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TITLE**:** **A Micro-Coil Based Cortical Visual Prosthesis**

PRINCIPAL INVESTIGATOR**:** **Shelley Fried, PhD**

CONTRACTING ORGANIZATION**:** **Boston VA Research Institute (BVARI)**

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14. ABSTRACT

We are developing a cortical visual prosthesis that can restore vision to the blind. Our approach is based on the recent development of micro-coils, small implantable inductors that magnetically activate neurons. Much proof-of-concept testing has shown that coils are more selective and maintain consistency longer than conventional micro-electrodes. The Aims here focus on the design and development of a device that can be safely implanted into humans, the initial testing of the new prototypes, and then establishing safety and efficacy of the implants. Here, we describe our ongoing progress with the design of the device, a wide range of safety and performance testing as well as progress towards psychophysical testing in non-human primates.

15. SUBJECT TERMS

NONE LISTED

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TABLE OF CONTENTS

1. INTRODUCTION:

Despite some early clinical success, progress with cortical visual prostheses has been limited by an inability to selectively target specific neuronal sub-populations as well as by the foreign body responses that can compromise long-term efficacy. Our goal here is to advance efficacy and reliability by developing an array of implantable micro-coils. Much previous work has shown that coils are more selective and will remain stable over longer periods of time (vs. implanted electrodes). The Aims here are the design and development of the array, initial testing of the new prototypes and then establishing safety and efficacy of the implants.

2. KEYWORDS:

Visual prostheses; cortical stimulation; magnetic stimulation; cortical implants

3. ACCOMPLISHMENTS:

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

What were the major goals of the project?

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

Aim 1: Design and development of a micro-coil array suitable for implantation into human visual cortex

- Aim 1.1: Establish thresholds of human pyramidal neurons to magnetic stimulation
- Aim 1.2: Develop design specifications for the array
- Aim 1.3: Development of driving electronics optimized for use with coils
- Aim 1.4: Fabrication of prototype micro-coil devices

Aim 2: Establish efficacy of the WFCA via physiological testing

- Aim 2.1: Verify functionality of WFCA prototypes via physiological testing

Aim 3: Establish safety and efficacy of implanted devices

- Aim 3.1: Assess the effectiveness of device implantation into cortex.
- Aim 3.2: Evaluate long-term safety and efficacy of the implant via a conditioned avoidance paradigm.
- Aim 3.3: Establish the ability of WFCAs to elicit psychophysical percepts in non-human primates.
- Aim 3.4: Determine the spatial extent of activation in human cortex *in vivo*.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and

negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Introduction:

We continue to develop two distinct coil designs for use as a cortical visual prosthesis. The first is wired directly to the power supply ('wired' approach), an approach that is technologically simpler and useful for much proof of principle testing. The second design is a wireless version in which power and data are transmitted wirelessly between the portion of the device in contact with the brain and the portion that sits external to the skull. The second approach is considerably more complex technologically but will likely be highly advantageous for devices that remain implanted chronically. The two approaches were referred to as 1st generation and final generation in the original proposal and the SOW, and that terminology will be used here as well. The SOW describes efforts to advance both approaches and both are covered in this update.

The lab shutdowns during the Covid pandemic resulted in delays to the original schedule and we continue to work around ongoing slowdowns. Fortunately, many expenditures have been also reduced during this time, so all tasks are still expected to be completed by the end of the project. Despite the shutdown, we made substantial progress with the design and testing of the coil-based device.

We also ran into unforeseen problems when the site at which the non-human primate (NHP) testing was supposed to be performed, closed. We have identified an alternative site and had made much preliminary discussion to formulate a new plan that will allow us to meet all of the original goals laid out in the original Aims and SOW. We describe the proposed changes below.

Aim 1.1 (thresholds of human PNs):

To evaluate the effectiveness of a given micro-coil design, we measure the strength of the stimulus needed to activate individual neurons; we refer to the minimum strength needed for activation as the threshold and compare thresholds across designs. We have performed extensive threshold testing in mouse cortex but needed to better understand the sensitivity of human neurons, i.e., will the coils be similarly effective when tested clinically.

Fortunately, we are able to obtain small pieces of human cortical tissue, resected from medically necessary neurosurgical procedures, that allowed us to measure thresholds in individual (human) neurons. Using test protocols that were essentially identical to those performed in mice, we determined that thresholds for activating human cortical neurons are only about 15% higher than those from mouse. Note that in mouse we had access to all cortical regions and therefore could test a specific class of neurons, referred to as Layer 5 pyramidal neurons, from a portion of cortex referred to as V1 (or primary visual cortex). V1 is almost never resected during clinical surgery and so we worked with Layer 5 pyramidal neurons from other cortical regions (mostly the temporal lobe). Nevertheless, our experiments in mouse suggest that most L5 pyramidal neurons have similar

thresholds, regardless of region, and so the similarity in threshold levels (between mouse and human) is highly encouraging because it suggests that our ongoing animal testing does indeed directly inform the design of clinical devices.

Initial experiments with human tissue were performed prior to the start of this CDMRP award. However, since human tissue becomes available on a regular basis at MGH, we proposed to continue our *in vitro* testing and applied for HRPO approval (received March 2020). The additional measurements will add to existing cell counts for basic threshold measurements (Aim 1.1) but also help to evaluate whether other response characteristics, identified in rodent neurons, persist in human neurons (Aim 2). The additional experiments for this sub-Aim will not interfere with any of the other Aims.

HRPO reviewed and approved the most recent Continuing Review from the MGH IRB on January 25th, 2021.

Aim 1.2 (Design optimization of coils):

- We have established design specifications for the wired and wireless versions. Samples of both versions have been produced (Aim 1.4, described below) and physiological testing is ongoing (Aim 2, *in vitro* and Aim 3, *in vivo*); summaries of this testing are reported in the corresponding sections below.
- Although originally confined to months 1-6 in the original SOW, design efforts to enhance the efficacy, enhance selectivity and reduce power consumption will continue for the duration of the project. In general, this effort consists of computational modeling of coil efficacy, e.g., how do changes to coil shape, change stimulation waveforms and the addition of specialized cores influence the field strength and gradients produced by the coil, followed by fabrication of prototypes (for promising designs) and then physiological testing. This ongoing effort does not adversely impact progress on the rest of the Aims.

Aim 1.3 (Development of electronics):

- The first-generation hardware for wireless power delivery was completed in December 2019 (Sigenics) and has been tested at MGH. Tests were successful, i.e., neural responses were elicited by wireless stimulation of in brain slices. The *in vivo* testing of the wireless system that was scheduled to begin in March of 2020 was delayed significantly by the shutdown; experiments were re-started in September 2020. The power supply is working as designed but two additional modifications are needed: (1) there is a large amount of electrical noise that impedes analysis of the neuronal responses, and (2) it is desirable to increase power levels slightly so that we can test the full range of responses. These have been discussed with the group at IIT and Sigenics and are scheduled for completion in Q9.

Aim 1.4 (coil fabrication):

- The first 4 steps in the SOW (Develop coil fabrication processes; Fabrication of 1st generation coils; Develop coil testing procedures; Fabrication of 2nd generation coils) have all been completed. We continue to refine the designs and to develop and test new coils (see details below).

- There are now two versions of the wired device – one for use in *in vitro* experiments and one for use in *in vivo* (chronic) testing. Devices produced by MicroProbes for Life Sciences (MLS, one of the sub-contracts sites for this award) reliably meet design specifications and perform consistently. As of 1/31/21, MicroProbes has made over 70 *in vitro* devices and ~40 *in vivo* devices. They continue to refine the production process and coils are now made reliably and repeatably.
- Quality checks remain in place to ensure that key elements of the design (e.g., impedance, lead integrity, tip orientation, etc.) are all consistent (validated by testing at the vendor and at MGH). Additional improvements in the fabrication process continue to be implemented on an ongoing basis.
- The wired device for use in NHP testing (Aim 3.3) had been completed previously. Our decision to move the NHP experiments to a new site (Greger lab at ASU) resulted in some additional design changes that were worked on in Q8. Samples for the first NHP experiments will be evaluated in early Q9 and will be ready for the first experiments currently scheduled in April 2021.
- Fabrication of the wireless coils are behind schedule. Most of the delay is due to pandemic-related vendor slowdowns, e.g., delays in obtaining the ceramic base of the samples. Prototypes of the new design were not fabricated by 11/30/20 as we originally anticipated but are in progress now. Fortunately, the delays will not impact subsequent Aims as long as they are completed by the end of Q9. The fact that the earlier versions of the wireless design have already been shown to be effective strongly suggests that the final versions will work as well.

<u>Aim 2 (establish efficacy via physiological experiments)</u>

- Much testing of effectiveness using *in vitro* experiments in mice has been completed (MGH). The results are encouraging in that devices consistently drive neuronal activation, impedance levels are low (and consistent), the devices are robust, e.g., they are used in many consecutive experiments with no loss of function so far.
- Power levels remain higher than we would like, and so effort continues to refine the coil design (Aims 1.2 and 1.4). Note that higher power levels do not impede progress with these Aims or even testing up to and including clinical trials. If the quality of artificial vision arising from coil-based devices exceeds that of conventional electrode devices, the engineering design of the coil and power supply can be overhauled to incorporate advanced electromagnetic design features.
- We suspect that part of the reason that thresholds are high is due to testing in anesthetized animals. Much previous work with electric stimulation has shown that sensitivity increases in some neural circuits under anesthesia and so we are awaiting results from Aim 3.2 (chronic testing in awake animals) and Aim 3.3 (psychophysical testing in awake NHPs) before we make a final determination of whether thresholds are satisfactory.

<u>Aim 3.1 (Establish efficacy of implanting)</u>

- Coils have been safely and reliably inserted into mouse, rat and NHP cortex. A large number of acute mouse experiments have been performed without significant problem. Testing of insertion into rat cortex (n=~30) has also been relatively straightforward to date. Prior to the start of this grant, coils were inserted into visual cortex of

anesthetized monkeys (after craniotomy and removal of dura); insertion was relatively easy, and we were able to detect surface responses (ECoG) arising from stimulation of the coils. Additional implantation testing will take place as part of the ongoing NHP psychophysical testing (Aim 3.3).

- Additional implantation testing into NHP cortex will take place as part of the psychophysical testing of Aim 3.3. Discussion with team members at the new NHP experiment site (Aim 3.3) indicated a preference for coils that were functionally similar but with a thinner diameter and more rigid; these samples will be available by 2/28/21 and will be insertion tested in the first NHP experiments (scheduled for April 2021).
- While much of the Aim has been completed, final testing will extend beyond the date in the SOW; this is largely due to issues with the original NHP site (see below for details). It is not expected to adversely affect any of the key milestones or other goals of this grant.

Aim 3.2 (Evaluate long-term safety and stability)

- Preliminary psychophysical testing of chronic (wired) coils took place in collaboration with Kevin Otto and his lab at the University of Florida. As per the testing plan, responses to chronic implantation of electrodes were completed first and included measurement of thresholds, dynamic range, signal-to-noise ratio, etc. Repeated capture of these measurements allowed the stability of responses over time to be evaluated. The results convincingly show that thresholds do indeed vary over time, i.e., the performance of implanted electrodes is not stable.
- Following completion of the electrode measurements, coils were implanted, and the same measurements repeated. Animals could consciously detect coil-based stimulation indicating that implanted coils were functional. We began to capture thresholds and dynamic range over time with coils, but the experiments were cut short by the shutdown in March of 2020, i.e., the data needed to evaluate stability of coils was not completed. The stability testing was re-started in August (once the labs re-opened) and we are now collecting data in new animals. We expect to have this study completed in early 2021. As mentioned previously, the UF efforts focus on somatosensory cortex (i.e., not visual) but we expect these to be highly similar to the V1 experiments (at MGH) and will help with our efforts to optimize coil performance.
- The pandemic also delayed the start of implantation experiments at MGH. Since July however, we have implanted devices into visual cortex of animals and demonstrated stability and viability. The psychophysical test rig was completed in October 2020 and experiments are in progress. Whereas we originally anticipated completion at the end of Year 2 (by February 2021), the actual completion date will likely be closer to August 2021 (much of this delay is pandemic related, e.g., we could not get into the lab to run experiments).
- Despite this delay, the initial results are encouraging in that coils have been implanted up to 60 days so far in rats without incident. We will begin sacrificing the first round of animals and will have the initial histology results in the next quarter.
- We have also made considerable progress towards the safety component of this sub-Aim. The design protocol has been completed and outlines a series of experiments to evaluate coil function and tissue integrity over time. The protocol includes measurements that will help demonstrate safety of the coils as we ready for human

testing. For example, we are measuring temperature, pressure waves, tissue response, etc. in response to chronic implantation. The tissue response will consist of a number of immunochemical markers analyzed in the immediate vicinity of the coil implant and findings will be compared to those from electrodes.

- The temperature measurement portion of the study is mostly complete, and figures are being readied for publication. We found that coil-based stimulation could induce relatively large temperature changes but that neural responses arose even from parameter sets that did not induce large temperature changes. Thus, observed neuronal responses are not mediated through a temperature-related mechanism. Pressure waves also do not appear to play a significant role in the activation process.
- The protocol for immunochemical testing has been developed and we will test the tissue from the first few animal implants in the next quarter (Q9) of this award.

Aim 3.3 (Psychophysical testing in non-human primates)

- These experiments were originally scheduled to take place during Year 2 (Quarters 5-8) but have not started yet. Most of the delay is due to closure of the original site at which NHP experiments were supposed to take place (the Born laboratory at Harvard Medical School in Boston, MA). Additional details of these events are described in Section 3.
- As a result, we propose some significant changes to this sub-Aim that are detailed in Section 3 (below). Briefly, while we thought originally that we could move this work to an existing site (the laboratory of Seungwoo Lee, PhD, at Massachusetts General Hospital), we realized there was too much risk in such an approach (lack of specific experience in the Lee lab). We therefore identified a new laboratory (PI: Bradley Greger, PhD, at Arizona State University, ASU) to perform the NHP psychophysical testing. We have had much discussion about the project with Dr. Greger and his team, and have made significant progress, e.g., the IACUC protocol has been developed and approved at ASU, the animal is being trained, the headpost will be installed later this month and the craniotomy will be performed early next month, the coil design has been optimized for their set-up, animal training is ongoing, and the first experiments are scheduled for April 2021.
- As detailed in Section 3 (below), we are hereby requesting approval to add the Greger Lab at ASU as an approved site for this work; we are also requesting some funds be allocated. The work to date at ASU is funded by the NIH and there will be no testing of the coils developed in this grant, or any other work specific to this grant, until the new site has been approved, and the protocol has been reviewed and approved by ACURO.

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

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist

others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

There are several opportunities for Training as well as for Professional Development

- Sang Baek Ryu, PhD, a post-doc in the lab is working with Seung Woo Lee (site-PI for the MGH sub-contract) to obtain greater proficiency with micro-coil design, development and testing.
- Aditya Datye, M.S. is a research assistant in the lab and has been trained on how to model the effectiveness of coil-based stimulation; his efforts are contributing to the goal of optimizing coil design. Drs. Lee and Fried are providing most of the training but are also making additional resources available, e.g. electromagnetic experts.
- Andrew Whalen is a post-doc in the lab and is working with Drs. Fried and Lee to learn how to perform *in vitro* and *in vivo* electrophysiological experiments. He has performed much of the temperature and stability testing of Aim 3.2.
- Vineeth Raghuram, M.S., is a graduate student at Tufts University who is working with Drs. Fried and Lee to learn how to perform *in vitro* and *in vivo* electrophysiological experiments. He is a student in the lab of Brian Timko (Tufts, Department of Biomedical Engineering) and they are collaborating with Dr. Fried on the development of coil arrays; Vineeth will be testing the arrays and his results will help to optimize the array features of the clinical device. He is also developing the immunochemical assays for evaluating the tissue response of the implants.
- Jae-Ik Lee is a post-doc in the lab and was trained on how to perform coil-based electrophysiological experiments. He is now part of a collaboration between the PI (Fried) and Konstantina Stokjovic, MD/PhD to develop a coil-based cochlear implant and learned how to perform the complex *in vivo* measurements needed to test such a device. He has recently completed his first study and results encouragingly show that coil-based cochlear implants show great promise.

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

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

Dissemination has been achieved through publications, conference presentations and abstracts. A full list of presentations and abstracts is provided below.

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

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

Our plan is to continue to follow the schedule outlined in the SOW. Because there were some delays in getting the project started (e.g. implementing sub-contracts), several items on the schedule have been slightly behind schedule. The shutdown associated with the pandemic has resulted in additional delays. As such, we continue to work on a few items originally scheduled to be completed already (details below). Note that many action items extend through multiple reporting periods. Specific action items include:

- Aim 1.4 (Fabrication of prototype devices). Most tasks are completed but the fabrication of 2nd generation (wireless) coils is still in progress. The design is largely finalized for small animals and the new modifications for NHPs will be finalized in Q8.
- Aim 2 (Verify functionality of prototypes). Testing is ongoing at MGH with the prototypes. We continue to look at efficacy, consistency, stability, functionality, power usage and selectivity. Modeling efforts are being incorporated to help optimize design. This effort focuses on continuous improvement of the designs and will continue throughout the course of this project.
- Aim 3.1 (Implant testing in rats). As described above, we have initial results from implant testing (electrodes) in S1 (somatosensory cortex) and the same testing with coils is now underway in primary visual cortex (V1). Implant testing in visual cortex is ongoing in rats; initial results will be available in Q9. We are encouraged by the fact that coils have remained stable for > 60-days.
- Aim 3.2 (evaluate long-term safety). The temperature and vibration testing will be completed in early Q9 and we expect to have a publication submitted on our findings shortly after that. The first tissue evaluation results will be available in Q9 and we expect to continue this work through Q9 and into Q10.
- Aim 3.3 (NHP testing). We will discuss the revised plan for the NHP testing portion with the Program Officers and then complete all necessary documentation in support of the proposed changes. Training of the animal will continue; all surgeries will take place in Q9 and the first psychophysical experiment is scheduled for April 2021.

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

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

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

Implantable micro-electrodes have been the standard for delivering artificial stimulation to targeted regions of the CNS. The micro-coils we are developing as part of this project represent an alternative to conventional electrodes and may have some important advantages, e.g., enhanced performance stability over time as well as the ability to more precisely target specific neuronal populations. We continue to present our work at meetings focused on the development of neural prostheses so that those in the field can learn of the potential benefits of this approach. We are currently collaborating with a group

in the University of Florida to develop implants for their work on stimulation of the somatosensory cortex and a group at the Massachusetts Eye and Ear Infirmary focused on development of a next-generation cochlear prosthesis.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Many efforts to develop a neural prosthesis that targets the CNS are faced with similar challenges: maintaining stability and enhancing selectivity of stimulation. We are presenting this work to those in the broad field of stimulation with the hope that others will find the approach advantageous to their project. This work is not likely to have a significant impact outside the field of neural prostheses other than the human-interest aspect if we can restore function to a non-working part of the CNS.

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

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

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

We have begun discussion about forming a company. Efforts are still in the initial stages and the company is not likely to get started until reports from the first clinical tests are complete. However, the goal is to be able to rapidly move the technology forward at that point. Preliminary discussions about a company to develop a next-generation cochlear prosthesis are also continuing.

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

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

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

Nothing to report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are*

significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

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

1. As reported in Q6, we were given notice that Dr. Born was ceasing all NHP electrophysiology experiments and would not be able to complete the psychophysical testing of NHPs with coils (work associated with Aim 3.3) as he originally committed.
2. This left us in a jam, and we tried to respond quickly. We opted to move this testing into the lab of the Co-I from MGH (Seungwoo Lee). Although Dr. Lee had not previously done these specific experiments, he has extensive expertise performing electrophysiological experiments in other animals and is highly proficient at designing and building test rigs. We were also able to enlist the help of John Pezaris PhD, an expert in visual psychophysical testing of NHPs and on the same floor at MGH as the Lee lab. We spent a good deal of time discussing the start-up of these experiments, meeting with IACUC and the Veterinarians, developing the IACUC protocols, talking with outside experts, etc. While we made significant progress from these efforts, we became convinced that the scope of the effort was beyond the capabilities of the Lee lab, even with added help from the team and Dr. Pezaris, at least in the timeframe of the present award, and looked for additional options.
3. We contacted Bradley Greger, an Associate Professor in the Department of Biomedical Engineering at Arizona State University. Dr. Greger has 20+ years of performing these exact types of experiments (with electrodes) and was interested in collaborating with us on this project.
4. We were able to divert some NIH funding to Dr. Greger to help him get up and running (this required a formal application and approval from NIH) and have since developed the IACUC protocol, acquired a monkey for these experiments, begun training the animal, and have been evaluating their experimental set-up to make sure it is ready for testing with coils.
5. We have completed the IACUC protocol (January 2021), and anticipate performing the craniotomy and head-post surgeries in February and/or March of 2021, performing the first NHP psychophysical experiments in April and will have the basic phosphene experiments completed by June (first component of Aim 3.3).
6. We will review these proposed changes with CDMRP personnel and obtain approval before we begin testing of the coils developed here.

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

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

Detailed above

Changes that had a significant impact on expenditures

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

Nothing to report

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

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

As described above, we propose to test coils in non-human primates at a new site.

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

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

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

1. Paulk, A.C., Yang, J.C., Cleary, D.R., Soper, D.J., Lee, S.H., Ganji, M., Ro, Y.G., Oh, H., Hossain, L., Rogers, N., Kilic, K. Ryu, S.B., Lee, S.W., Hermiz, J., Gilja, V., Lee J.W., Maus, D., Devor, A, Fried, S.I., Jones, P.S., Nahed, B.V., Ben-Haim, Sharona, Raslan, A.M.T., Siler, D.A., Cahill, D.P., Williams, Z.M., Cosgrove, G.R., Dayeh, S.A., Cash, S.C., (2021), Microscale physiological events on the human cortical surface detected with PEDOT:PSS Electrodes, Cerebral Cortex, (accepted).
2. Ryu, S.B., Paulk, A.C., Yang, J.C., Ganji, M., Dayeh, S.A., Cash, S.C., Fried, S.I., Lee, S.W. (2020), Spatially confined responses of mouse visual cortex to intracortical magnetic stimulation from micro-coils, J. Neural Eng. PMID: 32998116.

3. Rathbun, D, Shivdasani, M, Guo, T, Fried, SI, Lovell, N, Hessburg, P (2020), The eye and the chip 2019 – Conference report." Journal of Neural Eng., 2020: 17 (1), 010401. PMID: 31965978.
4. Ryu, SB, Werginz, P, **Fried, SI**, (2019), Response of visual cortical neurons in the mouse to electric stimulation of the retina, Frontiers in Neuroscience, 04 April 2019 https://doi.org/103389/fnins.2019.00324. PMID: 31019449.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report

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

Other Publications:

1. Werginz, P, Raghuram, V, **Fried, S.I.** (2020), The relationship between morphological properties and extracellular electric stimulation in alpha RGCs, J.Neural Eng., 2020;10.1088/1741-2552. PMID: 32736374.
2. Werginz, P, Raghuram, V, Fried, S.I. (2020), The relationship between morphological properties and extracellular electric stimulation in alpha RGCs, J.Neural Eng., 2020;10.1088/1741-2552. PMID: 32736374.
3. Yoon, Y.J., Lee, J.I., Jang, Y.J. An, S., Kim, J.H., Fried, S.I., Im, M. (2020), Retinal Degeneration Reduces Consistency of Network-mediated Responses Arising in Ganglion Cells to Electric Stimulation, IEEE-Trans Neural Syst Rehabil Eng. PMID: 32746297.
4. Muralidharan, M., Guo, T., Shivdasani, M.N., Tsai, D., Fried, S.I., Li, L., Dokos, S., Morley, J.W., Lovel, N.H. (2020), Neural activity of functionally different retinal ganglion cells can be robustly modulated by high-rate electrical pulse trains, J. Neural Eng., 2020 Jun 8, doi: 10.1088/1741-2552. PMID: 32512555.
5. Yu, H., Enayati, S., Chang, K., Cho, K., Lee, S.W., Talib, M., Zihlavnikova, K., Xie, J., Achour, H., Fried, S.I., Utheim, T.P., Chen, D.F. (2020), Noninvasive electrical stimulation improves photoreceptor survival and retinal function in mice with inherited photoreceptor degeneration, IOVS Apr 9;61(4):5. PMID: 32271885.
6. Raghuram, V, Werginz, P, Fried, SI (2019), Somatodendritic and AIS scaling in retinal ganglion cells helps to regulate spike properties and maintain response consistency,

Front. Cell. Neurosci, https://doi.org/10.3389/fncel.2019.00436. PMID: 31611777

7. Werginz, P, Fried, SI (2019), Comparison of electrically elicited responses in rabbit and mouse retinal ganglion cells, Conf Proc IEEE Eng Med Biol Sci. 2019 Jul; 2019:1813-1816. Doi: 10.1109/EMBC.2019.8857504. PMID: 31946249.
8. Lee, SW, Thyagarajan, K, Fried, SI, (2019), Micro-coil design influences the spatial extent of responses to intracortical magnetic stimulation. IEEE-Trans BioMedical Engineering. DOI: 10.1109/TBME.2018.2877713

Talks:

1. Artificial Vision: The International Symposium on Visual Prosthetics, Aachen, Germany, “Progress in the development of micro-coil based cortical visual implants”, December 15, 2019.
2. Artificial Vision: The International Symposium on Visual Prosthetics, Aachen, Germany, “Location-dependent AIS variations influence activation thresholds in mouse RGCs”, December 15, 2019.
3. 11th World Congress on Visual Prostheses, Detroit, MI, Invited Talk, “Towards the development of a micro-coil based cortical implant”, November 11, 2019.
4. Society for Neuroscience, Chicago, IL, Tools and Techniques Session, “Micro-coils for cortical stimulation”, October 20, 2019,
5. Electronics and Information Technologies for Bionic Human (collaboration with BioCAS2019), Osaka, Japan, Invited Talk, “Implantable micro-coils for neural modulation”, October 16, 2019
6. Neurotechnology for Dementia (Workshop), Buckinghamshire, England, Invited Talk, “Implantable microcoils for neurorehabilitation”, May 15, 2019
7. Bioelectronic Medicine Forum, New York, NY, ‘A cortical visual implant to restore vision to the blind’, April 4, 2019.
8. V. Raghuram, P. Werginz, S.I. Fried [2019]. The Spike Initiation Zone in Mouse ON and OFF Alpha sustained RGCs Scales with Cell Size. The Eye and the Chip World Congress on Artificial Vision. Detroit, MI.
9. P. Werginz, V. Raghuram, S.I. Fried [2019]. Location-Dependent AIS variations and Their Influence on Preferential Activation of RGC Subclasses. The Eye and the Chip World Congress on Artificial Vision. Detroit, MI.
10. S. I. Fried, S. W. Lee, S. B. Ryu, [2019], Development of a Micro-Coil Based Visual Prosthesis. Military Health System Research Symposium, Kissimmee, FL.
11. S.I. Fried, S.B. Ryu, A.C. Paulk, J.C. Yang, M. Ganji, S.A. Dayey, S.S. Cash, S.W. Lee, [2019]. Spatially confined evoked responses of mouse visual cortex by magnetic stimulation using micro-coils. Association for Vision in Research and Ophthalmology Annual Meeting, Vancouver, BC, Canada.
12. S. B. Ryu, S. I. Fried, S. W. Lee, [2019], Focal activation of mouse visual cortex by magnetic stimulation using micro-coils, International IEEE EMBS Conference on Neural Engineering, San Francisco, CA.
13. S. W. Lee, S. B. Ryu, S. I. Fried, [2019], Optimizing micro-coil designs for precise activation of primary visual cortex, International IEEE EMBS Conference on Neural Engineering, San Francisco, CA.

14. S. B. Ryu, S. I. Fried, S. W. Lee [2019], Spatially confined evoked responses of mouse visual cortex by magnetic stimulation using micro-coil, 71st Annual MGH Scientific Advisory Committee Meeting.
15. S. W. Lee, K. Thyagarajan, S. I. Fried [2019], Optimization of micro-coil designs for precise activation of primary visual cortex,71st Annual MGH Scientific Advisory Committee Meeting. Notable Poster Award

Posters / Abstracts:

1. S.W. Lee, S.B. Ryu, S.I. Fried [2019]. Optimization of Micro-Coil Designs for Selective Cortical Stimulation. The Eye and the Chip World Congress on Artificial Vision. Detroit, MI.
2. S.B. Ryu, S.I. Fried, S.W. Lee [2019]. Spatially Confined Evoked Responses of Mouse Visual Cortex by Magnetic Stimulation Using Micro-Coils. The Eye and the Chip World Congress on Artificial Vision. Detroit, MI.
3. S. B. Ryu, S. I. Fried, S. W. Lee [2019], Focal activation of mouse visual cortex by magnetic stimulation using micro-coils, IEEE NER Meeting.
4. S. W. Lee, K. Thyagarajan, S. I. Fried [2019], Optimizing micro-coil designs for precise activation of primary visual cortex, IEEE NER Meeting.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities.

  friedlab.mgh.harvard.edu
  (the web-site of the PI)

  A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

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

  BRAIN Initiative Investigators meeting (2020): coils were presented at the Tools and Technologies workshop.

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

  1. One existing patent has been obtained on coils prior to the onset of this grant

and a second patent application is currently under review. These were developed prior to the onset of this award.
2. Two additional patent applications are under development.

- **Other Products**

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

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

1. An animation that conceptually describes the coil approach has been developed
2. Microprobes for Life Sciences, LLC (Gaithersburg, MD) is a for-profit electrode manufacturing company; they are now developing coils for use as an alternative to electrodes.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

Name:	Shelley Fried, PhD
No change	
Name:	Seung Woo Lee, PhD
No change	
Name:	Vineeth Raghuram, MS
No change	
Name:	Jae-Ik Lee, PhD

Project Role: Post-doctoral research fellow
Researcher Identifier (e.g. ORCID ID): ecommons ID: N/A
Nearest person month worked: *6*
Contribution to Project: *in vivo* testing of implanted coils, protocol development
Funding support *DoD Grant (and other grants)*

Name: *Aditya Datye*, MS
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): ecommons ID: N/A
Nearest person month worked: *6*
Contribution to Project: design improvements, modeling
Funding support *DoD grant (and other grants)*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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

The PI (Fried) received a new award from the BRAIN Initiative (NINDS; R01-NS110575) to investigate the fundamental biophysics of neuronal activation. Aims include study capturing detailed anatomy of retinal and cortical neurons, including a new technique we've developed to study the axon initial segment, and incorporating the measurements into realistic biophysical models. Model predictions will be verified by *in vitro* measurements.

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

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

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

- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

- Sub-contracts have been issued to the same four organizations listed in the original proposal (Illinois Institute of Technology, Sigenics Inc., Massachusetts General Hospital and MicroProbes for Life Sciences).
- We continue to collaborate with Kevin Otto, PhD, in the Department of Biomedical Engineering at the University of Florida. Kevin is investigating the response of somatosensory cortex to electric stimulation and will perform some preliminary evaluations of coils to see how they compare to his electrode measurements. We supply Kevin with coils for this work and he has helped us to become more proficient with the process.

8. SPECIAL REPORTING REQUIREMENTS

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

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

9. APPENDICES:

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

A micro-coil based cortical visual prosthesis

ERMS/Log Number: N/A
Award Number: W81XWH1910057

PI: Shelley Fried **Org:** Boston VA Research Institute (BVARI) **Award Amount: $2.1 MM**

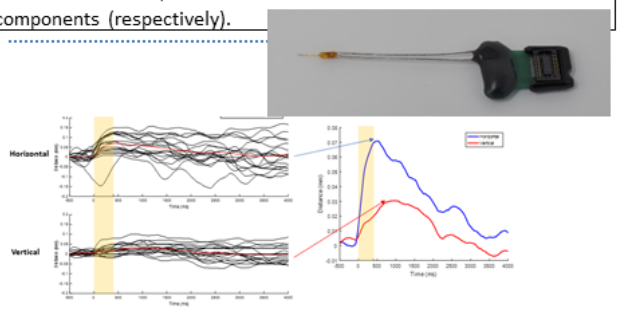
Study/Product Aim(s)

- Design and development of a micro-coil array suitable for implantation into human visual cortex
- Establish functionality of the device via physiological testing
- Establish safety and efficacy of implanted devices

Approach

The use of magnetic stimulation from coils offers several important advantages over conventional electrode-based stimulation and we think our approach overcomes many of the limitations that have hindered progress with electrode-based prostheses in the past. We target visual cortex because it makes treatment available to the widest range of blind subjects, including soldiers and others that have suffered traumatic eye injury and/or damage to the optic nerve or optic radiation. The Specific Aims focus on optimizing the device design, establishing manufacturing processes that will consistently produce high-quality devices, and safety and efficacy testing in preparation for clinical trials.

Inset shows the in vivo device currently implanted in animals for chronic testing. Main plot shows eye movements elicited from cortical stimulation; blue and red are horizontal and vertical components (respectively).



Timeline and Cost

Activities / CY	19	20	21	22
Dev. of human device				
Prototype testing				
Safety and Effectiveness				
IRB / IDE Development				
Estimated Budget ($K)	**$500k**	**$800k**	**$600k**	**$200k**

Updated: (January 31, 2021)

Goals/Milestones

CY19 Goal – Development of human device
☐ Human in vitro testing; develop design specifications
☐ Prototype fabrication
CY20 Goals – Prototype testing; proof of efficacy
☐ Chronic implantation study
CY21 Goal – Safety and effectiveness testing
☐ Human testing (acute); behavioral activation and spatial spread
☐ Psychophysical testing of coils in NHPs
CY22 Goal – IRB/IDE Development
☐ IRB & IDE preparation

Comments/Challenges/Issues/Concerns
Psychophysical testing of coils in NHPs – relocation to ASU

Budget Expenditure to Date
Projected Expenditure: $2.1 MM
Actual Expenditure: ~$1.1 MM