AWARD NUMBER: W81XWH-18-1-0399

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

PRINCIPAL INVESTIGATOR: Dr. Michael Kilgard

CONTRACTING ORGANIZATION: University of Texas at Dallas
Richardson, TX 75080

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TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER
W81XWH-18-1-0399

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. Seth Hays, Dr. Crystal Engineer Dr. Michael Kilgard

E-Mail: kilgard@utdallas.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

UNIVERSITY OF TEXAS AT
DALLAS800 W CAMPBELL
RDRICHARDSON TX 75080-1407

8. PERFORMING ORGANIZATION REPORT NUMBER

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U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	56	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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:** *Provide a brief list of keywords (limit to 20 words).*

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

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

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

Milestones achieved: Obtain ACURO approval

Upcoming milestones: Documentation of the ability of VNS+Speech to significantly improve recovery of speech discrimination after noise trauma compared to speech exposure alone, 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

Upcoming milestones: Documentation of the ability of VNS+Speech to reverse maladaptive plasticity in auditory networks after noise trauma, submission of manuscript detailing experimental results to a peer-reviewed journal

This is the first annual report for the proposed project. We are on schedule to complete all milestones as originally proposed.

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 the present quarter. Subtask 1.3: 'finalize behavioral data collection for speech discrimination +/- VNS after noise trauma in all subjects (n = 10 per group)', is currently in progress, and is more than 50% complete.

Specific Aim 2 is to characterize auditory network plasticity in noise-exposed rats following VNS-sound pairing. This quarter, we completed Subtask 2.1: 'complete high-density microelectrode mapping of multiple auditory brain areas +/- VNS after noise trauma in n = 5 per group'. Subtask 2.2: 'finalize high-density microelectrode mapping of multiple auditory brain areas +/- VNS after noise trauma in all subjects (n = 10 per group)', is currently in progress, and we anticipate completing Subtask 2.2 on schedule.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

In the initial phase of the project, we developed a reliable model of noise exposure to induce hearing loss (Fig. 1).

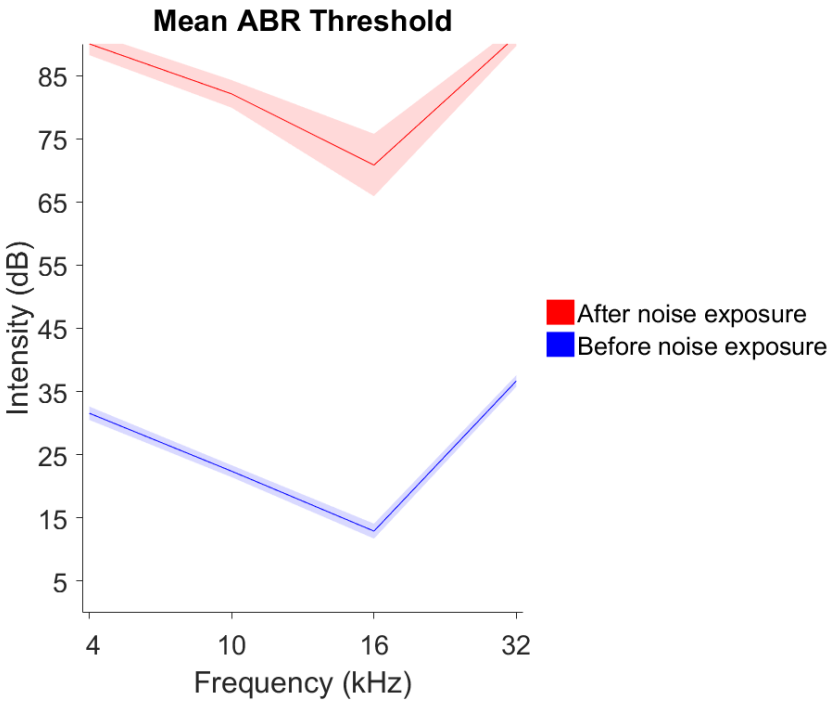

Figure 1. Noise exposure produces significant, long lasting elevation of hearing thresholds. *The blue line indicates rat hearing thresholds prior to noise exposure. The red line indicates rat hearing thresholds one month after noise exposure. Colored patching indicates standard error across rats. These results confirm that noise exposure produces significant, long lasting elevation of hearing thresholds, which are comparable to those that occur in military and civilian populations*

We then applied this model of noise exposure to induce hearing loss to rats trained to perform a speech detection task. As in our previous studies, rats successfully acquire the task and demonstrate stable performance well above chance. Behavioral performance on the task is significantly reduced following noise exposure, indicating loss of speech discrimination (Fig. 2).

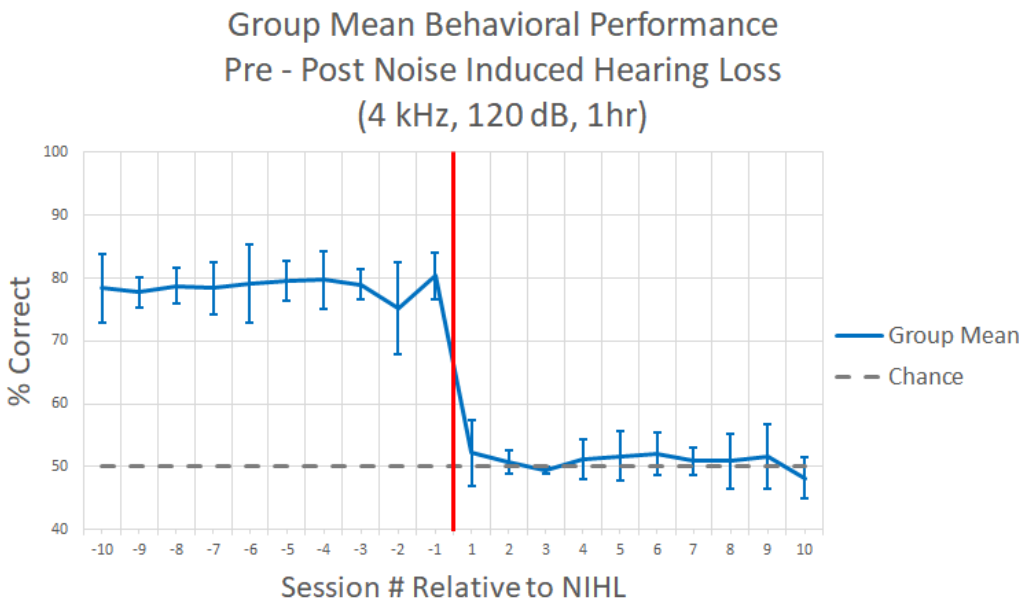

Figure 2. Behavioral performance is reliably impaired following noise induced hearing loss. *The blue line indicates the mean behavioral performance on an auditory detection task. Prior to noise induced hearing loss the rats consistently detected the presentation of a speech sound. One month after noise induced hearing loss the rats consistently struggle to detect the same auditory cue. The red line delineates pre- and post- noise induced hearing loss phases of testing while the dashed gray line indicates chance performance on the task. This is the most extreme hearing loss group and we expect the next groups to have less complete hearing loss. These results confirm that noise exposure produces significant, long lasting behavioral impacts, which are comparable to those that occur in military and civilian populations.*

We next tested whether VNS paired with sound therapy would improve speech discrimination performance after noise trauma (Fig. 3). Before noise exposure, rats can accurately detect the presentation of a speech sound (Fig. 3, 'Pre'). Rats were then exposed to one-octave broadband noise for one hour at 120 dB. The rats were then implanted with VNS cuffs and received VNS-sound pairing or sham therapy. Following therapy, rats were tested on their ability to discriminate between speech sounds. As expected, noise exposure substantially impaired speech discrimination in both groups. On Week 1 of behavioral testing, rats in both the Sham and VNS groups were unable to accurately discriminate between speech sounds (Fig. 3, 'Week 1'). However, on Week 6 after therapy, VNS paired with sound therapy improved the ability of rats to accurately discriminate between speech sounds (Fig. 3, 'Week 6'). These findings providing initial proof-of-concept data that VNS paired with sound therapy can restore speech processing in the context of hearing loss.

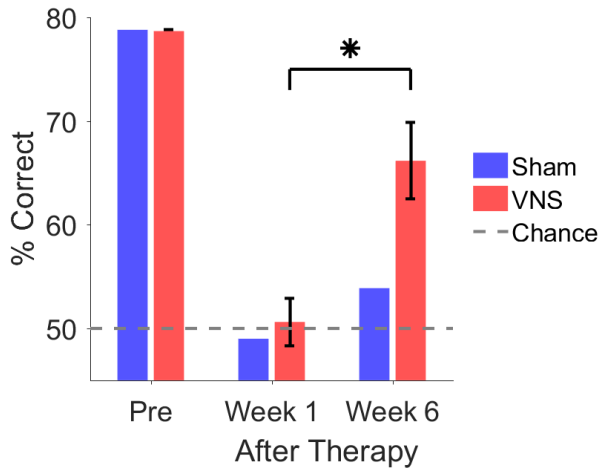

Figure 3. Behavioral discrimination performance is restored following VNS-sound pairing therapy. *Prior to noise induced hearing loss the rats consistently detected the presentation of a speech sound (Pre). Following noise exposure and sham or VNS-sound pairing therapy, rats were tested on their ability to discriminate between speech sounds. The dashed gray line indicates chance performance. While both experimental groups were unable to discriminate between speech sounds on Week 1, by Week 6, VNS-sound pairing rats were able to reliably discriminate between speech sounds. These results provide an initial demonstration confirming that VNS-sound pairing therapy can significantly improve recovery of speech discrimination after noise trauma.*

We next sought to evaluate neural changes that accompany VNS dependent restoration of speech processing after hearing loss. To do so, we performed high-density microelectrode mapping of auditory cortex in animals that had received noise trauma and either NVS paired with sound therapy or sham stimulation and sound therapy, as well as naïve rats. Initial data suggests that VNS paired with sound therapy improves neural responses after noise trauma (Fig. 4). Before noise exposure, rats respond robustly to the presentation of tones (Fig. 4a, 'Naive'). Noise trauma substantially decreased the response strength to tones (Fig. 4a, 'Sham'). However, following VNS paired with sound therapy, the response strength to tones was strengthened (Figure 4a, 'VNS'). Similarly, the neural response strength to speech sounds is decreased following noise exposure (Fig. 4b, 'Sham'). VNS therapy significantly strengthens the response of neurons in auditory cortex to speech sounds (Fig. 4b, 'VNS').

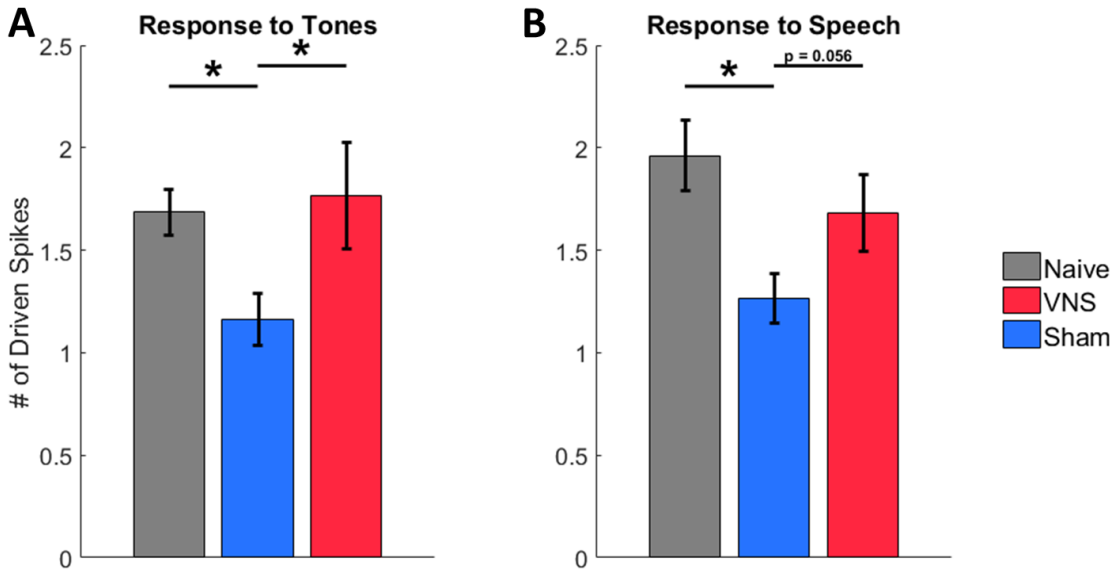

Figure 4. Neural responses to sounds are strengthened following VNS-sound pairing therapy. *A) The neural response to tones in primary auditory cortex (A1) was weaker in noise exposed rats following sham therapy (blue line) compared to experimentally naïve rats (black line), but was strengthened in noise exposed rats following VNS-sound pairing (red line). B) The response to the speech sound 'shad' presented at 75b dB intensity is decreased following noise exposure (NIHL + Sham, blue bar), and this response is strengthened in noise exposed animals following VNS-sound pairing therapy (NIHL + VNS, red bar).*

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This project provided the opportunity to participate in the International Hearing Loss Conference and the 23rd International Congress on Acoustics.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Results have been disseminated at the following conferences: International Hearing Loss Conference in Ontario, Canada and the 23rd International Congress on Acoustics in Aachen, Germany.

- May 2019
    - Cortical and Subcortical Effects of noise intensity and frequency on noise induced hearing loss in rats
    - International Hearing Loss Conference- Ontario, Canada
- May 2019
    - Vagus nerve stimulation paired with sounds alters auditory processing in rats
    - International Hearing Loss Conference- Ontario, Canada
- September 2019
    - Targeted neuroplasticity in rat primary auditory cortex with vagus nerve stimulation and near-threshold tones
    - 23rd International Congress on Acoustics- Aachen, Germany
- September 2019
    - Reversing degraded auditory processing using targeted plasticity
    - 23rd International Congress on Acoustics- Aachen, Germany

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

During the next reporting period, noise exposed and sham control rats will continue progressing through the VNS-sound pairing therapy protocol. We will continue collecting speech discrimination data from these rats. We will continue collecting high-density microelectrode mapping of multiple auditory brain areas.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to Report

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to Report

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

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: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

- Michael S. Borland, Will A. Vrana, Nicole A. Moreno, Elizabeth A. Fogarty, Elizabeth P. Buell, Sven Vanneste, Michael P. Kilgard, and Crystal T. Engineer; Pairing vagus nerve stimulation with tones drives plasticity across the auditory pathway; Journal of Neurophysiology; Volume 122, Issue 2, August 2019, Pages 659-671; **https://doi.org/10.1152/jn.00832.2018**

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time*

conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

- May 2019 Jonathan Riley- presented VNS work
    - Cortical and Subcortical Effects of noise intensity and frequency on noise induced hearing loss in rats
    - International Hearing Loss Conference- Ontario, Canada
- May 2019 Crystal Engineer- presented VNS work
    - Vagus nerve stimulation paired with sounds alters auditory processing in rats
    - International Hearing Loss Conference- Ontario, Canada
- 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)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://www.utdallas.edu/txbdc/engineer/: This website provides an overview of current research, publications, recent news, as well as biographical information of the lab members.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

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 once data collection and analysis is complete.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Michael Kilgard
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-6699-1818
Nearest person month worked: 0
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: 0
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: 1
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: 2
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: 3
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: 3
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: 3
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: 1
Contribution to Project: Collin has performed work in the area of behavioral and physiology 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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Kilgard Active Award Updates

Awards that Ended

Rett,
Wings for Life Research Grant
Caruth

Updated Performance Period

Aged Stroke
NIH R01NS085167-01
Performance Period: 6/1/14-4/30/**20 (on NCE)**

Updated Time Commitments, Performance Period, Level of Funding, and Added an Aim

ElectRx
DARPA ElectRx N66001-15-2-4057
Time Commitments: 2 months per year in years 1 and 2, 0.5 months per year in years 3 and 4, **2 months per year in years 5 and 6**
Performance Period: 9/1/15-**9/21/21**
Level of Funding: **$6,995,309**
Aims:
…
5 Clinical Evaluation of VNS Therapy for PTSD
5.1 Gain Regulatory Approval for a Pilot Trial of VNS Therapy for PTSD
5.2 **First-in-human Pilot Trial of VNS Therapy for PTSD**

Updated Time Commitments, Performance Period, Level of Funding, and Added Aims

TNT
DARPA TNT N66001-17-2-4011
Time Commitments: 1.5 months per year for years 1-4, **1 month for year 5**
Performance Period: 4/4/17-**9/30/21**
Level of Funding: **$7,245,817**
Aims:
…
1.1.5 **Evaluate whether optimized VNS parameters provide a greater enhancement of speech discrimination**
…
2.5 **Patient Enrollment and Implantation**
2.5.5 **Implant at least 10 patients to enter the accelerated learning study**
2.6 **VNS-dependent Acceleration of Learning**
2.6.5 **Determine if VNS paired with training accelerates learning by at least 30% compared to training without stimulation**
2.6.6 **Determine if TNT-dependent benefits are long-lasting**
3 **Evaluation of VNS-Dependent Accelerated Learning in SCI Participants**
3.1 **Obtain Regulatory Approval to Evaluate VNS-dependent Accelerated Learning in SCI Participants**
3.2 **Evaluation of VNS-dependent Accelerated Learning in SCI Participants**

New Award

SCI

NIH 1R01NS103803-01

Title: Enhancing Recovery after Chronic Bilateral Cervical Spinal Cord Injury with Targeted Plasticity Therapy
Time commitment: 2 months
Supporting Agency: National Institutes of Health
Name and Address of Contracting/Grants Office:

Grants Management Branch
National Institutes of Neurological Disorders and Stroke
6001 Executive Boulevard, Suite 3290, MSC 9537
Bethesda, MD 20892-9537

Performance Period: 6/1/2018-5/31/2023
Level of Funding: $218,750
Brief Description of Project Goals: Evaluate the effectiveness of vagus nerve stimulation paired with physical rehabilitation to enhance neuroplasticity and motor recovery in a model of severe bilateral cervical SCI in the rat.
Aims:

1. To test the hypothesis that VNS paired with rehabilitative training enhances forelimb motor recovery after chronic bilateral cervical SCI.
2. To test the hypothesis that VNS paired with rehabilitative training restores motor cortex function after chronic bilateral cervical SCI.
3. To test the hypothesis that VNS paired with rehabilitative training promotes anatomical plasticity in motor networks after chronic bilateral cervical SCI.

Role: PI

Hays Active Award Updates

Awards that Ended

International Rett Syndrome Foundation

Caruth

Updated Performance Period

Aged Stroke

NIH R01NS085167-01

Performance Period: 6/1/14-4/30/**20 (on NCE)**

Updated Level of Funding

Mechanisms

NIH R01NS094384

Level of Funding: **$1,338,752** of anticipated $1,673,422 award

Updated Time Commitments, Performance Period, Level of Funding, and Added an Aim

ElectRx

DARPA ElectRx N66001-15-2-4057
Time Commitments: 2 months per year in years 1 and 2, 0.5 months per year in years 3 and 4, **2 months per year in years 5 and 6**
Performance Period: 9/1/15-**9/21/21**
Level of Funding: **$6,995,309**
Aims:
…
6 Clinical Evaluation of VNS Therapy for PTSD
6.1 Gain Regulatory Approval for a Pilot Trial of VNS Therapy for PTSD
6.2 **First-in-human Pilot Trial of VNS Therapy for PTSD**

Updated Time Commitments, Performance Period, Level of Funding, and Added Aims

TNT

DARPA TNT N66001-17-2-4011
Time Commitments: 1.5 months per year for years 1-4, **1 month for year 5**
Performance Period: 4/4/17-**9/30/21**
Level of Funding: **$7,245,817**
Aims:
…
3.2.5 **Evaluate whether optimized VNS parameters provide a greater enhancement of speech discrimination**
…
4.5 **Patient Enrollment and Implantation**
4.5.5 **Implant at least 10 patients to enter the accelerated learning study**
4.6 **VNS-dependent Acceleration of Learning**
4.6.5 **Determine if VNS paired with training accelerates learning by at least 30% compared to training without stimulation**
4.6.6 **Determine if TNT-dependent benefits are long-lasting**
5 **Evaluation of VNS-Dependent Accelerated Learning in SCI Participants**
5.1 **Obtain Regulatory Approval to Evaluate VNS-dependent Accelerated Learning in SCI Participants**
5.2 **Evaluation of VNS-dependent Accelerated Learning in SCI Participants**

New Award

NIH UG3 NS109497-01

Title: *Wireless Nerve Stimulation Device To Enhance Recovery After Stroke*
Time Commitments: 3 months per year
Supporting Agency: National Institutes of Health
Name and Address of Contracting/Grants Office:
Grants Management Branch
National Institutes of Neurological Disorders and Stroke
6001 Executive Boulevard, Suite 3290, MSC 9537
Bethesda, MD 20892-9537
Performance Period: 2/15/2019-1/31/2021
Level of Funding: $464,499
Brief Description of Project Goals: Conduct pre-clinical and clinical testing of a novel low-cost, clinical-grade VNS system to provide tangible improvements in the lives of stroke patients.
Aims:
1. Validate the VNS System to FDA Standards

2. Complete Biocompatibility and Package Sterility Testing
3. Gain Regulatory Approval for a Clinical Study
4. Evaluate Wireless VNS Therapy Device in Chronic Stroke Patients

Overlap: There is no overlap between this project and the current proposal.
Role: PI

Engineer Active Award Updates

Award that Ended

Rett

New Award

NARSAD
2018 NARSAD Young Investigator Grant

Title: Enhancing Speech Processing in a Rat Model of Autism Using Vagus Nerve Stimulation
Time Commitments: 1 month per year
Supporting Agency: Brain & Behavior Research Foundation
Name and Address of Contracting/Grants Office:
Brain & Behavior Research Foundation
747 Third Avenue, 33rd Floor
New York, NY 10017
Performance Period: 1/15/2019-1/14/2021
Level of Funding: $70,000
Brief Description of Project Goals: Evaluate whether VNS paired with auditory training can enhance the efficacy of rehabilitation in a genetic model of autism by determining whether VNS paired with auditory training can reverse the neural and behavioral auditory processing deficits observed in heterozygous Mecp2 rats.
Aims:

1. To test the hypothesis that VNS paired with auditory training improves discrimination ability in VPA exposed rats.
2. To characterize auditory cortex plasticity during auditory training in VPA exposed rats with or without VNS.

Overlap: There is no overlap between this project and the current proposal.
Role: PI

New Award

Autism
NIH R01 DC017480-01

Title: Enhancing Speech Processing in a Rat Model of Autism Using Vagus Nerve Stimulation
Time Commitments: 3 months per year
Supporting Agency: National Institutes of Health
Name and Address of Contracting/Grants Office:
Grants Management Branch
National Institute on Deafness and Other Communication Disorders
6001 Executive Boulevard, Suite 3290, MSC 9537
Bethesda, MD 20892-9537
Performance Period: 12/1/2018-11/30/2023

Level of Funding: $250,000
Brief Description of Project Goals: Evaluate whether VNS paired with auditory training can enhance the efficacy of rehabilitation in an environmental model of autism by determining whether VNS paired with auditory training can reverse the neural and behavioral auditory processing deficits observed in VPA exposed rats.
Aims:

1. To test the hypothesis that VNS paired with auditory training improves discrimination ability in VPA exposed rats.
2. To characterize auditory cortex plasticity during auditory training in VPA exposed rats with or without VNS.
3. To test the hypothesis that the cholinergic and noradrenergic systems are required for alterations in auditory learning and auditory cortex plasticity in VPA exposed rats.

Overlap: There is no overlap between this project and the current proposal.
Role: PI

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*

- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*