Mini-Symposia Title:

Recent Advances in Cortical Visual Prostheses

Theme:

- (●) 01. Biomedical Signal Processing
- ( ) 02. Biomedical Imaging and Image Processing
- ( ) 03. Micro/ Nano-bioengineering; Cellular/ Tissue Engineering &
- ( ) 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ( ) 05. Cardiovascular and Respiratory Systems Engineering
- ( ) 06. Neural and Rehabilitation Engineering
- ( ) 07. Biomedical Sensors and Wearable Systems
- ( ) 08. Biorobotics and Biomechanics
- ( ) 09. Therapeutic & Diagnostic Systems and Technologies
- ( ) 10. Biomedical & Health Informatics
- ( ) 11. Biomedical Engineering Education and Society
- ( ) 12. Translational Engineering for Healthcare Innovation and Commercialization

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Mini-Symposia Synopsis— Max 2000 Characters

Visual prostheses strive to restore vision to the blind. While devices that target the retina and optic nerve have undergone considerable developmental effort and attention over the last two decades, a large percentage of blind subjects are not candidates for a retinal device. As an alternative, devices that target the visual cortex offer hope to those with nearly all forms of blindness. There has been much recent progress with the efforts to develop a cortical visual prosthesis and this Mini Symposium will highlight several of the leading efforts. The talks will cover a number of different approaches and promising technologies; the presentations will span early stage efforts through clinical tests.

Progress with the Orion Cortical Visual Prosthesis

Jessy D. Dorn, Ph.D., Second Sight Medical Products, Inc.

***Abstract*— The Orion System is a first-in-human device intended to induce visual perception in patients with profound acquired blindness. One year results for the first five subject indicate that the device is well tolerated and successfully creates visual perception as measured by a suite of assessments.**

I. INTRODUCTION

The Orion Visual Cortical Prosthesis System is a chronically-implanted subdural electrode array intended to induce visual percepts in patients who are profoundly blind from various causes of non-cortical etiology. The System leverages the technology and platform of the Argus II Retinal Prosthesis System, the only visual prosthesis approved for commercialization in the United States.

The Orion System consists of an array of electrodes that is placed on the medial surface of the occipital lobe; a hermetically sealed electronics package and receiving antenna that are recessed into the skull; and external components consisting of glasses with an embedded video camera and a body-worn video processing unit (VPU). The visual scene is captured in real time by the camera, processed and translated into stimulation patterns by the VPU, and transmitted wirelessly to the implant. Activation of the electrodes creates percepts in blind patients; training and visual rehabilitation allow them to interpret the percepts and perform functional vision tasks.

II. METHODS

The Orion System is being studied in an Early Feasibility Study (EFS) in six subjects at two sites in the U.S., UCLA and Baylor College of Medicine. Key inclusion criteria are: bilaterally blind with bare light or no light perception due to non-cortical etiology; a history of useful form vision; between the ages of 22 – 74; and medically fit for neurosurgical intervention. Full inclusion and exclusion can be found at clinicaltrials.gov (NCT03344848).

Adverse events are collected throughout the study and are classified for seriousness and relatedness. The functionality, stability, and utility of the system are evaluated with stimulation thresholds, Square Localization (SL), Direction of Motion (DOM), and Grating Visual Acuity (GVA), and the Functional Low-vision Observer Rated Assessment (FLORA). All visual function and functional vision assessments are performed both with the System ON and OFF.

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For SL and DOM, a two-tailed t-test compares the mean performance over all trials ON and OFF to determine if performance with the Orion System is significantly different than when subjects use their residual vision only. For GVA, results are reported on a logMAR scale (1.6 – 2.9 logMAR); if subjects are unable to perform the test, their score is "worse than 2.9 logMAR). For the FLORA, independent assessors rate the benefit received by subjects from the Orion on a five-point scale: positive, mild positive, neutral, mild negative, and negative.

III. RESULTS

As of October 28, 2019, six subjects have been implanted an average of 17.3 ± 4.1 months (range 9 – 21 months). Reasons for vision loss include two congenital glaucoma, two trauma, and two other causes. Adverse events due to the device or procedure as of July 10, 2019 occurred in two subjects and included one serious event (seizure) and five non-serious events.

Table I summarizes the number of subjects (out of 5 who have reached one-year post-implant) who performed significantly better with the System ON than OFF (SL and DOM); scored on the scale with the System ON (GVA), and were rated as receiving positive or mild positive benefit from the Orion (FLORA).

TABLE I.

Performance at 12 Months Post-Implant	
Square Localization	80% (4 of 5)
Direction of Motion	100% (5 of 5)
Grating Visual Acuity	40% (2 of 5)
FLORA	100% (5 of 5)

IV. DISCUSSION & CONCLUSION

Interim results of the Orion EFS study indicate that the System is safely providing some visual perception to a small sample of profoundly blind patients.

ACKNOWLEDGMENT

This work requires a large team including the implanting surgeons Nader Pouratian, M.D., Ph.D., and Daniel Yoshor, M.D., their study teams, and the scientists at Second Sight Medical Products, Inc. Many thanks also to the six subjects enrolled in the Orion EFS, without which none of this work could be done.

Implantable microcoils for cortical visual prostheses

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***Abstract*—Electric stimulation of the primary visual cortex (V1) via electrodes implanted in cortex has been suggested as a means to restore vision to patients suffering from a wide range of visual impairments. Despite the success in eliciting visual perception in human subjects, the stability of electrode-based cortical implants remains limited, in part due to the complex biological and chemical reactions that can diminish the effectiveness of individual electrodes over time. Further, electric stimulation via conventional electrodes is unable to avoid activation of the passing axons of distant neurons, thereby reducing the potential acuity that can be achieved from implanted devices. Magnetic stimulation from microcoils is a potentially attractive alternative to conventional electrodes because the use of induction to activate neurons provides for a long-term stable interface and further, the spatially asymmetric fields arising from coils can be oriented to avoid the unwanted activation of passing axons. Here we present novel implantable microcoils, and demonstrate the effectiveness via *in vitro* and *in vivo* animal experiments.**

IX. Introduction

Electric stimulation of V1 via electrodes implanted in cortex has been suggested as a means to restore vision to patients suffering from a wide range of visual impairments [1]. Despite the success in eliciting visual perception in human subjects, the stability of electrode-based implants remains limited, in part due to the complex biological and chemical reactions that can diminish the effectiveness of individual electrodes over time [2, 3]. Further, electric stimulation via conventional electrodes is unable to avoid activation of the passing axons of distant neurons, thereby reducing the potential acuity that can be achieved from implanted devices [4]. Magnetic stimulation from micro-coils is a potentially attractive alternative to conventional electrodes because the spatially asymmetric fields that arise from coils can be oriented to avoid the unwanted activation of passing axons [5, 6] and further, because the use of induction to activate neurons provides for a more stable interface over time. Here, we describe a series of novel microcoils that allow precise cortical activation and demonstrate their effectiveness via modeling, *in vitro* and *in vivo* animal experiments.

X. Methods

Computational modeling was conducted to compare the effectiveness of several microcoil designs; the optimum designs were selected for use in electrophysiology experiments. *In vitro* patch-clamp recording and calcium imaging (GCaMP6s) were performed to measure responses of pyramidal neurons in brain slices. A custom microelectrode array was used to measure the spatial extent of cortical activation in response to stimulation in anesthetized mice.

XI. Results and Discussion

Consistent with the modeling results, both *in vitro* and *in vivo* experiments showed that magnetic stimulation from the microcoils confined activation to a focal region, approximately 300-µm in diameter. In contrast, electric stimulation from conventional electrodes produced a widespread activation, extending more than 1-mm from the site of stimulation. Our findings suggest that magnetic stimulation from an implantable microcoil can improve the ability to focally activate cortex and thus may offer advantages over conventional electric stimulation from microelectrodes.

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Development of a Cortical Visual Neuroprosthesis for the blind: Preliminary results in human

Eduardo Fernández, University Miguel Hernández and CIBER BBN (Spain)

Abstract— **Visual prostheses are implantable medical devices that are able to provide some degree of useful vision to individuals who are functionally blind. Retinal prostheses have been the most successful approach to date and several visual prostheses systems have been already approved to treat some eye diseases. However, this approach is not suitable for pathologies affecting the entire retina, optic nerve or thalamus. We are facing the challenge of creating an intracortical visual neuroprosthesis designed to interface with the occipital cortex as a means through which a limited but useful visual sense could be restored to these blind patients.**

V. INTRODUCTION

Visual impairment is one of the ten most prevalent disabilities and poses extraordinary challenges to individuals in our society, which is heavily dependent on sight. Drug development and genetic engineering have had only marginal success as possible treatments but new hope has been generated by recent advances in neuroscience, micro-fabrication technologies, biomaterials, neuromorphic engineering and information and communication technologies leading to the development of highly sophisticated neural prosthetic devices which interact with the nervous system. Such assistive devices have already allowed thousands of deaf patients to hear sounds and acquire language abilities and the same hope exists in the field of visual rehabilitation [1].

In spite of this progress, a number of important questions regarding this approach remain. To answer some of these questions, we are performing a Clinical Trial (Identifier: NCT02983370) to evaluate the usefulness of a cortical visual prosthesis based on intracortical microelectrodes. These experiments have been designed to learn if blind volunteers can learn to integrate the electrical stimulation of brain visual areas into meaningful percepts.

VI. METHODS

A 57-year-old female with bilateral optic neuropathy and no light perception for 16 years was implanted for 6 months with an array of 100 intracortical microelectrodes based on the Utah Electrode Array (UEA). The UEA was implanted in the right visual cortex, nearby the occipital pole (O1) using a minicraniotomy. We collected multielectrode recordings and descriptive feedback regarding thresholds, features of evoked perceptions and stimulation parameters to investigate if the volunteer could integrate the electrical stimulation of visual cortex into meaningful perceptions. All the experiments were carried out at the Hospital IMED Elche during the early post-surgical period and, afterward, in a human neurophysiology laboratory at the Miguel Hernández University (Spain).

VII. RESULTS

The surgical implantation was performed without complications and high-quality simultaneous recordings were consistently obtained. It was necessary a training period until the subject was able to distinguish between natural (spontaneous phosphenes) and artificial visual perceptions. Microstimulation mainly evoked elementary phosphenes at stable locations in visual space, described as isolated and spatially localized spots of light. Less frequently shadows or black spots were induced. All the phosphenes were in the left visual field. When several electrodes were stimulated simultaneously the subject reported the perception of several complex patterns.

After 6 months the subject was reanesthetized and a craniotomy was performed in order to explant the UEA. Because there was negligible fibrosis around the implanted electrode array, the UEA and the external connector were easily explanted without complications. The subject has been followed periodically and no adverse effects have been reported to date.

VIII. DISCUSSION & CONCLUSION

Our preliminary results suggest that electrical microstimulation of occipital cortex in long-term blind individuals is able to provide meaningful visual perceptions. However, there are still a relevant number of open questions and more experiments should be done to achieve the clinical goals envisioned by this new technology.

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The Monash Vision Group cortical vision prosthesis

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***Abstract*— Cortical vision prostheses aim to restore visual sensations by directly applying electrical stimulation the visual cortex. The Monash Vision Group has developed one such cortical vision prosthesis (Gennaris) that can be wirelessly powered and controlled. Each device can deliver stimulation through one of 43 electrodes with up to 11 devices able to be controlled by a single transmitter. This device has successfully undergone pre-clinical testing.**

I. Introduction

For patients who have lost vision from diseases such as retinitis pigmentosa, electrical stimulation of surviving retinal ganglion cells can generate visual perceptions similar to a spot of light (phosphenes) [1]. However, for patients suffering vision loss that arises from damage that does not leave surviving retinal ganglion cells, cortical approaches offer a viable alternative for intervention. Early studies in cortical vision prostheses have demonstrated that electrical stimulation delivered to the visual cortex could effectively generate multiple punctate phosphenes [2].

The Monash Vision Group has developed and tested a fully implantable wireless stimulating device that is ready for a first-in-human trial (**Figure 1a**, and **b**). We will present some pre-clinical results demonstrating the efficacy and safety of the device [3].

II. Methods & Results

Each wireless implant (Gennaris array) contains an Application Specific Integrated Circuit (ASIC) that is wirelessly powered and controlled via a receiving antenna and supporting electronics. These components were encased in a ceramic (tetragonal zirconia polycrystal) capsule (**Figure 1b**) [4]. Each implant has 43 electrodes (127 µm diameter platinum-iridium wire with a sub-micron tip tapered at a 6˚ angle, **Figure 1c**) connected to the ASIC via a printed circuit board. Electrodes were insulated with ~ 3 µm of parylene-C, with a cylindrical electrical contact (70 µm height) opened 1.5 mm from the base of the device. The device (excluding the electrodes) measured 9 x 9 x 2.8 mm and weighed 1.02 ± 0.01 g.

Devices were implanted chronically in sheep for up to 9 months and electrical stimulation was delivered. Cortical slices around the devices were taken and astrocytes and neurons labelled. Reactive astrocytes were mostly seen around electrode tracks and there was minimal cortical damage.

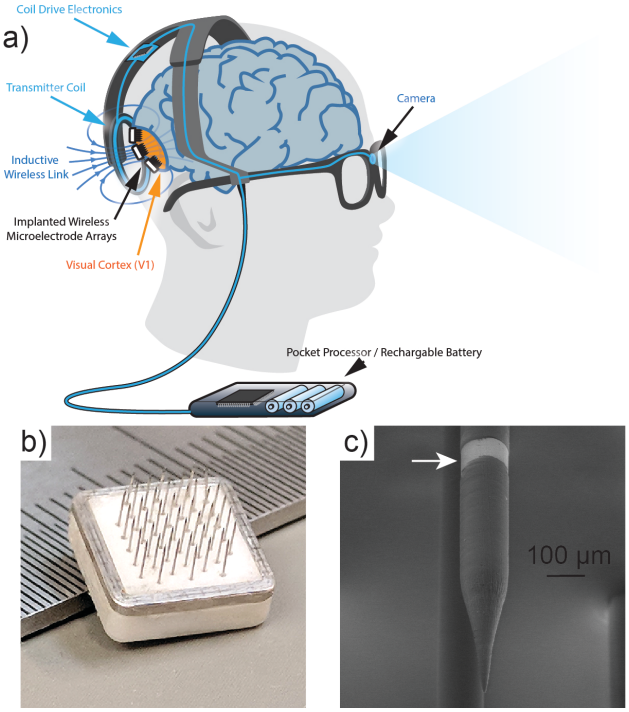

Figure 1. a) Schematic of the Monash Vision Group cortical vision prosthesis. A pocket processor turns images of the world captured from a camera into stimulation commands that are sent to the implanted device via a transmitter coil. **b)** The Monash Vision Group cortical vision prosthesis. **c)** A single stimulating electrode with the contact highlighted with an arrow.

III. Discussion & Conclusion

We present a clinically viable cortical vision prosthesis that can be controlled and powered wirelessly. This device has been tested on the benchtop and shown to be able to reliably deliver charge [4] as well as chronically *in vivo*.

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Visual prosthesis employing a neuromorphic retina

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Abstract— **In the visual cortical prosthesis, ambient image has to be processed to effectively evoke the coherent visual perception. We propose to use a neuromorphic retina that reproduces spatio-temporal distribution of ganglion cell responses for image processing module. The neuromorphic retina can not only mimic the retinal input to the cortex but also can greatly reduce the data communication rate between the external system and the implanted internal system.**

XII. INTRODUCTION

The retina is a sophisticated neuronal network that dynamically extracts visual events from ambient image. In the cortical visual prosthesis, electrical stimulations are delivered directly to the visual cortex bypassing the retina. This indicates that the computation more or less similar to the one conducted by the retinal circuit is necessary to effectively evoke the visual perception. Here, we propose a prosthesis design in which a neuromorphic (NM) retina is used to dynamically process the image and to control the electrical stimulations delivered to the visual cortex.

XIII. NEUROMORPHIC RETINA

In conventional visual prostheses, ambient image is sampled and filtered with a CCD camera and a digital system unit. And then the processed image is transmitted wirelessly to the stimulation electrode array implanted to the visual cortex. However, the image processing with the digital architecture and the algorithm, e.g. the contour extraction on each sampled frame, is not appropriate taking into account of the computation carried out in the retina. Moreover, it requires the prosthesis to deal with excessive amount of data that is transmitted to the implanted system.

Recent physiological experiments on the retina indicated that the retinal computation is much more efficient with the aid of the event-driven image sampling [1]. We previously developed a neuromorphic (NM) retina that can reproduce the spike timing of the ganglion cell response [2]. The NM retina consists of a VLSI silicon retina [3] and a field programmable gate array (FPGA) module. The VLSI silicon retina and the FPGA module mimic the spatial filtering and the temporal filtering of the retinal circuits, respectively. The FPGA module also computes the spike timing of the ganglion cell with a precision of millisecond order, which can be regarded as event driven.

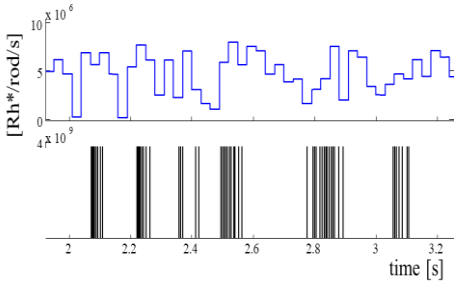

Figure 1. Spike response of the NM retina (lower panel) to randomly modulated intensity of light (lower panel).

Fig. 1 is an example of the dynamic computation of the NM retina. We reproduced the spike response of a transient OFF type ganglion cell of the mouse. In this case, the NM retina was illuminated with a spot of light whose intensity was randomly modulated. The size of the spot was adjusted to the receptive field center. Even for such favorable stimulation, this NM ganglion cell responds intermittently for brief periods as was observed in the previous physiological experiment [1]. The maximum instantaneous spike rate of the NM ganglion cell is about 200-300 Hz, which is comparable to the stimulus frequency commonly used to excite the cortical circuits in the visual prosthetic [4]. These observations suggest that our NM retina is an appropriate image processing unit to efficiently stimulate the cortical circuits and to mitigate the data communication bottle neck of the cortical prosthesis. Furthermore, it can provide more natural electrical stimulations to the visual cortex than the conventional digital image processing system.

XIV. DISCUSSION & CONCLUSION

Neuromorphic retina is considered to be necessary for designing the cortical prosthesis in order to effectively excite the cortical circuits and to reduce its power consumption.

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The Intracortical Visual Prosthesis (ICVP): Aspects of the Inaugural Clinical Trial

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***Abstract*— After decades of research and preparation the Intracortical Visual Prosthesis (ICVP) is poised for testing in a clinical trial. The experiences leading to this outcome may be instructive to others who work to advance novel neural interface technology to clinical translation. The completion of preclinical testing needed for the ICVP IDE application proved extremely challenging owing mainly to lack of definition about what tests were needed, how standardized test methods needed to be adapted to an unconventional device, and which non-standard tests were appropriate to establish safety.**

XV. INTRODUCTION

The ICVP project dates back to 1970 when it was started as an intramural NIH project for the purpose of providing artificial vision to those people with blindness. Inspired by the work of Brindley [1], during 1970-2000 extramural fundamental and developmental studies directed towards clinical testing of an implanted intracortical interface for artificial vision were funded under the NIH Neural Prosthesis Program. As part of the intramural work, a human subject was implanted with intracortical electrodes in the occipital lobe, accessed by percutaneous wires. Starting in 2000, the ICVP project pursued a pathway of developing a fully-implantable system for providing multichannel intracortical stimulation via wireless arrays of metal microelectrodes. This work culminated in the development of the Wireless Floating Microelectrode Array [2] (WFMA – Fig.1). The ICVP system has received FDA approval for testing in a clinical trial.

XVI. METHODS

Preclinical testing for implantable medical devices is typically defined through ISO standards in which test types and methodologies are described. These standards include ISO 10993, ISO 11706, ISO 14708, EIC 61000 and EIC 60601. However, many of these ISO-defined tests are suitable for implantable devices similar to pacemakers which are much larger than the WFMA and use coiled lead wires to connect a central package to the electrodes. In addition, ISO 10993 biocompatibility tests require a device minimal surface which far exceeds the WFMA area. To accommodate these, and other test methods, equivalent test methods had to be developed, and justified, for the IDE application. In other cases, the FDA requested non-ISO tests to evaluate safety of cortical tissue subjected to electrical stimulation. The most difficult part of the preclinical process was establishing an adequate set of tests for establishing ICVP safety.

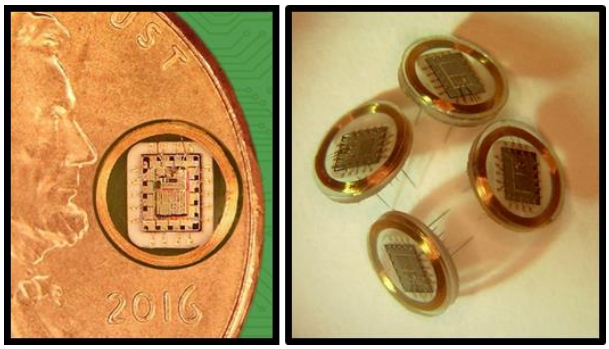

Figure 1. Wireless Floating Microelectrode Array (WFMA) used as a modular intracortical interface for the ICVP. Size: 5mm diam x 0.75mm thick. Each module is wirelessly powered and has a unique electronic address for setting pulse-by-pulse stimulation parameters. Up to 40 WFMAs may be implanted on the dorso-lateral surface of the occipital lobe.

XVII. RESULTS

While the results of the tests did provide a satisfactory basis for use of the ICVP in a clinical trial, interpretation and analysis of non-standard test results required interaction with the FDA, and this interaction improved the scientific quality and subject safety of the approved clinical trial.

XVIII. DISCUSSION & CONCLUSION

Planning translation of novel medical devices involves extensive test definition and methods which should not be underestimated. Although often non-standard in form, emerging technology requires an adequate level of testing to confirm safety. Current testing and regulatory approval processes must be adapted and these can add considerable schedule time to the preclinical phase of translational work.

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