AWARD NUMBER: W81XWH-16-2-0015

TITLE: Central Visual Prosthesis with Interface at the Lateral Geniculate Nucleus

PRINCIPAL INVESTIGATOR: Joseph F. Rizzo, MD

CONTRACTING ORGANIZATION: Massachusetts Eye and Ear Infirmary
Boston, MA 02114

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

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6. AUTHOR(S)
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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Ophthalmology, 9th Floor, 243
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8. PERFORMING ORGANIZATION REPORT NUMBER

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

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14. ABSTRACT

The goals of this project are to:
- *Modify microfabrication methods to produce 256 channel, implantable electrode arrays for the Lateral Geniculate Nucleus (LGN)*
- *Adapt visual neuroprosthesis RF coil and titanium package to fit in small hole in skull; update external controller software*
- *Develop surgical insertion tool to deliver the electrodes to LGN*
- *In vitro bench testing of electrode arrays and insertion tools*
- *In vivo implantation and psychophysical testing in non-human primate animal model*

The main accomplishments under this award were a) the development of viable, microfabricated deep-brain stimulation electrodes and the means to deploy them using a unique, custom surgical insertion tool; this assembly was the subject of a provisional patent application filed by sub-awardee Bionic Eye Technologies, Inc. and b) the development of very low-stress Silicon Nitride material for the substrate on which the penetrating electrodes were micro-fabricated. This material was tested extensively in agarose gel models of brain tissue.

15. SUBJECT TERMS
Visual Prosthesis; Lateral Geniculate Nucleus

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	11	**19b. TELEPHONE NUMBER** *(include area code)*

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1 **INTRODUCTION:**

The scope of this award concerned the adaptation of a high density implantable neurostimulation system for a visual prosthesis, for the application of providing visual input to the brain's Lateral Geniculate Nucleus (LGN). This device had originally been developed by the PI and his colleagues for application in a sub-retinal visual prosthesis. A thalamic interface for visual input could have far reaching implications, since it would be usable to treat patients with blast induced eye trauma, glaucoma, or diabetic retinopathy who would otherwise not be able to benefit from a prosthesis that introduces artificial vision by interfacing with the retina. To achieve an LGN device, deep-brain electrode technology and means for surgical deployment of arrays of such electrodes in brain tissue needed to be developed via a specialized surgical implantation tool.

2 **KEYWORDS:**

Visual Prosthesis; Lateral Geniculate Nucleus

3 **ACCOMPLISHMENTS:** .

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

The goals of this project are to:
• *Modify microfabrication methods to produce 256 channel, LGN-implantable electrode arrays*
• *Adapt visual neuroprosthesis RF coil and titanium package to fit in small hole in skull; update external controller software*
• *Develop surgical insertion tool to deliver the electrodes to LGN*
• *In vitro bench testing of electrode arrays and insertion tools*
• *In vivo implantation and psychophysical testing in non-human primate animal model*

The first milestone at month 4 was the selection of a process for microfabricating the LGN electrodes; this was done (100% complete)

- **What was accomplished under these goals?**

Major Activities / Specific Objectives for the Program:
-Mask design and initial microfabrication of ultra-microelectrode (UME) arrays made from Silicon Carbide and Polyimide at the Cornell NanoScale Facility and the University of Texas, Dallas
-Optimization of surgical insertion tool design for LGN arrays that are compatible with UMEs and the Bionic Eye 256-channel implantable neurostimulator platform
-Refinement of SiC UME design and materials based on initial findings: changed to Crystalline Silicon based penetrating electrode shafts and later, to Low-Stress Silicon Nitride
-Fabrication of complete surgical insertion systems comprised of optimized SiC LGN electrodes and micro-fabricated 'ribbon cables in surgical delivery/insertion devices
-In vitro testing of insertion of SiC UMEs in agarose gel models of brain tissue
-3D model development of the entire peri-operative surgical scheme for device implantation in non-human primate models, and the post-operative device structure, adapting the designs of sub-awardee Bionic Eye's high density neurostimulator

Significant Results:

-Sub-awardee Bionic Eye Technologies, Inc. completed fabrication of Silicon based microelectrode arrays made from Silicon-On-Insulator (SOI) starting wafers and Polyimide at the Cornell NanoScale Facility. These were later substituted with Silicon Nitride based arrays, when the crystalline Silicon ones were found to be too stiff to achieve the desired splaying characteristics

-A surgical insertion tool design for the LGN arrays that are compatible with our microelectrodes and the Bionic Eye implantable neurostimulator platform was developed, and a provisional patent application was made.

-Mock surgical insertion systems comprised of Si-based LGN electrodes and micro-fabricated ribbon cables were prepared, followed by SiN-based devices (whose fabrication is still in progress). This builds on a documented process developed by sub-awardee Bionic Eye for fabricating 256 channel flexible electrode arrays

-In vitro testing of insertion of SiC, Si and SiN-based microelectrodes in gel models of brain tissue was performed to observe splaying behavior of the arrays upon deployment at two sites; by Dr. John Pezaris at Massachusetts General Hospital, and by Dr. Doug Shire and colleagues at Bionic Eye Technologies, allowing duplication and confirmation of results. The Crystalline Si-based electrodes were found to be too brittle and stiff for practical use, but the later SiN-based structures performed satisfactorily (and were the subject of a provisional patent).

-3D models were developed of the entire peri-operative surgical scheme for device implantation in non-human primate models, and the post-operative device structure, adapting the designs of sub-awardee Bionic Eye's high density neurostimulator.

-Manual bonding of ribbon cables to Si-based microelectrode arrays was performed. This task was sufficiently difficult that an alternative approach of fabricating the electrodes and their lead wires/ribbon cables together was adopted, and fabrication of integrated assemblies is underway.

-From the initial in vitro insertion studies, design changes were made to improve the stiffness, flexibility and splaying and assembly characteristics of the penetrating electrode arrays by replacing the crystalline silicon with extremely low stress plasma-deposited Silicon Nitride as the insulating electrode substrate. New electrode models were created and insertions were successfully tested in agarose gel.

-Based on these results, sub-awardee Bionic Eye developed new CAD and electrode designs to incorporate the above material changes into 32-channel integrated electrode arrays using the same processes that were developed for 256-channel arrays; the 32-channel arrays are for proof-of-concept but may easily be scaled to higher densities using the same processes, such as the 256-channel arrays that Bionic Eye has previously published

-We are now near completion of the manufacture of new 32-channel Silicon Nitride based microelectrode arrays at the Cornell NanoScale Facility. Of particular note is that these new microelectrode arrays have been developed as a one-piece design, and hence do not require separate bonding to flexible ribbon cables to make assemblies that can carry stimuli and data into/out of the brain. This move to a single microfabrication process will lead to stronger, more resilient devices that are less prone to assembly difficulties and, as stated, the processes may readily be scaled to higher densities

-Due to the findings of the initial gel brain model insertion studies, a change in electrode materials was indicated, which was completed and tested in 2018 Q1

-We will shortly complete manufacture of the one-piece microelectrode / ribbon cable assemblies, in preparation for follow-on non-human primate studies. (Fabrication ongoing as of 2018 Q3)

-Approval was obtained from Massachusetts General Hospital's Institutional Animal Care and Use Committee for the animal trials of the one-piece microelectrode assemblies. These studies were not yet completed as of the official end of the award period, however.

New discoveries, Inventions, and Patent Disclosures

-A provisional patent application was made by sub-awardee Bionic Eye Technologies, Inc. on behalf of all parties to this award in December, 2017 concerning the LGN electrode array and surgical inserter design.

Cost Variances

There are no cost variances to report.

Narrative Description

We have improved upon the electrode array fabrication methods from those that were originally selected in the first year of the award. The thick-film Silicon Carbide based LGN electrode tines originally fabricated, were first replaced by Crystalline Silicon-based arrays made using a deep reactive ion etching process. Sub-awardee Bionic Eye's process engineer Dr. Marcus Gingerich performed these studies under the supervision of Dr. Doug Shire. They also developed very low-stress Silicon Nitride protective films to enable processing on top of etched structures fabricated from Silicon-On-Insulator (SOI) wafers to form electrodes. The resulting penetrating electrodes for LGN use were tested in gel models of brain tissue in all cases (figures below).

We since continued to improve upon the design and fabrication processes of the LGN microelectrode devices. In particular, the results of our *in vitro* gel insertion studies suggested that the crystalline silicon-based electrodes, while workable, were too stiff. Around this time, Bionic Eye engineers discovered a process for making virtually stress-free, thick Silicon Nitride films, which provided a much better balance between flexibility and insertability/splaying in brain tissue. Thus, this change of substrate was made. Our current arrays are a "one-piece" part, with both the electrode tines and the ribbon cable leads being produced simultaneously using novel nanofabrication techniques at the Cornell Nanofabrication Facility.

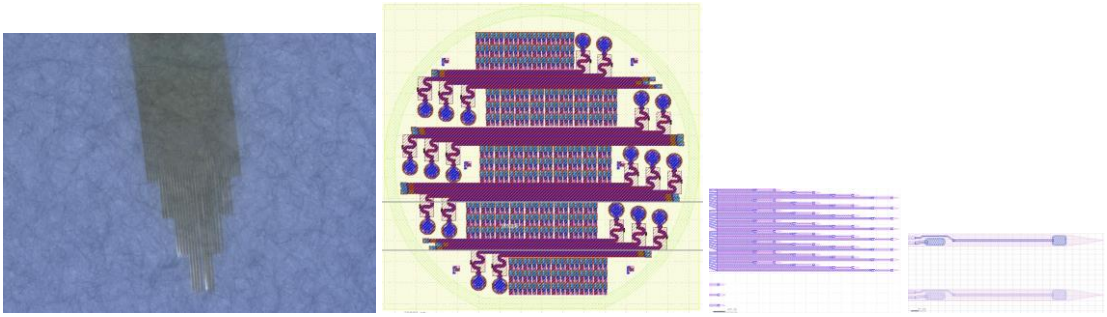


Figure 1. Sub-awardee Bionic Eye Technologies Inc. (BET) has developed and manufactured an improved SiN microelectrode array (left) based on the results of in vitro testing of the original SiC/Si based penetrating electrodes (together with John Pezaris at MGH). Integrated SiN electrode – ribbon cable assemblies are now being fabricated for LGN implantation in upcoming preclinical non-human primate trials; CAD images of these integrated designs are shown (center, right). It was found that hand assembly of ribbon cables to the microelectrode arrays was quite challenging, which led to the current integrated design that is implemented on 6 inch diameter host Si substrates.

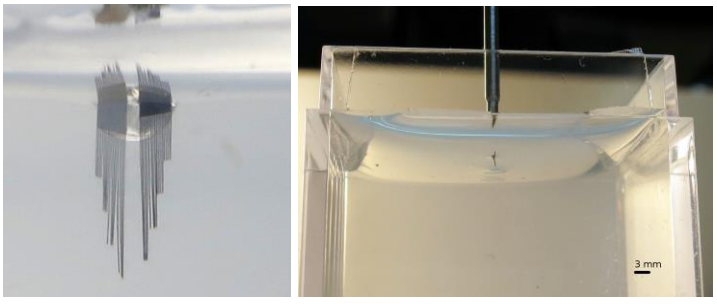


Figure 2. Sample insertion of Crystalline Silicon based electrode tines into an agarose gel by Dr. John Pezaris at Massachusetts General Hospital at 12 microns/second. Note the slight deflection of the tines but otherwise excellent insertion into the LGN model. Silicon was found to be too brittle and was abandoned for the more forgiving low-stress Silicon Nitride material.

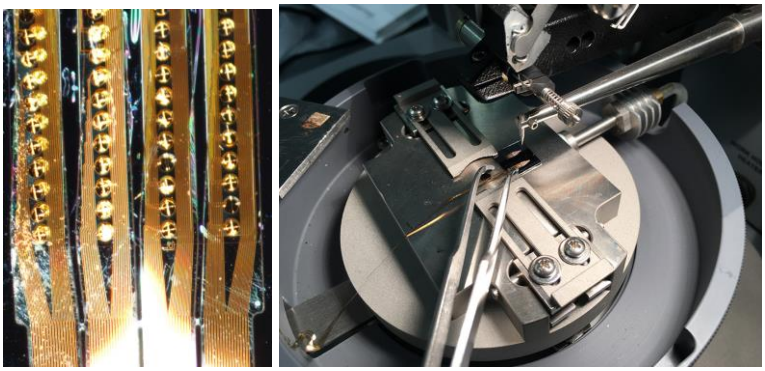


Figure 3. Left: Bonded region showing the interconnection between a ribbon cable that brings signals into/out of the brain (gold color, exiting at bottom) and a microelectrode array (exiting top). This design was tedious to bond using the K&S manual bonder (at right), and this led us to the integrated ribbon cable / electrode assembly shown in Fig. 1.

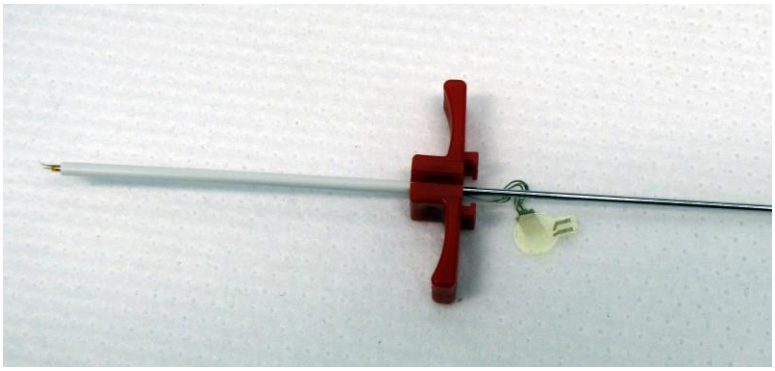
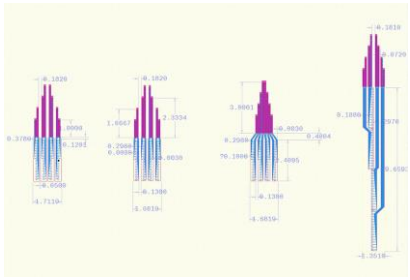
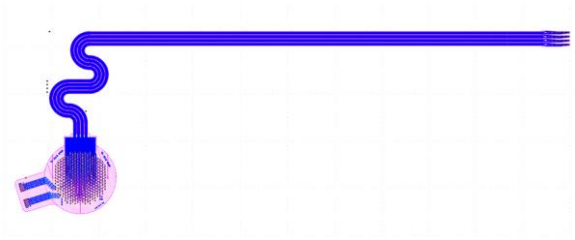
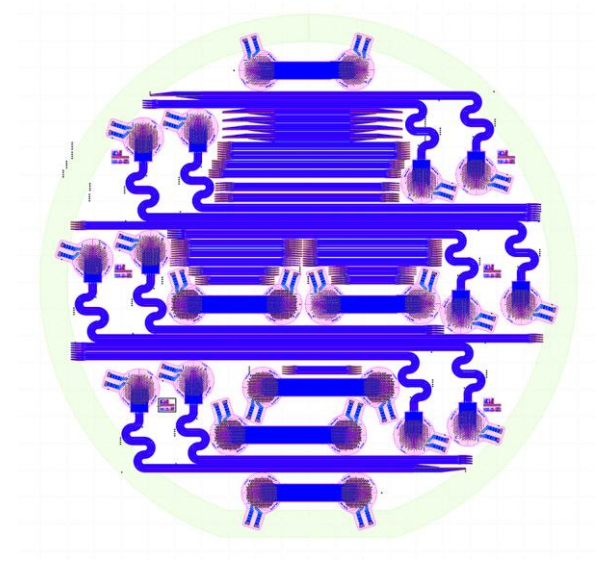
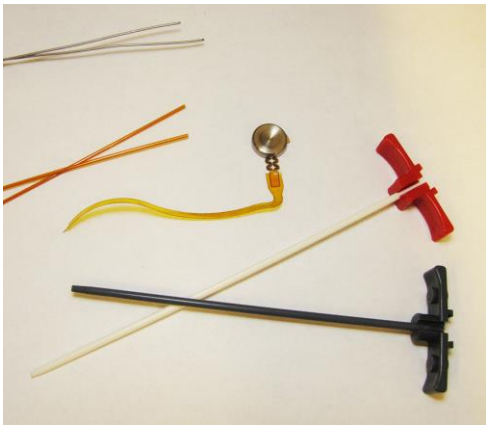


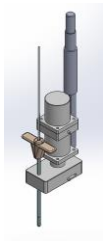
Figure 4. Complete LGN electrode mounted in split-sheath surgical insertion device. The contact pad array for connecting the Bionic Eye or lab stimulator is at right. The insertion procedure is to retract the electrode tines within the inserter tube and advance it through the brain to the desired location. A microdrive is then connected to the tungsten push rod (exiting to the right) which is then advanced at ~3 microns/second, slowly inserting the electrode tines into the LGN. Afterward, the inserter is split and removed, and the push rod withdrawn, leaving only the electrode assembly and the flexible ribbon cable lead in the brain. A 3D model of the entire LGN electrode deployment system for the brain is also shown below in Figure 5.

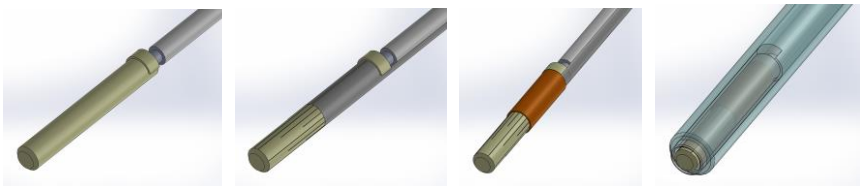












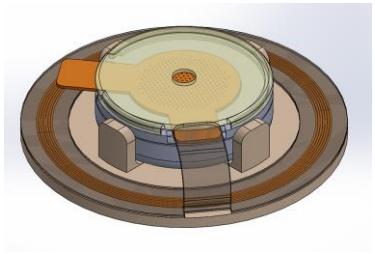


Figure 5, clockwise from upper left:

CAD drawings of the original penetrating SiC electrodes for the LGN, and the original, separate ribbon cable to connect the electrodes to the signal feedthroughs on sub-awardee Bionic Eye Technologies' high density implantable neurostimulator; electrode array and split sheath surgical inserters prior to assembly; 3D models showing assembly sequence for mounting the penetrating electrode array on the surgical insertion and loading it into the split-sheath device; scaffold holding the round titanium micro-package for the visual prosthesis and the RF coil that receives power and data from the external controller; split sheath inserter mounted on a micro-drive motor; and, a CAD drawing showing the layout of the ribbon cable arrays on a silicon wafer.

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

Nothing to report; however, PI Dr. Rizzo and sub-award PI Dr. Pezaris of Massachusetts General Hospital presented on this project at The Eye And The Chip Conference in Detroit, MI in September, 2017.

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

A provisional patent application was made by sub-awardee Bionic Eye Technologies, Inc. concerning the LGN electrode technology and the related surgical insertion tool design to access deep brain structures.

- **What do you plan to do in the future to accomplish the goals of this program?**

Future Work

Sub-awardee Bionic Eye's Dr. Doug Shire and microfabrication engineer Dr. Marcus Gingerich will assemble the integrated Silicon Nitride based electrode arrays shown above for this study into finished devices, for potential animal testing at Massachusetts General Hospital (MGH). These arrays will be attached to neurostimulator systems in the lab of PI Dr. Pezaris at MGH upon their implantation in a non-human primate animal model, after first being inserted in gel models of the brain to ensure that the parts are compatible with the neurosurgery equipment at hand. *In vitro* bench testing of the devices will continue in parallel as well.

4 **IMPACT:**

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

If successful, a viable LGN based visual prosthesis would not only provide useful vision restoration for millions of potential patients who would otherwise not benefit from a retinal prosthesis. Apart from the microfabrication advances made, an equally significant advance was the development of a surgical insertion tool capable of safely accessing deep brain structures and subsequently inserting penetrating tines into the target tissue using a hydraulic micro-drive.

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

The LGN surgical insertion tool and electrode assembly may readily be adapted to other advanced neuromodulation systems, such as improved deep brain stimulation devices for other medical conditions.

- **What was the impact on technology transfer?**

A patent application on the LGN surgical insertion tool and electrode assembly was submitted; this will be co-authored by the PI and the sub-award PIs, and will be further developed by startup company Bionic Eye Technologies, Inc.

- **What was the impact on society beyond science and technology?**

Nothing to report

5 **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

  The originally-conceived Silicon Carbide based penetrating electrode technology for this effort turned out not to be viable, and this led our team to subsequently evaluate Crystalline Silicon and then low-stress Silicon Nitride based electrode substrates. The latter was quite successful, though the crystalline tines were too stiff and did not exhibit the desired splaying behavior.

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

  The net effect of the materials and microfabrication developments was that the originally-projected nonhuman primate trial was not able to be completed as part of this effort.

- **Changes that had a significant impact on expenditures**

  There was an initial delay in establishing the two major sub-awards under this program to Massachusetts General Hospital and to Bionic Eye Technologies, Inc. that resulted in a request to carry some Year 1 funds over into Year 2.

- **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.**

  An IACUC protocol for the non-human primate study was submitted by sub-award PI Dr. Pezaris at Massachusetts General Hospital and approved, but the trial was not able to be completed within the originally projected time-frame.

  - **Significant changes in use of biohazards and/or select agents**

  Nothing to report

6 **PRODUCTS:**

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

  - **Journal publications.**

  Nothing to report

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

  Nothing to report

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

  Presentations by PI Rizzo and sub-award PI Pezaris on the topic of this work at the Eye And The Chip conference in Detroit, MI were made in September, 2017.

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

  Nothing to report

- **Technologies or techniques**

  The LGN electrode and surgical insertion tool technology developed under this program could have far reaching implications for future deep brain stimulation devices; see Patent Application below.

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

  A patent application was submitted by PI Rizzo and sub-award partners Dr. Pezaris at MGH and Dr. Shire at Bionic Eye on the LGN surgical insertion tool and associated electrode technology in December 2017.

- **Other Products**

  Nothing to report

7 PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

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

Name: Dr. Joseph Rizzo, MD
Project Role: Principal Investigator, Massachusetts Eye and Ear Infirmary
Researcher Identifier: N/A
Nearest person month worked: 1
Contribution to Project: Coordinating, negotiatiating, and supervision of two major sub-awards to Massachusetts General Hospital and to Bionic Eye Technologies, Inc.

Name: Dr. Douglas Shire, Ph.D.
Project Role: PI on Sub-Award to Bionic Eye Technologies, Inc.
Researcher Identifier: N/A
Nearest person month worked: 3
Contribution to Project: Coordinating of vendors, collaborators and Bionic Eye staff for the production, testing and programming of implantable high-density LGN stimulators for delivery to sub-awardee Massachusetts General Hospital for non-human primate studies

Name: Dr. Marcus Gingerich, Ph.D.
Project Role: Microfabrication Engineer under Sub-Award to Bionic Eye Technologies, Inc.
Researcher Identifier: N/A
Nearest person month worked: 3
Contribution to Project: Dr. Gingerich is responsible for the micro-fabrication of ultra-microelectrode arrays for use in the LGN and the interfacing of such arrays to the HD Bionic Eye implantable neurostimulator

Name: Dr. John Pezaris, Ph.D.
Project Role: PI on Sub-Award to Massachusetts General Hospital
Researcher Identifier: N/A
Nearest person month worked: 2
Contribution to Project: In-vitro testing of provided UME electrode arrays and submission of a non-human primate animal surgical protocol for implantation of the HD LGN neurostimulator components provided by sub-awardee Bionic Eye Technologies, Inc.

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

Nothing to Report

- **What other organizations were involved as partners?**

Nothing to Report

8 **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** N/A
- **QUAD CHARTS:** The most recent Quad Chart for this project is attached as an Appendix.

APPENDICES:.1. Quad Chart covering the period 6/15/2016-6/14/2018

Appendix 1. Quad Chart covering the period 6/15/2016-6/14/2018

Central Visual Prosthesis with Interface at the Lateral Geniculate Nucleus
Award W81XWH-16-2-0015
Vision Research Program: Pilot Technology Development

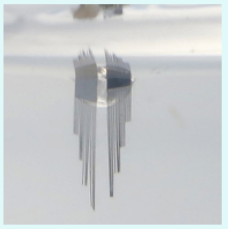
PI: Joseph F. Rizzo, MD **Org: Massachusetts Eye and Ear Infirmary** **Award Amount: $408,707**

Study/Product Aim(s)

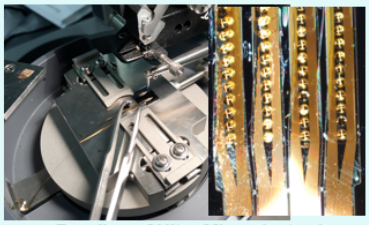
- Modify microfabrication methods to produce 256 channel, deep brain implantable electrode arrays
- Adapt visual neuroprosthesis RF coil and titanium package to fit in small hole in skull; update external controller software
- Develop surgical insertion tool to deliver the electrodes to LGN
- In vitro bench testing of electrode arrays and insertion tools
- In vivo implantation and psychophysical testing in non-human primate animal model

Approach

The purpose of this proposal is to adapt a record high density 256 channel retinal neurostimulation system previously developed by the PI and his colleagues, to a new visual prosthesis that will interface with the deep brain at the lateral geniculate nucleus, and to validate the design by testing the device.



New silicon nitride (SiN)- based ultra-microelectrode tines in gel model of brain tissue



Bonding of Ultra Microelectrode Arrays to Ribbon Cables for Insertion into Tissue Models

Figures: In this program, sub-awardee Bionic Eye Technologies Inc. (BET) has developed and manufactured an improved SiN microelectrode array based on the results of in vitro testing of the original Si/SiC based penetrating electrodes (together with John Pezaris at MGH). Integrated SiN electrode – ribbon cable assemblies were fabricated and are the subject of a patent application by Bionic Eye.

Timeline and Cost

Activities CY	15	16	17	18
Electrode Array Fabrication				
Develop Surgical Insertion Tool				
In Vitro Bench Testing of Devices				
In Vivo Implantation and Testing in Monkey Animal Model				
Estimated Budget ($K)		**$150**	**$100**	**$160**

Updated: 09/30/2018

Goals

CY16 Goals – Hardware Adaptation, Surgical Tools

- ☑ Develop Initial Fabrication Methods for HD LGN Electrode Arrays
- ☑ Initial Design of Surgical Insertion Tool for LGN Electrode Arrays

CY17 Goals – In Vitro Tests; Software Updates & Device Assembly

- ☑ Test Design of Electrode Arrays & Surgical Tools in Gel models of Brain Tissue, Assemble & Bench-top Testing of LGN Devices
- ☑ Update External Controller Software Code for LGN Application

CY18 Goal – Complete Animal Study at MGH under Sub-Award

- ☐ Perform biocompatibility and psychophysical testing

Comments

- Nonhuman primate trials of the final SiN based LGN device are not completed at this time due to long development time for underlying micro-fabrication technology