PHYSIOLOGICAL RESPONSE IN OVIS ARIES RESULTING FROM ELECTRICAL STIMULI DELIVERED BY AN IMPLANTABLE VISION PROSTHESIS

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Abstract – **An implantable vision prosthesis has been developed to deliver externally controlled, charge balanced, constant current, biphasic electrical stimuli to the inner retina. The device is intended as a treatment to blindness. Specifically, degenerative disorders of the retina such as retinitis pigmentosa, macular degeneration, choroideremia, etc. would be treated with such a device.**

Many profoundly blind patients suffering from the aforementioned conditions are plagued with sleeping disorders associated with the loss of photic input. Restoration of light and dark perception may serve to restore circadian rhythm and thus this has been set as the initial goal for the device.

In an effort to confirm the device's ability to provide light and dark perception an implantable electrode with a 3.9 mm^2 contact area was inserted into the posterior eye chamber of the *Ovis aries* (common name: sheep). Using this electrode, stimuli from the implant were applied to the inner retina and an ensemble averaged evoked potential was successfully recorded from the visual cortex using sub-dural electrodes. This resulted in an electrically induced visual evoked potential with peak amplitude of 140 $\pm$ 20 μV (N=3) that was qualitatively similar to a visual evoked potential evinced using stroboscopic light stimuli.

Keywords -**Visual prosthesis, neurostimulation, visual evoked potential**

I. INTRODUCTION

Development of neuroprostheses for the purpose of restoration of vision is taking place at a number of research centers [1,2,3,4,5,6,7,8]. Of these neuroprostheses, each has its own unique attributes but all have in common the goal of restoration of vision in some form. One such device is being developed at the University of New South Wales (UNSW).

The implant system is comprised of: an external transmitter powering a radio frequency (RF) telemetry trans-tissue link for power and data delivery to the implant; an intra-ocular implant device containing an application specific integrated circuit (ASIC) capable of delivering controlled, constant current, charge balanced, biphasic stimuli to 100 unique sites; and an electrode array in intimate contact with the inner retina. The system has been described in detail elsewhere [9,10,11].

Profoundly blind patients frequently suffer from sleeping disorders, presumably as a result of their loss of light and dark perception. Photic input plays a key role in melatonin secretion from the body's endocrine system and serves to maintain circadian rhythm [12].

As the sleeping disorders suffered by these patients are often severe and distressing, it is the initial goal to confirm that the neuroprosthesis is capable of delivering electrical stimuli such that it may restore light and dark perception.

Beyond the initial goal, the neuroprosthesis is designed to deliver rudimentary patterned vision from successive stimulation of the 100 electrode sites. Confirmation of delivery of patterned vision is the topic of ongoing study.

The present study focuses upon determining whether or not the device is capable of delivering the appropriate stimulus to evoke a physiological response (an electrically-induced visual evoked potential or EIVEP) in a mammal as a first step towards restoring vision. These EIVEPs were qualitatively compared with a visual evoked potential (VEP) induced by stroboscopic light.

II. METHODS

A. Animal Model

The *Ovis aries* species (common name: sheep) (N=3) was chosen as the animal for the present study owing primarily to the relative similarity (geometrically) in its ocular anatomy to that of humans. The study has been carried out under the authority of the UNSW Animal Care and Ethics Committee.

B. Stimulator and Electrode
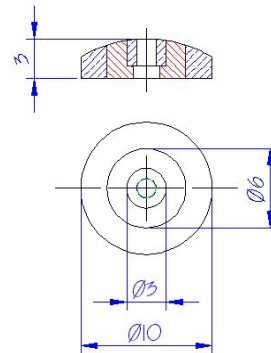
Fig. 1. Concentric electrode fabricated of stainless steel and PTFE (insulator). Stimulating electrode at center is 3 mm in diameter. The center of the stimulating electrode is threaded (M2) for connection to a micromanipulator subsequent to insertion. The tissue contacting area is approximately 3.9 mm^2. Outer ring is used as reference electrode. All dimensions in mm. Wires not shown.

Report Documentation Page

Report Date 25OCT2001	Report Type N/A	Dates Covered (from... to) -

Title and Subtitle Physiological Response in Ovis Aries Resulting from Electrical Stimuli Delivered by an Implantable Vision Prosthesis	**Contract Number**
	Grant Number
	Program Element Number
Author(s)	**Project Number**
	Task Number
	Work Unit Number
Performing Organization Name(s) and Address(es) Graduate School of Biomedical Engineering University of New South Wales, Sydney, Australia, 2052	**Performing Organization Report Number**
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research Development & Standardization Group (UK) PSC 802 Box 15 FPO AE 09499-1500	**Sponsor/Monitor's Acronym(s)**
	Sponsor/Monitor's Report Number(s)

Distribution/Availability Statement
Approved for public release, distribution unlimited

Supplementary Notes
Papers from the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, October 25-28, 2001, held in Istanbul, Turkey. See also ADM001351 for entire conference on CD-ROM., The original document contains color images.

Abstract

Subject Terms

Report Classification unclassified	**Classification of this page** unclassified
Classification of Abstract unclassified	**Limitation of Abstract** UU

Number of Pages
4

In order to stimulate a relatively large area of the retina and thus evoke and record a correspondingly large VEP, a relatively large concentric electrode was utilized. Fig. 1 shows the electrode utilized in this experimentation.

The stimulation delivered to the retinal tissue is derived from two stimulation channels of the 100 channel neurostimulation electronics [9]. Power and configuration data was sent by way of RF telemetry with every effort made to duplicate the operating conditions of the implant as it would be in its final configuration *in-situ*.

C. Visual Evoked Potential Measurement

Five hundred stroboscopic light flashes were delivered to the dilated eye at a rate of 2 Hz. Recording and ensemble averaging techniques are described in subsequent sections and were identical to those used for recording the EIVEP.

D. Surgical Technique

Having on previous occasions successfully implanted a non-functional model of the implant's final form [13], a very similar technique was applied in order to implant the electrode. Following lensectomy and total vitrectomy, the electrode was inserted within the ocular anatomy by way of a corneal incision. Via one of the holes made in the orbit in the process of carrying out the vitrectomy, a guide rod, threaded at its tip, was inserted and joined (by way of threads) with the electrode so as to facilitate micromanipulation of the electrode at the inner retinal surface.

E. Recording Technique
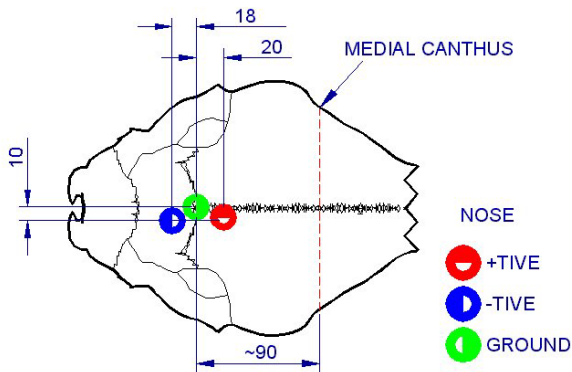
Fig. 2. Diagram of sheep skull and recording electrode placement. Ground electrode (bone screw) is located at the lambda formed by the intersection of the lambdoid and sagittal sutures. Positive recording electrode is a 0.450 mm diameter Pt sphere situated 20 mm nasal and 10 mm lateral to the lambda. Negative electrode is also a 0.450 mm Pt sphere, 18 mm dorsal and 10 mm lateral to the lambda. All dimensions are in millimeters. Dashed line passes through the medial canthi.

The VEP and EIVEP were measured using a similar technique to that described by Gregory and Wotton [14]. In brief, spherical, platinum recording electrodes of 0.450 mm diameter were placed sub-durally and a grounding bone screw was attached to the skull in the locations shown in Fig. 2.

Amplification of the VEP and EIVEP signals was performed by a Grass Instruments P511K amplifier (Grass Instruments, Quincy MA) with low and high frequency filters set to 3 Hz and 1 kHz respectively, digitally recorded via the analogue to digital converter facility of a National Instruments AT-MIO-16F (National Instruments, Austin TX) and stored using customized software. Routines written in MATLAB 5.3 (Mathworks, Natik MA) were used to perform post-processing, including zero-phase forward and reverse digital filtering, and ensemble averaging.

F. Stimulus Delivery

With the electrode mounted upon a micromanipulator and its associated lead wires exiting the globe via a small remaining incision at the cornea (following suturing of the initial, larger incision made to facilitate implantation), the implant electronics were attached to the electrode. 'Power only' RF (RF containing no instructions to deliver stimulus) was broadcast to the implant so as to maintain a stable power supply in anticipation of subsequent stimulation events.

In each data acquisition event, a series of 500 stimulation events consisting of a charge balanced, biphasic, constant current stimulus waveform was delivered to the retina at approximately 800 ms intervals. Power and stimulation data were provided via the RF link.

G. Electrode Size Study

Applying identical recording methods to those described in the foregoing, separate experimentation (N=4) was performed using a pair of 450 µm diameter, spherical platinum electrodes. These electrodes were approximated to the retina by means of a micromanipulator and identical stimulus was applied using the UNSW neurostimulation circuit and, for purposes of comparison, a commercially available Grass S88F stimulator with PSIU8 stimulus isolation unit (Grass Instruments, Quincy MA).

III. RESULTS

Fig. 3 shows an ensemble average VEP for purposes of comparison with the EIVEPs.
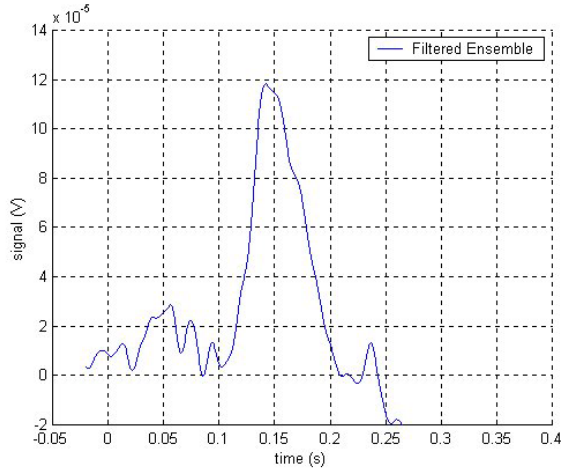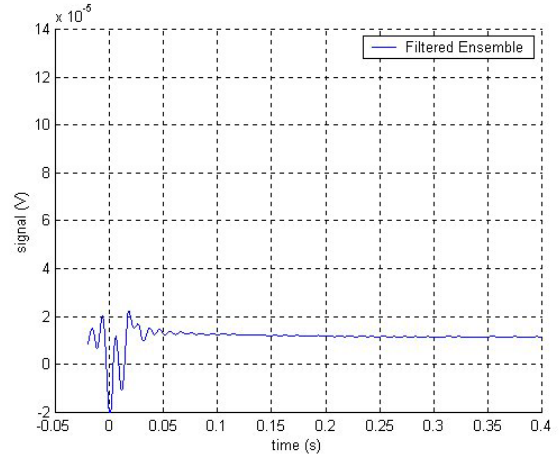
Fig. 3. Ensemble averaged VEP recording from the delivery of 500 stroboscopic light flashes.
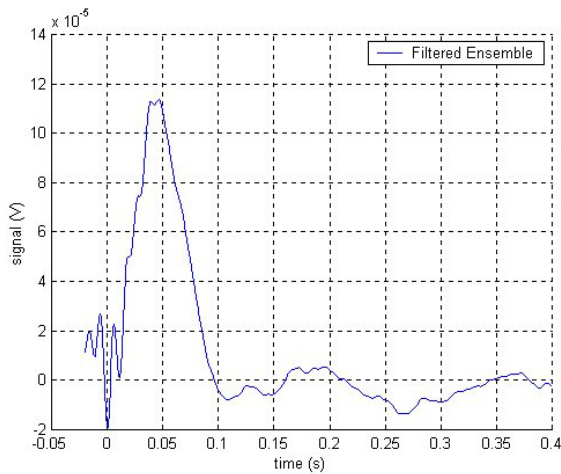
Fig. 4. Ensemble average EIVEP recording from the delivery of 500 stimulation events of 845 μA current, 1 ms per phase (biphasic).

In an effort to obtain an accurate comparison of pre- and post-mortem EIVEP recordings, no attempt was made to determine stimulation threshold levels or optimal stimulus parameters as doing so would prolong the duration of the experiment, raising the probability of inadvertent retinal detachment thus invalidating the pre and post mortem comparison. The primary objective was to determine whether or not the electronics were capable of evoking a physiological response at the visual cortex as a direct result of electrical stimulation of the inner retina.

Rather than start the stimulus delivery at low levels and gradually work upward until a response was obtained, for the reasons discussed above, the stimulus began at a moderate current amplitude and pulse width.

Fig. 5 Post mortem ensemble average EIVEP recording from the delivery of 500 stimulation events of 845 μA current, 1 ms per phase (biphasic). Recording taken 5 minutes post injection of a lethal dose of sodium pentobarbital.

Fig. 4 shows a representative EIVEP recording resulting from stimulation using 845 μA current, 1 ms per phase. Fig. 5 shows the EIVEP from the same animal after euthanasia. The single electrode of 3 mm diameter employed in this study resulted in an EIVEP with peak amplitude of 140 ± 20 μV (N=3).

Electrode size experimentation did not yield conclusive results with no discernible EIVEP (N=4).

IV. DISCUSSION

Fig. 4 indicates a prominent peak in the recording at approximately 45 ms after the delivery of stimulus. The post mortem recording under otherwise identical conditions (Fig. 5) contains only the stimulus artifact. Comparing these two figures, it is clear that the peak in Fig. 4 is the EIVEP.

It must be noted that it is difficult to distinguish which of the several neuronal types within the retina are being stimulated electrically and which are simply functioning as per their normal role in the chain of events leading to the VEP. This is an important issue in developing a vision prosthesis as degenerative disorders of the retina often destroy the photoreceptor layer yet leave higher order neurons intact.

One could argue that the short latency of the EIVEP in Fig. 4 (relative to light evoked VEPs with typical peaks several tens of milliseconds later (Fig. 3)) indicates that at least some neurons other than the photoreceptor layer are being stimulated electrically. These findings correlate well with the observed and calculated latency of ganglion cell response to photic stimulation (19 to 56 ms), as compared to the retino-cortical conduction time (3 to 10 ms), in the cat [15]. Localization of the target cell, however, must be

confirmed with further study, perhaps following injection of sodium iodate, a known photoreceptor toxin [16].

An obvious extension of this work is to implant an electrode grid of multiple electrodes (up to the 100 electrodes that the implant electronics can service). Naturally the diameter of these electrodes will be smaller but care will need to be taken to ensure that the electrodes are not so small as to result in current densities at the electrode-tissue interface that may damage the retinal tissue. To this end a ten-by-ten electrode grid of 8 mm square with an electrode pitch of 888 μm, has been developed. Each electrode is of spherical shape with an approximate diameter of 450 μm.

In our study using electrodes of this size, initial results from four additional sheep indicate that electrical stimulation is not able to evoke a measurable EIVEP. This may be due to multiple factors. Firstly, it may be because the electrodes were not appropriately positioned. Secondly, the electrode-tissue interface may have been of too high impedance for the implant to supply the appropriate constant current given that the power supply of the UNSW implant is fixed in this study to 5.1 V. Lastly, the number of neurons being stimulated with this electrode configuration may have been too few to result in a discernable EIVEP. This is the most likely reason as many different electrode positions were attempted. To discount the supply voltage limitations of the UNSW stimulator as being the cause, the Grass S88F stimulator and PSIU was employed in lieu. Again, it was not possible to evoke an EIVEP distinguishable from background noise. Further studies will be necessary with differing electrode geometries to determine the limitations of this particular EIVEP recording method.

V. CONCLUSIONS

The present study has established that the electronics of the UNSW prosthesis are in fact functioning and capable of evoking a physiological response *in vivo*.

The existence of the peak in Fig. 4 at approximately 45 ms latency and the absence of the same peak in the post mortem response of Fig. 5 indicate that the origin of the peak is in fact a living function. As the latency and duration of the peak compares favorably to the VEP from similar studies [14], we may then conclude that the prosthesis is indeed evoking a physiological response in the vision system of the *Ovis aries*.

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