Noninvasive Cochlear Stimulation System

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IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Michael J. Cevette, Ph.D.
Co-Principal Investigator: Gaurav Pradhan, Ph.D.

Study Title: Noninvasive Cochlear Stimulation System

Protocol version number and date: Protocol version 4, September 12, 2024

Research Question and Aims

Hypothesis: Can our team develop a potentially groundbreaking means of delivering sound that could change the way in which hearing care professionals can deliver hearing intervention as well as the way immersive reality systems communicate sound.

Aims, purpose, or objectives:

1. Develop a portable wearable hardware headset using a computer-based software that can establish the optimal stimulation parameters appropriate for medical and consumer environments for individuals with hearing impaired and normal hearing individuals.
2. Incorporate a noise cancellation technology for the cochlear system
3. Establish speech intelligibility above 90% for normal hearing individuals in quiet and 8/10 satisfaction of music.
4. Develop a surround sound system for entertainment and media

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Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Noninvasive electrostimulation of the cochlea has notable benefits for normal hearing and hearing-impaired individuals that extend well-beyond conventional acoustic and bone conducted enhancements of sound. Although the technique has been known since the 19th century little clinical attention or application of the technique has occurred, particularly related to a wearable technology for individual use. The present project will gather experts in the fields of clinical audiology, engineering, and acoustics to design and develop a wearable amplification device with the capability of an extended high frequency range for improved fidelity, directionality, noise cancellation, and surround sound. The markets targeted with this technology span the domains of hearing amplification, noise reduction, and entertainment and media.

Initial studies for an Army funded grant in 2019 showed excellent speech intelligibility in quiet and noise. The technology had the limitations of a single channel of stimulation reducing directionality, non-portability, and a reduced dynamic range of amplification. With the design and development of a new head worn system all the major limitations will be addressed widely enhancing the benefit to users and the markets they represent. [redacted]

The conventional transmission of sound is through air and bone conduction. Acoustic receivers and bone conduction transducers offer the capability to enhance hearing for a variety of uses in the world of sound. However, there is another approach to create the perception of sound that is largely ignored despite its notable and unique capabilities. Auditory electrostimulation has been known since the early 1800's when it was shown that electrical energy fields applied to the skin could create the perception of sound. Well known 19th century physicists, Volta and Fechner, experimented with "neurophonic hearing" to create a perception of sound. In the 1970's scientists discovered that the perception of sound could also be created through an electrode system with amplitude modulated electromagnetic signals to stimulate the cochlea directly.

A new technique of electrostimulation utilizes an audio signal to modulate a high frequency carrier wave (60 to 80 kHz) (Tonndorf and Kurman, 1984; Cevette et al, 2019). The combined signals are transmitted to the listener through pairs of externally applied electrodes at or near the head. The striking result is the perception by the listener of extremely high-fidelity broad-spectrum signals, ranging up to 20,000 Hz, without involvement of traditional acoustic transducers or the influence of the outer and middle ear structures. Because multiple pairs of electrodes are possible notable directionality using time and level of current through lateralization can create a surround sound experience. The outcome of this capability is a new product that addresses complex problems in hearing abnormalities inadequately addressed with conventional hearing devices by by-passing outer and middle ear structures and overcoming the limitations of currently available frequency ranges. The capability to provide localization of sound enhances the hearing experience for those individuals unfortunate to have asymmetrical hearing loss and single-sided deafness (SSD).

In 2019 the Aerospace Medicine and Vestibular Research Laboratory (AMVRL) and Vivonics won an award from the Department of Defense to use our technique to investigate whether we could provide a very high degree of speech intelligibility in quiet and extreme background noise (95 dB SPL) using our cochlear stimulation system. The military is interested in alternate modes of communication that will provide better

[redacted]
security in field applications. AMVRL successfully provided the benefits required by the Army by showing that through a one channel electrode array we were able to achieve 95.6% word recognition ability in quiet and 84.4% in the presence in a high noise level using appropriate ear protection. The non-portable system employed was fixed hardware instrumentation tethered to an electrical source.

[redacted]

The Mayo Clinic team has a long history of taking an idea from conception to commercialization. Over the past 15 years the team has completed a variety of topics but with notable development using galvanic vestibular stimulation (GVS) integrated with flight simulation to enhance training fidelity and reduce the reduction of simulator sickness [redacted] and the HearHook

[redacted]

Preliminary Results

The Mayo Clinic/Vivonics team demonstrated that speech could be delivered to the subject through the skin electrodes in a manner that allowed the subject to recognize 95.6% in quiet and 84.4% in extreme noise of the words in a 50 word Modified Rhyme Test (MRT). Additionally, a small battery powered breadboard prototype was developed demonstrating that the system was capable of being transformed into a portable system, which will be used to optimize the system prior to full miniaturization. Given these results, the team considers this initial effort highly successful and is the first step to realizing a potentially groundbreaking means of delivering sound that could change the way in which hearing care professionals can deliver hearing intervention as well as the way immersive reality systems communicate sound. The ability to lateralize electroacoustic sound with different electrode placement in conjunction with forehead bone conduction is shown in the Figure 1 below. The blue highlighted areas represent where the sound was perceived under the various conditions creating a pathway for surround sound with a multiple electrode array.

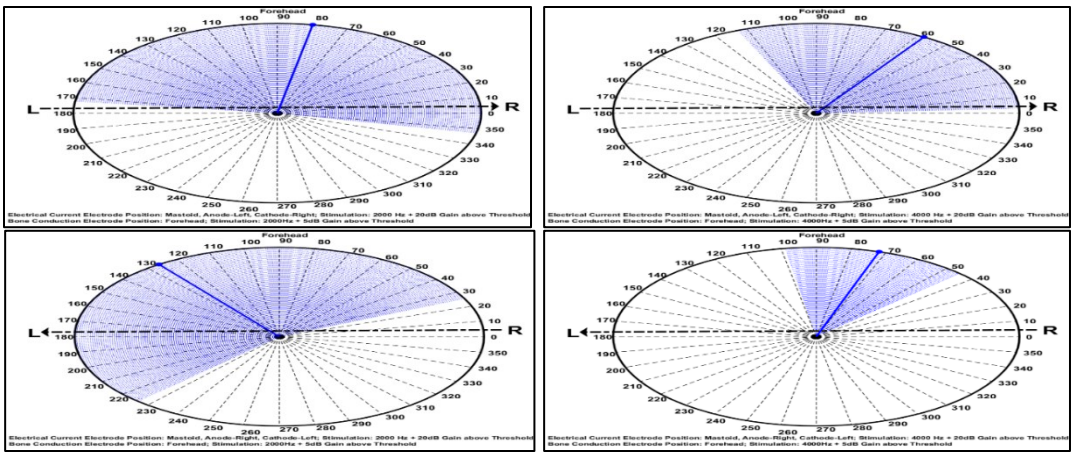

Figure 1. Lateralization plots by electrode placement using forehead bone conduction.

Key Objectives

1. Leverage the promising preliminary results with the overall objective to fully characterize the non-invasive cochlear stimulation system with multiple inputs and finalize concepts.
2. Based on the feedback from the initial study with the Army the team at Vivonics shall upon direction from Mayo Clinic upgrade, test, and demonstrate a benchtop system optimized for clinical studies.
3. Conduct comprehensive clinical trials that include amplitude requirements, threshold and suprathreshold studies, lateralization, and word recognition with 30 participants.
4. Integrate electrode inputs with multimicrophone noise cancellation.
5. Finalize systems with universal headset.
6. Conduct clinical trials integrating noise cancellation in the context of word recognition and lateralization for 20 normal hearing, 20 bilateral sensorineural, and 20 single-sided deafness participants

[redacted]

Specific Objectives	Quarter after Award								
	1	2	3	4	5	6	7	8	**Responsible**
1. ***Gather inputs and Finalize Concepts***									Mayo and Vivonics
2. ***Optimize Clinical System***									Mayo and Vivonics
3. ***Execute technology characterization study (n=30)***									Mayo Clinic
4. ***Integrate electrode inputs with microphone array***									MCK and Vivonics
5. Finalize systems with universal headset clinical trial									Mayo Clinic
6. Prepare technology for commercialization									Mayo Clinic

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Collaborators:

[redacted]

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Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

Following informed consent Mayo Clinic staff will evaluate the auditory perception of electrical stimulation by comparing the responses to traditional audiological threshold measures and word recognition. Each threshold from 250Hz through 20 KHz will be determined with a method of limits approach for both acoustic and electrostimulation. Once these thresholds are established then we will measure percent correct in standardized word recognition testing using isophonemes and words at a suprathreshold level of 60dB HL.

Of primary interest is the assessment of lateralization of sound within the head by employing 4 channels of electrostimulation to determine the place and degree of separation of sound compared to the traditional lateralization of ear-to-ear with traditional acoustic hearing. These measures will be conducted by changing the level and timing of current between electrode pairs. Given there are four electrode pairs we will establish the critical parameters for timing and current that yield specific patterns of lateralization. Data will be recorded on a spherical plot representing perception within the head.

Lateralization.
Subjects will have skin electrodes affixed to locations around their body (wrist, forearm, and base of the neck) and head (mastoids, forehead and nape of the neck) and will be placed in an acoustically sealed test room at Mayo Clinic. Two or more pairs of electrodes will be chosen until all 12 possible combinations are tested for current level and timing. At each test point, the perception threshold will be evaluated by increasing the amplitude of the current input until the subject can hear a tone. The threshold will be recorded as the perception threshold at that electrode pair and frequency.

Once the threshold is determined, the user will be asked to identify where they hear the sound and recorded on a 3-dimensional spherical plot. This angle will be recorded as the lateralization point at that electrode pair and frequency.

Modified Rhyme Test
The MRT is a speech intelligibility test consisting of a set of 50 six-item wordlists. Each word list contains single syllable words with a consonant-vowel-consonant sound sequence. Each group of words either rhymes (e.g., led, shed, red, bed, fed, wed) or starts with the same sound (e.g., sud, sum, sub, sun, sup, sung). The MRT is one of the speech intelligibility tests referred to in the American National Standard Method for Measuring the Intelligibility of Speech Over Communication Systems and is often used to test military communication systems.

First phase clinical trial:
1) 30 normal hearing participants will be recruited to measure amplitude, threshold, lateralization, and speech intelligibility using the prototype compared to conventional acoustic measures.

2) Parameters for electrode interaction between two channels of electrical stimulation by level of current and timing will be measured in the same participant pool.
3) Algorithms will be established for surround sound based upon the electrode interaction data.

Subjects will be seated in a comfortable chair in a sound treated test room (100dB of attenuation from outside sound). Standard insert earphones and surface electrodes will be used in acoustic and electrostimulation respectively. Acoustic signals will be generated by a standard diagnostic audiometer used in hearing evaluations. Electroacoustic signals will be generated by the Vivonics programmable prototype. The participant will respond to the auditory signals to indicate the lowest level of perception, the location of the signal within the head, and word recognition using a standard work recognition test.

Second phase clinical trial:
1) 15 bilateral hearing impaired, and 15 asymmetrical hearing-impaired participants will be recruited to evaluate directionality of the surround sound system for speech and music,
2) 30 normal hearing participants will be recruited to implement amplitude adjustments to offset simulated cochlear hearing loss with narrowband masking noise and compare the findings to standard acoustic measures of threshold and speech recognition.

Subjects will be seated in a comfortable chair in a sound treated test room (100dB of attenuation from outside sound). Standard insert earphones, bone conduction, and surface electrodes will be used in acoustic and electrostimulation respectively. Acoustic signals will be generated by a standard diagnostic audiometer and bone conduction used in hearing evaluations. Electroacoustic signals will be generated by the Vivonics programmable prototype. The participant will respond to the auditory signals to indicate the lowest level of perception, the location of the signal within the head, and word recognition using a standard work recognition test.

Standard clinical narrowband masking noise will be used to simulate hearing loss and assess the suprathreshold perception of electric signals. Narrowband masking noise will be introduced via earphones and will be presented at suprathreshold levels between 25-50 dB HL at all frequencies. The masking noise of a maximum of up to 50 dB HL is below than the sound levels categorized as " loud sound (> 85 dB SPL). In fact, the sound levels of normal speech are around 60 dB SPL. While this is occurring, the skin electrodes will be used as reported above, and the perception of the threshold will be evaluated with the addition of masking noise. This is to simulate a higher hearing threshold and assess if the electric signal can still be heard over the masking noise. This protocol is to further develop the modeling from the first phase that will be used to predict electric thresholds using air conduction threshold inputs.

In the second phase 8-space will be utilized which is an 8-speaker system that provide independent sound source as an evaluation of localization. The localization experiment will include electrostimulation data from the first phase in combination with a prototype multi-microphone headset to evaluate the necessary parameters for precise localization for bilateral, unilateral, and normal hearing participants. A signal-to-noise ratio of various levels will be adjusted to evaluate the efficacy of the noise cancellation system developed my MCK Audio. Participants will be asked to rate the quality of music of the electroacoustic system on a 1-10 scale.

Third phase clinical trial:

1) 30 normal hearing participants will be recruited to evaluate parameters of electrical stimulation for body-worn electrodes. Laterality and amplitude measures will be assessed for tone and speech stimuli.
2) All of the methods used in Phase 3 have been previously described and approved for Phases 1 and 2, with the difference lying in where the electrodes are placed on the body for Phase 3.

Following informed consent, the investigators will evaluate the auditory perception and magnitude of electrical stimulation at the wrist, forearm, and base of the neck by comparing the responses to those established at the forehead, mastoids, and neck. Each threshold from 250Hz through 20 KHz will be determined with a method of limits approach for both acoustic and electrostimulation. Once these thresholds are established, then we will test speech recognition at these distal locations by measuring percent correct in MRT testing at a suprathreshold level.

Of primary interest is the assessment of lateralization of sound when the electrodes are placed on the wrist, forearm, and back by employing unique channels of electrostimulation to determine the place and degree of separation of sound compared to the traditional lateralization of ear-to-ear with traditional acoustic hearing. Participants will have electrodes affixed to the three locations on their body (wrist, forearm, and base of the neck), and a matrix of possible combinations will be tested for perception threshold and location. At each test point, the perception threshold will be evaluated by increasing the amplitude of the current input until the subject can hear a tone. The location of the sound will be recorded on the three-dimensional spherical plot.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 100 subjects (30 for phase 1, 60 for phase 2, 30 for phase 3)

Subject population (children, adults, groups): Adults over the age of 21

Inclusion Criteria: Age range of 21-75

Exclusion Criteria: Pregnant, cochlear implants, history of fluctuating sensorineural hearing loss, skin diseases of the head, history of acute paroxysmal tachycardia, history of trigeminal neuralgia, recent of paralysis of the facial nerve, recent cerebrovascular stroke

Biospecimens-NOT APPLICABLE TO THIS STUDY

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

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☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: Not applicable at this time, technology currently in development

Data Analysis Plan: This

Data Analysis Plan: This systematic approach will provide the electrical hardware needs for prototype development, will characterize the electrode location dynamics, and will demonstrate the feasibility of clear speech understanding using the proposed concept. Furthermore, the resultant data can be extrapolated across other frequencies and input currents to deliver a highly effective and safe prototype at the end of this effort.

Endpoints:
Primary: Fully functional cochlear stimulation 2 channel headset with directivity and noise cancellation
Secondary: Fully functional cochlear stimulation 4 channel headset with directivity and noise cancellation
Related proprietary algorithms and software

[redacted]

Previous commercial successes
AMVRL and MCK Audio developed the HearHook and Amplified Surgical Face Mask that is currently available commercially [redacted] These hearing

[redacted]
systems allow for high intelligibility between 2 to 4 people up to 30 feet. The technology is currently being used in operating rooms to ensure optimal communication among surgical personnel overcoming noise, distance, and reverberation negatively impacting communication. AMVRL developed GVS virtual reality and flight simulation technology to enhance fidelity and mitigate motion sickness
[redacted]

Commercial applications
High fidelity hearing enhancement in unilateral, and bilateral hearing loss
Surround sound experience in entertainment and media
Noise cancellation in medical, military/aerospace, and entertainment environments.

References
Tonndorf, J, Kurman B. High Frequency Audiometry. Annals of Otology, Rhinology, and Laryngology 93(1984) 576-582.
Cevette MJ, Stepanek J, Pradhan G, Brookler K. Cochlear Stimulation System with Surround Sound and Noise Cancellation. US Patent application #16/083,656. Mayo Clinic.