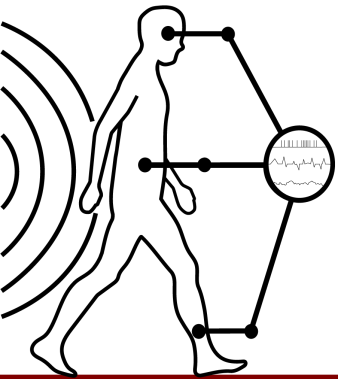
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Department of Biomedical Engineering

Department of Otolaryngology–Head & Neck Surgery

University of Minnesota–Twin Cities, U.S.A.

<http://soniclab.umn.edu>



T E S S L a b

Translational Energy Stimulation-Sensing Laboratory

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Lions Hearing Foundation, UMN CTSI ODAT program, UMN MnDRIVE, Neuromod Devices Limited*

Disclaimers

I am serving as the Chief Scientific Officer of Neuromod Devices, which is developing tinnitus treatment technologies. I receive compensation from and hold equity in this company.

I am serving as the Chief Scientific Officer of SecondWave Systems, which is developing wearable ultrasound neuromodulation technologies for various health conditions. I receive compensation from and hold equity in this company. These interests have been reviewed and managed by the University of Minnesota in accordance with its Conflict of Interest policies. No content in this talk is associated with SecondWave Systems.

Clinical trial data presented in this talk were generated in studies sponsored by Neuromod Devices Limited.

Real world data presented in this talk were provided by the German Hearing Center in Hannover, Germany associated with Hannover Medical School.

Outline

- Brief background on tinnitus
- Concept of bimodal neuromodulation
- University of Minnesota findings
- University of Michigan findings
- Neuromod Devices findings: TENT-A1 (Lenire) clinical trial
- Real world Lenire data at an independent clinic
- Conclusions

What is Tinnitus?



- Subjective tinnitus: phantom sound perception without any external sound source
- 10-15% of general population struggle with tinnitus
- Major health issue in society

How Do We Treat Tinnitus?

- Sound devices such as maskers, music therapy and hearing aids
- Convenient, take-home devices that can be easy to use
- Insufficient clinical trial evidence to recommend solely for tinnitus (e.g., Tunkel et al., AAO, 2014), but sound treatments can be helpful for some tinnitus patients
- Improvements in tinnitus can be short-term or transient after sound stimulation

How Do We Treat Tinnitus?

- Patient centered and psychological/behavioral approaches:
 - Education and counseling
 - Mindful-based approaches
 - Tinnitus Retraining Therapy
 - Tinnitus Activities Treatment
 - Combination approaches customized to each patient
 - Cognitive Behavioral Therapy (CBT) – recommended in clinical guidelines (e.g., Tunkel et al., AAO, 2014) based on clinical trial evidence
 - Tinnitus Handicap Inventory (score: 0 to 100; 7 points clinically meaningful):
Improvement of 10 points at 8 months (e.g., Cima et al., Lancet, 2012)
- Typically longer lasting benefits than sound-only approaches

New Concept for Treating Tinnitus – Bimodal Neuromodulation

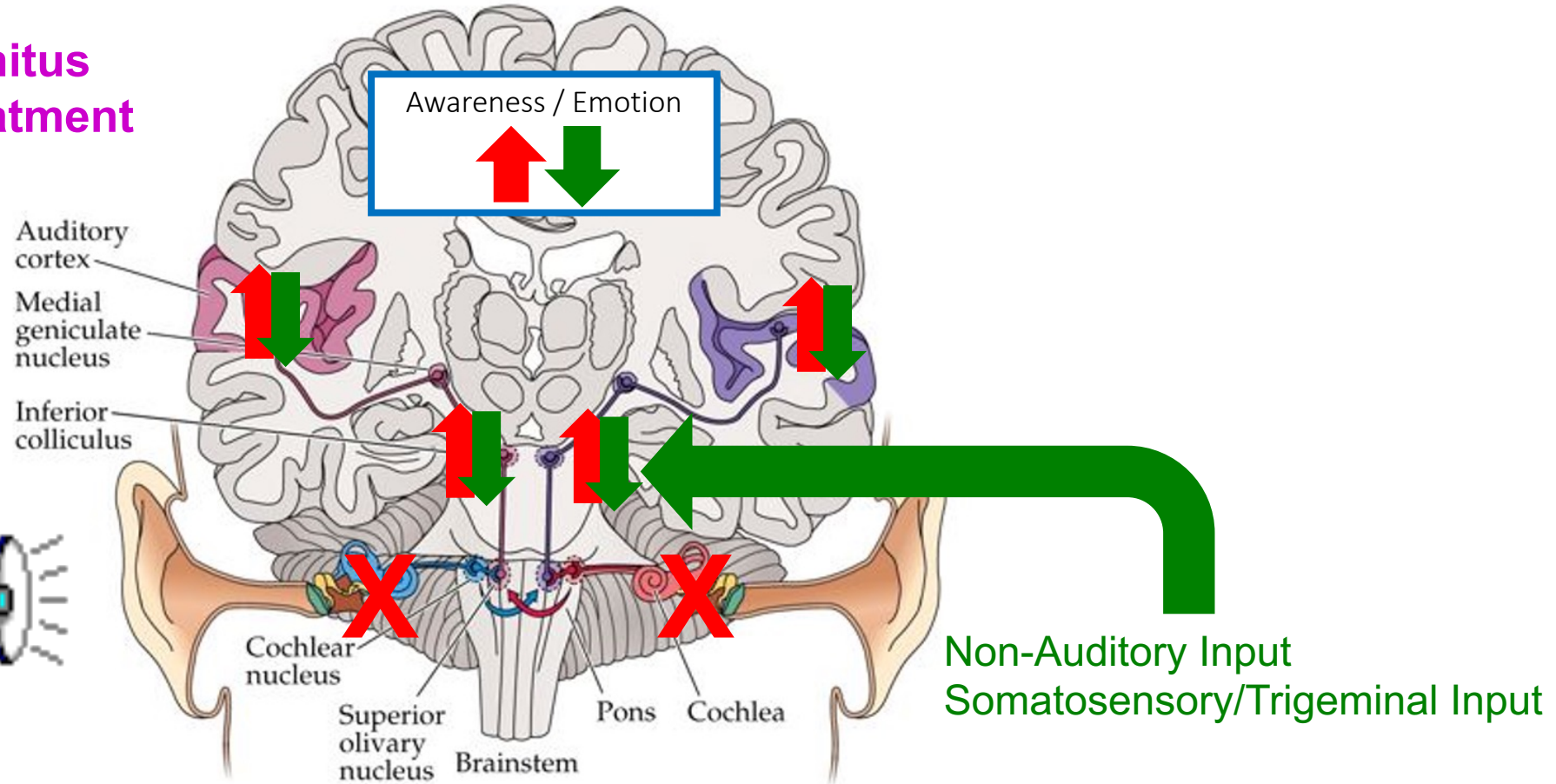
Goal: To achieve long-term tinnitus relief as is possible with CBT (i.e., reduce tinnitus awareness/reaction) but with a convenient take-home treatment like sound devices

Potentially long-term tinnitus relief with short-term treatment

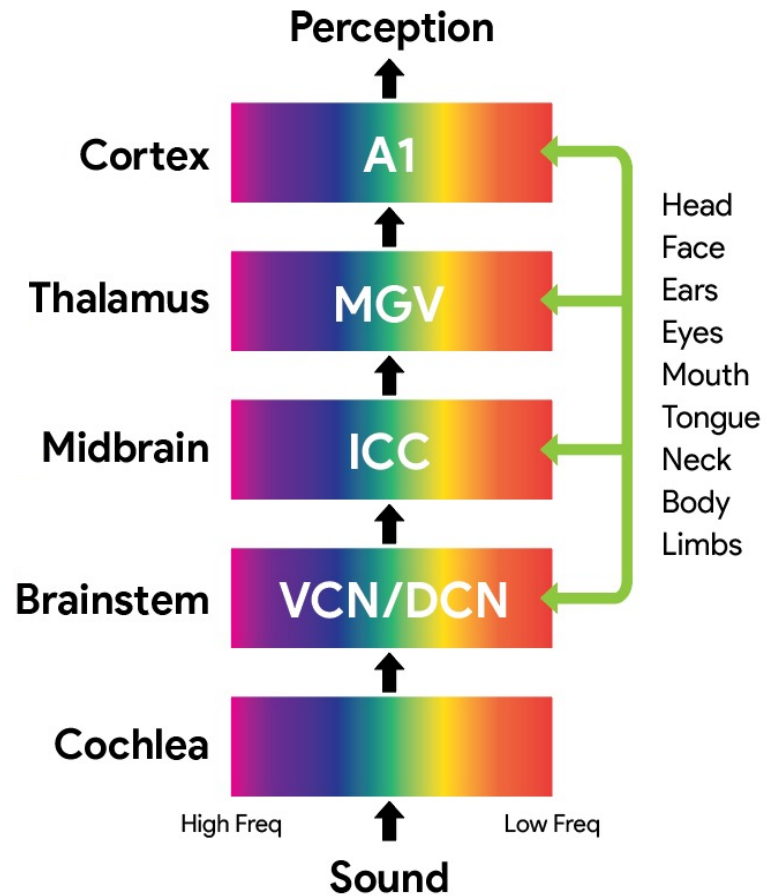
Hebbian Plasticity:
“neurons that fire together wire together” – Dr. Donald Hebb



Sound Input Synchronized with Somatosensory Input



University of Minnesota Research into Bimodal Neuromodulation



University of Minnesota Research into Bimodal Neuromodulation



*Cory Gloeckner, PhD
Asst. Prof. – UMN Duluth*



*Craig Markovitz, PhD
Abbott / Inari Medical*



*Ben Smith
UMN Medical School*



*Yezihalem Mesfin
BME Ph.D. Candidate*



*Elizabeth Batman
Speech-Lang-Hear Student*



*Jennifer Wittman, AuD
Audiology at HealthPartners*

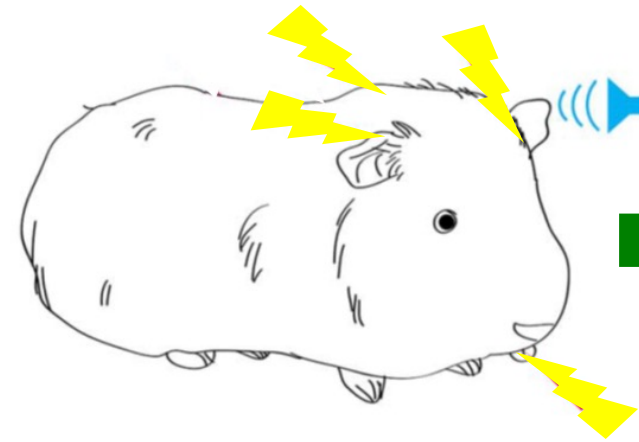
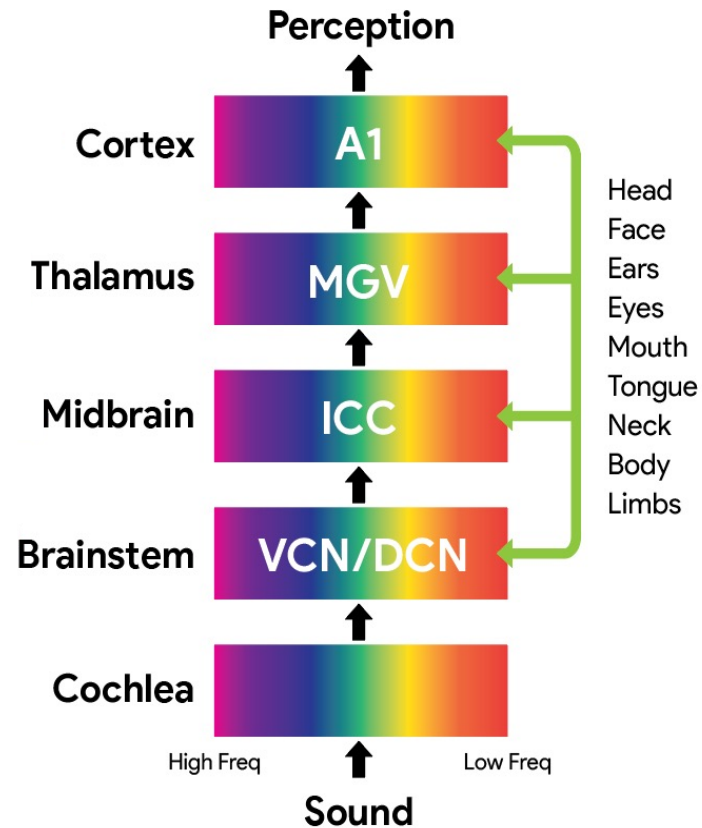


*Martha Westman
Audiology Doctoral Student*



*Caitlin Brehmer
Speech-Lang-Hear Student*

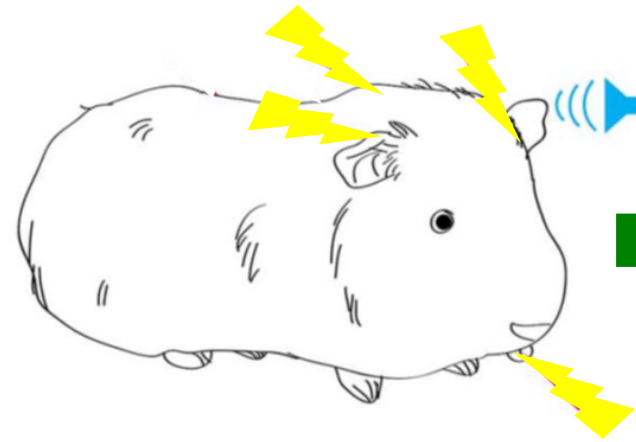
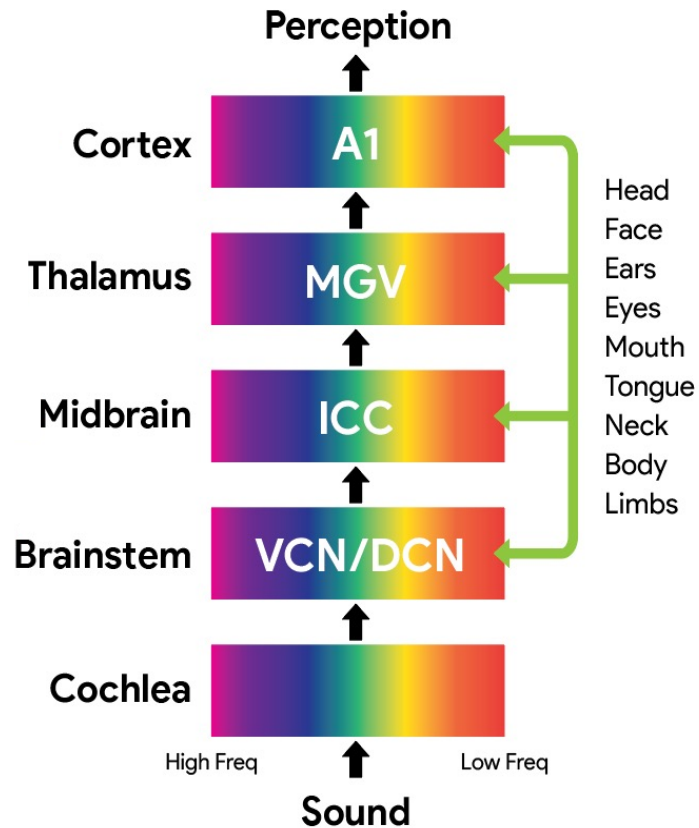
University of Minnesota Research into Bimodal Neuromodulation



Record activity in auditory brain (midbrain & cortex)

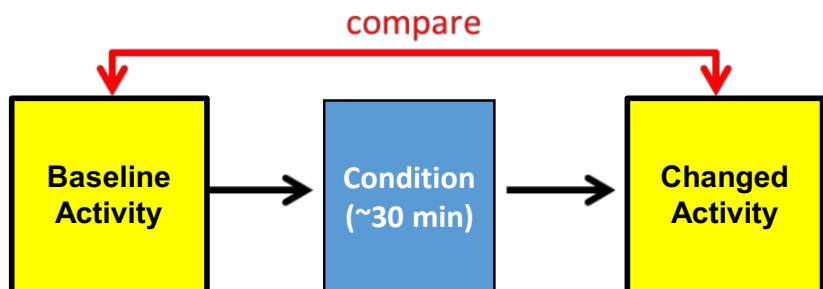
Noise (also tones) combined with electrical stimulation of tongue, ear regions and neck

University of Minnesota Research into Bimodal Neuromodulation



Record activity in auditory brain (midbrain & cortex)

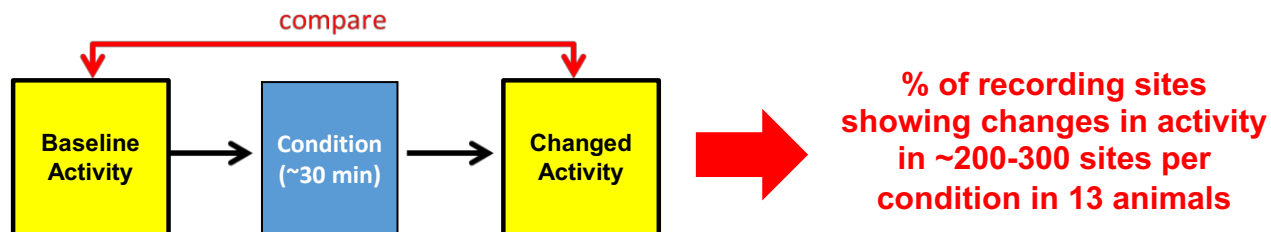
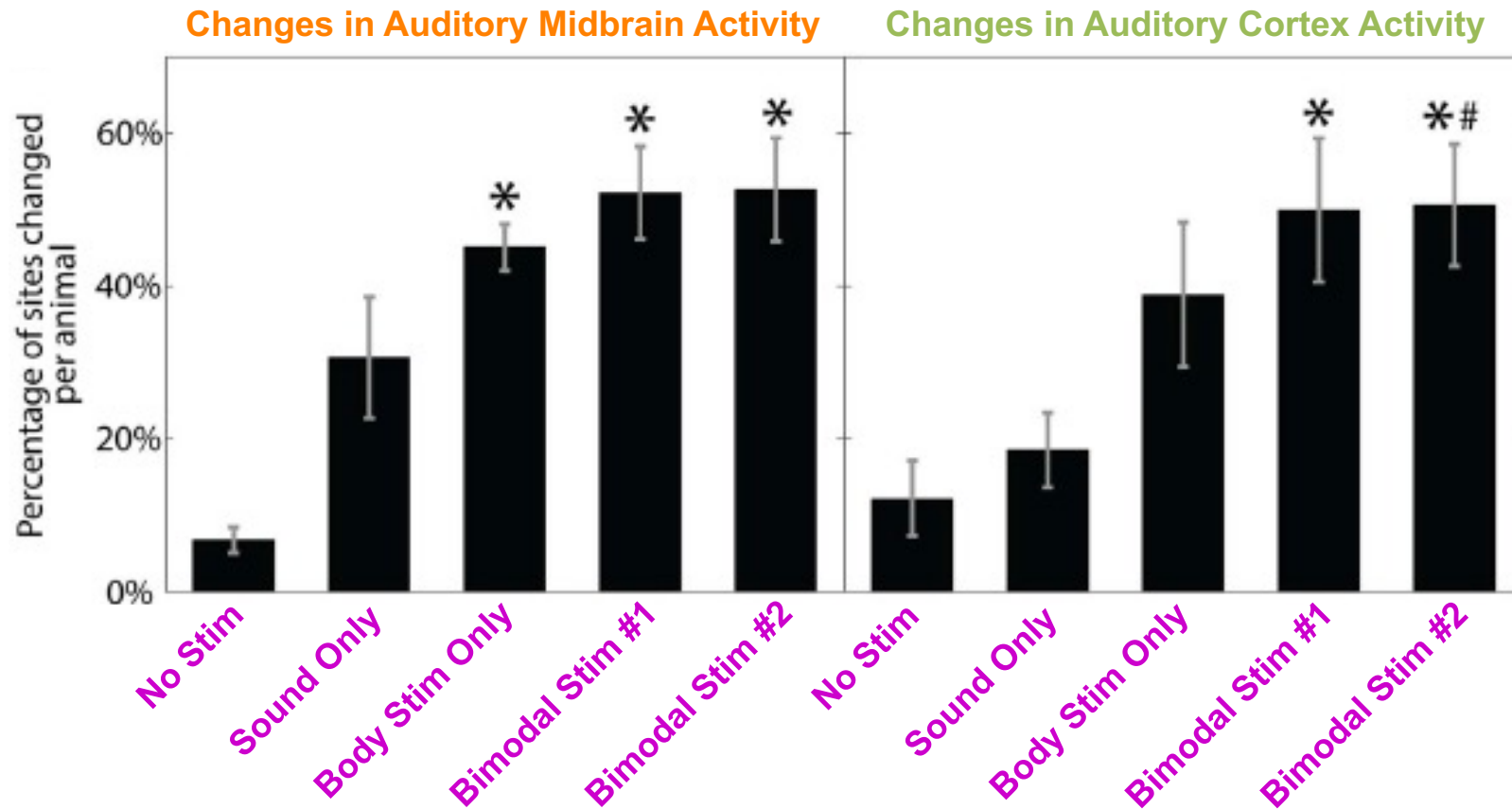
Noise (also tones) combined with electrical stimulation of tongue, ear regions and neck



Demonstrate we can change activity in auditory brain

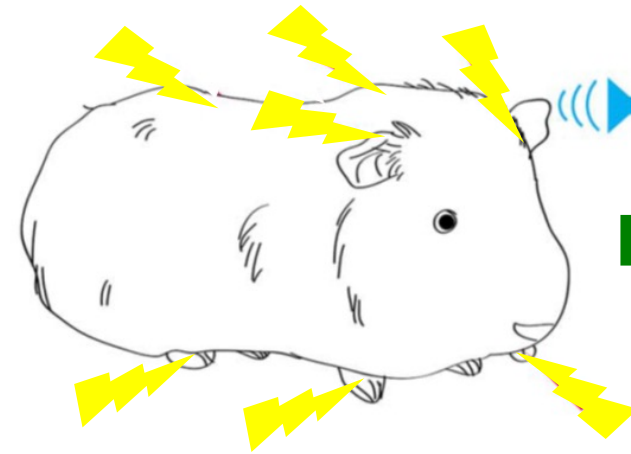
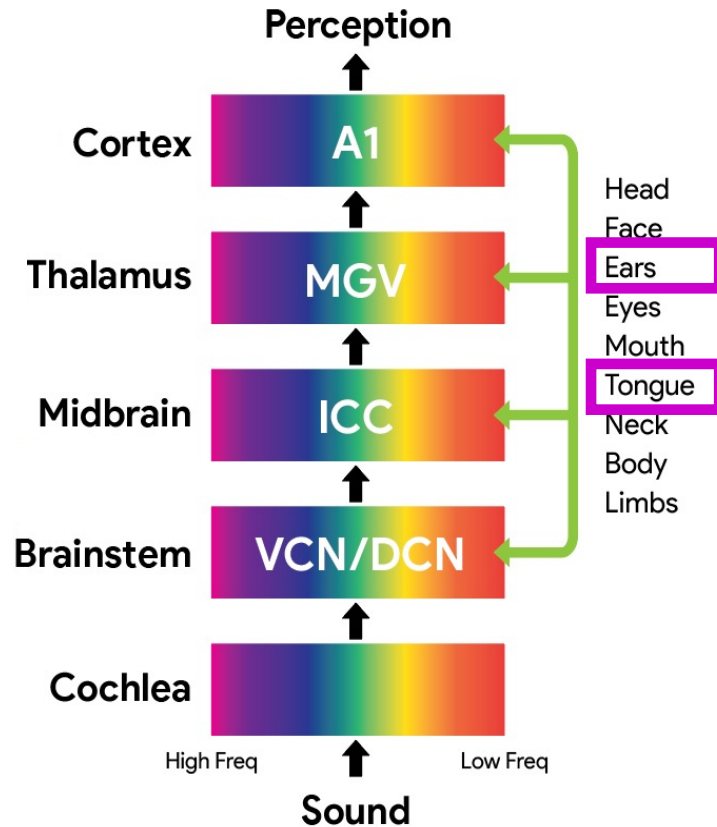
Markovitz...Lim, Nature Scientific Reports, 2015

University of Minnesota Research into Bimodal Neuromodulation



Markovitz...Lim, Nature Scientific Reports, 2015

University of Minnesota Research into Bimodal Neuromodulation

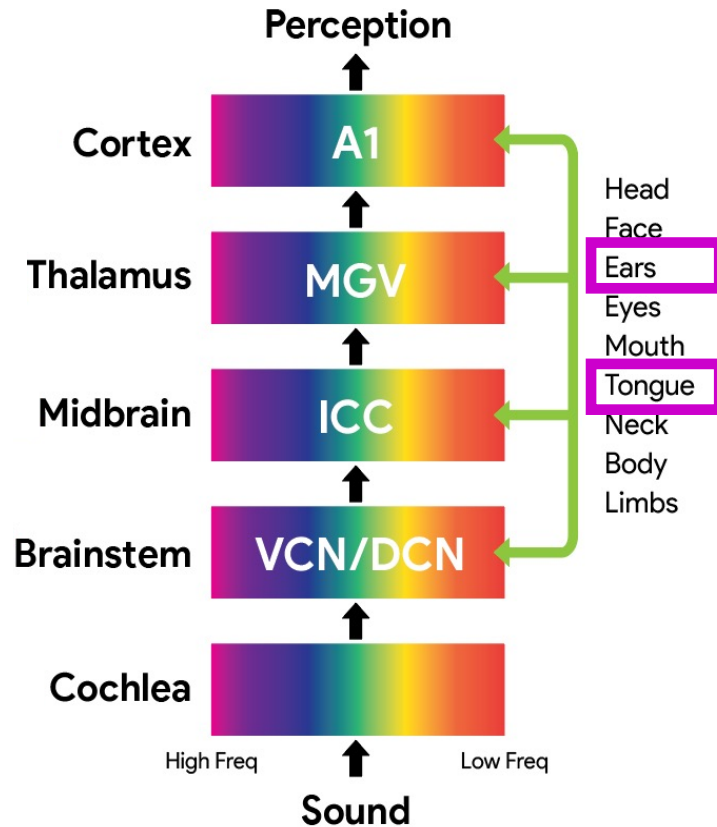


**Record activity in
auditory brain
(midbrain & cortex)**

Noise (also tones) combined with electrical stimulation of different body and head locations

Electrical stimulation of tongue or ears/mastoid combined with sound showed strong changes in the auditory brain relevant for tinnitus treatment

University of Minnesota Research into Bimodal Neuromodulation



Positive findings in several tinnitus subjects with electrical ear and sound stimulation in Dr. Lim's lab at University of Minnesota

Consistent Findings by a Separate Group at University of Michigan

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

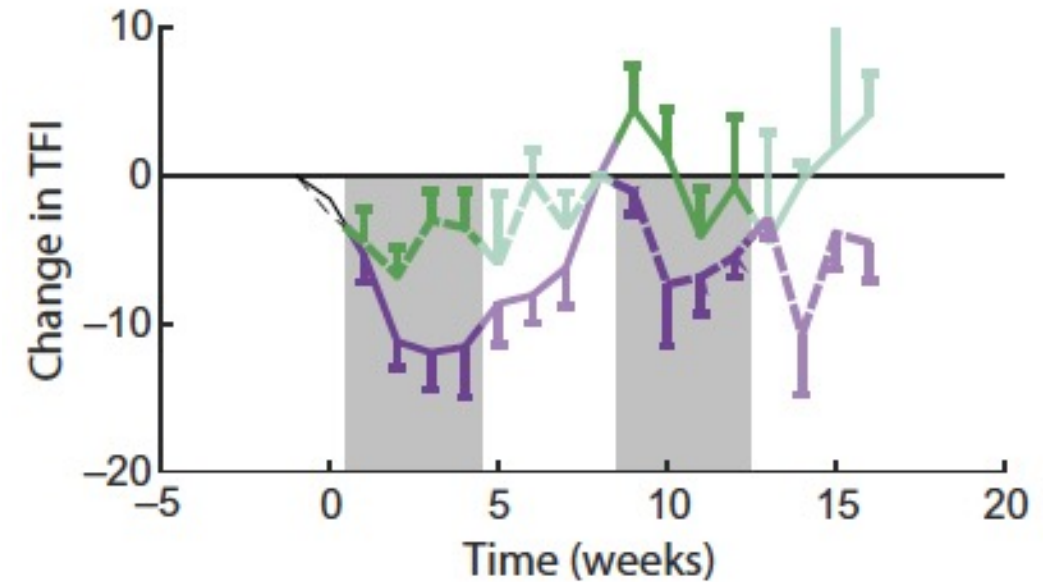
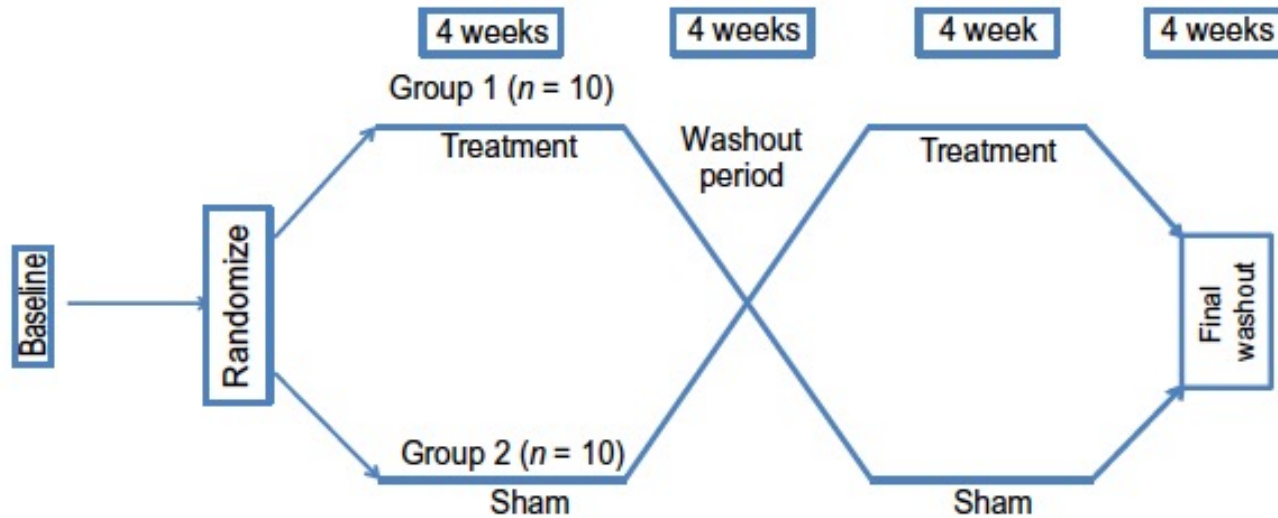
TINNITUS

Auditory-somatosensory bimodal stimulation desynchronizes brain circuitry to reduce tinnitus in guinea pigs and humans

Kendra L. Marks,^{1*} David T. Martel,^{1,2*} Calvin Wu,^{1*} Gregory J. Basura,¹ Larry E. Roberts,³
Kara C. Schvartz-Leyzac,¹ Susan E. Shore^{1,2,4†}

- Electrical stimulation of cheek or neck combined with pure tones in guinea pigs induced extensive plasticity within the auditory brainstem and can treat tinnitus
- Similar approach used in humans and achieved improvements in tinnitus symptoms with 4 weeks of treatment that could last up to 3 weeks post-treatment

Consistent Findings by a Separate Group at University of Michigan



- **Bimodal stimulation** for 30 minutes per day of treatment for 4 weeks
- **Sham (acoustic only):** same setup as treatment with ear inserts for sound stimulation and surface pads for electrical stimulation but no electrical pulses were presented
- **Bimodal stimulation showed greater improvements in tinnitus symptoms compared to acoustic-only condition consistent with animal neural plasticity findings from Lim lab and Shore lab**



Lenire™ — Bimodal Neuromodulation Treatment for Tinnitus from Neuromod Devices

Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

Real World Data

Overall Conclusions



LENIRE™

Lenire™ [Len - ear]

Derived from Latin; lēnīre, present active infinitive
of lēniō (to soften, soothe, appease, pacify)



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Two Large-Scale Randomized and Double-Blinded Clinical Trials (TENT-A1 and TENT-A2)

TENT-A1

Open Access

Protocol

BMJ Open Bi-modal stimulation in the treatment of tinnitus: a study protocol for an exploratory trial to optimise stimulation parameters and patient subtyping

Shona D'Arcy,¹ Caroline Hamilton,¹ Stephen Hughes,¹ Deborah A Hall,^{2,3}
Sven Vanneste,⁴ Berthold Langguth,^{5,6} Brendan Conlon^{1,7,10,8}

Due to time, I will focus on TENT-A1 data today

TENT-A2

JMIR RESEARCH PROTOCOLS

Conlon et al

Protocol

Noninvasive Bimodal Neuromodulation for the Treatment of Tinnitus: Protocol for a Second Large-Scale Double-Blind Randomized Clinical Trial to Optimize Stimulation Parameters

Brendan Conlon^{1,2,3}, FRCSI; Caroline Hamilton², BSc, MSc; Stephen Hughes², BSc; Emma Meade², BA, MSc; Deborah A Hall^{4,5,6}, BSc, PhD; Sven Vanneste^{3,7}, PhD; Berthold Langguth⁸, MD, PhD; Hubert H Lim^{2,9}, MSE, PhD



Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

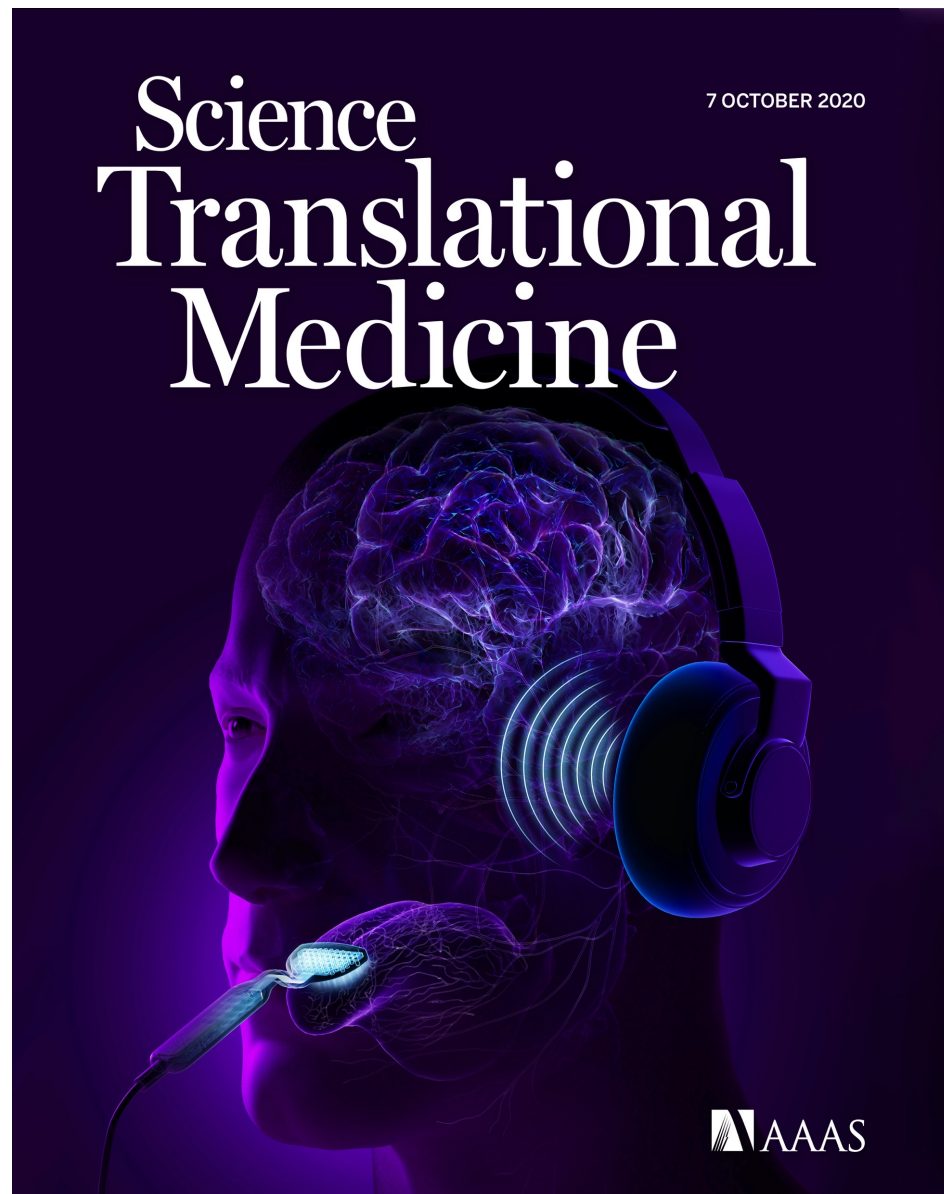
TENT-A1 Subtyping

TENT-A1 Conclusions

Real World Data

Overall Conclusions

TENT-A1 Clinical Trial Results Available in Science Translational Medicine



Conlon, Brendan, et al. Bimodal neuromodulation combining sound and tongue stimulation reduces tinnitus symptoms in a large randomized clinical study. *Science translational medicine*. 12: 564, eabb2830 (2020).

Co-Authors of TENT-A1 Study



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Scientific Advisory Board



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Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

TENT-A1 Subtyping

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TENT-A1 Clinical Trial Objectives

Stimulus
Optimization

Investigate effectiveness of different spectral and temporal patterns of acoustic and tongue stimulation

Subject
Subtyping

Identify subtypes of subjects most responsive to specific stimulus settings of bimodal sensory neuromodulation



Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

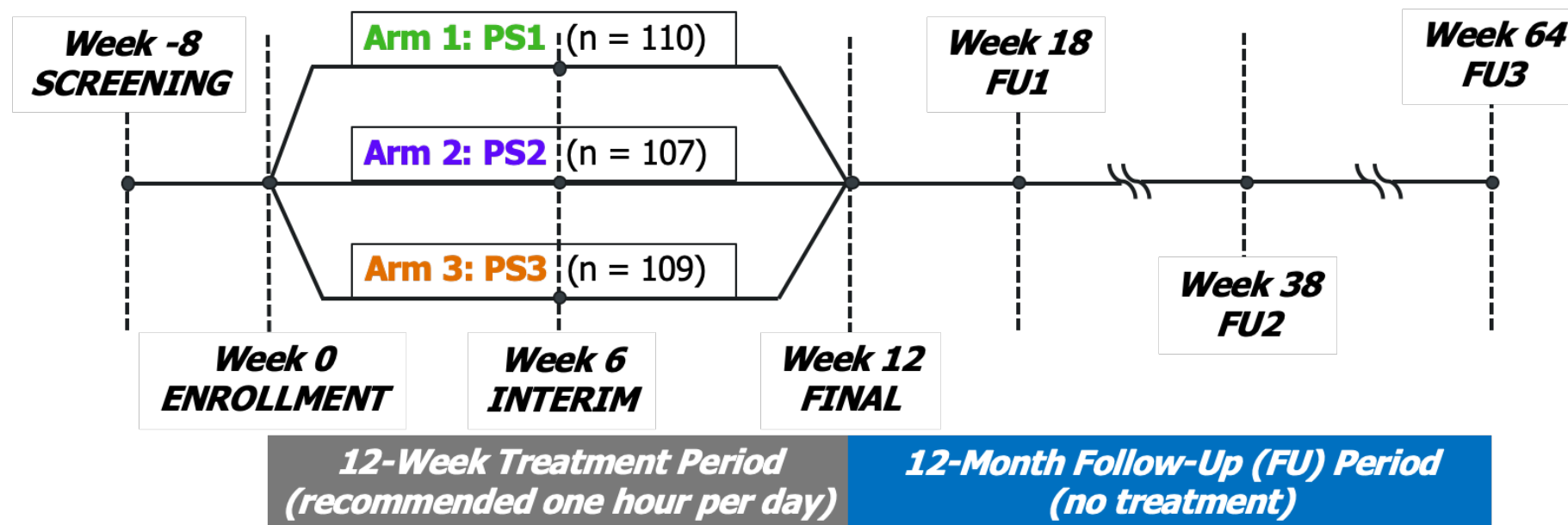
TENT-A1 Subtyping

TENT-A1 Conclusions

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Overall Conclusions

TENT-A1 Clinical Trial Design (two-site, randomized, 3-arm, double-blinded study)



Primary Outcome Measures

- Tinnitus Handicap Inventory (THI)
- Tinnitus Functional Index (TFI)

Baseline = average of screening & enrollment

Several of the Key Inclusion Criteria

- 18 to 70 years of age
- Experiencing subjective tinnitus
- Experiencing chronic tinnitus for 3 months to 5 years
- THI score of 28 to 76



Background

TENT-A1 Objectives

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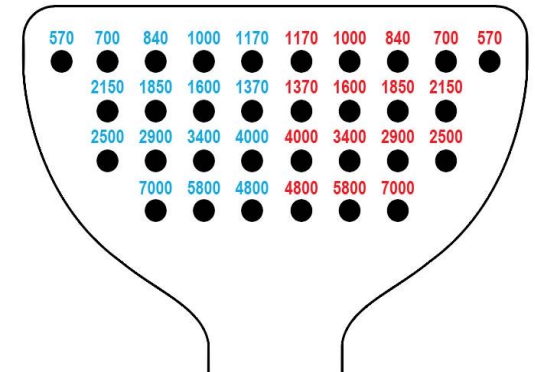
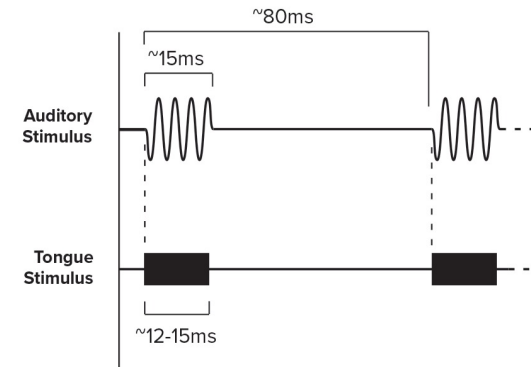
TENT-A1 Protocol: Key Differences Between Stimulation Settings

Each arm was intended to serve as an active and blinded control to each other

Arm 1 (PS1)

(synchronized; based on pilot study)

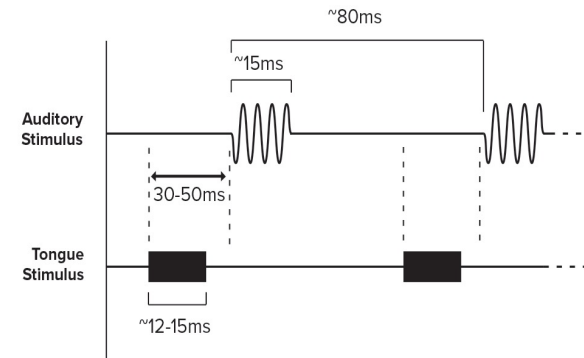
- Broad range of frequency tones (500-8000 Hz)
- Synchronous bimodal stimulation
- Systematic tone-to-tongue-location map
- Background noise



Arm 2 (PS2)

(short delays)

- Broad range of frequency tones (500-8000 Hz)
- Varying short delays
- Randomized tone-to-tongue locations
- Background noise

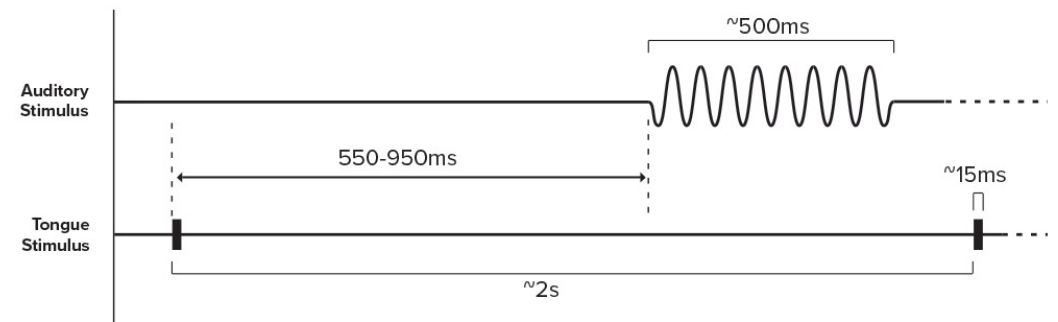


Example sound for PS1 & PS2

Arm 3 (PS3)

(long delays; lower frequencies)

- Lower frequency tones (100-500 Hz)
- Varying long delays
- Randomized tone-to-tongue locations
- Background noise





TENT-A1 Results: Significant Improvements in THI for All Arms

synchronized, tone-tongue map

short inter-stimulus delays

long delays, lower frequencies

Background

TENT-A1 Objectives

TENT-A1 Protocol

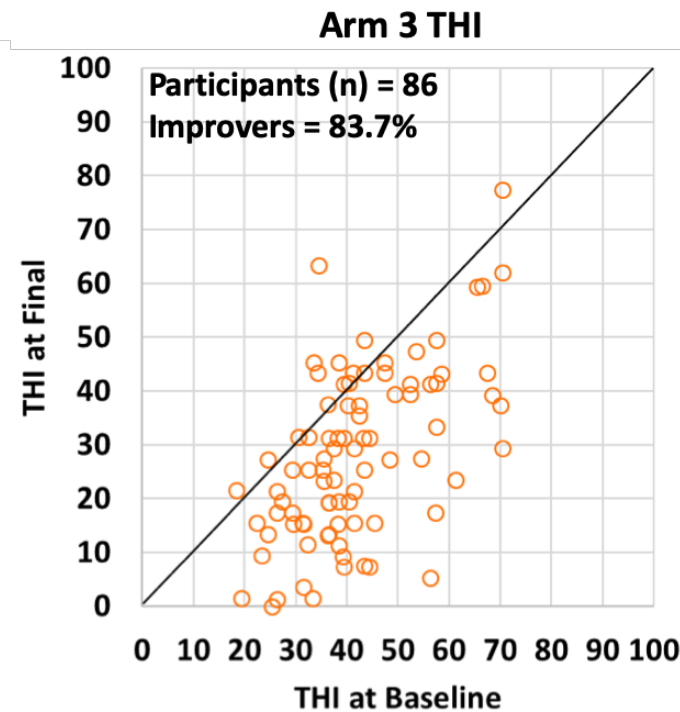
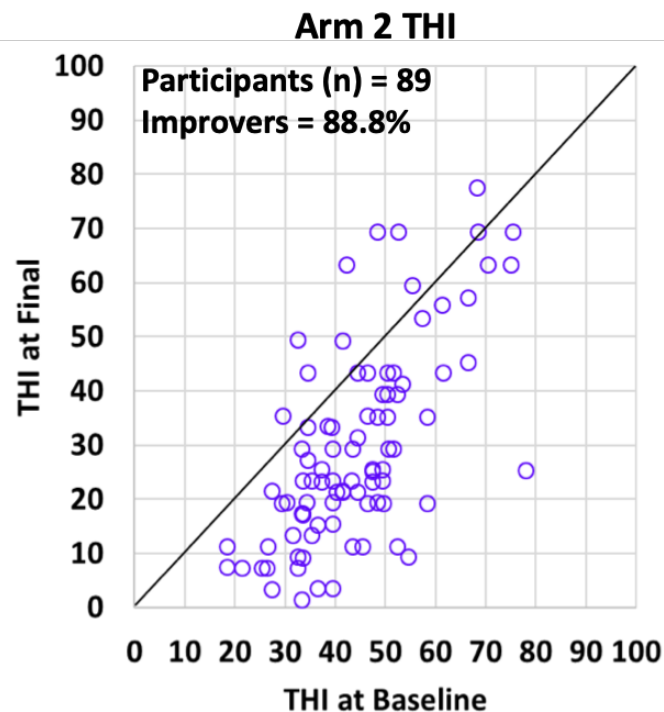
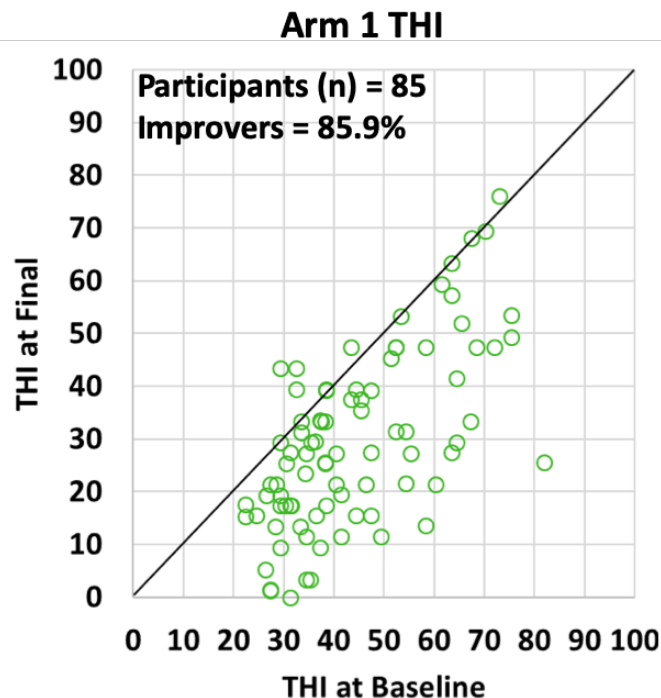
TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

Real World Data

Overall Conclusions



Mean THI Improvement:

14.6 points (p<0.001)

14.5 points (p<0.001)

13.5 points (p<0.001)

*Minimal Clinically Important Difference = 7 points
(MCID; Zeman et al. 2011)*

n = treatment-compliant participants for whom final visit data available and who had used the device per protocol for ≥ 36 hours.



TENT-A1 Results: Fast Acting and Sustained Therapeutic Effects Across Treatment Arms

*Arm 1 exhibits more sustained effects than Arm 3**

Background

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TENT-A1 Protocol

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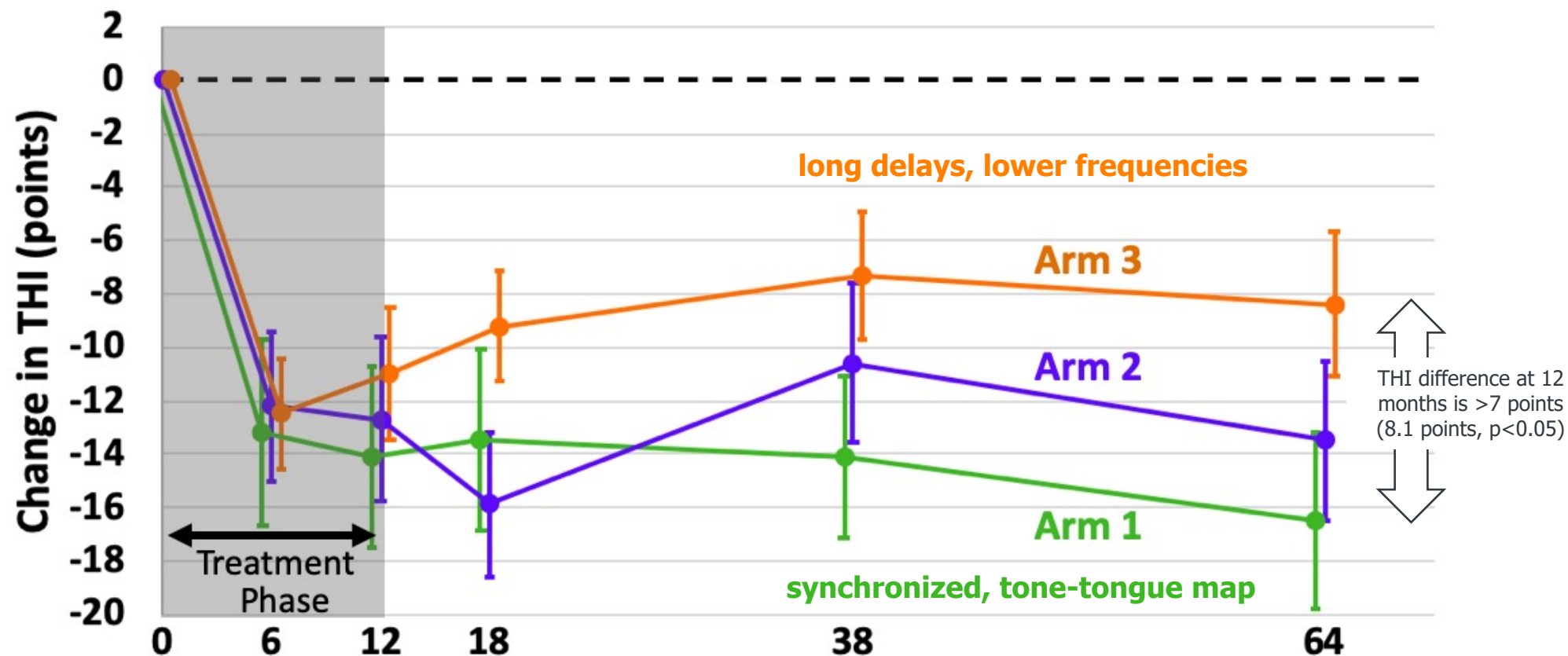


Figure includes subjects who came to all visits up to 12-months and who used the device per protocol for ≥ 36 hours. Arm 1 ($n=31$), Arm 2 ($n=41$), Arm 3 ($n=32$); mean and SEM bars shown. *Post-hoc analysis



TENT-A1 Results: Therapeutic Effects Last 12 Months After Completing Treatment

Background

TENT-A1 Objectives

TENT-A1 Protocol

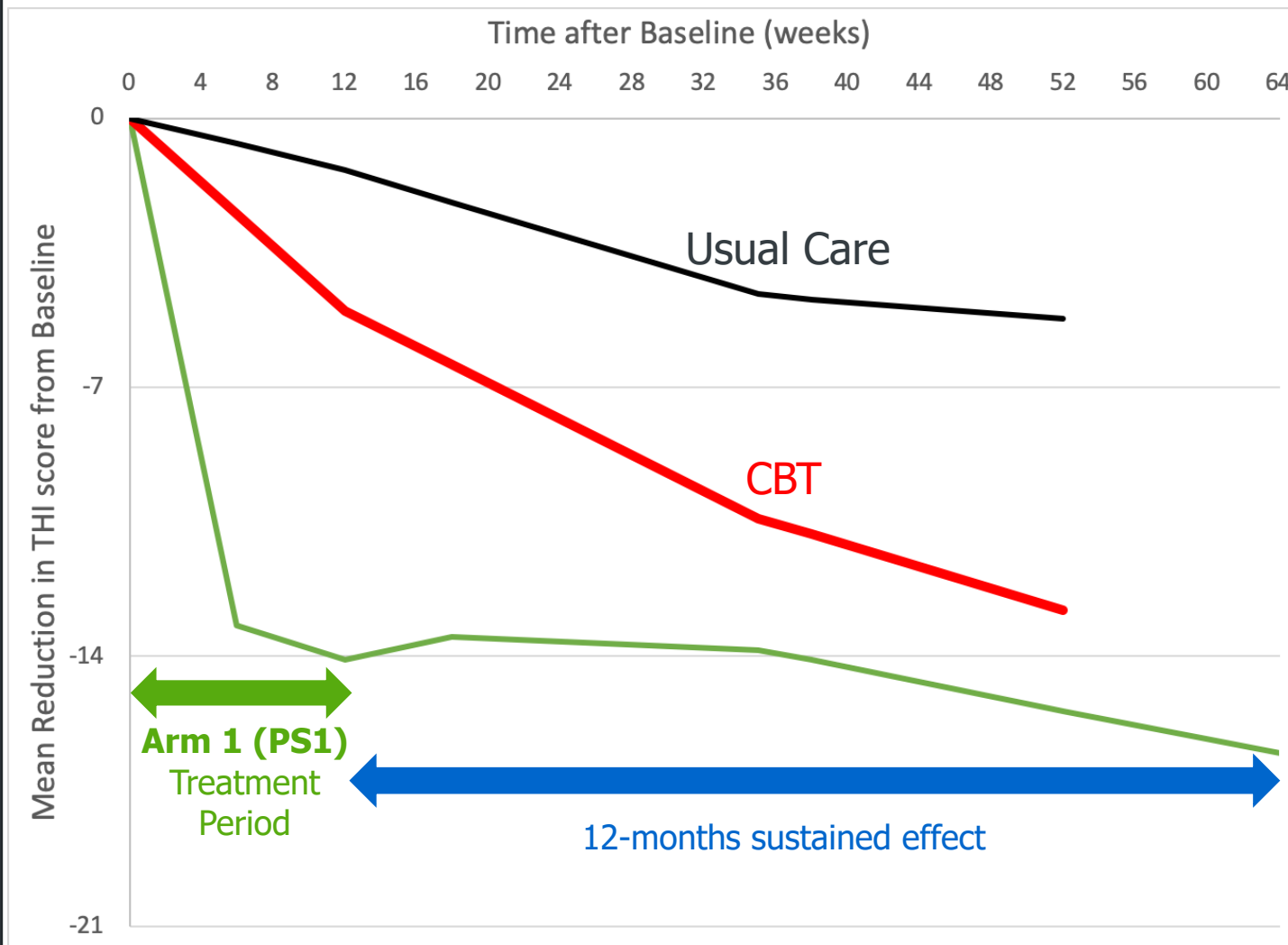
TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

Real World Data

Overall Conclusions



- Achieves our goal of fast-acting therapy like sound therapies but long-lasting effects like CBT
- Michigan study showed significant improvement with 4 weeks of treatment but tinnitus returned back to baseline after 3 weeks
- Is the long-term 12-month benefit in Neuromod study due to longer treatment (12 weeks vs. 4 weeks) or achieved by using tongue stimulation (vs. cheek or neck)?



TENT-A1: High Compliance (≥ 36 hours over 12 weeks) and Satisfaction Rates

Background

TENT-A1 Objectives

TENT-A1 Protocol

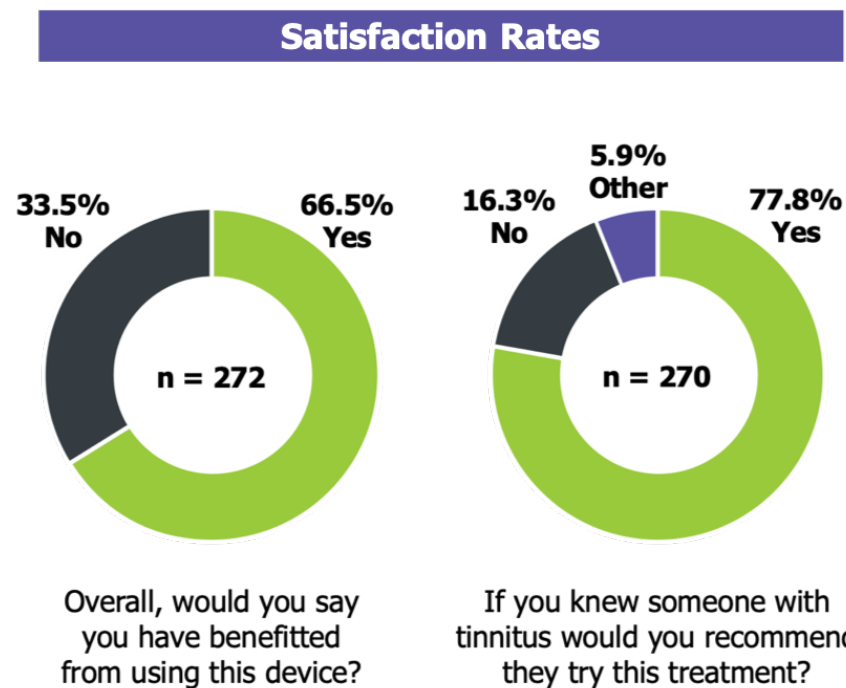
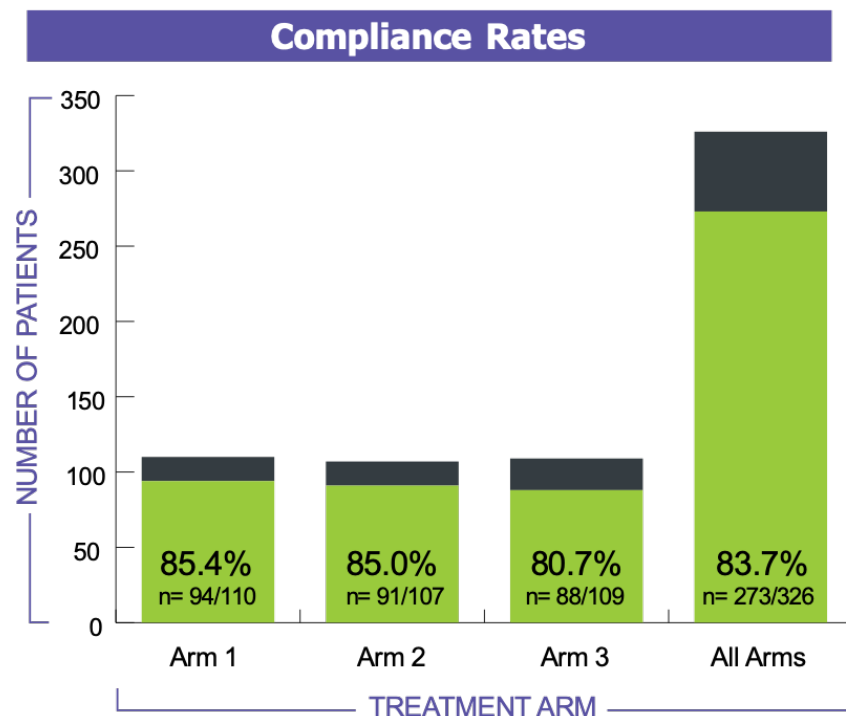
TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

Real World Data

Overall Conclusions





Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

TENT-A2 Objectives

TENT-A2 Protocol

TENT-A2 Results

Overall Conclusions

TENT-A1 Subtyping: Pre-Defined Subject Subgroups

- Subtyping results have been presented at previous conferences
- We will publish the subtyping results in a future publication



Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

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TENT-A1 Conclusions

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Overall Conclusions

TENT-A1 Conclusions: Full Cohort Results

- Overall, non-invasive bimodal neuromodulation combining sound and electrical somatosensory stimulation shows promise in the management of the symptoms of tinnitus, supported by findings from studies performed by three separate research groups
- For sound and tongue stimulation, we observed statistically significant improvements in tinnitus within 12 weeks of treatment
- The therapeutic effects could be sustained for 12 months after treatment, especially for Arm 1 (synchronized, tone-tongue mapped stimulation)
- Treatment appears to be safe with no treatment-related serious adverse events and with high satisfaction rates

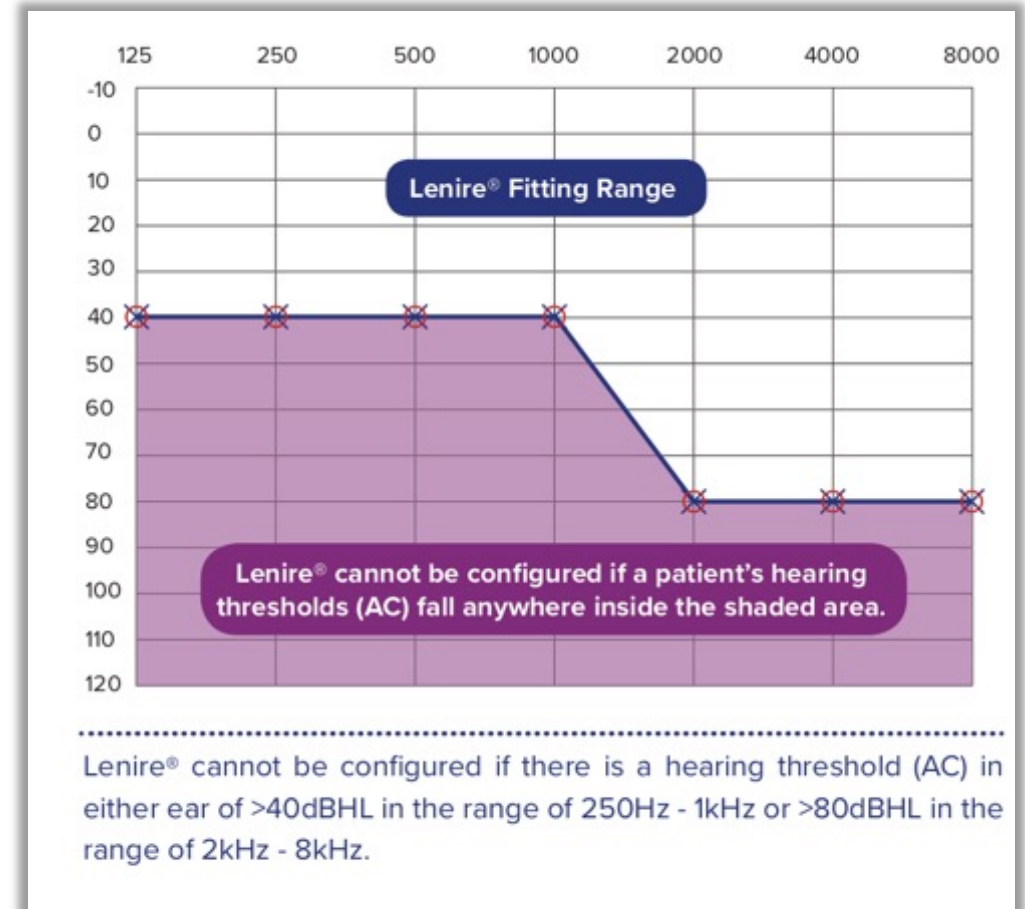
Real world data on the Lenire system at an independent clinic at Hannover Medical School (German Hearing Center)

A. Büchner, T. Frank, T. Lenarz
Hannover Medical School
Dept. Otorhinolaryngology
Chairman: Th Lenarz, MD PhD

Real World Lenire Data from Hannover Medical School/German Hearing Center

Lenire – Contraindications

- Active implantable devices
- Pregnancy
- Under 18 years old
- Lesions, sores or sensitivity of the tongue
- Epilepsy or other neurological conditions that lead to a loss of consciousness



Real World Lenire Data from Hannover Medical School/German Hearing Center

Patient Characteristics (**13 patients**; PS1 treatment)

TENT-A1 Criteria:

- 18 to 70 years of age
- Tinnitus duration: 3 months to 5 years

Real World Lenire Data from Hannover Medical School/German Hearing Center

Time between pre-treatment and follow-up assessment

Hannover Data (PS1)

TENT-A1 Data (PS1/Arm 1 Group)

Real World Lenire Data from Hannover Medical School/German Hearing Center

Change in Tinnitus Handicap Inventory (THI) Scores

Hannover Data (PS1)

TENT-A1 Data (PS1/Arm 1 Group)

- Significant improvements in tinnitus symptoms in patients who purchased the Lenire device in Hannover consistent with findings from TENT-A1 study

Real World Lenire Data from Hannover Medical School/German Hearing Center

Change in Tinnitus Handicap Inventory (THI) Scores: Individual Data

Hannover Data (PS1)

TENT-A1 Data (PS1/Arm 1 Group)

- Overall, distribution of THI scores are consistent between TENT-A1 study and the real world data



Background

TENT-A1 Objectives

TENT-A1 Protocol

TENT-A1 Results

TENT-A1 Subtyping

TENT-A1 Conclusions

Real World Data

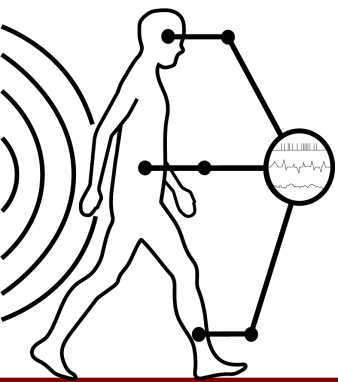
Overall Conclusions

Overall Conclusions

- Overall, non-invasive bimodal neuromodulation combining sound and electrical somatosensory stimulation shows promise in the management of the symptoms of tinnitus, supported by findings from studies performed by three separate research groups and one independent clinic
- For sound and tongue stimulation, we observed statistically significant improvements in tinnitus within 12 weeks of treatment
- The therapeutic effects could be sustained for 12 months after treatment, especially for Arm 1 (synchronized, tone-tongue mapped stimulation)
- Treatment appears to be safe with no treatment-related serious adverse events and with high satisfaction rates
- Real world data for Lenire treatment in an independent clinic at Hannover Medical School with 13 patients has been consistent with the results from the TENT-A1 clinical trial
- Improvements in tinnitus symptoms were slightly less, on average, in the real world data that may reflect the greater diversity in tinnitus patients coming to the clinics (i.e., narrower inclusion & exclusion criteria in TENT-A1). This question will be further investigated with larger real world datasets through additional clinical sites.

Bimodal Neuromodulation for Tinnitus Treatment

Thank you for your attention!
Questions?



TESSLab

Translational Energy Stimulation-Sensing Laboratory