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TITLE: Hearing Restoration Through Synaptic Plasticity Directed by Vagus Nerve Stimulation

PRINCIPAL INVESTIGATOR: Dr. Michael Kilgard

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14. ABSTRACT Individuals with hearing loss lack any consistently effective interventions to restore normal hearing, especially in noisy environments. The goal of this study is to produce a novel therapy to improve speech intelligibility for people with noise-induced hearing loss. This project will provide the critical proof-of-concept demonstration that vagus nerve stimulation (VNS) paired with auditory therapy can direct highly effective synaptic plasticity to restore speech processing in a rat model of hearing loss. Our results confirm that noise exposure produces significant, long lasting behavioral impairments and degraded neural responses to sound. Initial preliminary results indicate that VNS-sound pairing therapy can restore speech discrimination ability and strengthen neural responses to sounds. The development of this therapy to improve hearing function would yield clear benefits for patients with hearing loss, most notably enhanced communication and increased quality of life. Successful development and translation of this flexible platform technology has the potential to fundamentally impact the treatment of hearing impairments.					
15. SUBJECT TERMS Vagus nerve stimulation; hearing loss; noise exposure; speech; auditory processing; cortex					
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1. INTRODUCTION:

Hearing loss is the second most common service-connected disability, and most patients are not satisfied with the current technology developed to treat it. Individuals with hearing loss lack any consistently effective interventions to restore normal hearing, especially in noisy environments. Rather than trying to treat the damage done to the ear, the goal of the study is to develop a method to improve the way the brain processes speech after hearing loss. The goal of this study is to produce a novel therapy to improve speech intelligibility for people with noise-induced hearing loss. By pairing vagus nerve stimulation with speech, we expect to drive neural plasticity mechanisms to more effectively compensate for cochlear damage and more efficiently encode critical acoustic information required for high fidelity speech processing. There is every reason to believe that neural plasticity mechanisms can be harnessed so that patients can benefit more from the hearing that they have left. The goal is to restore productivity and quality of life for individuals with moderate hearing loss. Successful treatment could yield benefits for years without further therapy. The proposed study will provide the initial proof-of-concept rat study needed to begin human clinical trials. Our group has twice converted proof-of-concept rat studies into successful clinical trials in three years' time. If the project is successful in rats, it is reasonable to expect that this therapy would be tested in patients within the same timeframe. The proposed research project represents the critical next step to testing a completely new approach to treat one of the most common and debilitating conditions in the world.

2. KEYWORDS:

Vagus nerve stimulation; hearing loss; noise exposure; speech; auditory processing; cortex

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Aim 1: To document improved speech discrimination in noise-exposed rats following VNS+Speech pairing

Milestones achieved: Obtain ACURO approval, Complete behavioral data collection for speech discrimination +/- VNS after noise trauma in n = 5 per group, Finalize behavioral data collection for speech discrimination +/- VNS after noise trauma in all subjects, and Complete analysis of speech discrimination behavioral data and draft manuscript and submission of manuscript detailing experimental results to a peer-reviewed journal.

Aim 2: To characterize auditory network plasticity in noise-exposed rats following VNS+Speech pairing

Milestones achieved: Complete high-density microelectrode mapping of multiple auditory brain areas +/- VNS after noise trauma in n = 5 per group, Finalize high-density microelectrode mapping of multiple auditory brain areas +/- VNS after noise trauma in all subjects, and complete analysis of VNS-dependent plasticity in multiple brain areas after noise trauma and draft manuscript.

Upcoming milestones: Submission of manuscript detailing experimental results to a peer-reviewed journal.

This is the final report for the project.

Specific Aim 1 is to document improved speech discrimination in noise-exposed rats following VNS-sound pairing. We completed the milestone for subtask 1.1: ‘submit and obtain ACURO approval’, on 7/26/2018. We completed Subtask 1.2: ‘complete behavioral data collection for speech discrimination +/- VNS after noise trauma in n = 5 per group’ in a previous quarter. Subtask 1.3: ‘finalize behavioral data collection for speech discrimination +/- VNS after noise trauma in all subjects (n = 10 per group)’ was completed during a previous quarter. Subtask 1.4: ‘complete analysis of speech discrimination behavioral data and draft manuscript’ was completed during the previous quarter.

Specific Aim 2 is to characterize auditory network plasticity in noise-exposed rats following VNS-sound pairing. We completed Subtask 2.1: ‘complete high-density microelectrode mapping of multiple auditory brain areas +/- VNS after noise trauma in n = 5 per group’ in a previous quarter. Subtask 2.2: ‘finalize high-density microelectrode mapping of multiple auditory brain areas +/- VNS after noise trauma in all subjects (n = 10 per group)’ was completed during a previous quarter. Subtask 2.3: ‘complete analysis of VNS-dependent plasticity in multiple brain areas after noise trauma and draft manuscript’ complete and will be submitted to a peer-reviewed journal this summer.

What was accomplished under these goals?

We recently submitted a manuscript detailing the behavioral deficits observed following noise-induced hearing loss (NIHL). One month after noise exposure, we stratified rats into three distinct deficit groups based on their auditory brainstem response (ABR) thresholds. These groups exhibited markedly different behavioral outcomes across a range of tasks. Rats with moderate hearing loss (30 dB shifts in ABR threshold) were not impaired in speech sound detection or discrimination (Figure 1a,d). Rats with severe hearing loss (55 dB shifts) were impaired at discriminating speech sounds in the presence of background noise (Figure 1b,e). Rats with profound hearing loss (70 dB shifts) were unable to detect and discriminate speech sounds above chance level performance (Figure 1c,f).

Each of these groups had distinct alterations in their ABR profiles following NIHL (Figure 2a). One hour of high intensity noise substantially altered ABR amplitudes (Figure 2b) and thresholds (Figure 2c). Across groups, ABR threshold accurately predicted behavioral performance on all tasks (Figure 3).

All 3 groups reflect clinically relevant conditions. The profound group reflects deaf and nearly-deaf patients with little ability to detect and discriminate sounds. The severe group mirrors the chief complaints of patients with noise-induced hearing loss: difficulty discriminating speech sounds—especially in noisy environments. The moderate group echoes observations of physiological changes in patients without overt behavioral manifestations. These models, individually and as a whole, provide a framework for investigations into the broad range of physiological and behavioral outcomes associated with NIHL as well as the development of novel plasticity-based treatments.

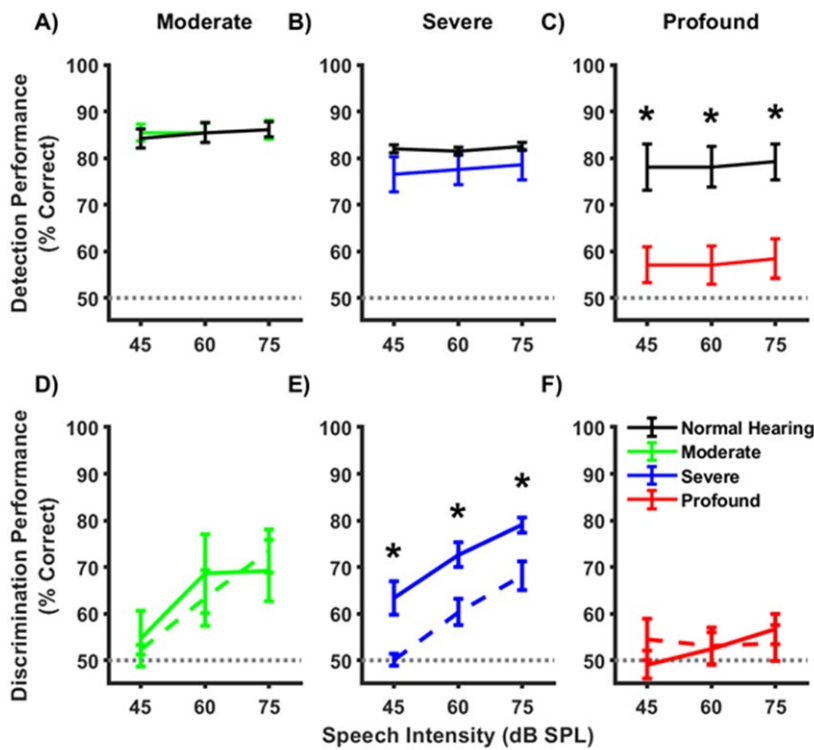


Figure 1. Behavioral performance on detection and discrimination tasks. Performance on detection in quiet before noise induced hearing loss (A-C, solid black lines) and after noise induced hearing loss (A-C, colored lines). Performance on discrimination in quiet (D-F, solid colored lines) and in noise (D-F, dashed colored lines). Stars represent significant impairment in behavioral performance after either noise exposure (C) or in presence of noise (E) ($p < 0.01$, Bonferroni corrected). Data are the average performance from 10 sessions each for normal hearing before noise exposure (week 4, top row), detection performance after NIHL (week 14, top row), discrimination in quiet (week 20, bottom row), and discrimination in noise (week 23, bottom row). Error bars represent SEM and the dashed line at 50% correct indicates chance performance.

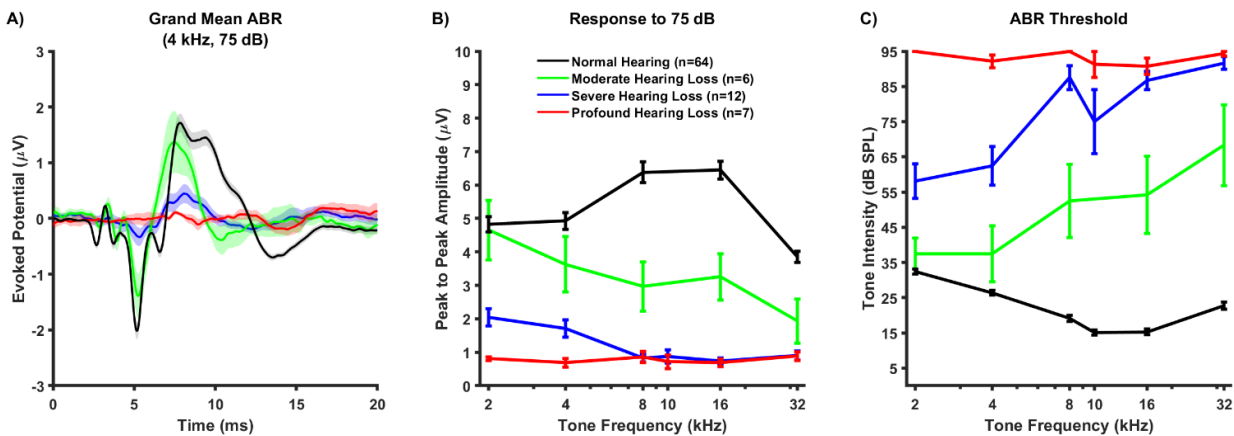


Figure 2. ABR outcome metrics for normal hearing, moderate hearing loss, severe hearing loss, and profound hearing loss groups 4 weeks after noise exposure. A) Grand mean average evoked potentials for a 4 kHz, 75 dB SPL tone with gray shading indicating SEM across rats. B) Peak-to-peak amplitudes for maximal evoked potential for 75 dB tones as a function of tone frequency from 2-32 kHz. C) ABR threshold as defined by the minimum tone intensity required to reliably elicit an evoked response as a function of tone frequency from 2-32 kHz with error bars indicating SEM.

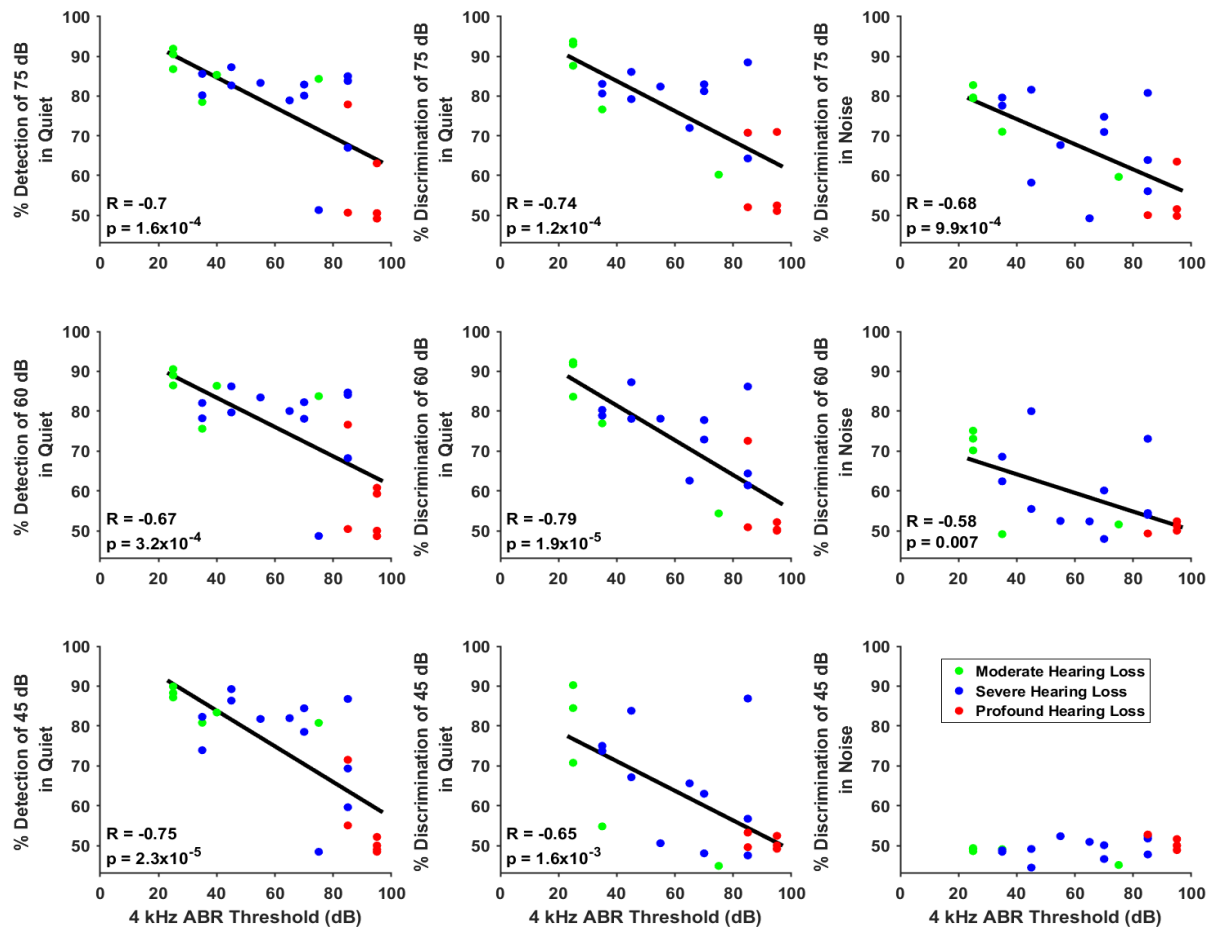


Figure 3. Correlations between 4 kHz ABR threshold and behavioral performance at 45, 60, and 75 dB on detection in quiet (left column), discrimination in quiet (center column), and discrimination in noise tasks (right column). Solid black lines denote significant correlations between 4 kHz ABR threshold and behavioral performance on each of the tasks and are fitted as least-squares. Each dot represents a single animal's ABR threshold and behavioral performance and least-squares regression lines (black line) are plotted where $p < 0.05$.

Additionally, we are currently preparing a manuscript for submission that details the improvement in neural responses following VNS-sound pairing therapy. Our results indicate that the subcortical inferior colliculus responses to sounds are improved in noise-exposed rats following VNS-sound pairing therapy compared to sham therapy (Figure 4).

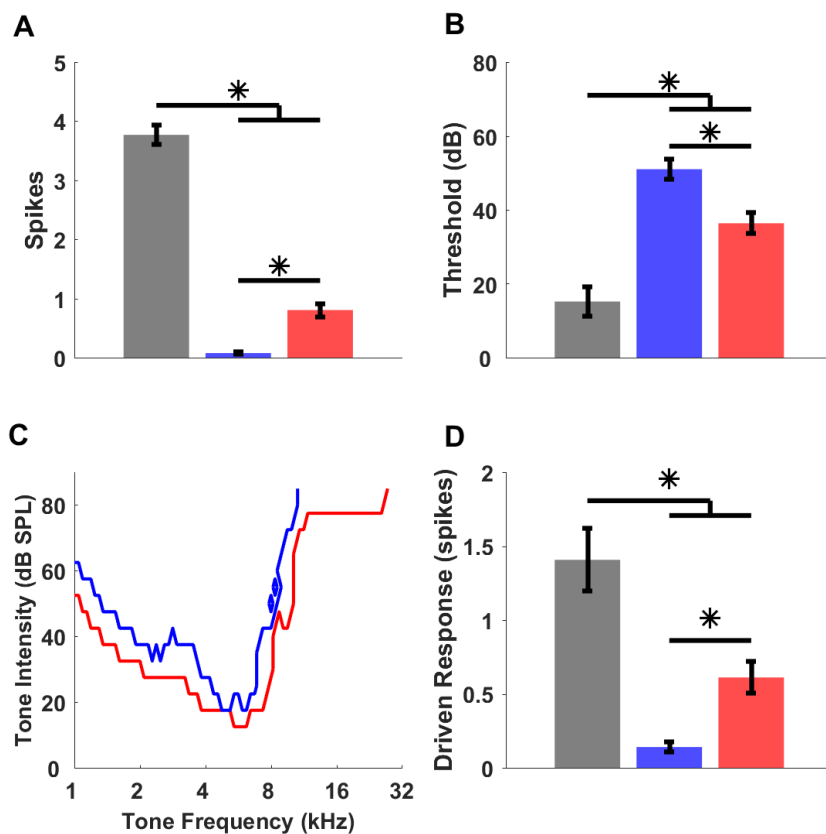


Figure 4. VNS-sound pairing improves the inferior colliculus response to sound. A) The IC response strength to high frequency tones is greatly diminished following noise exposure, and partially restored following VNS-sound pairing. Asterisks indicate statistically significant differences between groups. Error bars indicate SEM across rats ($n=4$ rats per group). B) The IC response threshold across the tested frequency range (1-32 kHz) is increased following noise exposure, and partially restored following VNS-sound pairing. C) The IC response threshold is plotted by tone frequency for sham therapy rats (blue) and VNS-sound paired rats (red). VNS-sound pairing lowered the response threshold and increased the frequency range that responded to tones. D) The IC response strength to the paired speech sound 'shad' was greatly reduced following noise exposure, and partially restored following VNS-sound pairing.

What opportunities for training and professional development has the project provided?

This project provided the opportunity to participate in the 23rd International Congress on Acoustics.

How were the results disseminated to communities of interest?

Results have been disseminated at the following conference: the 23rd International Congress on Acoustics in Aachen, Germany in September 2019.

- Targeted neuroplasticity in rat primary auditory cortex with vagus nerve stimulation and near-threshold tones
- Reversing degraded auditory processing using targeted plasticity

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to Report.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The initial findings from this study indicate that pairing stimulation of the vagus nerve with the presentation of sound therapy may restore the ability to discriminate speech in subjects with hearing loss. The proof-of-concept preclinical data collected as part of this project has motivated the submission of a subsequent funding application to translate this innovative therapy to clinical evaluation. We fully expect to continue the development of this promising therapy for use in patients with hearing loss.

What was the impact on other disciplines?

The development of VNS paired with sensory training to restore lost sensory function has led to further development of VNS strategies to treat other domains of sensory dysfunction. Based on findings from the present project, we are pursuing the use of VNS paired with sensory retraining to restore tactile sensation in a model of peripheral neuropathy.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Nothing to Report.

Changes in approach and reasons for change

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Not applicable.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

• **Publications, conference papers, and presentations**

Journal publications.

Riley JR, Borland MS, Tamaoki Y, Skipton SK, Engineer CT. Auditory brainstem responses predict behavioral deficits in rats with varying levels of noise-induced hearing loss. Submitted to the journal *Neuroscience*. Acknowledgement of federal support: yes.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

- September 2019 Alan Carroll- presented VNS paired with quiet tones and how this approach can help design better clinical auditory treatments for conditions like tinnitus
 - Targeted neuroplasticity in rat primary auditory cortex with vagus nerve stimulation and near-threshold tones
 - 23rd International Congress on Acoustics- Aachen, Germany
- September 2019 Yuko Tamaoki- presented projects on how VNS paired with sound presentations can reverse the maladaptive plasticity acquired through noise trauma
 - Reversing degraded auditory processing using targeted plasticity
 - 23rd International Congress on Acoustics- Aachen, Germany

• **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

UTD 20004

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- **Other Products**

The initial findings from this study indicate that pairing stimulation of the vagus nerve with the presentation of sound therapy may restore the ability to discriminate speech in subjects with hearing loss. Additionally, we provide initial evidence of the neural mechanisms that support these benefits. These findings advance the field of hearing loss research and will be published.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Michael Kilgard
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-6699-1818
Nearest person month worked:	2
Contribution to Project:	Dr. Kilgard has performed work in the area of experimental design.
Name:	Seth Hays
Project Role:	co-I
Researcher Identifier (e.g. ORCID ID):	0000-0003-4225-241X
Nearest person month worked:	1
Contribution to Project:	Dr. Hays has performed work in the area of experimental design.
Name:	Crystal Engineer
Project Role:	co-I
Researcher Identifier (e.g. ORCID ID):	0000-0002-2188-2335
Nearest person month worked:	7
Contribution to Project:	Dr. Engineer has performed work in the area of experimental design.
Name:	Michael Borland
Project Role:	Postdoc
Researcher Identifier (e.g. ORCID ID):	0000-0002-0901-4965
Nearest person month worked:	22
Contribution to Project:	Dr. Borland has performed work in the area of noise exposure and data collection.
Name:	Jonathan Riley
Project Role:	Graduate student
Researcher Identifier (e.g. ORCID ID):	0000-0003-0129-3071
Nearest person month worked:	21
Contribution to Project:	Jonathan has performed work in the area of noise exposure and data collection.
Name:	Alan Carroll
Project Role:	Graduate student
Researcher Identifier (e.g. ORCID ID):	0000-0002-9917-6350
Nearest person month worked:	15
Contribution to Project:	Alan has performed work in the area of noise exposure and data collection.
Name:	Yuko Tamaoki
Project Role:	Student technician
Researcher Identifier (e.g. ORCID ID):	0000-0002-5102-9167
Nearest person month worked:	6
Contribution to Project:	Yuko has performed work in the area of noise exposure and data collection.

Name: Collin Chandler
Project Role: Student technician
Researcher Identifier (e.g. ORCID ID): 0000-0002-9375-990X
Nearest person month worked: 11
Contribution to Project: Collin has performed work in the area of behavioral and physiology data collection.

Name: Khalil AbedRabbo
Project Role: Laboratory Manager
Researcher Identifier (e.g. ORCID ID): 0000-0003-0943-3796
Nearest person month worked: 2
Contribution to Project: Khalil has facilitated noise exposure, surgical teams, and data collection.

Name: Tanya Danaphongse
Project Role: Research assistant
Researcher Identifier (e.g. ORCID ID): 0000-0003-2125-2082
Nearest person month worked: 3
Contribution to Project: Tanya has performed work in the area of surgical procedures and data collection.

Name: Alfonso Reyes
Project Role: Student Technician
Researcher Identifier (e.g. ORCID ID): 0000-0002-4913-1859
Nearest person month worked: 3
Contribution to Project: Alfonso has facilitated device development, testing, and data collection.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

1. Riley JR, Borland MS, Tamaoki Y, Skipton SK, Engineer CT. Auditory brainstem responses predict behavioral deficits in rats with varying levels of noise-induced hearing loss. Submitted to the journal *Neuroscience*.
Acknowledgement of federal support: yes.