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

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Shelley Fried, PhD

E-Mail: fried.shelley@mgh.harvard.edu

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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.

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None listed.

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1. INTRODUCTION:

Despite some encouraging clinical results, progress with cortical visual prostheses has been limited. Phosphenes (light percepts) are reliably elicited by stimulation from single electrodes, but their assembly into complex spatial patterns is much less consistent, likely because of an inability to create specific patterns of neuronal activation. There are also questions about how foreign body responses impact long-term efficacy. Our goal here is to advance efficacy and reliability by developing a device based on 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 focus on 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:

What were the major goals of the project?

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?

Introduction:

Although the pandemic continues to impact many aspects of the project, we have made good progress in some important areas. Some of the milestones on the original timeline have been delayed but we received approval for a no-cost extension (NCE) that will allow us to continue this work for another 12 months. All Aims are still scheduled for completion within the NCE period

As mentioned in previous quarterly reports, the site at which the non-human primate (NHP) testing was originally supposed to be performed was closed and the work was moved to Bradley Greger's lab at Arizona State University. Much effort was devoted this year to bringing this testing up to speed and we are starting to see encouraging results, e.g., magnetic stimulation from the implanted microcoil is eliciting phosphenes.

Progress and remaining challenges for all Aims are listed 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 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 several types of wired device and one wireless version. Multiple samples of all types 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 design of the ASIC was finalized during Q11. There were several meetings to review the final design and it was signed off in late Q10. Despite several delays in chip fabrication, we are still expecting the ASIC in April. The ASIC will control stimulus delivery for up to 16 channels on the implantable device. We are working to complete fabrication of the rest of the chronic implant so that the chip can simply be inserted and we are ready to go.
- To recoup some of the time lost due to the pandemic and to the transfer of NHP testing from HMS to ASU, the initial ASIC testing will operate with wired devices. Use of wires (vs. the wireless design) will enable more precise temporal control of all channels and also enable a wider range of stimulus amplitudes to be tested. In addition, much less design refinement will be needed with a wired device, allowing us to quickly establish proof-of-principle for the multi-channel chronic implant. This will also allow us to focus more narrowly on evaluating the performance of the chronic implant rather than on the development of wireless technology.

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. To date, MicroProbes has made over 100 *in vitro* devices and ~40 *in vivo* devices. They continue to refine the production process and coils are now made reliably and repeatedly.
- 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 acute NHP testing (Aim 3.3) had been completed previously. Our decision to move the NHP experiments to a new site (Greger lab at ASU) necessitated some additional design changes that were worked on in Q8. Samples for the first NHP experiments were developed in Q8 and revised in Q9; they have been tested in >20 experiments to date. Although much additional testing is required, preliminary results strongly suggest that the acute, single channel device is working.
- The final device that will be fabricated is the chronic, multi-coil implant. The design has been completed and 2-, 4- and 8-channel devices have been prototyped. All were tested for penetration and worked well. Individual channels have been functionally tested in vitro and

function as expected and we are assembling the chronic design; we expect to have it ready in Q13.

Aim 2 (establish efficacy via physiological experiments)

- 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.
- Much of our focus now has shifted to psychophysical testing in awake behaving NHPs. Results are summarized in Aim 3.3. Thresholds there appear to be significantly lower than those from anesthetized rodent experiments; while encouraging, we are still actively working to lower thresholds further.

Aim 3.1 (Establish efficacy of implanting)

- 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.
- Initial implantation of single channel devices into NHP cortex has been successful in ~ 15 experiments to date. The design has worked well and ongoing testing is in progress (see Aim 3.3). 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.
- The multi-channel chronic design was also successfully inserted into mouse cortex. Devices containing 2-, 4- and 8-channels have all been inserted successfully, and are not impacted by the presence of the dura, i.e., insertion works well regardless of whether the dura is removed. 16-channel devices are currently under development and insertion testing will take place during Q12.
- Testing of the multichannel device will also take place in sheep cortex to confirm that insertion works well in larger brains with thicker dura/pia. This work has been delayed significantly due to the pandemic (our access to the institution was restricted) and we are working to get this testing rescheduled for Q13.
- In the most recent round of NHP testing, we have observed some bending of the coil shaft for single channel devices. Initial observations suggest that it may be due to incomplete penetration of the cortex by the cannula, but we are still investigating. If necessary, we can fill the shaft with epoxy to add rigidity. This concern will not adversely impact the design and development of the chronic multichannel implant as the coil for these devices is embedded in a SU-8 housing that provides rigidity and greatly reduces the likelihood of buckling.

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. This first study has been published (Urdaneta et al. 2021) and two additional manuscripts are currently under development.

- Following completion of the electrode measurements, coils were implanted into a second set of animals, 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, 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 data was collected in new animals but they could not collect enough data to reach meaningful conclusions. Rather than continue the efforts in somatosensory cortex at UF, we have transferred the rodent in vivo testing to the Lee lab at MGH with a focus on V1 stimulation. Although the pandemic has delayed both the start of experiments as well as ongoing progress, experiments are ongoing and initial results are encouraging in that coils have been implanted up to 7 months so far in mice. We were originally planning to sacrifice animals in Q9 but performance stayed stable longer than expected and so we delayed euthanasia until they fail. This caused some additional delay but seemed prudent given the ongoing performance of the first implants. Initial histology testing has been completed and is currently being analyzed. Whereas we originally anticipated completion at the end of Year 2 (by February 2021), the actual completion date will be in Q14.
- We have also made considerable progress towards the safety component of this sub-Aim. The design protocol has been completed and experiments to evaluate coil function and tissue integrity over time have been performed. This includes measuring temperature, pressure waves, tissue response, etc. in response to chronic implantation. The tissue response consists of a number of immunochemical markers analyzed in the immediate vicinity of the coil implant and findings will be compared to those from electrodes. This testing will provide much of the safety validation as we prepare for human testing.
- The temperature measurement portion of the study is largely complete, and a manuscript is largely developed. We found that coil-based stimulation could induce relatively large temperature changes but that neural responses arose from parameter sets that did not induce large temperature changes. Thus, observed neuronal responses are not mediated through a temperature-related mechanism. This research led to a design change that greatly reduces temperature increases. Pressure waves also do not appear to play a significant role in the activation process.
- We were originally hoping to have the manuscript on temperature measurements submitted for publication by Q12, but we developed an additional control experiment that we think will show unequivocally how temperature and magnetic fields interact. The new experiments required additional coil prototypes. Those arrive on 11/22 and all experiments were scheduled for Q12 but were delayed by the pandemic; they were completed in mid-February and the manuscript is finally being prepared.
- Chronic implantation experiments have continued at MGH; implantation durations of up to 7 months continue to show stable performance although some devices have been extruded (ejected) after implantation. We think the cyanoacrylate used in some early experiments was sub-optimal as the new material seems to have stabilized the situation.

<u>Aim 3.3 (Psychophysical testing in non-human primates)</u>

- The site change from HMS to ASU, the associated delays, have been described previously.

- Following the initial round of magnetic stimulation experiments at ASU, the animal had a setback and we had to go back to basic chair training. This took about 5 weeks, but the animal recovered and was behaving well midway through Q12. Psychophysical testing with light stimuli now shows excellent results with the animal reliably discerning light stimuli from control testing.
- Results from the first few experiments with microcoils were encouraging, e.g., the animal reliably reports detection when magnetic stimulation is delivered. In addition, relatively low power levels were required (much less than that required in anesthetized rodent experiments).
- The pandemic significantly delayed some of the experiments we were hoping to perform in Q12, and they were on hold for almost half the Quarter. We have made significant progress in the last few weeks and even though some of this work occurred at the start of Q13, the results are encouraging, and we will provide some details here. We have been able to ensure that coil depth is within visual cortex via implantation of a recording electrode, i.e., we can hear the neural background signal when we get to the correct depth. We can also detect light responses. Inserting coils to the same depth has proved fruitful. Now that the monkey can reliably report light stimuli from control trials, we have a lot more confidence in what he is telling us in response to magnetic stimulation trials. Bottom line is that we are getting poor detection for control trials (no current supplied) and very good detection once stimulation currents reach 100 mA. Above 100 mA, response consistency decreases somewhat but detection levels remain good for stimulation levels up to 500 mA (the highest levels tested so far). We have not tested below 100 mA (other than 0 mA) and so it is possible that threshold levels are actually below 100 mA; we will test this during Q13. We have also begun to explore different stimulus rates and are finding that rates of about 100-200 Hz are most effective.

<u>Aim 3.4 (Spatial extent of activation in humans)</u>

- We will begin to assemble all safety data and anticipate having sufficient efficacy data as well (in Q13) to begin discussion with the IRB about intrasurgical testing of coils.

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

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

- Sang Baek Ryu, PhD is working with Seung Woo Lee (site-PI for the MGH sub-contract) to obtain greater proficiency with micro-coil design, development and testing.

He has become quite adept in all of these and has completed 3 first-author studies to date and is proceeding with additional work. He was recently promoted from post-doctoral fellow to Research Associate.

- 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.
- 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 Julie Arenberg, PhD (along with Christian Brown and Dan Lee, all at MEE) to develop a coil-based cochlear implant and learned how to perform the complex *in vivo* measurements needed to test such a device. Results from the first study are encouraging, e.g., they show that coil-based stimulation of the cochlea is effective and further, that it better confines activation than electric stimulation, thus offering the potential for narrower spectral channels. A manuscript on this work has been submitted for publication and is currently under review.

How were the results disseminated to communities of interest?

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?

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 have been completed. The design of the final device, the multi-channel implant for chronic use, is largely complete. Details of packaging are still being worked out and the first prototypes are expected to be completed shortly after the ASIC arrives (expected in May of 2022).

- 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 rodents). 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) and superior colliculus. Implant testing is ongoing in mice; we are encouraged by the fact that thresholds with implanted coils have remained stable for 7+ months.
- Aim 3.2 (evaluate long-term safety). The temperature and vibration testing will be completed in early Q12 with submission of a publication submitted on our findings in Q13. The tissue evaluation will continue through Q13 into Q14.
- Aim 3.3 (NHP testing). Psychophysical experiments will continue. We hope to have threshold profiles for both stimulation rate and the depth of insertion in Q13.

4. IMPACT:

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

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 at the Massachusetts Eye and Ear Infirmary focused on development of a next-generation cochlear prosthesis.

What was the 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?

We are not actively discussing forming a company – the pandemic brought so many new challenges that it was tough enough to keep up with our existing workload. We may revisit this again at some point in the near future. Outside the scope of this grant, we are talking to a Danish company (Oticon) about working together to develop a next-generation cochlear prosthesis.

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

The covid pandemic continues to increase challenges and was especially problematic during the Omicron phase. We ran into supply chain issues from several vendors and also had a small shut-down at MGH, one of the sub-contract sites, where their animal support staff were so decimated by covid that we could not order new animals. This impacted our schedule somewhat and we are working to catch up.

Last year's Annual Report along with several additional quarterly reports during the past year have detailed the changes we've made with NHP testing, moving from the originally proposed site (Born Lab at Harvard Medical School) to a new site (Greger

Lab at ASU). This was reviewed and approved by DoD/CDMRP personnel and the new site is up and running and producing results. No additional issues have occurred and so I am not reiterating all of the material covered previously.

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

Detailed above

Changes that had a significant impact on expenditures

As mentioned in quarterly reports throughout the year, we have added Bradley Greger at Arizona State University as a new sub-contract. Dr. Greger is performing the NHP experiments that were originally slated to be performed in the laboratory of Richard Born at Harvard Medical School. The change necessitated supplying funding to ASU and the budget was amended. Expenditures were reduced to the some of the existing sub-contractors as well as at the VA. Given the importance of the NHP experiments, we wanted to find a way to make this happen and the bottom line is that we were able to find a compromise that works. Experiments have been proceeding at ASU for several months now and we are seeing clear evidence of device function.

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

As mentioned in quarterly reports throughout the year, we have added Bradley Greger at Arizona State University as a new sub-contract. Dr. Greger is performing the NHP experiments that were originally slated to be performed in the laboratory of Richard Born at Harvard Medical School. The change was reviewed and approved through a formal request to the DoD and IACUC protocols from ASU were reviewed and approved by ACURO.

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. Lee, J.I., Seist, R., McInturff, S., Lee, D.J., Brown, M.C., Stankovic, K.M., Fried, S.I. (2022), Magnetic stimulation of the cochlear nerve: towards next-generation cochlear implants. (under review)
2. Raghuram, V., Datye, A.D., **Fried, S.I.,** Timko, B., (2021), Transparent and conformal microcoil arrays for spatially selective neuronal activation, BioRxiv (on-line).
3. Raghuram, V., Werginz, P., Fried, S.I., Timko, B., (2021), Morphological factors that underlie neural sensitivity to simulation in the retina, Advanced NanoBiomed Research (Awaiting publication).
4. Lee, S.W., Fried, S.I., (2021), Micro-magnetic stimulation of primary visual cortex induces focal and sustained activation of secondary visual cortex, Phil. Trans. of the Royal Soc. A (Awaiting publication)
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Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Other Publications:

1. Otgondemberel, Y., Roh, H., **Fried, SI**, Im, M (2021), Spiking Characteristics of Network-Mediated Responses Arising in Direction-Selective Ganglion Cells of Rabbit and Mouse Retinas. IEEE-Trans Neural Syst Rehabil Eng. 2021. PMID: 34784280.
2. Urdaneta, M.E., Kunigk, N.G., Delgado, F., **Fried, S.I**., Otto, K.J. (2021), Layer-Specific Parameters of Intracortical Microstimulation of the Somatosensory Cortex, J.Neural Eng. PMID: 33706301.
3. Werginz, P, Raghuram, V, **Fried, S.I.** (2020), Tailoring of the axon initial segment underlies reliable conversion of synaptic inputs into spiking output in OFF-Alpha T retinal ganglion cells, Science Advances, 2020 Sep 11;6(37):eabb6642. doi:10.1126. PMID: 32917708.
4. 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.
5. 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.
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Posters (last 12 months):

1. P. Werginz, V. Raghuram and S.I. Fried [2021], “Customized AIS properties in OFF α-T ganglion cells”, EMBO Workshop: Axons 2021: structure and function, Virtual.
2. E. C. Szoka, J. C. Werth, S. Lee, J.-I. Lee, A. J. Cortese, T. A. Cleland, S. I. Fried, and A. Molnar, “Neural probe utilizing programmable microcoil magnetic stimulation,” in 2021 10th International IEEE/EMBS Conference on Neural Engineering (NER), 2021, pp. 651–654
3. A.D. Datye, S.N. Makarov, A. Nummenmaa, S.I. Fried, [2021]. A computational model of a micro-coil based magnetic cochlear implant. SAC Poster Competition, Massachusetts General Hospital.
4. S.B. Ryu, A.C. Paulk, S.S. Cash, S.I. Fried, S.W. Lee [2021]. Comparison of spread of cortical activation for electric and magnetic stimulation. SAC Poster Competition, Massachusetts General Hospital. ***Poster of Distinction Award.

Presentations (last 12 months):

1. Minnesota NeuroSpin Initiative, Virtual, Invited Talk, “Micro-coil-based activation of CNS neurons”, December 7, 2021, Invited Speaker.
2. 12th World Congress on Visual Prostheses, Virtual, Invited Talk, “Micromagnetic stimulation of primary visual cortex elicits focal activation of secondary visual cortex”, (Author, S. W. Lee Presenter), October 5, 2021.
3. 12th World Congress on Visual Prostheses, Virtual, Invited Talk, “Towards the development of a micro-coil based cortical implant”, (Invited speaker) October 5, 2021.
4. 12th World Congress on Visual Prostheses, Virtual, Invited Talk, “Morphological features of RGCs and their influence on threshold to electric stimulation”, (Author, D. B. Shire

Presenter), October 5, 2021.
5. 12th World Congress on Visual Prostheses, Virtual, Invited Talk, “Microfabrication and biocompatibility of subretinal electrode arrays”, (Author, J. I. Lee Presenter), October 4, 2021.
6. 12th World Congress on Visual Prostheses, Virtual, Invited Talk, “Mechanisms underlying differential RGC responses to low vs. high rate stimulation”, (Author, P. Werginz Presenter), October 4, 2021.
7. 10th International IEEE/EMBS Conference on Neural Engineering (NER), Virtual, 2021, “Neural probe utilizing programmable microcoil magnetic stimulation”. (Author, E. C. Szoka Presenter), May 4-6, 2021.
8. MOMRP (DoD) – Auditory, Visual and Vestibular prosthesis Review meeting (Virtual), “A micro-coil based cortical visual prosthesis”, July 20, 2021 (Invited speaker).
9. Transducers’21 (Virtual), “Neural stimulation: new strategies for enhanced control”, June 23, 2021. (Invited speaker).
10. Neuroprosthetics of today and tomorrow (Virtual), Danish Society for Neuroscience, “Visual Prostheses”, June 11, 2021.
11. Korean Society for Brain and Neural Sciences, 24th Annual Meeting (Virtual), “Selective targeting of ON vs. OFF retinal ganglion cells with hi-rate stimulation”, May 19, 2021.
12. IEEE EMBS Conference on Neural Engineering (Virtual), “Towards a micro-coil based cortical visual prosthesis”, May 5, 2021.
13. IEEE EMBS Conference on Neural Engineering (Virtual), “Neural Probe Utilizing Programmable Micro-Coil Magnetic Stimulation”, Author, May 5, 2021.

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

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

- **Technologies or techniques**

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

- **Inventions, patent applications, and/or licenses**

1. A second patent application was approved:

Application #: 11,007,372
Title: Selective activation of cortex using bent micro-wires to magnetically stimulate neurons
Publication date: May 18, 2021
Inventors: Lee, Fried
Summary
The design consists of one or more bends in a micro-wire and can be used to magnetically stimulate cortical neurons. Precise arrangements of the bends can facilitate the creation of stronger field gradients in one direction with much smaller gradients in orthogonal directions, thus allowing for selective targeting, or avoiding, of specific cell types within a targeted region. In exemplary versions, a micro-wire stimulator may be implanted into the cortex of the brain to selectively stimulate nearby neural cells having a particular orientation relative to the stimulator. The micro-wire design results in a reduced cross-sectional surface area of the micro-wire stimulator; the smaller area helps to minimize both the trauma arising from implantation as well as the level of biological response that arises over time.

2. One additional application has been submitted and is currently under review.

- **Other Products**

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?

Name: Shelley Fried, PhD
No change

Name: *S*eung Woo Lee, PhD
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?

The PI (Fried) has received 2 new-subcontracts: one is from an NIH R01 award to Tatjana Jakobs at Schepens Eye Institute ("Cell biology of astrocyte-ganglion cell interactions") – our role is to perform physiological recordings from retinal ganglion cells in the PI's animal model of glaucoma. There is no overlap with the present work. The second is from a foundation from NovoNordisk, a Danish Foundation, to Anpan Han PhD, a PI at the Danish Technical Institute in Copenhagen ("Micro-coil-based cortical implant for restoration of vision to the blind"). Dr. Han is trying to develop next-generation coils in which intensifying cores are used to enhance the effectiveness of stimulation. This could help to reduce thresholds and would enable many more channels. Even though the titles are similar, there

is no overlap with the present work.

Previously reported:
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?

- 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).

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

A micro-coil based cortical visual prosthesis

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

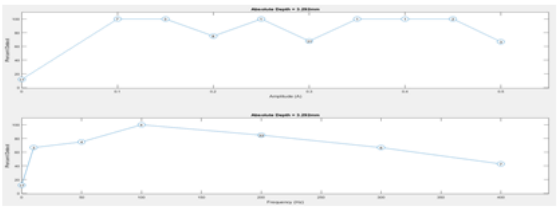
PI: Shelley Fried **Org:** Boston VA Research Institute (BVARI) **Award Amount: $2.1 MM**

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.



Summary of initial NHP testing. (top) Performance as a function of stimulus amplitude. Poor detection for control experiments (0 mA) and good activation for magnetic stimulation amplitudes > 100 mA. (bottom) performance as a function of the rate of stimulation suggesting rates ~ 100 Hz are optimal. More repetitions are needed as are controlled experiments for each variable. Nevertheless, the findings strongly suggest coil-based stimulation of monkey V1 is eliciting percepts.

Timeline and Cost

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

Updated: (February 28, 2022)

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
- ☐ Psychophysical testing of coils in NHPs

CY22 Goal – IRB/IDE Development
- ☐ Psychophysical testing in NHPs (continues)
- ☐ IRB & IDE preparation
- ☐ Human testing (acute); behavioral activation and spatial spread

Comments/Challenges/Issues/Concerns

Psychophysical testing of coils in NHPs will continue into 2022; IRB development is underway

Budget Expenditure to Date

Projected Expenditure: $2.1 MM
Actual Expenditure: ~$1.3 MM