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TITLE: Mechanism-Based Prevention of Noise-Induced Tinnitus:
Protection and Repair of Peripheral Auditory Neuropathy

PRINCIPAL INVESTIGATOR: Dr. Richard Altschuler

CONTRACTING ORGANIZATION: Regents of the University of Michigan, Ann Arbor, MI

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14. ABSTRACT Studies test a potential treatment for noise-induced tinnitus in the rat model. We hypothesize that noise-induced loss of synaptic connection between Inner Hair Cells (IHC) and the auditory nerve (AN) contributes to the induction of tinnitus and rapidly repairing this loss will therefore decrease the incidence of tinnitus. Treatment with the neurotrophic factor NT-3 was previously shown by our consultant Dr. Corfas to induce significant IHC-AN synapse reconnection after a different type of noise in his mouse model (Suzuki et al., 2016). During the first year of studies we have found that we can duplicate these results using a more military relevant small arms fire (SAF)-like noise in the rat model, showing a large and significant re-connection (described later in Section 3 of the Results Section). NT-3 in poloxamer was applied to the round window with the trans-tympanic approach that has been successfully applied in people for other treatments. These results show that it is possible to reverse noise induced synaptic loss from a military relevant noise exposure with a treatment paradigm that can be applied to those in the service. Such noise-induced synapse loss can cause a "Hidden Hearing Loss" that can impair speech understanding (Liberman et al., 2016, 2017). Therefore, the ability to repair and reverse Hidden Hearing Loss has immediate impact. The major goal, however, is to test if such reconnection will decrease or prevent the later development of tinnitus and that is the focus of the next stage of our ongoing studies. Studies are now underway to determine if this rapid reconnection from NT-3 treatment will decrease the incidence of noise induced tinnitus compared to noise exposed rats without treatment. If successful, this would provide a military relevant treatment to prevent and treat noise-induced tinnitus.					
15. SUBJECT TERMS Tinnitus, Deafness, Neurotrophins, NT-3, Synaptopathy, Noise, Small Arms Fire, Cochlea, Auditory, Hidden Hearing Loss					
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes / Problems	6
6. Products	6
7. Participants & Other Collaborating Organizations	6
8. Special Reporting Requirements	9
9. Appendices	9

1. INTRODUCTION:

Studies test an underlying mechanism and potential mechanism-based treatment for noise-induced tinnitus in the rat model. We hypothesized that noise-induced loss of synaptic connection between Inner Hair Cells (IHC) and the auditory nerve (AN) contributes to the induction of tinnitus and repairing this loss will decrease the incidence of tinnitus. Treatment with the neurotrophic factor NT-3 was previously shown by our consultant Dr. Corfas to induce significant IHC-AN synapse reconnection after a different type of noise in his mouse model (Suzuki et al., 2016). In our first phase of studies we reported we can duplicate these results using a more military relevant small arms fire (SAF)-like noise in the rat model, showing a large and significant re-connection when this treatment is applied 1 day after the noise. During Years Two and Three we tested NT-3 treatment beginning after a delay of 1 week to determine if it remains effective in inducing re-connection of IHC-AN synapses. We find a more variable, less consistent, re-connection, effective in some treated rats and not others, and also see variability across different regions of the cochlear spiral. This has relevance to those in the field that might not be able to get immediate treatment. Current studies testing if the NT-3 in poloxamer treatment given one day after noise (when re-connection is more consistent) reduces the incidence of tinnitus began in Year Two and are still in progress (see section on Unanticipated Problems for reasons behind delay). Reconnection could reduce the incidence of tinnitus but could also be effective in treating “Hidden Hearing Loss” that can impair speech understanding (Liberman et al., 2016, 2017). Either or both would provide benefit to Veterans and those in general population exposed to noise.

2. KEYWORDS:

Tinnitus, Deafness, Neurotrophins, NT-3, Synaptopathy, Noise, Small Arms Fire, Cochlea, Auditory, Hidden Hearing Loss

3. ACCOMPLISHMENTS

A. MAJOR GOALS for YEAR FOUR (EXTENSION)

Studies in all Aims have continued

Aim 1: Test the hypothesis that rapid reconnection of Inner Hair Cell –Auditory Nerve (IHC-AN) synapses that are lost as a consequence of a Small Arms Fire (SAF)-like impulse noise, will prevent chronic tinnitus from appearing.

TASK 1: Determine if (Subtask 1) NT-3 elevation treatment beginning 1 day after a SAF-like noise induces effective reconnection of lost IHC-AN synapses and (Subtask 2) if this will subsequently prevent Tinnitus from appearing (compared to noise-exposed rats without NT-3 elevation treatment).

- **Subtask 1:** Determine the influence of NT-3 elevation treatment given 1 day after SAF-noise on noise-induced changes to IHC-AN synapses. Will NT-3 elevation induce IHC-AN reconnection so that the significant noise-induced loss found in non-treated cochlea is reversed?
- **Subtask 2:** Determine the influence of NT-3 elevation treatment given 1 day after SAF-like noise on the appearance of tinnitus based on the Gap Detection metric compared to noise-exposed rats without NT-3 elevation treatment. Will there be reduced incidence of tinnitus in rats where NT-3 treatment induces re-connections compared to rats where IHC-AN connections remain lost?

Task 1 Milestones: 1. Determine efficacy in inducing re-connection.
2. Determine treatment effects on tinnitus

Aim 2: Test the hypothesis that a later reconnection of the IHC-AN synapses that are lost as a consequence of noise will be less effective in preventing tinnitus. First (Subtask 1) determine the effectiveness of NT-3 treatment given at 1-2 (Aim 2A) or 6 (Aim 2B) weeks following SAF-like noise in inducing repair of IHC-AN synaptic connections. Then (Subtask 2) determine efficacy in reducing the incidence of Tinnitus.

Task 2A: Determine if NT-3 elevation treatment beginning 1-2 weeks after a SAF-like noise induces effective reconnection of lost IHC-AN synapses and if this will subsequently prevent Tinnitus from appearing (compared to noise-exposed rats without NT-3 elevation treatment).

- **Subtask 1:** Determine the influence of NT-3 elevation given 1-2 weeks after SAF-like noise on Noise-Induced changes to Inner Hair Cell –Auditory Nerve (IHC-AN) synaptic connections. Determine the efficacy in inducing IHC-AN synaptic ‘re-connection’ compared to when the treatment is given 1 day after noise (results from Aim 1B – Subtask 1)
- **Subtask 2:** Determine the influence of NT-3 elevation given 1-2 weeks after SAF-like noise to prevent the appearance of tinnitus based on Gap Detection and behavioral (operant conditioning) metrics. Compare the efficacy to treatment 1 day after noise (results from Aim 1B – Subtask 2)

Task 2B: Determine if NT-3 elevation treatment beginning 6 weeks after a SAF-like noise induces effective reconnection of lost IHC-AN synapses and if this will subsequently prevent Tinnitus from appearing (compared to noise-exposed rats without NT-3 elevation treatment).

- **Subtask 1:** Determine the influence of NT-3 elevation beginning 6 weeks after SAF-like noise on Noise-Induced changes to Inner Hair Cell –Auditory Nerve synaptic connections, loss of Inner and Outer Hair Cells and loss of Spiral Ganglion Neurons. Compare the efficacy of ‘re-connection’ to treatment 1 day or 1-2 weeks after noise.
- **Subtask 2:** Determine the influence of NT-3 elevation 6 weeks after SAF-like noise to prevent appearance of tinnitus based on Gap Detection and behavioral (operant conditioning) metrics. Compare the efficacy in reducing incidence of tinnitus to treatment beginning 1 day or 1-2 weeks after noise.

Task 2 Milestones: 1. Determine efficacy of re-connection at 1-2 or 6 weeks after noise
2. Determine treatment effects on tinnitus

B. Unanticipated Problems: These were discussed in our request for a no-cost extension, as given below: First, as mentioned in previous Progress Reports, there were delays in manufacturers (e.g. Kinder) providing all the critical components of behavioral tinnitus testing stations resulting in delays of our getting the systems and stations functional. Because of these delays we needed to postpone the start of the study tasks involving testing for tinnitus by over 6 months. These tasks (given below) were the sub-tasks that involved testing if reconnection of inner hair cell – auditory nerve connections lost following noise would influence the subsequent appearance of tinnitus:

- **Aim 1 - Subtask 2:** Determine the influence of NT-3 elevation treatment given 1 day after Small Arms Fire (SAF)-like impulse noise on the appearance of tinnitus based on Gap Detection & and behavioral (operant conditioning) metrics compared to noise-exposed rats without NT-3 elevation treatment
- **Aim 2 - Subtask 2:** Determine the influence of NT-3 elevation given 1 week after SAF-like noise to prevent the appearance of tinnitus based on Gap Detection and behavioral (operant conditioning) metrics. Compare the efficacy to treatment 1 day after noise (results from Aim 1 – Subtask 1).

Second, there was a “ramping down” of research activities at the University of Michigan starting in February 2020, because of the COVID-19 pandemic. We were able to continue testing animals already in study, but at a reduced level due to staffing constraints. We were not able to order new animals or do any new procedures. We were able to begin a “ramp up” at the University of Michigan in mid 2021 and were able to order new animals, do surgeries and begin new studies, but constraints on the number of staff that can be in at one time continued and kept us from operating at full capacity. We were able to reduce spending commensurate with the reduced activities and carry over sufficient dollars to fund these studies for the additional months. However, the No Cost Extension had a reduction in budget that required reduction in staff efforts. This influenced the subtasks listed above

Because of these delays we were allowed additional time to carry out studies as proposed.

C. Major Activities:

Major Activities 2: Because of the delay (mentioned above) in being able to use the needed metrics to test rats for tinnitus, the studies first focused on the assessing synaptic connections, since this does not require tinnitus testing stations to be utilized to generate initial results. Studies first examined NT-3 treatment given one day after the SAF-like noise for repair of lost IHC-AN synapses (Groups 5 – 8) and compared this to the efficacy we

found using anti-excitotoxicity treatments given before the noise (for preventing loss). The analysis examining anti-excitotoxicity treatment given before the SAF-like noise was completed in Year One and results were published in 2019 (Altschuler et al, 2019). Studies examining efficacy of trans-tympanic NT-3 in poloxamer applied at the round window 1 day following the SAF-like noise in inducing reconnection of lost IHC-AN synapses in Groups 5-8 were completed in Years One – Two with assessment completed in Year Two. This was followed up by examining NT-3 elevation treatment given 1-2 weeks after the noise (Task 2 - Groups 9 and 10). This is being prepared for publication. The Subtask 2 studies testing for influence of treatment on incidence of tinnitus based on the Gap Detection metric remain in progress.

Rats received base-line measures of auditory brain stem response (ABR) and Gap Detection (GD). Animals were then randomly divided into groups receiving either Sham noise or SAF-like noise in one ear (left ear only). Animals in each group were then again randomly divided and received either Poloxamer containing NT-3 or Poloxamer only (no NT-3), delivered with a trans-tympanic approach into the left middle ear by the round window, done one day after the noise or sham (Groups 7 & 8) or one to two weeks after the noise or sham (Groups 9 & 10). In each aim the rats for Sub-Task 1 previously received euthanasia and assessment of IHC-AN connections two weeks after the NT-3 or no-NT-3 treatment. The rats in each group for Sub-Task 2 remained “in-life” and received 6-10 weeks of testing with GD as metric for the presence of tinnitus beginning 2 weeks after the NT-3 or no NT-3 treatment. These rats are then tested for ABR and euthanized. Cochleae are processed to determine hair cell loss and loss of IHC-AN synaptic connections.

TASK 1 (Aim 1)

1. Base-line Auditory Brain Stem Response (ABR), Gap Detection (GD)
2. Noise exposure (or sham noise)
3. NT-3 treatment (or poloxamer only without NT-3) one day after the noise
4. Testing for tinnitus (using GD) for two months
5. Final ABR

TASK 2 (Aim 2)

1. Base-line Auditory Brain Stem Response (ABR), Gap Detection (GD)
2. Noise exposure (or sham noise)
3. NT-3 treatment (or poloxamer only without NT-3) one to two weeks after the noise
4. Testing for tinnitus (using GD) for two months
5. Final ABR

After the in-life phase animals are then euthanized and assessed for hair cell loss and loss of Inner Hair Cell – Auditory Nerve synaptic connections

Major Activities AIM ONE Task 1:

- | | |
|-------|---|
| Aim 1 | Group 5 – Sham Noise – no NT-3 |
| Aim 1 | Group 6 – SAF-like Noise – no NT-3 |
| Aim 1 | Group 7 – Sham Noise – NT-3 elevation treatment given 1 day after noise |
| Aim 1 | Group 8 – SAF-like Noise – NT-3 elevation treatment given 1 day after noise |

Major Activities AIM TWO Task 2:

- | | |
|-------|---|
| Aim 2 | Group 5 – Sham Noise – no NT-3 |
| Aim 2 | Group 6 – SAF-like Noise – no NT-3 |
| Aim 2 | Group 9 – Sham Noise – NT-3 post-treatment 1-2 weeks after noise |
| Aim 2 | Group 10 – SAF-like Noise – NT-3 post-treatment 1-2 weeks after noise |

Animals from each group for Sub Task 1 are euthanized 2 weeks after NT-3 or no NT-3 treatment and assessed for the number of IHC-AN connections

Animals from each group for Sub Task 2 received 6-10 weeks of tinnitus assessment starting 2 weeks after the NT-3 or no NT-3 treatment and then were euthanized assessed for the number of IHC-AN connections

RESULTS:

Studies examining pre-treatment with anti-excitotoxicity agents were published (Altschuler et al., 2019). Studies comparing pre-treatment to NT-3 post treatment 1 day after noise were completed during Year One, assessed in Year Two and are summarized below:

Sprague Dawley rats were tested for ABR and only rats with normal responses were placed in study. The SAF-like impulse noise groups received 50 biphasic impulses over 2.5 minutes at 154 dB SPL given unilaterally (with a speculum) to the left ear. They received a second ABR within one hour following the noise and were then randomly divided into a group receiving NT-3 in poloxamer 1 day after the noise or a group receiving poloxamer only 1 day after the noise. Eight μ l of Poloxamer with or without NT-3 was placed in the middle ear by the round window of the left cochlea with a trans-tympanic approach 1 day after the noise. Animals received a third ABR assessment 7 days later and were then euthanized. Cochleae received intrascalar fixation with 4% paraformaldehyde fixative and were then processed for assessment of hair cell loss and loss of IHC-AN synaptic connections, using CTBP2 ribbon immunolabeling as a marker for IHC synapses.

SAF-like noise exposed rats showed a significant temporary threshold shift in the left ear of ~25 dB at 8 kHz and no shift at 16 and 32 kHz when assessed an hour following the noise. There was complete recovery of ABR thresholds and DPOAE (at the frequencies tested) 10 days after the noise exposure in both NT-3 treated and non-treated SAF-like noise exposed rats. There was no loss (over normal baselines) of inner or outer hair cells at 10-11 days following the SAF-like noise in either NT-3 treated or untreated rats. CTBP2 synaptic labeling (number of synapses per IHC) was assessed in regions of the cochlear spiral 5.0 mm and 6.5 mm from the apex. These regions were chosen for examination based on finding an SAF-like noise induced loss of synapses that was prevented by anti-excitotoxicity pre-treatment in Altschuler et al. (2019). Results showed SAF-like noise produced a large loss of IHC-AN synaptic connections compared to shams and our normative data base. In the region of the cochlea 5 mm from the apex, the “normal” number of synapses per inner hair cell is 21.7 +/- 2.8. The SAF-like noise exposure significantly ($P<0.05$) reduced this to 11.1 +/- 9.7 synapses per inner hair cell. The NT-3 treatment restored this to 22.8 +/- 0.6 comparable to normal and significantly greater ($P<0.05$) than without treatment. This suggests almost complete reconnection of lost IHC-AN synapses. The numbers were also highly comparable to what was seen with anti-excitotoxicity pre-treatment to prevent loss

Conclusions: Our results show that a clinically relevant trans-tympanic application of NT-3 in poloxamer on the round window can induce a significant re-connection of IHC-AN synaptic connections that are lost following an SAF-like noise exposure, even when treatment is one day following the noise. This treatment paradigm would be more applicable to those in the service than pre-treatment and could provide recovery from Hidden Hearing Loss following noise exposure.

Subtask One studies are examining re-connection when NT-3 treatment is delayed and given 1-2 weeks after the noise. Results show less consistent reconnect, with some treated rats showing substantial reconnection but others none. We also see variability across different regions of the cochlear spiral. This suggests that re-connection with treatment 1 week after noise exposure is possible, but earlier treatment would be recommended when possible. Results are being finalized and the comparison of 1 day versus 1-2 weeks will be submitted for publication.

Subtask Two studies are still ongoing and testing whether the rapid (and more consistent) reconnection will reduce the incidence of noise-induced tinnitus as well as the influence of later reconnection (1-2 weeks after the noise). Studies will also correlate efficacy in reducing tinnitus with the efficacy in inducing re-connection and require a larger ‘n’ for this purpose. Substantial data on the NT3 treatment influence on tinnitus has been obtained but many animals are still in study (because of the unanticipated delays) and remain blinded.

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

Nothing to Report

How were the results disseminated to communities of interest?

- One publication:

Altschuler RA, Halsey K, Kanicki A, Martin C, Prieskorn D, DeRemer S, Dolan DF.(2019) Small Arms Fire-like noise: Effects on Hearing Loss, Gap Detection and the Influence of Preventive Treatment. Neuroscience - [Epub ahead of print] PMID:30053484

- One Invited Platform Presentation by Dr. Altschuler:

Altschuler RA: “Noise Induced Hearing Otopathology and Tinnitus: Mechanisms and Strategies for Prevention and Repair” at the International Hearing Loss Conference at the Niagara on the Lake, Ontario, Canada, May 5-9, 2019.

Progress

Year Four of the no-cost extension did assessment of Task 1 from Aims 1 and 2 (influence of NT-3 on reconnection comparing 1 day after noise and 1-2 weeks after noise. Task 2 from Aim 1 remains in progress with rats in all the groups entering and completing an “in-life phase” of noise exposure (or sham) and NT-3 with testing for indication of tinnitus.

4. IMPACT:

There were three important results that impact hearing research and rehabilitation:

- Our studies show that a military relevant small arms fire (SAF) – like impulse noise that does not cause a permanent hearing loss or loss of sensory cells in the cochlea will still produce a large loss of synaptic connections between the sensory cells and the auditory nerve in the rat model. Other studies have shown such loss can influence hearing processing and speech understanding in a noisy environment
- We published results showing that pre-treatment with anti-excitotoxicity agents can prevent the small arms fire-like noise from causing this loss of connections.
- Our more recent results show that a treatment with NT-3 even one day following the SAF-like impulse noise will induce re-connection and repair of the lost connections, comparable to what was found with prevention prior to noise. Treatment following noise will be more applicable and the trans-tympanic middle ear approach to applying NT-3 is feasible for clinical application. Our more recent results show that treatment at a later time (1-2 weeks) following noise can still be very effective in some subjects, but results are less consistent and approximately 1/3 of subjects do not have significant re-connection. This would support treatment as soon as possible after noise, but with some potential for effectiveness even 1 week after the noise

There is also more general impact for study results:

- demonstrated NT-3 can induce re-connection of lost synapses
- effective anti-excitotoxicity treatments

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

REFERENCES

Altschuler RA, Halsey K, Kanicki A, Martin C, Prieskorn D, DeRemer S, Dolan DF (2019) Small arms fire-like noise: Effects on hearing loss, gap detection and the influence of preventive treatment, Neuroscience 2019 May 21;407:32-40. PMID: 30053484

Liberman MC, Epstein MJ, Cleveland SS, Wang H, Maison SF. (2016) Toward a Differential Diagnosis of Hidden Hearing Loss in Humans. PLoS One. 11(9):e0162726. PMID:27618300

Liberman MC, Kujawa SG. (2017) Cochlear synaptopathy in acquired sensorineural hearing loss: Manifestations and mechanisms. Hear Res.;349:138-147. PMID:28087419

Suzuki J, Corfas G, Liberman MC. (2016) Round-window delivery of neurotrophin 3 regenerates cochlear synapses after acoustic overexposure. Sci Rep. 6:24907. PMID:2710859

5. CHANGES / PROBLEMS:

There was delay in being able to apply metrics for the presence of tinnitus significantly delaying tinnitus assessments so that completion of Tasks will be delayed and a no-cost extension into a Year Four was provided to allow completion of tasks

6. PRODUCTS:

Other publications, conference papers, and presentations.

Nothing additional over what was reported above

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	Richard Altschuler
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	richardaltschuler
Nearest person month worked:	3
Contribution to Project:	Responsibility for the supervision of the histopathology, quantitative assessments of hair cells and the connection between hair cells and auditory nerve. He will interpret results; trouble shoot methods and make decisions on directions.
Funding Support:	Changes Since Last Report New Awards: I01 RX003250-01A2 (Altschuler) 03/01/21 – 02/28/25 3.0 calendar months* Ann Arbor VA Medical Center Year 1 Direct Cost Total Direct Costs: Source of Support: USA Intense Noise Exposure Impacts Performance of Vestibular Dependent Behaviors

	<p>Noise exposure as a risk factor for vestibular loss has obvious and significant veteran health implications, but there are few, if any studies that (1) provide insights into the physiology that underlies noise-induced vestibular loss and (2) provide guidance for preventative or rehabilitative strategies for veterans with balance disorders. The proposed studies will show in a rat model, that noise exposure at levels encountered by veterans during their military service and during daily life can cause vestibular dysfunction that includes deficits in vestibular reflexes and vestibular signaling that increase fall risk and reduce head stability and visual acuity during movement.</p> <p>Ended Award: T32 NS076401 (Satin) 07/15/16 – 06/30/21 0.6 calendar months NIH/NINDS Annual Directs: Source of Support: USA Total Award: Early-Stage Training in the Neurosciences (ESTN) The purpose of this grant is to foster training and development of the next generation of researchers in neuroscience, who will devote their careers to address the basic science and biomedical research needs of the nation across the broad field of Neuroscience. Role: Co-Director</p>
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Name:	David Dolan
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0
Contribution to Project:	Responsible for directing the auditory brain stem response (ABR) measures including thresholds and input-output function and overseeing the assessment of gap detection and pre-pulse inhibition of the acoustic startle reflex as well as the assessment and interpretation of these results. He will also oversee the noise exposures.
Funding Support:	Effort removed from this award during the No Cost Extension

Name:	Bryan Pfingst
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0
Contribution to Project:	Dr. Pfingst is an expert in behavioral psychophysical evaluation of hearing. He provide guidance on the operant conditioning test for tinnitus.
Funding Support:	No Changes

Name:	Susan Shore
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Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0
Contribution to Project:	Provide advice and assist in interpretation of data
Funding Support:	No Changes

Name:	Diane Prieskorn
Project Role:	Research Lab Specialist Senior
Nearest person month worked:	1
Contribution to Project:	Ms. Prieskorn is responsible for all animal surgeries and drug delivery (by poloxamer on the round window niche) at KHRI and training the Partnering PI staff at WSU in this method. She also assists in ABR measures and assessment.
Funding Support:	N/A

Name:	Hannah Beck
Project Role:	Research Lab Technician Intermediate
Nearest person month worked:	12
Contribution to Project:	Ms. Beck (100% effort) is responsible for animal surgeries and drug delivery (by poloxamer on the round window niche) at KHRI, ABR measures and assessment as well as carrying out the Gap Detection an operant conditioning metrics to test for tinnitus.
Funding Support:	N/A

Name:	Ariane Kanicki
Project Role:	Research Lab Specialist
Nearest person month worked:	4
Contribution to Project:	Ms. Kanicki is responsible for animal surgeries and drug delivery (by poloxamer on the round window niche) at KHRI, ABR measures and assessment as well as carrying out the Gap Detection an operant conditioning metrics to test for tinnitus.
Funding Support:	N/A

What other organizations were involved as partners?

Wayne State University, Detroit Michigan, is a Partnering Institution to this project. They will be sending in their collaborative Progress Report separately.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

9. APPENDICES:

Nothing to Report