AWARD NUMBER: W81XWH-19-1-0609
RH180042

TITLE: Measurements of Cochlear Synaptopathy Using Electrocochleography

PRINCIPAL INVESTIGATOR: Douglas C Fitzpatrick

CONTRACTING ORGANIZATION: University of North Carolina at Chapel Hill

REPORT DATE: SEPTEMBER 2021

TYPE OF REPORT: Annual

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 2021	ANNUAL	15AUG2020 - 14AUG2021

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)
Douglas C Fitzpatrick

E-Mail:dcf@med.unc.edu

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. Animal results with neurotoxins and human studies in subjects with various degrees of hearing loss are showing effects of synaptopathy on ECochG potentials recording from the round window that can be detected with our specialized analyses. The methods are being extended to ear canal recording with should have a broader clinical applicability. New results are also showing an unexpected sensitivity of responses to distortion products of multione stimuli to be sensitive to cochlear synaptopathy produced by neurotoxins.

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)*

TABLE OF CONTENTS

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

Distortion Products

Hearing loss

Inner hair cells

Noise Exposure

Outer hair cells

Summating Potential

Synapse

Tympanic Membrane

Ear Canal ECochG

3. ACCOMPLISHMENTS

What were the major goals of the project?
(NOTE: numbering is congruent between this section, the parallel section on accomplishments, and the figures in the attached Powerpoint file)

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 the biomarker 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). Human hearing in the range for speech is dominated by low frequencies (<~1500 Hz) where neural phase-locking to the fine structure of the sound waveform is present. The evoked potential correlate of this phase-locking is the ANN, which is mixed with CM from hair cells in the fine structure of the ECochG response. We have developed novel techniques to estimate the relative magnitudes of each in the recorded response. This separation relies on the use of fitting model based on the biophysics that produce the CM and ANN. With this model, the degree of cochlear synaptopathy, or relative paucity of neural compared to hair cell activity, should be measurable.

1a. 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. 3) The delivery of a model showing further development at the end of the second year.

Major Task 2 - Measuring the CM and CAP in response to high frequency sounds. Similar to Major Task 1 except that to high frequencies (i.e., >~1500 Hz) the neural component is a different feature called the compound action potential (CAP). Here, the CAP is separable from the CM in time. 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.

1b. Subtasks. Similar to 1a.

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.

1c Subtasks. Develop a gerbil model of cochlear synaptopathy

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.

1d. Subtasks. HRPO and IRB approval. Intraoperative recordings from CI subjects and other subjects where the round window is approachable intraoperatively.

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.
2a, Subtasks. HRPO and IRB approvals. Concurrent recordings.

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

2b Subtasks. HRPO and IRB approvals. Ear canal recordings.

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

Subtasks. HRPO and IRB approvals. Obtain behavioral and ECochG data from the same young adult subjects with normal hearing.

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 report delivered for year 1 included many details of our approach used to resolve the contributions of the ANN and CM in the combined signal. The approach is to use modeling based on the waveform shapes and principles of the biophysics that produce each of the potentials. A two-step modeling effort was described where the waveform was first evaluated for the presence of any ANN compared to a purely CM waveform, and if some was detected, by evaluating the waveform shape to measure the proportions with a biophysically-based model. In the current version from this year, we have replaced the algorithm for the initial, detection step with a deep-learning algorithm as will be briefly described (additional details available in previous quarterly reports). The deep learning algorithm works with high sensitivity and specificity on the data set from normal hearing animals where the categories "has ANN" or "No ANN" are well-defined by the frequency range. That is, responses to frequencies within the range of neural phase-locking have ANN, while to frequencies above the phase-locking range there is no ANN, so these represent a perfect training set to identify the presence of the ANN in the input waveforms. The second step of the model estimates the proportions of CM and ANN using a model based on the biophysics of the production of the hair cell (CM) and neural (ANN) responses. The basics of the current, two-step model are shown in Fig. 1a-1, and the legend in the notes provides additional details.

Some results using this two-step approach in normal hearing animals are shown in Fig. 1a-2. The high specificity and sensitivity are shown by the confusion matrix (top left), where 98.0% of cases where ANN was present were detected, and 99.1% were also correctly identified where it was not present. When considered on a frequency-by-frequency basis, the proportion of recordings identified by the DLA as having ANN was >95% for 0.25 to 0.75 kHz, which then dropped to <5% for frequencies of 1.5 kHz and higher (Fig. 2, bottom left). The proportion at 1 kHz was about 75%. The overall phase-locking to 1 kHz may be reduced because it is near the cut-off frequency for phase-locking (for both gerbils and humans), but a reduction in the ANN may also be because the width of a unit potential begins to exceed the width of a stimulus cycle.

Further validation of the analytic model, or second stage, for determining values for the CM and ANN was provided by a new analysis (Fig. 1a-2, right). Here, the output of the model in terms of ANN proportion was compared to that of an independent method of analyzing an average cycle which did not make assumptions about the shapes that make up the CM and ANN. For each low-frequency average cycle from the normal-hearing animals, we performed a cross-correlation with all the average cycles to high frequencies (which can have a range of shapes even though they are only CM). We then measured the root-mean square value of the residuals in the case with the closest overall fit. The idea was that the smaller the residuals, the closer a match to a CM-only case, and the less ANN would be present. That is, these residuals should be proportional to the amount of ANN but cannot produce values for each. We found that this metric correlated well (r=0.883) with the ANN proportion from the analytic model (Fig. 1a-2, right), indicating that the values derived from the analytic model scale with actual rather than far distant values. This result indicates that the model is not simply curve-fitting but is instead fitting with plausible actual values.

Once constructed and validated in normal hearing animals, using data independent from the training set (e.g., Fig. 1a-2), the approach was applied to additional animal and human data sets. Another animal model where we have applied this two-step approach is animals exposed to intense (122 dB SPL for 2 hours) high pass (4 kHz cutoff) noise exposure that produces a sloping hearing loss (i.e., loss of high frequency but preserved low frequencies) that mimics that of CI subjects. These are termed HP-NIHL animals, for high-pass noise-induced hearing loss. Then both the normal and HP-NIHL animals were also tested after kainic acid, a neurotoxin, was applied to the round window, for additional data sets. The humans were CI subjects recorded from the round window intraoperatively and other subjects where the round window was approachable during surgery. These 'other subjects' include primarily Meniere's patients undergoing labyrinthectomy to treat their vertigo and patients where vestibular Schwannoma's are being removed.

Using the deep learning algorithm, or step 1 or the approach (Fig. 1a-3, left), the average cycles to low frequencies (<1000 Hz) in normal hearing and HP-NIHL animals almost all showed ANN. This was shown previously for the NH animals (Fig. 1a-2, left) but was not necessarily expected for the HP-NIHL animals. After the KA, both animal groups showed a large increase in the proportion judged to have no ANN. A partial synaptopathy is expected to low frequencies since the drug has to diffuse to the apex of the cochlea for complete loss of neural activity, and a complete loss of neural activity is infrequent. *Of note is that is that both human groups showed a high proportion of average cycles judged to have no ANN.* Thus, the humans studied, both groups of which had substantial hearing loss, resembled animals treated after neurotoxins, a hallmark of cochlear synaptopathy. (Please note that scientifically speaking the line in this figure has no meaning since the groups are not connected in a causal way but is used for illustrative purposes.)

The results from the analytic portion of the model are similar, in that after the neurotoxin the proportion of ANN decreased overall for both NH and HP-NIHL animals, as would be expected. Interestingly, the HP-NIHL animals before the KA showed an *increase* in ANN. We attribute this paradoxical result to different rates of spread of excitation of the CM and ANN, with the CM in a normal hearing animal showing greater increases as larger parts of the cochlear are recruited than for the ANN. In the HP-NIHL animals the spread of excitation to the basal cochlea is blocked by the loss of hair cells, so the CM and ANN are more nearly equal in size. *Again, the most interesting part of this plot is that relative amounts of ANN in the human groups closely resemble the animal groups after treatment with neurotoxin*. In the bottom figure we show the means and standard errors used for post-hoc tests of significance (alpha=0.083 after correcting for multiple comparisons) employed after a Kruskal-Wallace test showed significant differences between the six groups (Chi sq=320, df=5, 1608, p<0.0001). The human groups were distinct from both the animal groups prior to the neurotoxin but were not distinct from the animal groups after the neurotoxin. These results are novel results in the field of cochlear synaptopathy for two reasons 1) they show cochlear synaptopathy to be present in subjects with a high degree of hearing loss, and 2) it extends the effect of cochlear synaptopathy to low frequencies – to date it has been treated as a purely high frequency phenomenon in both animals and human. It also represents a novel approach to identifying cochlear synaptopathy using ECochG.

Additional work The basics of these results were presented in last year's report, and we spent much of this past year providing additional val**idation of the methods as well as producing a manuscript that was sent to Science Translation. Unfortunately, it was not reviewed so we are submitting to Hearing Research, a more specialized journal.**

In addition, we are continuing to work on improvements to the approach and have recently been focusing on improving the equations in the analytic model for both the CM and ANN. In particular, the equations we have been using are largely phenomenological, e.g., for the CM we used a truncation step which allowed the saturation of the peak and trough of response to be hard cut-offs and independent, and for the ANN we used a 1100 Hz sine wave to model the unit potential. We have recently begun to implement equations that more accurately fit the biophysics.

Nearly all post stimulus time histograms (PSTH) in the literature describing the EcochG focus on the modeling of the compound action potential (CAP), which occurs before the steady state of the EcochG we are interested in. Most of these include a delay term, a peak, and a long tail and are intended to model the entire EcochG, rather than the average cycle of the steady state.

To attempt to model the average cycle rather than the CAP, we implemented a PSTH for the average cycle described by a gaussian distribution with the mean in the middle of the cycle, and a spread of excitation parameter influencing the standard deviation.

Previously, we had been normalizing the CM and scaling it using an amplitude parameter in the same way we had for the Auditory Nerve Neurophonic (ANN). This makes sense for the ANN because we are modeling the response of a single fiber and then multiplying it by the number of fibers responding. However, this does not translate to the CM, as we are modeling the total response of the hair cells. The amplitude should be controlled by the P_{sat} parameter from the equation describing the cochlear transducer. The equation controlling the shape of the CM is below for reference.

$$h(t) = -P_{sat} + \frac{2P_{sat}}{1+e^{z(P+P_0)}}$$

where P_{sat} is the saturation voltage, z is the sensitivity and P_0 is the operating point.

These changes are attractive because they reduce free parameters and in theory should provide more accurate estimates of the biophysics being modeled. To test how well the changes in the model are working we used the 'residual's test' described in Fig. 1a-2 (right). The r value with the new equations is 0.735, which is good, but is actually less than the value from before, where r=0.883. The reason is because in some cases the CM is particularly small, and believe that the changes to the bounds discussed in the previous section will increase this fit.

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, that can also be measured in relation to the CM to estimate cochlear synaptopathy. Unlike the ANN, the CAP can be separated from the CM in time, with the CAP occurring at the onset and the CM being analyzed later after reaching steady-state. The analyses to date remain more preliminary than those of the ANN, primarily because the CAP is a less prominent feature in our human groups with a high degree of hearing loss. We will show some results in the next sections that use analyses of the CAP, however, and expect to incorporate it more formally over the next few reports.

A problem has been the form of the dynamics of the summating potential (SP) which we have found through the use of neurotoxins can mimic the shape of the CAP even when no neural responses are present (Figure 2a-1, from year 1's report). The dynamics are that an early phase of the SP is driven by the OHCs and has negative polarity, while the SP from IHCs comes in slightly later and has positive polarity. Thus, its transient, negative peak resembles the CAP. There are differences, however, in particular that the CAP will decrease in latency with intensity while the hair cell latencies will not. We are in the process of developing tools to deal with this, possibly in the form of a deep learning algorithm, where we can use recordings from NH animals that include both the SP and CAP, and other after neurotoxins that are purely SP, as a training set.

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, and in previous reports detailed our ability to use immunofluorescent methods with confocal microscopy to identify and quantify synaptic terminals on gerbil inner hair cells exposed to various noise exposures. When analyzed, we were perplexed to find that the unexposed control animals were themselves distinct from 'normal'. Instead, we observed a pattern of inner hair cell loss and synapse counts well below that expected from previous studies and a few of our best cases. This inconsistency in controls led us to be unable to conclusively demonstrate synaptopathy in the exposed animals, despite physiological evidence that were in fact producing synaptopathy over a well-defined range of intensities.

To further address the issue of animal quality, we are examining animals of different ages and sexes from the from the same supplier of research animals (Charles River). We have generally used fully adult animals (6-8 months) and generally male, because in past experience these do well under surgery. We have begun ordering younger males and females to determine if these have this same issue. To date, we have observed hair cells on 2 young females and 1 young male, and have not seen as much IHC loss.

However, in terms of impact on the overall study the problem is manageable. That is, we can produce a greater degree of any already-present synaptopathy with neurotoxins in a reproducible manner.

An example of how this capability with neurotoxins is extending our approach to new areas is with our analyses of distortion products. We showed some early results in last years annual report but our methods have been refined with different stimuli to produce a greater degree of sensitivity than described there. We presented a poster on this work at the ARO meeting in February 2020, that is included in the attachment, and the current state of the study is briefly described below.

Distortion Product (DP) Analysis

There is a new finding that has come out of the gerbil synaptopathy via neurotoxin studies that we have been pursuing. In last year's report we provided results with two-tone stimuli, i.e., frequencies (F1) from 1000 to 16000 Hz presented simultaneously with a second frequency (F2) at 1.2x the F1 at either identical levels or with F2 10 dB lower. These data were obtained in the same experiments with responses to tones and noise exposure described above. Recently we have switched to the approach of using neurotoxins and changed the stimuli to a multitone complex which allows investigation of numerous DPs simultaneously. We use six tones, carefully chosen so that each of the distortions produced by each interaction can be tied to specific F1 and F2 combination tones.

An example of the pattern of response is shown in Fig. 1c-1 (top). That experiment shows the responses to the primaries (F1-F6, from 4300-7034 Hz) and the F2-F1 DPs. Of particular note is that to this low intensity (20 dB SPL), the responses to the DPs prior to the neurotoxin are larger than to the primaries. In contrast, after the neurotoxin the responses to the DPs have disappeared, indicating they are of neural origin. Thus, reduced DPs to low-level stimuli appear to be a hallmark of cochlear synaptopathy.

To describe the pattern more fully, the pre-neurotoxin results are shown for a range of intensities in the bottom panels of Fig. 1c-1. To high intensities the DPs are relatively small compared to the primaries, while to low intensities the DPs dominate. In Fig. 1c-2, we show more complete results across the ranges of frequency and intensity tested.The behavior of the primaries, measured as the peaks on the FFTs, was largely linear with intensity (left). In contrast, the DPs to high frequencies (1607 Hz and higher) was linear, but that to lower frequency DPs was not. This test therefore appears to identify a range similar to that of neural phase-locking.

At this point there were essentially two hypotheses for the source of these potentials. It is possible that, like some parts of the distortion product otoacoustic emissions, the distortions at the site of the primaries sent traveling waves toward the more apical locations where the responses to the lower frequency DPs could be produced. However, the levels where these DPs are prominent are so low that it seems unreasonable for a DP to excite a remote region. With DPOAEs, the intensities used are much higher, and generally such low frequency DPs (<1000 Hz) are not detectable anyway because they are below than the noise floor. Alternatively, the DPs could be generated by distortions within the IHC receptor potentials, in which case they would derive from the CF region of the primaries, with the distortions modulating the spontaneous and driven rates of the neurons to produce the responses we see.

In Fig. 1c-2, we show evidence for this latter hypothesis, i.e., that the low frequency DPs derive from the sites of the high frequency CF regions associated with the primaries. On the left is a series of panels with results from the Carney model for producing auditory nerve action potentials to a two-tone stimulus with F1=4000 Hz and F2=4800 Hz. The blue traces are the vector-strengths (degree of phase-locking) energy for fibers with CF frequencies from 200 to 38000 Hz to the DPs shown, either F2-F1 frequency (800 Hz), 2F1-F2 (3200 Hz) and 2F2-F1 (5600 Hz). The panels above with cyan traces show the uncorrected p-values of the vector strength peaks to each frequency and show that the largest significant peaks are to the F2-F1 frequency (below the red lines, which is the p-value for significance after multiple comparisons). Most importantly, the *fibers showing these significant peaks are at the CF of the primaries* rather than the lower frequency DPs. In the panels on the right, we show directly by using neurotoxins that the source of the F2-F1 DPs is from the CF

region of the primaries. Here, the neurotoxin (kainic acid) was applied to the round window and allowed to diffuse from base to apex while recordings to tones and to the multitone complex were taken. The top panel plots the CAP to tones, a purely neural potential which disappears in sequential fashion from high to low frequencies as the neurotoxin spreads. The bottom panel shows the loss of the DPs, which clearly occurs over a range where the CAPs to high frequencies associated with the primaries are also disappearing. Significantly, the DP that was lost first (arrow on purple curve) was the DP associated with the highest frequencies and the DP that was lost last was associated with the lowest frequency primaries. The actual DP frequencies, however, are adjacent to each other (arrows on legend).

Finally, it remained to be demonstrated that these DPs are also relevant in human ECochG. In Fig. 1c-3 we show an example of intraoperative round window recording from a CI subject to 2-tone stimuli. We used low frequencies as the primaries because many CI subjects have only responses to low frequencies remaining. The response to F1=500 Hz and F2=750 Hz (left) shows a large peak at 250 Hz which corresponds to both the F2-F1 and 2F1-F2 DPs. The response to F1=1000 Hz and F2=1250 Hz (right) also shows a large peak to the F2-F1 DP to 250 Hz and a peak to 500 Hz that corresponds to the 2F2-2F1 DP. Notably, these peaks to the DP frequencies are larger than to the primaries, which are small, similar to the results in gerbils. However, the intensities used were large (90 dB nHL), so we cannot rule out traveling waves to the low frequency part of the cochlea, even though the tones were not less than 20 dB above the response thresholds. Further human work is necessary to make the connection more parallel to that in gerbils.

We think that in general these DPs observed with ECochG show properties that distinguish them from DPOAEs, and that have also not been well-described in the ECochG literature. The F2-F1 DPs in gerbils that defined the range of phase-locking (Fig. 1c-2, right) is similar to the ANN but is evoked by an entirely different stimulus that can used to define the phase-locking over a wide range of CFs. Consequently, we think these DPs represent a novel stimulus/response paradigm that deserves further characterization.

Aim2. Develop extra-tympanic recording techniques to optimize non-invasive ECochG measurement.
2a. *Concurrent recordings from the round window and ear canal.*

Our initial idea of recording round window and ear canal ECochGs fully concurrently is not feasible, because the SNR at the round window is so high that too few repetitions are taken for ear canal recordings to show anything. Operative time being what it is, it is not possible to obtain more averages. However, there are times before drilling or after the facial recess is exposed to play more stimuli without interrupting the surgery. This is not fully concurrent with the round window recordings but at least is in the same subject so we will have a good idea of how the two potentials are related which was the main purpose of this experiment.

2b. Ear Canal recordings in young adults

In the Q6 report we showed the first data from ear canal recordings, including examples of the CM and ANN to low frequencies and some test/retest data. This data is reproduced in Fig. 2b-1. The stimuli used are 250 Hz tones, 2000 Hz tone, and clicks. Each is presented at 80 dB nHL, with 2000 repetitions. The low frequency enables the measurement of the CM and ANN using our two-step modeling approach, and the high frequency is used to measure the CM and CAP.

To date we have ear canal recordings from 14 young adult subjects, all with normal hearing, i.e., audiometric thresholds <20 dB HL for frequencies from 250 Hz to 8 kHz. Distributions of the relevant measurements to the 250 Hz tone burst at 80 dB SPL are shown in Fig. 2b-2, which were also provided with the Q7 report. We have recorded from 3 additional subjects since then but the results are not yet included. The top row is the sum of the CM and ANN, so it shows the largest responses, followed by the CM alone (second row). The ANN (third row) was much smaller. This pattern is similar to what we observed from the round window. The bottom row is the ANN divided by sum of the CM and ANN for each case, expressed as a percent.

As would be expected, these responses are much smaller than many that are recorded from the round window in CI and other subjects. That is, the ear canal is much further from the cochlea, and therefore the responses are smaller. However, it is noteworthy that in each case our deep learning algorithm (step 1) detected that an ANN was present, and the analytic model (step 2) indicated that it was at least 10% of the total, and in other cases were nearly 40%.

In Fig. 2b-2, right, we show the distributions of the CM and ANN as a function of the ANN proportion. The inverse relationship of the CM means that the larger the CM gets, the smaller is the proportion of ANN. In contrast, the larger the proportion of ANN the larger its size. These relationships are the same as seen in our round window recordings. Similarly, in Fig. 2b-3, the measurements of ANN proportion show a strong correlation (r=0.8) with the residual RMS from the best-fit CM-only curve, identical to the results from normal hearing gerbils that helped to validate the approach (see Fig. 1a-2, right). Thus, our current preliminary results indicate that the methods used for the round window recordings are suitable for the ear canal.

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

We have speech data for the same 14 subjects with ear canal ECochG. There are two behavioral tasks involved, which are modulation masking release (MRM) and spatial masking release (SRM). Both are speech in noise tests that are hypothesized to be affected by cochlear synaptopathy. The subjects all have normal thresholds over the usual range of audiometric frequencies (250 Hz – 8 kHz, HL thresholds <20 dB). The MRM task measures the improvement in speech perception threshold when speech-shaped maskers are modulated vs. unmodulated, and the SRM task measures the improvement when the target speech is spatially separated (45 degrees to either side) from the masker speech (please note that more complete experimental details for the behavioral experiments were provided in the Q7 report and are reproduced in the legend of Fig. 3-1. The ECochG is the ear canal responses from the same subjects to 250 Hz and 2 kHz tones. From the 250 Hz tones we can measure the CM and ANN using our two stage modeling approach, and from the 2 kHz tone we can measure the CM and CAP. Each of these stimuli takes about 10 minutes of recording (2000 repetitions). We also use clicks to compare to published responses.

Results are shown in Fig. 3-1. The rows are the two behavioral tasks, MRM (top) and SRM (bottom). The row are the correlations with different response magnitudes, either all of the responses measured summed (Resp_all, left) or each response individually. The individual responses are the CM and ANN to 250 Hz (both derived from the two-stage modeling approach), the CM to 2 kHz CM and the CAP to 2 kHz (if significant). None of the plots show a relationship between ECochG and behavior. We also examined measures such as the ANN proportion or CAP/CM proportion with similar results.

Possible reasons for a lack of correlation between the ECochG and behavioral measures are that none of these young subject's measure to date has much synaptopathy to detect. The range of the speech detection thresholds to the individual stimuli (e.g., to the modulated and unmodulated maskers) are small for both stimuli, less than about 6 dB. As the number of subjects increases we should have more range to work with.

However, there are some positive results that may prove interesting and important in this regard. In addition to taking thresholds to the standard audiometric frequencies, we also used high frequencies, i.e., 10000, 12500 and 16000 Hz. There was no requirement that these be in the normal range. In Fig. 3-2, we show some examples of the correlation to the 2 kHz CM (2 left plots). The CM to 2 kHz did not correlated to the behavioral threshold to the low frequency (500 Hz) but did not correlate to the high frequency (12.5 kHz). The panel on the right shows the correlation to with the, but the To the low frequency (500 Hz) there Audiometric thresholds compared to the high frequency (2000 Hz) CM measured with ECochG. Results from 14 subjects are shown in the two left panels, for 500 Hz and 12.5 kHz audiometry, respectively. The correlation was not significant (p=0.29) to 500 Hz but was significant (p<0.001) for 12.5 kHz. Across all audiometric frequencies tested, the correlation was significant for frequencies of 10,12.5 and 16 kHz, but not for any lower frequencies.

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 on the distortion products and a podium talk on the demonstration of cochlear synaptopathy using ECochG in animal and human subjects were presented at the (virtual) Association for Research on Otolaryngology Midwinter meeting in February 2021 (files are in the attachments).

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 two-step modeling approach is at a high level of development and results are in the process of publication. Still, some further interesting advancements are in progress. We intend to further advance the CAP analyses which have progress in other areas (distortion products and ear canal recordings) but has only been applied in preliminary form to the larger data sets.

The ear canal recordings to date have shown that the methods used for the round window work well despite the much lower SNR. We will continue to examine the range of the various potentials in young adults with normal hearing. We will begin ear canal recordings in human CI subjects to compare the low SNR site with high SNR as further validation for the ear canal measurements.

Although the ECochG results are not yet showing a relationship with speech in noise tests in young adults, we are mindful that to date the range of behavioral variation is small. We think that over time the variation will increase with a better chance to show the hypothesized correlations. We are encouraged that the ear canal measurements work as well as they do, and also that the ECochG is showing correlations with audiometric thresholds to high frequencies above the standard audiometric range.

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 will have a substantial impact because they are the first clear demonstration of a physiological correlate of cochlear synaptopathy in humans with a high degree of hearing loss and to low frequencies. To the extent we are expanding our finding to the ear canal the tests and methods being developed should be applicable to a wide range of subjects.

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

As mentioned here and in a previous report our ‘normal’ gerbils are not entirely normal in terms of inner hair cells and synapse accounts. However, physiologically both hair cells and neural responses are large and we can increase the amount of any pre-existing synaptopathy in a reliable and reproducible manner with neurotoxins.

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

None anticipated

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, all ACURO, HRPO, IRB and IACUC protocols are in place and experiments are progressing.

6. PRODUCTS

Publications, conference papers, and presentations

Two presentations at the midwinter meeting at the Association for Research on Otolaryngology Midwinter meeting (virtual) in February, 2021. The title of the abstract is “Probable Cochlear Synaptopathy in Cochlear Implant Subjects.” A manuscript was submitted to Science Translation but not reviewed, it will be resubmitted to a more specialized hearing journal (Hearing Research).

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

In the year 1 report we included our code for separating the ANN from the CM, as attachments. Additional code has been developed and is fully available.

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* *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* *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:	*Meredith Hamby*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	12 calendar months
Contribution to Project:	*Meredith performs animal and human ECochG*
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 is the site where most of the recordings from non-CI subjects are occurring. They have recorded from 11 new subjects since full approval was obtained this year.

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

  None

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 1077 Patchel St., Bldg 1077 Fort Detrick, MD 21702
Project Dates:	08/15/2019-08/14/2022
Funding Amount:	
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):	1.8 cal mon, 15% 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:	
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 Laubisruetistrasse 28 8712 Stäfa Switzerland
Project Dates:	10/01/2018-09/30/2021
Funding Amount:	
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:	
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 1077 Patchel St., Bldg 1077 Fort Detrick, MD 21702
Project Dates:	08/15/2019-08/14/2022
Funding Amount:	
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

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 31 Center Dr. Bethesda, MD 20892-2320
Project Dates:	12/01/1992-08/31/2019

Funding Amount:	
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. 2. To test the hypothesis that the fidelity of envelope encoding of complex stimuli declines with age and hearing loss. 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 31 Center Dr. Bethesda, MD 20892-2320
Project Dates:	04/01/2015-03/31/2020
Funding Amount:	
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. 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'. 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 31 Center Dr. Bethesda, MD 20892
Project Dates:	04/01/2016-03/31/2021
Funding Amount:	
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 1077 Patchel St., Bldg 1077 Fort Detrick, MD 21702
Project Dates:	08/15/2019-08/14/2022
Funding Amount:	
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:	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 Laubisruetistrasse 28 8712 Stäfa

	Switzerland
Project Dates:	10/01/2018-09/30/2021
Funding Amount:	
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 NSC BG RM 8309 6001 Executive Blvd, Rockville, MC 20852
Project Dates:	08/01/2020-07/31/2025
Funding Amount:	
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:
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:
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:
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:
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), 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:
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:
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:
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:
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: A new quad chart is attached

9. APPENDICES

1. Figures for the ‘Accomplishment’ section in Powerpoint format (w legends in notes).

2. Poster presented at ARO.

3. Podium presentation at ARO.

4. Quad Chart