AWARD NUMBER: W81XWH-19-1-0609
RH180042

TITLE: Measurements of Cochlear Synaptopathy Using Electrocochleography

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CONTRACTING ORGANIZATION: University of North Carolina at Chapel Hill

REPORT DATE: SEPTEMBER 2020

TYPE OF REPORT: Annual Technical Report for Year 1

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

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| SEPTEMBER 2020 | ANNUAL | 15AUG2019 - 14 AUG 2020 |

**4. TITLE AND SUBTITLE**
Measurements of Cochlear Synaptopathy Using Electrocochleography

**5a. CONTRACT NUMBER**
W81XWH-19-1-0609

**5b. GRANT NUMBER**
RH180042

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
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**5d. PROJECT NUMBER**
0011338434-0001

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

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

UNIVERSITY OF NORTH CAROLINA
AT CHAPEL
OFFICE OF CONTRACTS & GRANTS
104 AIRPORT DR STE 2200
CHAPEL HILL NC 27599-5023

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

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

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT** Cochlear synaptopathy is a condition where hair cell function remains viable even though synaptic connection with the auditory nerve has been severed. As a means to test for the presence of this condition, it has long been recognized that electrocochleography (ECochG) provides an unparalleled and highly informative window into cochlear function. Experiments in animals using ototoxins and neurotoxins have allowed us to identify unique signatures of responses from hair cells and the auditory nerve, respectively. These have allowed us to identify unique metrics that are associated with synaptopathy. The goal of this project is to develop an innovative approach to use ECochG to serve as the centerpiece of a battery of differential tests focused on cochlear synaptopathy and its perceptual sequelae. This objective aligns itself precisely with the FY18 HRRP FARA Focus Area that calls for the development of methods to assess auditory dysfunction related to synaptopathy and hidden hearing loss. The plan is to develop ECochG measures that provide a detailed picture of the functional properties of an individual's hair cells and neural elements, and to relate this cochlear profile to auditory performance. The study includes both animal and human studies. The animal studies are ongoing and the human studies to date are based on analyses of existing data with approval for new studies pending. Animal results with neurotoxins and human studies in subjects with various degrees of hearing loss are showing effects of synaptopathy on ECochG potentials and models developed to analyze the results are producing reliable metrics of its presence. Development of an animal model of synaptopathy with noise exposure is under active development in terms of response magnitudes, measures of indices of synaptopathy, measures of distortion products, and anatomical counts of immunolabeled synapses.

**15. SUBJECT TERMS**
Cochlea, Hearing Loss, Cochlear Implants, Auditory System

| 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 | 28 | 19b. TELEPHONE NUMBER *(include area code)* |

**Standard Form 298 (Rev. 8-98)**
**Prescribed by ANSI Std. Z39.18**

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## 1. INTRODUCTION

Hearing loss is typically defined as an increase in the threshold sound levels required for detection of different frequencies. Hidden hearing loss is an impairment of complex auditory function, such as understanding speech in noise, with little or no change in detection thresholds. A major hypothesis recently developed based on animal studies is that hidden hearing loss may be due to prolonged overstimulation which causes loss of auditory nerve connections to the hair cells that detect sound vibrations. In this view, detection thresholds can be maintained with a limited number of connected auditory nerve fibers, but complex processing is impaired without the complete complement of connected fibers. This mechanism of cochlear synaptopathy is difficult to observe in humans, but anatomical evidence in the form of loss of auditory nerve synapses and fibers seen post-mortem indicates that it occurs. Physiological tests to demonstrate it in living subjects are lacking. For this project, we will use the technique of electrocochleography (ECochG) to study and describe cochlear function in detail in living subjects. ECochG involves recording the electrical responses from the cochlea in response to sounds. The two sources of these electric potentials are the hair cell receptors that detect vibrations and the auditory nerve that transmits the information to the brain. Consequently, the technique is ideal to study the relative proportions of connections between hair cells and the auditory nerve, with any imbalance toward hair cells being an indication of cochlear synaptopathy. Our project has three aims. The first aim is to develop metrics of cochlear synaptopathy using data from animal models and apply them to human subjects recorded under similar conditions. Using animals, ototoxins or neurotoxins can be applied to selectively eliminate hair cells or neural contributions, respectively. These experiments have allowed us to identify unique signatures of responses from each source, and to develop models based on biophysical properties that generate the responses that report the magnitudes of each component. The working models are relatively early versions not specifically designed for detecting cochlear synaptopathy, and so development for this purpose is a main activity of this aim. In addition, new animal work is needed to characterize synaptopathy in the noise-exposure model that has been used in previous studies and to separate the hair cell and neural responses into their constituent components, which are not incorporated in the current models. Finally, recordings in human subjects recorded under comparable signal-to-noise conditions are available only for subjects undergoing cochlear implant surgeries. To better characterize the distribution of cochlear synaptopathy we need subjects with less compromised hearing. Consequently, recordings will be done intraoperatively in other subjects where access to the inner ear is available. The second aim is to develop the techniques for use with non-invasive recordings from the ear canal. These are needed so that they can be used routinely in the clinic. We can compare intraoperative and ear canal measurements directly by recording both at the same time. In addition, we can examine ear canal measurements in a cohort of young, normal hearing subjects, which are a good representation of many currently deployed service members. The third aim is to compare ECochG measures of cochlear synaptopathy to audiometric and speech-in-noise measurements. A link between the suspected synaptopathy and behavioral outcomes has been difficult to make. The ECochG can provide a scale of synaptopathy based on objective measurements, to better test correlations between synaptopathy and the expected deficits. These subjects will also be young adults and will have audiometric hearing within the normal range. The overall product expected from this endeavor is an advanced system for evaluating cochlear function using ECochG that can be applied to synaptopathy and hidden hearing loss or to assess cochlear function in general. This system should be scalable to the needs both of advanced diagnostics and for local measurements by clinical users at various levels of training. It is intended to provide a reliable, objective measure of hair cell and neural function on an individual level.

## 2. KEYWORDS

Auditory nerve

Auditory nerve neurophonic

Auditory system, Cochlea

Cochlear implants

Cochlear Microphonic

Compound Action Potential

Hearing loss

Inner hair cells

Noise Exposure

Outer hair cells

Summating Potential

Synapse

Tympanic Membrane

## 3. ACCOMPLISHMENTS

**What were the major goals of the project?**

The overall goal is to use electrocochleography (ECochG), or cochlear responses to sound, to measure relative degrees of hair cell and neural contributions to the recorded potentials. A reduced neural contribution is expected to be a specific marker for the presence of cochlear synaptopathy. There were three specific aims, with tasks related to each listed in the SOW.

*Aim1. Develop metrics of cochlear synaptopathy using data from animal models and apply them to ECochG from human subjects taken under similar conditions*

Major Task 1. Separating the cochlear microphonic (CM) from the auditory nerve neurophonic (ANN). The CM is a hair cell potential and the ANN is from the auditory nerve. The ANN is only present to low frequencies within the phase-locking range of auditory nerve fibers (below about 1500 Hz). To these low frequency stimuli the CM and ANN are mixed together, and methods must be developed for them to be separately measured. Once developed, the degree of cochlear synaptopathy, or relative paucity of neural compared to hair cell activity, should in principle be measurable.

*Subtasks*. 1) The recruitment of a post-doc to aid in the modeling effort 2) the delivery of a new version of the model to separate the CM from the ANN at the end of the first year. **These tasks have been accomplished as will be described below.**

Major Task 2 - Measuring the CM and CAP in response to high frequency sounds. Similar to Major Task 1 except that to high frequencies the neural component is a different feature called the compound action potential (CAP). Because the CAP is seen early in the stimulus it is not entangled with the CM but is entangled with the summating potential (SP) which is from a mixture of sources. Thus, methods to separate the CAP and SP are under development. To high frequencies the CM is not entangled with other potentials, so a hair cell metric is readily available.

*Subtasks*. As above, the recruitment of the postdoc and delivery at 1 year of a new version of the model. The model is available for the CAP and is working. In the 'accomplishments' section we present figures from the low frequency, ANN model because there is still one issue with the CAP, and it is that issue that we describe instead of the complete results.

Major Task 3 – Development of a gerbil model of cochlear synaptopathy and identification of physiologic biomarkers of the condition using ECochG. The goal is to identify anatomical metrics of synaptopathy following different levels of noise exposure in gerbils, and to test these known anatomical results of synaptic and hair cell losses against the physiological measurements of hair cell and neural contributions to the ECochG.

Subtasks. The milestones for the first year were to complete ACURO approval and characterize cochlear synaptopathy in the gerbil model to high frequencies similar to studies previously done in other species. These goals are well underway, despite the months-long delay in animal work due to COVID-19. **In the accomplishments section we will describe the state of the animal work.**

Major Task 4. Human Intraoperative ECochG. Round window measurements of cochlear synaptopathy using CM/ANN and CM/CAP indices developed earlier and as improved in Aim 1.

Subtasks. Early tasks were to complete HRPO review and begin initial intraoperative, RW measurements. An approved IRB from the Univ. of North Carolina was submitted to HRPO in September 2019. This part of the project with the IRB at UNC has moved to near completion recently, in that it has been entirely approved by HRPO and is back in the hands of our IRB, which had minimal stipulations so this should be done in a matter of days.

*Aim2. Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement.*

Major Task 1. Human Intraoperative ECochG. Ear Canal recordings concurrent with round window measurements of cochlear synaptopathy using CM/ANN and CM/CAP indices

Subtasks. Early tasks were to complete HRPO review and begin initial intraoperative, RW measurements. See above for issues with the UNC IRB; the one from OHSU is completed.

Major Task 2 Ear Canal ECochG from young adults to assess CM/ANN and CM/CAP indices from this non-invasive location.

See above for issues with the UNC IRB; the one from OHSU is completed. For the extension to ear canal recording the data will not be available until later in the study when we have optimized the modeling to best account for the results from the characterization of cochlear synaptopathy in the gerbil. Since it can be done in the laboratory the data can be relatively quickly obtained later in the study.

Subtasks. HRPO review. An approved IRB from the Univ. of North Carolina was submitted to HRPO in September 2019.

Two Subtasks to begin with HRPO approval.

Aim3. *Compare ECochG measures of cochlear synaptopathy to audiometric and speech-in-noise measurements*

Work for this aim is not scheduled to begin until year 2.

**What was accomplished under these goals?**

**NOTE: The figures referred to are in a Powerpoint format as 'Attachment 2 Figures.' Figure legends are in the note section for each slide.**

*Aim1. Develop metrics of cochlear synaptopathy using data from animal models and apply them to ECochG from human subjects taken under similar conditions*

*1a. Separating the CM from the ANN to low frequency sounds and measuring the degree of synaptopathy in human subjects*

The post-doc recruited is Dr. Raymond Haggerty (CV is Attachment 1). Dr. Haggerty has a background in bioinformatics and is well-trained in the type of modeling needed.

Dr. Haggerty has developed a new version of the model to separate the ANN and CM, which was the main deliverable for year 1. The code and spreadsheet of the data will be provided as part of the technical section. The initial model was described in Fontenot et al 2019. It starts with the biophysical principles behind the production of the CM from the opening and closing of channels in the stereocilia of hair cells that produces a current, the CM, that fluctuates with sound frequency and the ANN, from the firing of action potentials in the auditory nerve. The differences in the production of the CM and ANN result in different shapes in their time waveforms (Fig. 1 and 2). The focus of our analysis is the 'average cycle' or waveform shape to one fluctuation of the basilar membrane. Some features of analysis of the recorded ECochG responses, using human CI subjects with recordings from the round window as examples, are shown in Fig. 2. These examples each including an average cycle, one to a low frequency sound (Fig. 2C) within the phase locking range (<~1500 Hz), where the ANN is present, and the other(Fig. 2F) is to a high frequency sound above the range of phase-locking where no ANN is produced.

The basic form of the model used to separately identify and measure the CM and ANN is shown in Fig. 3. It takes as input an average cycle and uses a variety of parameters that describe the possible shapes to each stimulus to determine the best fit curve as an output. The magnitudes of the CM and ANN that produced the fit and the degree of correlation (r) and variance account for ($r^2$) of the fit are measured. Examples of the variety of responses observed in human RW recordings to low frequencies (Fig. 3B) show that the model is

able to fit the wide variety of shapes of the average cycle encountered, which vary from nearly sinusoidal to highly distorted and complex, and the distribution of $r^2$ shows the fits were typically quite good (Fig 3C).

Although the shapes were well fit in these examples and in most cases, an issue with the algorithm was that it typically reported a small proportion of ANN (up to about 10%) in all cases, even when none could be present, such as to high frequencies (>1500 Hz) above the phase-locking range of auditory nerve fibers. This flaw meant the model could not provide an accurate indication of cochlea synaptopathy, because to a large CM even a small proportion of ANN can be a large absolute amount. To fix this problem we now run the model in two stages, as shown in 3D. First, we run the input waveform through a 'CM only' front end, and if this model fits the input shape with an $r^2$ greater than a criterion value it is determined to have a no ANN, while if the $r^2$ is less than the criterion the complete model is run and amount of CM and ANN is reported.

This criterion level was determined with the CM-only model (Fig. 3D) run against data from normal hearing gerbils in two conditions: 1) to low frequencies (250, 375, 500 and 750 Hz), where the ANN is in known to be present (top), and 2) to high frequencies (2, 3, 4 and 6 kHz) where it is known to be absent (middle). Thus, this condition represents a standard with the ANN status known at least in binary form. When plotted as a proportion of the maximum (Figs. 4A and B) the criterion level was taken as the $r^2$ value of the difference between them where the likelihood of the response being all CM or containing some ANN was equal (0.995, Fig. 4C). Above this criterion value the response was more likely to be only CM and below it the response was more likely to contain ANN.

In the following, we will report the results of the model using a 'CM/ANN index,' defined as

(CM-ANN) / (CM+ANN).

With this index a response that is all CM has a CM/ANN index of 1, equal amounts have an index of 0, and a response that is all ANN has an index of -1. In the following I describe results from the model with six existing data sets, all with recordings from the round window, with four groups from gerbils and two from humans.

1) Normal hearing gerbils (Fig. 5A, top row). As described above, these animals provide the known condition where the ANN is present to low frequencies but not high frequencies. To low frequencies, the model incorrectly classified only a few responses (each symbol represent the CM/ANN index to one frequency/intensity combination) as having no ANN (open symbols above the line). *Otherwise, the proportion of the CM relative to the ANN increased with increasing intensity. This effect of intensity indicates that in the normal hearing condition the ANN saturates earlier than the CM from hair cells*. To high frequencies, the model correctly classified most as having no ANN, but to high frequencies at high intensities the model classed more as having an ANN than not having an ANN. The binary results are shown in summary fashion in the confusion matrix. The model had a high sensitivity, or correct identification of the ANN when it exists (97%), and a high specificity (71%), or correct rejection when it was not present.

2) Normal hearing gerbils after applying the neurotoxin kainic acid (KA) to the round window (Fig. 5A, bottom row). The potent neurotoxin is expected to reduce the amount of ANN but not CM, i.e., to produce partial or complete cochlear synaptopathy. As can be seen, to low frequencies the model reports the ANN to be absent at a higher rate than in the pre-KA condition, and this condition extended to lower intensities. Overall, the proportion of ANN was reduced, but the trend of decreasing proportion of ANN with intensity was similar. These variable effects to low frequencies are consistent with incomplete travel of the neurotoxin to the apex of the cochlea. To high frequencies the model continued to report CM-only in most cases, with most incorrect identification of an ANN occurring to high intensities. Note that this and each following data set is 'live' in the sense that it uses the criterion derived from the Pre-KA data but was not itself used to generate that criterion.

3) Gerbils with high pass noise induced hearing loss (HP-NIHL), pre-KA (Fig. 5B, top row). Here, a high-pass (4 kHz cut-off) noise at very high intensity (122 dB SPL) for four hours severely and permanently damages the basal half of the cochlea to the point where there is little or no CM or ANN produced from this region. This condition mimics human subjects where the high frequency hearing loss is typically greater than to low frequencies, and specifically mimics that of many CI subjects where responses to high frequencies are absent. As would be expected the CM values were reduced, with a maximum of less than 40 dB (=100 $\mu$V) compared to more than 60 dB (=1000 $\mu$V). As we will directly compare later, there was an enhanced degree of ANN compared to normal hearing animals. This result is produced because the loss of the basal half of the cochlea prevents spread of excitation to higher frequency regions that provide most of the

response recorded at the RW in NH animals. That is, in an NH animal the responses from basal regions being recorded have relatively less ANN because the ANN saturates to lower intensities than the CM. *In the HP-NIHL animals, where responses are restricted to the apical parts of the cochlea, the CM and ANN have similar saturation profiles and are more proportional in size.* The model continues to achieve a high sensitivity (99%) for detecting the ANN in responses to low frequencies.

4) HP-NIHL gerbils after KA (Fig. 5B, bottom row). The neurotoxin reduced the overall level of the ANN, and increased the number reporting no ANN to 16%. These differences are an indication of the synaptopathy produced by the neurotoxin.

5) Human subjects NOT receiving a cochlear implant where the RW is accessible during surgery. (Fig. 5C, top row). These are primarily subjects with Meniere's disease during a labyrinthectomy, or with a vestibular schwannoma that is being removed. They are expected to have some hearing loss but not to the degree of a typical cochlear implant candidate. The stimuli in the intraoperative recordings were typically to 90 dB nHl although a level series to 500 Hz was often taken as well. To low frequencies, there were cases with small or no ANN, and the overall rate (12%) was similar to that of post-KA animals (15% for normal and 16% for HP-NIHL). As we will compare directly below, the distribution of the CM/ANN index was also similar to that of post-KA animals. ***This is important evidence for the presence of cochlear synaptopathy to low frequencies in subjects with less hearing loss than a cochlear implant subject.*** The responses to high frequencies also show a high specificity (63%), similar to that in NH gerbils (71%).

6) Human subjects receiving a cochlear implant (Fig. 5C, top row). Here the recordings are from the RW during implant surgery just prior to insertion of the device. To low frequencies there is an even higher rate of responses with no ANN and a similar distribution in the CM/ANN index. ***This is important evidence for the an increase in cochlear synaptopathy to low frequencies in subjects with a higher degree of hearing loss.*** The responses to high frequencies also show a high specificity (75%).

These distributions of the CM/ANN index to low frequencies in these data sets are shown in Fig. 5. A one-way ANOVA showed a main effect of the group ($F=45.1$, $df=5,1167$). Pairwise comparisons showed the pre-K responses to have a significantly lower CM/ANN index, indicating relatively more ANN, than the post-KA animal or humans, and the index in the HP-NIHL animals was significantly lower than that of normal-hearing animals. The two post-KA and two human groups were not significantly different from each other. Again, ***these results indicate a high degree of cochlear synaptopathy in human subjects similar to that of post-KA animals.***

The results to this point are expected to produce our first paper under this award.

*1b. Separating the CM from the CAP to high frequency sounds and measuring the degree of synaptopathy in human subjects*

We are performing similar analyses for the high frequency part of the responses where the CAP, a purely neural response, can be measured in relation to the CM, which is not bound with the ANN to these frequencies. Combined with the ANN measurements we expect the CAP and CM comparisons to provide a complete picture of the physiological description of cochlear synaptopathy in these groups. The analyses are to date more preliminary than those of the ANN, in part because there is still a technical barrier in the form of the summating potential which can mimic the shape of the CAP (Figure 7). We are currently beginning to focus on this problem to complete our efforts with the previously existing data sets soon.

*1c Development of a gerbil model of cochlear synaptopathy and identification of physiologic biomarkers of the condition using ECochG.*

We have been noise exposing animals according to the cochlear synaptopathy protocol. To describe results from the dataset, we first describe the interface of the MATLAB app used for analysis (Fig. 8), since it can serve as a summary of the data to follow. Fig. 8. There are program control features for sharing data with Excel and choosing data sets to analyze, but the main working parts are shown by the numbers: 1) RespMags refers to analysis of response magnitudes of experimental cases compared to control (no noise) cases (see Fig. 9). 2) Synaptopathy evokes the analyses described in the previous figures which is used on the new data

sets as well (see Figs. 12 and 13). 3) DPs refers to analyses of distortions products in the recordings evoked by two tone stimulation (Figs. 13-16). 4) Synapses refers to synapse counts, the primary anatomical marker of cochlear synaptopathy (See Figs. 17-19). Each of these features can be analyzed concurrently as needed for a case or group of cases using this program interface.

A summary of all the animal cases to date is shown in Table 1.

Response magnitudes

Please refer to Fig. 9 for the following description of response magnitudes. In Q3 we reported that no consistent effects of the noise were being seen, and we thought we needed to increase the intensity of the noise until effects were seen. In Fig. 9 we show that with new data for noise at 115 dB SPL for 2 hr clear response losses were present. Comparison of response magnitudes in two subsets of cases are shown. Each panel shows recordings from the left (green) and right (red) ears of an experimental case compared to a series of control animals (blue) with no noise exposure taken prior to these experiments. The two columns on the left were reported for Q3, where it was concluded that we needed to increase the noise levels. In the right panels the new data are shown, and there are clear response losses for exposures of 115 dB SPL for 2 hrs. These effects occur across frequency, which is expected, even though the noise exposure is only to high frequencies, because ECochG in a normal hearing animal for a round window recordings is primarily derived from the basal part of the cochlea, which responds to all frequencies if sufficiently intense. The losses persisted strongly to at least 1 day and possibly to as long as 7 days. We are now further investigating this time course and, as subsequent figures will show, examining the data from other respects as well.

Synaptopathy: CM/ANN index

In Fig. 10 we show the data examined for CM/ANN index in the same manner as in Figs 5A-C. Animals with sham noise exposures (top row) show distributions and a confusion matrix similar to the normal, pre-KA animals in Fig. 5A. Similarly, animals with exposures of 112 dB SPL for 2 hrs, appear little changed (middle row). Animals with exposures of 115 dB SPL for 2 hrs show a CM that is reduced on average, but the proportion of low frequencies neurons with no ANN did not increase. A difference was a large number of high frequency neurons not having a correct rejection, which resembles results from the HP-NIHL animals which were not shown in Fig. 5B because of the extensive noise damage in high frequency regions.

The distributions of the CM/ANN index for the three groups of noise exposures compared with normal hearing animals both pre and post KA showed only small differences. An ANOVA with just the noise-exposed groups did not reveal significant differences in the means of the control animals (0 dB noise) compared to the 115 dB noise, but the 112 dB had a significantly higher proportion of ANN than either. This is an odd result that may not hold up with additional data, although we note that the HP-NIHL animals (Fig. 6) also showed a greater proportion of ANN than normal animals. By 115 dB we may be approaching the condition that most resembles post-KA responses.

Distortion products

Typically, distortion product otoacoustic emissions (DPOAEs) are used to measure outer hair cell integrity, and a hallmark of cochlear synaptopathy is preservation of these DPOAEs with loss of cochlear synapses. DPOAEs tend to be small and difficult to measure in animals, so we decided on investigating the distortion products from similar stimulation in the ECochG. A primary difference with otoacoustic emissions is that in the ECochG there will be a contribution of the ANN to distortion products in the range of phase-locking. Thus, it is possible that these recordings will enable an additional sensitive measure of the ANN as well as information on hair cell integrity.

Responses to two tone stimulation in a normal hearing animal (Fig. 12, 0 dB sham noise exposure) show peaks in the FFTs at frequencies corresponding to both primary tones (f1=2000 and f2=2400 Hz at -10 dB relative to f1) and to the distortion products related to the f2-f1 and 2f1-f2. The proportion of the f2-f1 steadily increased as the intensity was lowered. Since this distortion product at 400 Hz was withing the phase-locking range, we interpret this increased peak to the lower intensities as primarily due to the ANN. Furthermore, this result supports the view that the ANN undergoes more saturation than the CM, and is thus relatively smaller as the intensity is raised. The 2f1-f2 distortion becomes proportionally the smallest to 60 dB, and is larger on either side. It is an open question whether this peak is neural or hair cell in origin, or differs in origin over the two intensity ranges. This question can be addressed with kainic acid experiments. An important result was the high signal to noise ratio even to stimuli of low intensity, which would be difficult to achieve with DPOAEs.

Fig. 13 shows sizes of each peak across intensities for four ears with sham noise exposure. The results were quite reproducible across these cases.

Fig. 14 shows results from 6 ears stimulated at 115 dB SPL noise for 2 hrs This exposure lowered the responses to the f1, consistent with results on response magnitude in Fig. 9. Here, the f2-f1 was relatively larger at higher intensities than the normal hearing animals at the same sound level. This result is presumably due to the loss of outer hair cell activity and consequent relative increase of the ANN. The responses to the 2f1-f2 were more variable, being proportionally larger in two ears and smaller in the others.

Fig. 15 shows a mixture of results from a case with 112 dB noise exposure and a 7 day recovery period. Here, the responses to the two ears were dramatically different. For the left ear the response loss was very large while to the right ear it was much less, although still reduced from normal. The less than complete recovery to the right ear results in a larger proportional degree of ANN in the f2-f1 than in a normal ear and the curve to the 2f1-f2 was shifted to the right, indicating a larger stimulus was required but the same pattern was produced.

Finally, another unusual case is shown in Fig. 16. where 112 dB noise-exposure produced a large response loss in just one ear. Here, similar trends were observed in the affected ear as was the case to the 115 dB exposures. This was the only large loss seen to 112 dB.

Synapses

The hallmark of cochlear synaptopathy is loss of synapses from the auditory nerve to inner hair cells. During the past year we have developed the expertise to immunolabel the hair cells (myosin VIIa), synaptic ribbons (CtBP2) and nerve terminals (GluR2) as has been reported in previous reports. Here we report again briefly on these methods and our first results with counts in experimental animals.

Fig. 17 is low power confocal images showing the frequency map applied to a dissected cochlea (left) and the seven frequency regions (right) where synapses were counted (0.5, 1, 2, 4, 8, 16, and 32 kHz). In Fig. 18 we show a higher-power image of the labeled hair cells (gray), ribbons (red) and terminals (green). Sites where a ribbon and terminal were colocalized were counted, as in the example of the cell at the left.

The top panel in Fig. 19 shows two ears from one sham-exposed case, which was used as a template for a normal number of synapses. In the middle panel results from four ears in 3 cases exposed to 112 dB all had fewer synapses across the frequency range. While possibly indicating cochlear synaptopathy, we are cautious at this point because 1) the losses are across the frequency range, but should be restricted to frequencies at or above the noise exposure (gray bars), and 2) there was no physiological evidence of synaptopathy in these cases.

The bottom panel shows synapses in two ears (two different gerbils) after exposure to 115 dB SPL. These are also lower than the control across frequencies although one curve (green) shows a trend like that expected with greater losses at and above the frequencies of noise exposure.

*Aim2. Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement.*

Formal experiments await final IRB approval. We have achieved ACURO approval and the IRB protocol is resubmitted in response to minor modifications and resolution of an COI issue, so we think it is due any day (truly).

Summary and Conclusions to date:

1. Clear evidence of cochlear synaptopathy is shown by ECochG for both human populations, where the response distributions closely resemble post-KA gerbils. The synaptopathy appears to be greater in the CI subjects than non-CI subjects.

2. Noise levels have now been used that show physiological effects in gerbils. At present these have suggestive but not conclusive evidence of cochlear synaptopathy. In general the noise levels needed in the gerbils are quite high (115 dB SPL for 2 hrs) compared to anatomical and physiological measurements in mice (106 dB for two hours) or guinea pigs (109 dB for 2 hrs).

3. The synapse counts are suggestive of the presence of synaptopathy at lower levels, but more data is needed and is being obtained rapidly.

4. Distortion products as measured with ECochG may provide an additional sensitive window to both hair cell and neural integrity.

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

The postdoctoral fellow is being trained in the anatomy and physiology of the auditory system, which is a new direction for him.

**How were the results disseminated to communities of interest?**

A poster was presented at the Association for Research on Otolaryngology Midwinter meeting in San Jose, January 2020. The title of the abstract was “Probable Cochlear Synaptopathy in Cochlear Implant Subjects” and describes how neural responses from cochlear implant subjects are relatively small compared to hair cell responses, which is the expected pattern for cochlear synaptopathy.

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

As is clear from the data presented the CM/ANN model is at a high level of development and results from our existing data sets is in preparation for publication (Fig. 1-6). The next goal is to bring the CAP/CM model to a similar level.

As was mentioned in the report for Q3 we have initiated a collaboration with Dr. Frijns of Leiden Univ. in the Netherlands to reproduce his quantitative model of ECochG in the human to gerbils. This will be an adjunct to our own modeling and experimental methods.

As we have mentioned in the last 2 quarterly reports, a bit of a bombshell in the field of cochlear synaptopathy occurred at the 2020 ARO meeting, where reports from the Liberman lab and others indicated that the loss of synapses with noise exposure may not in fact be permanent as was previously indicated using a particular strain of mouse. If the losses are not permanent, it means the issue for humans may not be as severe as permanent loss of 50% of auditory nerve fibers without changes in audiometric thresholds, as was the fear. Consequently, we have shifted our focus to a study of the time course of synapse loss which we will be pursing in the next series of animals. In addition, we are piloting a chronic implantation of a recording electrode for other studies, and if applied here that could greatly speed the time course experiments, in that multiple physiological time points could be obtained in single animals. If we perfect the technique, we will apply for permission to adopt them here.

However, it should be pointed out that anatomical data supports the presence of cochlear synaptopathy in older adults, and our physiological data in the human data set supports that view.

## 4. IMPACT

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

The identification of cochlear synaptopathy as a potential cause of hearing loss is a recent development based on animal studies. There is some anatomical evidence that it occurs in humans, but physiological and behavioral correlates have proven elusive. Our studies in cochlear implant subjects reported at the recent ARO and expanded on here (Figs. 1-6) should have a substantial impact since they are the first clear demonstration of a physiological correlate of cochlear synaptopathy in humans. In addition, in conversation with Charlie Liberman about the impact of his current results of synapse recovery in guinea pigs, he expressed the view that the issue in humans may be most prevalent later in life, as seen in his anatomical studies of human nerve fiber loss, rather than earlier in life, as had been feared for the condition. Our findings that cochlear synaptopathy is common in adult CI subjects, most of whom are fairly old, fits well with this hypothesis.

**What was the impact on other disciplines?**

Nothing to report

**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

**Changes in approach and reasons for change**

In the last report we mentioned that we were not seeing response losses with the noise levels used and would be increasing them. Here we report that the increases did have an effect, so we do now have a working model where all of our analyses can be brought to bear.

As indicated above, the finding that synapses can recover in guinea pigs after noise exposure could have a critical impact on our results if it also occurs in gerbils. Consequently, we are pursuing time course experiments which were not part of the original design, because when developing the project, the literature suggested that the losses were permanent so one time point would suffice.

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

The CAP measurements have the technical problem described, which is that a dynamically changing SP can mimic the shape of a CAP to a high degree but does not reflect neural activity. We think we can overcome the issue by setting a minimum latency for a CAP which the SP will not reach, since it occurs earlier than the CAP. In addition, the shape of the dynamic SP is 'smoother' than the CAP, which might help differentiation.

**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**

Nothing to report

## 6. PRODUCTS

**Publications, conference papers, and presentations**

From last quarter, Presentation at the Association for Research on Otolaryngology Midwinter meeting in San Jose, January 2020. The title of the abstract is "Probable Cochlear Synaptopathy in Cochlear Implant Subjects." A manuscript begun is our human cochlear synaptopathy paper in CI subjects.

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

Nothing to report

**Other publications, conference papers, and presentations.**

Nothing to report

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

Nothing to report

**Technologies or techniques**

Here we include our code and spreadsheet for the model (Fig. 3) for separating the ANN from the CM, as attachments 3 and 4.

**Inventions, patent applications, and/or licenses**
Nothing to report

**Other Products**
Nothing to report

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

| | |
|---|---|
| Name: | Douglas Fitzpatrick |
| Project Role: | *PI* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 3.6 calendar months |
| Contribution to Project: | *Dr. Fitzpatrick has supervised the performance of animal experiments and performed and supervised data analysis* |
| Funding Support: | *National Institutes of Health*<br>*Advanced Bionics Corporation* |

| | |
|---|---|
| Name: | *John Grose* |
| Project Role: | *Co-Investigator* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 3.6 calendar months |
| Contribution to Project: | Dr Grose is assisting in the preparation of the IRBs and piloting ear canal and tympanic membrane recordings for other protocols that can provide relevant information to guide our data collection once approval is granted. |
| Funding Support: | *NA* |

| | |
|---|---|
| Name: | *Kendall Hutson* |
| Project Role: | *Neurotologist* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 6 calendar months |
| Contribution to Project: | *Dr, Hutson is performing or supervising the animal experiments* |
| Funding Support: | *National Institutes of Health*<br>*Advanced Bionics Corporation* |

| | |
|---|---|
| Name: | *Raymond Haggerty* |
| Project Role: | *Post Doctoral fellow* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 12 calendar months |
| Contribution to Project: | *Dr. Haggerty is improving the models used to separate the CM and ANN and the CM and CAP. He is using the models to analyze existing data sets and new data sets using noise exposures in gerbils and ultimately in new human recordings* |
| Funding Support: | *None* |

| | |
|---|---|
| Name: | *Amy Lee* |
| Project Role: | *Research Assistant* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 12 calendar months |
| Contribution to Project: | *Amy performs the noise exposures and animal recordings and does the confocal imaging and analyses to count synapses* |
| Funding Support: | *None* |

| | |
|---|---|
| Name: | *Stephan Pulver* |
| Project Role: | *Research Assistant* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 2.76 calendar months |
| Contribution to Project: | *Stephan does the cochlear dissections necessary for confocal imaging of gerbils cochleas* |
| Funding Support: | *None* |

| | |
|---|---|
| Name: | *Oliver F. Adunka* |

| | |
|---|---|
| Project Role: | *Neurotologist* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | 0.12 |
| Contribution to Project: | *Dr. Adunka has provided institution oversight for development and attainment of IRB approvals and protocol setup for The Ohio State University.* |
| Funding Support: | *National Institutes of Health-NIDCD (U01)- 20%* |

| | |
|---|---|
| Name: | *William J. Riggs* |
| Project Role: | *Audiologist* |
| Researcher Identifier (e.g. ORCID ID): | n/a |
| Nearest person month worked: | *2.4* |
| Contribution to Project: | *Dr. Riggs has worked on IRB approvals and protocol setup for The Ohio State University.* |
| Funding Support: | *National Institutes of Health-NIDCD (U01)- 20%* |

- **What other Organizations were involved as partners?**
  - The Ohio State University
  - Ohio State has gotten an approved IRB for the studies and will be beginning human data collection as soon as the UNC approval is in place

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

  See below:

**CURRENT-COMPLETED SUPPORT FOR DOD**

**LNAME, FNAME: Fitzpatrick, Doug**

*** W81XWH1910609, newly active funding**
***1U01DC018920-01, newly active funding**

**CURRENT/ACTIVE**

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Measurements of Cochlear Synaptopathy Using Electrocochleography/Fitzpatrick/ W81XWH1910609** |
| Effort (Calendar Months): | 3.6 cal mon, 30% effort |
| Funding Agency: | DOD |
| Grants Officer Name & the Address of Funding Agency: | Susan M Dellinger<br>1077 Patchel St., Bldg 1077<br>Fort Detrick, MD 21702 |
| Project Dates: | 08/15/2019-08/14/2022 |
| Funding Amount: | $1,464,807 |
| Project Goals: | The proposed work is targeted to unraveling the ECochG signal with the intent of improving accuracy of the feedback. |
| Specific Aims: | Aim 1: Develop metrics of cochlear synaptopathy using data from animal models and apply them to ECochG from human subjects taken under similar conditions<br>Aim 2: Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement<br>Aim 3: Compare ECochG measures of cochlear synaptopathy to audiometric and speech-in-noise measurements |
| Overlap | NONE |
| | |

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Clinical Utility of Residual Hearing in the Cochlear Implant Ear/Adunka/1U01DC018920-01** |
| Effort (Calendar Months): | 1.8 cal mon, 15% effort |
| Funding Agency: | NIH/NIDCD |
| Grants Officer Name & the Address of Funding Agency: | Kelly Anne King<br>NSC BG RM 8309 6001 Executive Blvd, Rockville, MC 20852 |
| Project Dates: | 08/01/2020-07/31/2025 |
| Funding Amount: | $921,686 |
| Project Goals: | The present proposal aims to improve cochlear implant outcomes for candidates with residual hearing. These hearing remnants often pose a barrier for potential candidates. Consistent preservation and subsequent ipsilateral electric acoustic stimulation will help to make this technology available to more patients suffering from substantial levels of hearing loss. |
| Specific Aims: | Therefore, the present protocol seeks to answer two critical clinical questions in cochlear implantation: (Specific Aim 1) Are cochlear implant electrode insertions using Electrocochleography (ECochG) feedback better for achieving hearing preservation (HP) and (Specific Aim 2) is combined ipsilateral EAS better than non-HP (conventional) cochlear implantation among CI candidates with substantial residual hearing (EAS candidates). |
| Overlap: | NONE |

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **The Optimization of Electrocochleography (ECochG) for Intra-Operative Monitoring and Post-Operative Management/Fitzpatrick** |
| Effort (Calendar Months): | 7.02 cal mon, 58.55 % Effort |
| Funding Agency: | Advance Bionics Corporation |
| Grants Officer Name & the Address of Funding Agency: | Advanced Bionics AG<br>Laubisruetistrasse 28<br>8712 Stäfa<br>Switzerland |
| Project Dates: | 10/01/2018-09/30/2021 |
| Funding Amount: | $234,325 |
| Project Goals: | The proposed work is targeted to unraveling the ECochG signal with the intent of improving accuracy of the feedback. |
| Specific Aims: | N/A |
| Overlap: | Effort will be reduced on this contract to accommodate the proposed effort on all pending grants. |

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Spatial Hearing in Complex Sound Fields/ Freyman/ R01DC001625** |
| Effort (Calendar Months): | 1.08 cal mon,9% effort |
| Funding Agency: | NIH/ University of Massachusetts at Amherst |
| Grants Officer Name & the Address of Funding Agency: | N/A |
| Project Dates: | 07/01/1992-/03/31/2021 |
| Funding Amount: | $146,326 |
| Project Goals: | The goal of this project is to advance the scientific understanding of binaural and spatial hearing in reverberant environments and apply this knowledge to the special problems faced by those with asymmetric hearing, leading ultimately, to better, evidence based treatment approaches for these individuals. |
| Specific Aims: | The aim is to examine the responses of neurons to stimuli used in perceptual studies of the precedence effect in an animal model. |
| Overlap | NONE |

**COMPLETED**

None

## CURRENT-COMPLETED SUPPORT FOR DOD

**LNAME, FNAME: Grose, John**

*** W81XWH1910609, newly active funding**
*** R01-DC001507, recently completed**
*** R01-DC014460, recently completed**

**CURRENT/ACTIVE**

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Measurements of Cochlear Synaptopathy Using Electrocochleography/Fitzpatrick/W81XWH1910609** |
| Effort (Calendar Months): | 3.6 cal mon, 30% effort |
| Funding Agency: | DOD |
| Grants Officer Name & the Address of Funding Agency: | Susan M Dellinger<br>1077 Patchel St., Bldg 1077<br>Fort Detrick, MD 21702 |
| Project Dates: | 08/15/2019-08/14/2022 |
| Funding Amount: | $1,464,807 |
| Project Goals: | The proposed work is targeted to unraveling the ECochG signal with the intent of improving accuracy of the feedback. |
| Specific Aims: | Aim 1: Develop metrics of cochlear synaptopathy using data from animal models and apply them to ECochG from human subjects taken under similar conditions<br>Aim 2: Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement<br>Aim 3: Compare ECochG measures of cochlear synaptopathy to audiometric and speech-in-noise measurements |

**COMPLETED**

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Complex sound analysis in normal and impaired ears/Grose/R01-DC001507** |
| Effort (Calendar Months): | 6.3 cal mon, 52.5% effort |
| Funding Agency: | NIDCD |
| Grants Officer Name & the Address of Funding Agency: | Castilla Mcnamara<br>31 Center Dr.<br>Bethesda, MD 20892-2320 |
| Project Dates: | 12/01/1992-08/31/2019 |

| | |
|---|---|
| Funding Amount: | $323,000 |
| Project Goals: | The goal of this project is to provide a multi-faceted framework within which significant advances will be made in understanding supra-threshold deficits occurring in the presence of audiometrically normal hearing. |
| Specific Aims: | 1. To test the hypothesis that older listeners with audiometric hearing within normal limits have auditory deficits consistent with compromised eighth nerve function.<br>2. To test the hypothesis that the fidelity of envelope encoding of complex stimuli declines with age and hearing loss.<br>3. To test the hypothesis that spectro-temporal integration of speech glimpses declines with age. |
| Overlap: | |

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Factors influencing the behavioral assessment of hearing during infancy and childhood/Buss/R01-DC014460** |
| Effort (Calendar Months): | .6 cal mon, 5% effort |
| Funding Agency: | NIDCD |
| Grants Officer Name & the Address of Funding Agency: | Eric Nunn<br>31 Center Dr.<br>Bethesda, MD 20892-2320 |
| Project Dates: | 04/01/2015-03/31/2020 |
| Funding Amount: | $323,000 |
| Project Goals: | The long-term goal of this research is to identify the factors responsible for immature auditory behavior in infants and children, and to develop techniques for differentiating the contributions of these factors in individual listeners. |
| Specific Aims: | 1: Test the hypothesis that self-generated noise elevates detection thresholds in young listeners, particularly at low frequencies.<br>2: Evaluate central auditory processing and general cognitive factors limiting performance of young listeners In developmental psychoacoustics, effects related to central auditory processing and general cognitive factors are often described in terms of 'efficiency'.<br>3: Evaluate novel procedures for improving behavioral assessment of hearing in infants, toddlers, and 'hard-to-test' children with hearing loss |
| Overlap: | |

## PREVIOUS-COMPLETED SUPPORT FOR DOD

**LNAME, FNAME: Hutson, Ken**

*** W81XWH1910609, newly active funding**

**CURRENT/ACTIVE**

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Spatial Hearing in Complex Sound Fields/Freyman/R01DC001625** |
| Effort (Calendar Months): | 1.08 cal mon, 9% effort |
| Funding Agency: | University of Massachusetts at Amherst/NIDCD |
| Grants Officer Name & the Address of Funding Agency: | Edward Myrbeck<br>31 Center Dr.<br>Bethesda, MD 20892 |
| Project Dates: | 04/01/2016-03/31/2021 |
| Funding Amount: | $146,326 |
| Project Goals: | N/A |
| Specific Aims: | The aim is to examine the responses of neurons to stimuli used in perceptual studies of the precedence effect in an animal model |
| Overlap: | |

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Measurements of Cochlear Synaptopathy Using Electrocochleography/Fitzpatrick/ W81XWH1910609** |
| Effort (Calendar Months): | 6 cal mon, 50% effort |
| Funding Agency: | DOD |
| Grants Officer Name & the Address of Funding Agency: | Susan M Dellinger<br>1077 Patchel St., Bldg 1077<br>Fort Detrick, MD 21702 |
| Project Dates: | 08/15/2019-08/14/2022 |
| Funding Amount: | $1,464,807 |
| Project Goals: | The proposed work is targeted to unraveling the ECochG signal with the intent of improving accuracy of the feedback. |
| Specific Aims: | Aim 1: Develop metrics of cochlear synaptopathy using data from animal models and apply them to ECochG from human subjects taken under similar conditions<br>Aim 2: Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement<br>Aim 3: Compare ECochG measures of cochlear synaptopathy to audiometric and speech-in-noise measurements |
| Overlap: | If awarded effort will be reduced on **Electrocochleography: Basic Science and Clinical Utility** |

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **The Optimization of Electrocochleography (ECochG) for Intra-Operative Monitoring and Post-Operative Management/Fitzpatrick** |
| Effort (Calendar Months): | 4.92 cal mon, 41 % Effort |
| Funding Agency: | Advance Bionics Corporation |
| Grants Officer Name & the Address of Funding Agency: | Advanced Bionics AG<br>Laubisruetistrasse 28<br>8712 Stäfa |

| | |
|---|---|
| | Switzerland |
| Project Dates: | 10/01/2018-09/30/2021 |
| Funding Amount: | $234.325 |
| Project Goals: | The proposed work is targeted to unraveling the ECochG signal with the intent of improving accuracy of the feedback. |
| Specific Aims: | N/A |
| Overlap: | Effort will be reduced on this contract to accommodate the proposed effort on all pending grants. |

**COMPLETED**

None

## PREVIOUS-COMPLETED SUPPORT FOR DOD

**LNAME, FNAME: Brown, Kevin**

***1U01DC018920-01, newly active funding**

**CURRENT/ACTIVE**

| | |
|---|---|
| Grant Title/Main PI's Last Name/Grant Number: | **Clinical Utility of Residual Hearing in the Cochlear Implant Ear/Adunka/1U01DC018920-01** |
| Effort (Calendar Months): | 0.36 cal mon, 3% effort |
| Funding Agency: | NIH/NIDCD |
| Grants Officer Name & the Address of Funding Agency: | Kelly Anne King<br>NSC BG RM 8309 6001 Executive Blvd, Rockville, MC 20852 |
| Project Dates: | 08/01/2020-07/31/2025 |
| Funding Amount: | $921,686 |
| Project Goals: | The present proposal aims to improve cochlear implant outcomes for candidates with residual hearing. These hearing remnants often pose a barrier for potential candidates. Consistent preservation and subsequent ipsilateral electric acoustic stimulation will help to make this technology availale to more patients suffering from substantial levels of hearing loss. |

| | |
|---|---|
| Specific Aims: | Therefore, the present protocol seeks to answer two critical clinical questions in cochlear implantation: (Specific Aim 1) Are cochlear implant electrode insertions using Electrocochleography (ECochG) feedback better for achieving hearing preservation (HP) and (Specific Aim 2) is combined ipsilateral EAS better than non-HP (conventional) cochlear implantation among CI candidates with substantial residual hearing (EAS candidates). |
| Overlap: | NONE |

**COMPLETED**

None

## CURRENT-COMPLETED SUPPORT FOR DOD

**ADUNKA, OLIVER F.**

*** W81XWH1910609, newly active funding**
***1U01DC018920-01, newly active funding**
***Cochlear Americas, completed**
*** R01DC008581, completed**

**Current**

**Grant Title/Main PI's Last Name/Grant Number**: Measurements of Cochlear Synaptopathy Using Electrocochleography/Fitzpatrick/ **W81XWH1910609**
**Effort (Calendar Months):** 0.12 cal mon, 1% effort
**Funding Agency:** DOD
**Grants Officer Name & the Address of Funding Agency**: Susan M Dellinger 1077 Patchel St., Bldg 1077 Fort Detrick, MD 21702
**Project Dates:** 08/15/2019-08/14/2022
**Funding Amount:** $1,464,807
**Project Goals**: The proposed work is targeted to unraveling the ECochG signal with the intent of improving accuracy of the feedback.
**Specific Aims:** Aim 1: Develop metrics of cochlear synaptopathy using data from animal models and apply them to ECochG from human subjects taken under similar conditions
Aim 2: Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement
Aim 3: Compare ECochG measures of cochlear synaptopathy to audiometric and speech-in-noise measurements
**Overlap:** NONE

**Grant Title/Main PI's Last Name/Grant Number**: Clinical Utility of Residual Hearing in the Cochlear Implant Ear/Adunka/1U01DC018920-01
**Effort (Calendar Months):** 0.14 cal mon, 1.68% effort
**Funding Agency:** NIH/NIDCD
**Grants Officer Name & the Address of Funding Agency:** Kelly Anne King
NSC BG RM 8309 6001 Executive Blvd, Rockville, MC 20852
**Project Dates:** 08/01/2020-07/31/2025

**Funding Amount:** $921,686
**Project Goals**: The present proposal aims to improve cochlear implant outcomes for candidates with residual hearing. These hearing remnants often pose a barrier for potential candidates. Consistent preservation and subsequent ipsilateral electric acoustic stimulation will help to make this technology availale to more patients suffering from substantial levels of hearing loss.
**Specific Aims:** Therefore, the present protocol seeks to answer two critical clinical questions in cochlear implantation: (Specific Aim 1) Are cochlear implant electrode insertions using Electrocochleography (ECochG) feedback better for achieving hearing preservation (HP) and (Specific Aim 2) is combined ipsilateral EAS better than non-HP (conventional) cochlear implantation among CI candidates with substantial residual hearing (EAS candidates).
**Overlap:** NONE

**Title:** Outcomes in Adults with Mixed or Conductive Hearing Loss Implanted with the Bonebridge
**Time Commitments:** 0.0 calendar
**Supporting Agency:** Med-EL
**Address:**
**Contracting/Grants Officer:** NA
**Performance period:** 11/18/2019-12/31/2020
**Level of funding:** $19,500
**Project Goals:** The major goals of this project are to 1) assess safety and effectiveness of the BONEBRIDGE implant in adults with mixed or conductive hearing loss, and 2) assess post-operative audiometric and speech perception outcomes with BONEBRIDGE, compared to unaided preoperative performance as well as report on intraoperative experience.
**Specific Aims:** NA
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

**Title:** The Ohio State University Neurofibromatosis Type 2 Clinic
**Time Commitments:** 0.0 calendar
**Supporting Agency:** Children's Tumor Foundation
**Address:**
95 Pine Street, 16th Floor
New York, NY 10005
**Contracting/Grants Officer:** Heather Radtke
**Performance period:** 01/01/2020 – 12/31/2020
**Level of funding:** $5,000
**Specific Aims:** The Ohio State University NFCN Affiliate Clinic supports NF activities that will benefit patient care and the local NF Community. Stipends to the clinic provide continued support of the local NF2 Crew in the organization and hosting of their annual gathering in Columbus, Ohio. The NF2 Crew is an online-based support community for patients and family members (or loved ones) with NF2.
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

**Title:** Cochlear Implantation during Vestibular Schwannoma Removal or During Labyrinthectomy Surgery for Treatment of Meniere's Disease
**Time Commitments:** 0.0 calendar
**Supporting Agency**: Advanced Bionics AG
**Address:**
Laubisrutistrasse 28
Stafa, ZH 8712
**Contracting/Grants Officer:** Mary Orshan
**Performance period:** 10/22/2018 – 10/22/2020
**Level of funding:** Providing cochlear implant devices only (total market value $154,565), no other funding is being received

**Project Goals:** The purpose of this study is to determine longitudinal benefits of listening with a cochlear implant placed during the time of tumor removal for patients with a vestibular schwannoma and/or with patients undergoing a labyrinthectomy for treatment of Meniere's disease
**Specific Aims:** The specific aim is to determine the effectiveness of cochlear implantation for a specific patient population with single-sided hearing loss using a battery of tests and questionnaires: Detection Testing Determination, Speech Perception Testing, Sound Localization Testing, Speech, Spatial and Qualities of Hearing Scale, and Nijmegen Cochlear Implant Questionnaire.
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

**Title:** Neural Encoding and Auditory Processing of Electrical Stimulation in Pediatric Cochlear Implant Users
**Time Commitments:** 0.12 calendar
**Supporting Agency:** NIH
**Address:**
NIH
9000 Rockville Pike
Bethesda, MD 20892
**Contracting/Grants Officer:** Christopher Myers
**Performance Period:** 04/01/2019-03/31/2024
**Level of Funding:** $2,025,282
**Project Goal:** To 1) understand neural encoding and processing of electrical stimulation in children with cochlear nerve deficiency (CND), and 2) develop an effective, evidence-based clinical practice managing this unique patient population.
**Specific Aims:** Aim 1. To determine the effects of poor cochlear nerve survival on neural representation of electrical stimulation in the cochlear nerve. Aim 2. To determine the effects of poor cochlear nerve survival on cortical neural encoding of temporal and spectral cues.
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

**Title:** Vestibular Oriented Research Meetings
**Time Commitments:** 0.0 calendar
**Supporting Agency:** NIH
**Address:**
NIH
9000 Rockville Pike
Bethesda, MD 20892
**Contracting/Grants Officer:** Edward Myrbeck
**Performance Period:** 03/15/2019 – 02/28/2022
**Level of Funding:** $120,000
**Project Goal:** To establish an annual vestibular oriented research meeting.
**Specific Aims:** Aim 1: Create and host a 3-day vestibular oriented research meeting. Aim 2: Create and host two 1-day satellite meetings.
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

**Completed**

**Title:** Clinical Evaluation of the Cochlear Nucleus® CI532 Cochlear Implant in Adults
**Time Commitments:** 0.0 calendar
**Supporting Agency:** Cochlear Americas
**Address:**
13059 E. Peakview Avenue
Centennial, CO 80111
**Contracting/Grants Officer:** Christine M. Menapace
**Performance Period:** 03/07/2017- 03/31/2020

**Level of funding:** $33,783
**Project Goals:** To evaluate pre- and post-implantation speech recognition in quiet and noise scores in the implanted ear alone and to evaluate pre- and post-implantation Health Utility (HUI).
**Specific Aims:** The specific aims are to determine the group mean CNC word recognition in quiet measured at 6 months post-sound processor activation in the best unilateral condition compared to the group mean score obtained in the pre-operative, unilateral aided –ear to be implanted condition, to determine the group mean AzBio sentence in noise score measured at 6 months post-sound processor activation in the best unilateral condition compared to the group mean score obtained in the pre-operative, unilateral aided –ear to be implanted condition, and to determine the group mean HUI3 score measured at 6 months post-sound processor activation in the best unilateral condition compared to the group mean score obtained in the pre-operative, unilateral aided –ear to be implanted condition.
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

**Title:** Infant-directed Speech and Language Development in Infants with Hearing Loss
**Time Commitments:** 0.6 calendar
**Supporting Agency:** NIH/NIDCD R01DC008581
**Address:**
NHLBI Center for Scientific Review
6701 Rockledge Drive
Room 1040-MSC 7710
Bethesda, MD 20892-7710
**Contracting/Grants Officer:** Eric Nunn
**Performance period:** 08/14/2015 – 06/30/2020
**Level of funding:** $2,901,403
**Project Goals:** To determine how real-world language input affects language development in infants with hearing loss and to determine the underlying factors of infant-directed speech (IDS) that might facilitate language development in these infants.
**Specific Aims:** The specific aims are 1) To assess the quantity and quality of real-world speech directed to infants with hearing aids (HAs) and cochlear implants (CIs) relative to normal hearing (NH) peers. We will use the Language Environment Analysis (LENA) system to obtain real-world IDS and adult-directed speech (ADS) samples from the homes of CI, HA, and NH infants and perform quantitative (e.g., amount of IDS in a day) and qualitative (mean F0 of IDS vs. ADS) measurements on a representative sample of the speech input; 2) To determine direct and indirect relations between properties of IDS and language outcomes. We will assess infants' speech processing efficiency and obtain several language outcome measures; 3) To determine the effects of IDS on novel word learning in infants with PHL compared to NH peers. We will assess CI, HA, and NH infants' ability to learn novel words in IDS and ADS conditions from 9 to 27 months after receiving a CI or HA; and 4) To determine which acoustic characteristics of IDS facilitate novel word learning in NH infants under conditions of natural speech and spectrally degraded speech. We will test word learning in NH infants using pitch-, timing-, and vowel-altered stimuli under varying levels of spectral degradation (unprocessed, 32 channel, 16 channel, 8 channel).
**Overlap:** No scientific or budgetary overlap with the proposed PRMRP proposal

## 8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A
QUAD CHARTS: The quad chart has not changed

## 9. APPENDICES

1. CV for Dr. Haggerty

2. Figures for the ‘Accomplishment’ section.

3. Paper from Dr. Frijns lab

4. Model for separating the CAP from CM. Note that this “ModelCalc’ code is a subroutine that can be called from a larger program that serves as an engine for all of our analyses. This engine can be described and provided as a working version if needed.

5. The spreadsheet contains all of the data for the analyses of older data sets (BiologicData_by_seq page) and noise exposures for cochlear synaptopathy (CS_by_seq and CS_by_case pages), as well as distortion products (DPs_by_seq) and synapse counts (Synapses_by_freq).