Perceptual Thresholds and Electrode Impedance in Three Retinal Prosthesis Subjects

Manjunatha Mahadevappa, James D. Weiland, Douglas Yanai, Ione Fine, Robert J. Greenberg, and Mark S. Humayun

***Abstract*—Three test subjects blind from retinitis pigmentosa were implanted with retinal prostheses as part of a FDA-approved clinical trial. The implant consisted of an extraocular unit that contained electronics for wireless data, power, and generation of stimulus current, and an intraocular unit that consisted of 16 platinum stimulating electrodes arranged in a 4 $\times$ 4 pattern within a silicone rubber substrate. The array was held to the retina by a small tack. The stimulator was connected to the array by a multiwire cable and was controlled by a computer based external system that allowed precise control over each electrode. Perception thresholds and electrode impedance were obtained on each electrode from the subjects over several months of testing. The electrode distance from the retina was determined from optical coherence tomography imaging of the array and retina. Across all subjects, average thresholds ranged from 24–702 μA (1-ms pulse). The data show that proximity to the retina played a role in determining the threshold and impedance, but only for electrodes that were greater than 0.5 mm from the retina.**

***Index Terms*—Electrical stimulation, implantable medical device, low vision, neural prosthesis, retinal prosthesis.**

I. Introduction

PHOTORECEPTOR loss from diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD) is the leading cause of retinal blindness [1], [2]. An electronic retinal prosthesis can potentially restore some vision to individuals with these diseases [3], [4]. One concern in the field has been that the amount of electrical charge needed to elicit the perception of light might be too high to permit long term stimulation without damage to the retina. Short-term acute studies (lasting less than 3 h) found that localized retinal electrical stimulation of blind patients with RP and AMD resulted in discrete percepts, however, the amount of electrical current required to elicit a response was relatively large compared to animal studies examining retinal responses to electrical stimulation [5], [6]. One possibility was that these high thresholds were due to difficulties inherent in acute human trials (for example, in laying an electrode array flush on the retinal surface). Alternatively, the high electrical thresholds found in human trials might be attributed to differences in the diseased human retina versus animal models of retinal degeneration. While there is strong evidence for preservation of cells within the inner layers in retinitis pigmentosa [7]–[9], it remains possible that wiring between these cells might nonetheless be severely altered. [10] Severe degeneration of the inner retinal layers in humans would have worrying implications for the ability to create percepts using safe levels of electrical stimulation. This study investigates perceptual thresholds for visual perception in blind humans who have been implanted with a permanent retinal prosthesis as part of a feasibility study of chronic retinal stimulation. Thresholds were obtained during follow up periods of 6–12 months, in three subjects.

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M. Mahadevappa was with the Doheny Eye Institute, Los Angeles, CA 90033 USA. He is now with the University of Kentucky, Lexington, KY 40506 USA.

J. D. Weiland, D. Yanai, and M. S. Humayun are with the Doheny Eye Institute, Los Angeles, CA 90033 USA (e-mail: jweiland@usc.edu).

I. Fine is with the Zilkha Neurogenic Institute, University of Southern California, Los Angeles, CA 90033 USA.

R. J. Greenberg is with the Second Sight Medical Products, Inc., Sylmar, CA 91342 USA.

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II. Methods

This study protocol was granted an investigational device exemption (IDE) by the FDA and was approved by the Institutional Review Board (IRB) at the University of Southern California. Los Angeles. This research adhered to the tenets of the Declaration of Helsinki.

Three subjects with severe RP participated in the study. Two subjects had light perception only in the worse eye (S2 and S3), and a third subject had no light perception (S1). After informed consent (the informed consent explicitly emphasized the investigational nature of both the study and the surgery, and emphasized that there was no expected short- or long-term benefit) we carried out a series of standard preoperative ophthalmological tests to confirm each patients' visual acuity and assess their general ophthalmological health. The preoperative evaluation included a complete eye exam, and electroretinogram (ERG), visual evoked potential (VEP), bright flash detection and electrically evoked responses, fluorescein angiography and fundus photography [11]. At the time of data analysis, S1 had been implanted for 18 months, S2 for 15 months, and S3 for 7 months. One subject (S2) was operated twice in the same eye since her retinal array separated from the retina after 11 months due to the subject falling and bumping her head (no retinal detachment occurred). In the second surgery, the array was simply reattached. When reporting results specific to her performance before attachment this subject is referred to as S2a, after attachment she is referred to as S2b.

Testing sessions lasted a maximum of 4 h with frequent rest periods. The number of sessions was limited by the subjects' availability and the protocol. In general, we carried out 1–2 sessions/week for each subject.

Fig. 1 shows the intraocular stimulating array consists of 16 platinum electrodes in a 4 $\times$ 4 arrangement, held in place within a clear silicone rubber platform [3]. The electrode diameter is

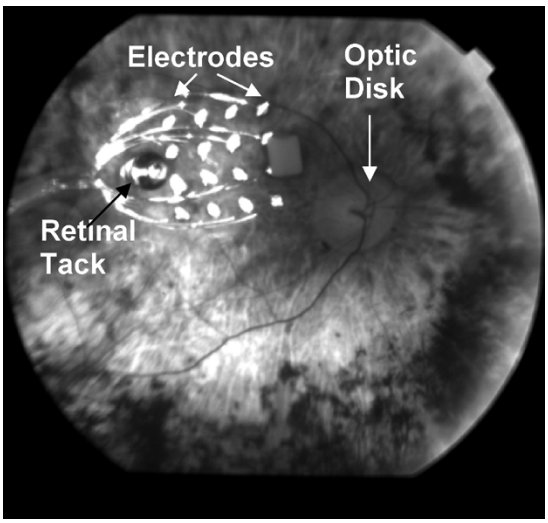

Fig. 1. Fundus photograph of an intraocular stimulating array viewed through a dilated pupil. Sixteen platinum electrodes are held on the retina with a single retinal tack.

500 μm in subjects S1 and S2, and 250 μm in subject S3 and the center to center separation is 800 μm in all subjects. The electrodes, therefore, cover between 2.65 $\times$ 2.65 and 2.9 $\times$ 2.9 mm of retinal surface. The array was held to the retina with a retinal tack. Several loops of wire were left in the orbit so that the eye could move freely without putting stress on the cable. A 16-wire subcutaneous cable connects the intraocular electrode array to the extraocular unit through the eyewall.

The extraocular component of the implant, which converts a radio frequency signal into electrical stimulation patterns, was surgically implanted in the temporal bone, similarly to a cochlear implant [12]. Input signals were provided via a 1-MHz inductive wireless link using an external antenna magnetically aligned over the electronic implant. The desired pulse pattern was sent to a custom-built video processing unit (VPU) that coded the data as a serial data stream, and transmitted it to the implant via the wireless link. In addition, the transmitted signal supplied power to the implant. A reverse telemetry function in the implant allowed direct measurement of 1-kHz impedance of each electrode. The subjects' unoperated eye was patched during all tests to ensure that subjects' performance was not aided by residual vision in the unoperated eye. The implant was only activated in the clinic.

The height of the array from the retinal surface was measured by using optical coherence tomography (OCT, STRATUSOCT; Carl Zeiss Meditec AG) to image cross-sections of the retina. The underlying principle is much like that of ultrasound, except that light is used instead of sound, thus permitting measurement of tissue and distance resolved to the scale of $\leq$ 10 μm. Cross-sectional images of retinal tissue across multiple depth planes are inferred from the profile of near infrared backscattered light.

Since our subjects suffer from nystagmus (uncontrolled eye movement) obtaining clear OCT images is physically and mentally demanding for the subjects. Consequently, OCT measurements could not be gathered at full resolution or for every electrode for every subject. These data, combined with indirect exams, provided an assessment of the proximity of each electrode to the retina. When testing S1, we did not have the OCT apparatus, so OCT data for this subject is not available.

Impedance was measured using the Second Sight VPU software with a back telemetry program, or with a hand held portable cochlear implant tester (PCIT, Advanced Bionics, Sylmar, CA). Both systems used the same diagnostic function of the implant by generating a 1 kHz, 10 μA sine wave on each electrode sequentially, recording the resulting voltage drop, calculating the impedance modulus in $k\Omega$ and transmitting this information from the implant to the external system via a reverse telemetry link. Impedance measurements were taken at the beginning and the end of each stimulating session.

We measured detection thresholds for each of the 16 electrodes using a "standard pulse" consisting of a 0.975-ms cathodic pulse followed by a 0.975-ms anodic pulse with a 0.975-ms interpulse delay between the cathodic and anodic components. All pulse waveforms were biphasic charge balanced.

Detection thresholds for all of the 16 electrodes were measured in most testing sessions. Due to time constraints, we used a relatively crude technique; on each trial subjects were given verbal feedback that a pulse was about to be presented, the subject was stimulated, and the subject was asked to verbally respond whether or not a percept was visible. At each intensity, the subject was stimulated three times, and the stimulation intensity was gradually increased until the patient saw the stimulation all three times. Occasional catch (nonstimulation) trials were interspersed randomly within the stimulation trials and confirmed that patients' false alarm rates were less than 10%.

We calculated thresholds by pooling data from each session, and then plotting the probability of the patient reporting seeing a percept as a function of the stimulation intensity. These data were then fit with a Weibull function and threshold was defined as the stimulation intensity at which the patient reported seeing a percept 75% of the time. [13] Over the last six months, a more sensitive protocol for threshold has been used (a yes-no procedure with half the trials being blank trials). These later tests confirmed that the method used in this study, despite using a small number of samples and a relatively small number of catch trials, produce reasonably accurate estimates of subjects' sensitivity. Note that, as described in the following, after an initial period of instability (usually a matter of weeks) the arrays appear to stabilize on the retina. The data shown here include this period of instability.

III. Results

Average thresholds for each electrode in the three subjects are shown in Fig. 2. The minimum-maximum range of these thresholds differed both within and between subjects, for example S1's thresholds varied between 139–702 μA and S2a's thresholds ranged between 130–575 μA. In contrast, subjects S2b and S3 had much lower thresholds; S2b's thresholds ranged between 25–79 μA, with 13 of the 16 electrodes having thresholds lower than 50 μA. S3's thresholds ranged between 24–143 μA, with 14 of the 16 electrodes having average thresholds lower than 100 μA.

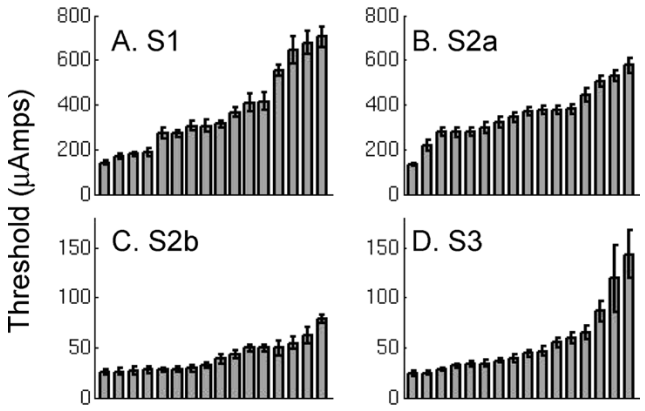

Fig. 2. Absolute thresholds (μA) for all 16 electrodes for each subject, ordered from lowest to highest. The data is averaged across all test sessions. Note the difference in scale along the y axis between subjects S1/S2a and subjects S2b/S3.

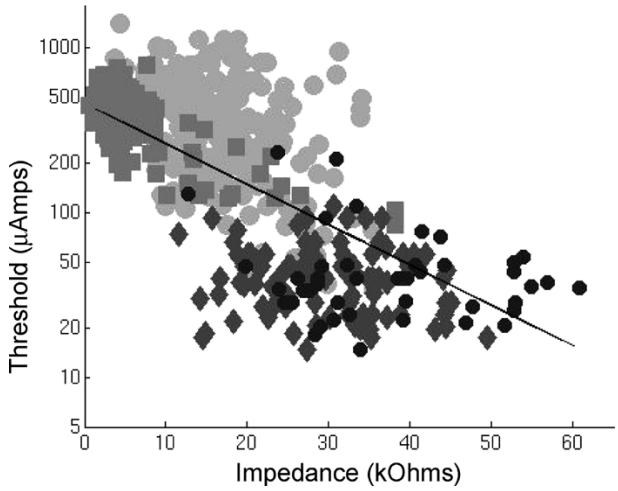

Fig. 3. Impedance versus threshold (on a log axis) for all of the four implantations. The best fitting linear trend for impedance versus log threshold is shown. Each subject is shown with a different symbol. S1-grey circle. S2A-squares. S2B-diamond. S3-black circle.

Phosphene appearance was typically white or yellow, and phosphenes were reported as being round or oval in shape. Occasionally, the subjects would report seeing a dark spot for very low stimulus current intensities. In these cases an increase in the stimulation current resulted in subjects seeing a light spot in the same location. In all subjects, phosphenes at threshold were not uncomfortable or unpleasant. In subjects S1 and S3, brighter phosphenes produced by suprathreshold stimulation were perceived with no discomfort, while in subject S2 suprathreshold stimulation occassionally created an uncomfortably bright phosphene.

After implantation we tend to see a positive correlation between patients' thresholds and time, i.e., patients thresholds tended to increase postoperatively, consistent with the electrode array lifting off the retina. This was particularly noticeable in the first postoperative weeks. We found (using a Wilcoxon 2-tailed t-test) that three of the four implantations showed statistically significant increases in thresholds over time (S2a, $p < 0.02$; S2b, $p < 0.02$; S3, $p < 0.05$), S1 showed no significant overall change in threshold over time (S1, $p > 0.05$): examination of the data suggests that there was a gradual increase in threshold over time, but that this was masked by strong variability in thresholds during the initial couple of months. This increase in threshold became significant when the first 60 preoperative days were excluded.

After implantation we also see significant variability in impedances during the first postoperative weeks which we again believe are due to the heights of individual electrodes changing relative to the retina. In most cases, the array seems to lifts off the retina, resulting in a drop in impedance. We measured whether these changes in impedance were significant across all electrodes by calculating the cross-correlations between impedance and time for each electrode, and then measured whether there was a significant overall increase or decrease in impedance using a Wilcoxon 2-tailed t-test. Three implantations showed significant decreases in impedances (S1, $p < 0.02$; S2a, $p < 0.05$; S3, $p < 0.05$). S2b showed no significant change in impedance over time (S2b, $p > 0.05$). Examination of the data suggests that an early rise in impedance in the first few weeks after implantation (consistent with the array settling on the retina) was followed by a very gradual drop in impedance as the array slowly lifted over the next several months. Both the increase ($p < 0.02$) and the decrease ($p < 0.02$) were significant when tested separately.

Fig. 3 plots impedance versus threshold (log axis) for all subjects. When data is collapsed across all four implants there is a significant negative correlation between impedance and log threshold (slope $= -0.06$, intercept $= 6.1$; $r^2 = 0.46$, $p < 0.001$); across subjects impedances predict thresholds fairly well. The best fitting linear-log fit is shown with a solid black line. This fit is clearly not perfect, but a linear log-log fit was even more unsuitable. It should be noted that the fit may be complicated by the fact that S3's electrodes were smaller than those of the other patients, and, therefore, tended to have slightly higher impedances. Somewhat surprisingly, the thresholds for S3 (250-μm electrodes) are not significantly different from S2b (500-μm electrodes). It is, therefore, not clear that a reduction in electrode size from 500 to 250 μm necessarily results in a decrease in the electrical stimulation threshold.

To look at the relationship between impedance and threshold over time for individual subjects we averaged data from days on which both impedance and threshold values were collected using 20-day time windows (e.g., a single data point represents mean impedance and threshold values collected between post-operative days 50–69 inclusive). Within individual subjects (graphs not shown) the correlation between impedance and log threshold (using a standard least squares regression analysis) is only significant for 2 of the implants (S1, slope $= -0.38$, intercept $= 0.14$, $r^2 = 0.22$, $p < 0.001$; S2a, slope $= -0.69$, intercept $= 0.47$, $r^2 = 0.49$, $p < 0.001$; S2b, slope $= -0.12$, intercept $= 0.015$, $r^2 = 0.043$, $p > 0.05$; S3, slope $= -0.17$, intercept $= 0.03$, $r^2 = 0.01$, $p > 0.05$).

Panel A in Fig. 4 shows a fundus image of the retina in patient S2b showing the OCT imaging light source (a single line). The arrow represents the direction in which the imaging was carried out. Panel B shows the cross-sectional OCT image in grayscale (analysis was carried out using color images). Broad

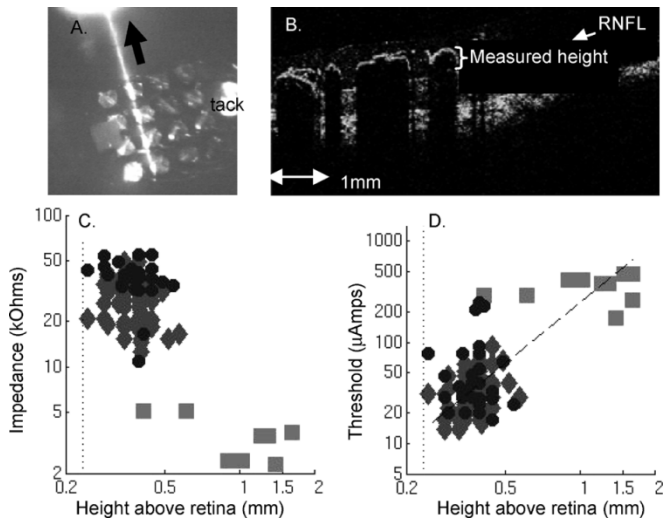

Fig. 4. (A) Electrode array is visualized through the pupil in S2b. The white line from the imaging source shows the cross section scanned. The arrow represents the direction in which the imaging was carried out. (B) Cross-sectional OCT image. The broad shadows are cast by electrodes, the narrow shadows by wires in the array. RNFL—retinal nerve fiber layer indicates the surface of the retina closest to the electrodes. (C) Impedance versus electrode height. (D) Threshold current versus electrode height. The dashed line in panel (D) shows the predicted increase in threshold with height based on electromagnetic field theory. S2A-squares. S2B-diamonds. S3-circles.

shadows are cast by electrodes; narrow shadows are cast by individual wires in the array. The small deviation between the fundus image and the OCT image is due to small eye-movements in the very short time interval between the two images. We measured the height of the array from the top of the shadow cast by the electrode to the surface of the retina. Our measurements therefore included the electrode thickness, which varied between 0.22–0.28 mm depending on the exact cross section of the electrode over which the OCT measurement was taken.

Panel C in Fig. 4 shows impedance as a function of height above the retina (measured using OCT) for the three subjects (S2A, S2B, and S3) for which OCT data were collected. Panel D shows threshold as a function of height above the retina. The dotted vertical line shows the amount of the height above the retina that can be attributed to the thickness of the electrode (0.23–0.28 mm). For each date on which OCT data were collected we averaged impedance and threshold data using a 20-day time window centered on the date the OCT data was collected (e.g., OCT data collected on October 15th would be associated with impedance and threshold data collected between October 5th and 25th). On three occasions either impedance or threshold data had not been collected within the specified time window, and we used data from the nearest possible date.

It has been suggested that that the electric field diminishes with the square of distance from the electrode during stimulation, as occurs in an isotropic medium with distant boundaries. If so, thresholds should also increase with the square of distance. Recent retinal electrophysiological data do indeed find that spike thresholds increase with distance according to a square law [14]. This prediction is plotted in Panel D as a dashed line, with the intercept minimized using a maximum likelihood procedure. While an exponent of 2 is not the best fitting slope (the best fitting slope is in fact 1.66), it can be seen that an exponent of 2 is perfectly consistent with the data. Thus, while we do not have enough data points to definitively prove a correlation between height and threshold, the results we do have are consistent with predictions based on field theory. Provided the array is within 0.5 mm to the retinal surface there seems to be little correlation between array height and either impedance or threshold, but where the array is more than 0.5 mm from the retinal surface, impedance tends to be lower and thresholds tend to be higher.

IV. Discussion

Our low thresholds values suggest that it may be possible to use smaller electrodes than those used in this study to deliver effective stimulus current, provided the array is relatively close to the retinal surface. The results from S2b and S3 both show thresholds consistently below 100 μA (1-ms pulse) on a majority of the electrodes. Assuming platinum has a safe stimulation limit of 0.35 mC/cm^2 [15], these data imply that an electrode of 200 μm diameter would be acceptable. More advanced materials such as iridium oxide, with a safe stimulation limit of 3 mC/cm^2 [16] could safely supply 100 μA (1-ms pulse) using an electrode only 65 μm in diameter. This will allow more selective stimulation of the retina, since the current electrodes (250–500-μm diameter) are assuredly stimulating hundreds of retinal cells simultaneously. Reducing the electrode size will permit more electrodes within the same retinal area as the current implant, which may translate into more pixels in the same degree of visual angle. Simulations of prosthetic vision predict that more electrodes in the central visual area of the retina will lead to a higher resolution image and better visual task performance [17], [18], though this prediction cannot be tested until a high resolution device is implanted in a human.

Our data confirms retinal electrophysiology data suggesting that the height of electrode from the retina is a significant concern [14]. It seems that the stimulus current requirements can increase significantly as the electrode lifts off the retina, resulting in large power consumption by the stimulator and a need for significantly larger electrodes to safely supply current. The electrode arrays used in this study were hand-made and relatively large and stiff (0.5-mm thick), thus the separation from the retina that we observed is not completely surprising. As thinner electrode structures are developed, it is to be hoped that maintaining stable proximity to the retina will become more manageable. [19], [20] More research into fixation methods for epiretinal arrays is also warranted, since the retinal tack may not be capable of close positioning. An electrode made adherent through coating may offer the best alternative to tacks in the future.

As illustrated by Figs. 2–4, thresholds and impedances do differ significantly across subjects. S1 and S2a both have much higher thresholds than the other subjects, and have lower impedances. As indicated by S2a in Fig. 4, this is almost certainly due to the array being lifted off the retina: her implant was significantly higher off the retina than the other two subjects. In fact, the array later separated from the retina in this subject after a jarring bump to her head, and impedances were much higher and thresholds much lower once the array was reattached. For

S1 we do not have OCT data, so we cannot confirm quantify the degree to which his array was lifted off the retina, but visual examinations through a dilated pupil suggested variability in electrode-retina proximity and correlation between impedance, threshold, and liftoff. Like S2a, his highest thresholds are also associated with low impedances. However, even where his impedances are within "normal" ranges, his thresholds remain very high. S1 had the most severely degenerated retina so it is possible that his high thresholds can also be partially attributed to retinal damage.

S2b and S3 both had relatively low thresholds and high impedances, and, as shown in Fig. 4, their arrays seemed to be resting relatively close to the retina. It seems that provided the surface of the electrode array is within 0.25 mm to the retinal surface there is little correlation between the height of the array, impedance, and threshold. Retinal physiology studies did find an increase in thresholds when stimulating electrodes were above 50 μm. [14]. It is perfectly possible that our OCT measurements, or the variability inherent in measuring a perceptual threshold, meant that we did not have sensitivity needed to demonstrate such correlations. We do find, across subjects, that thresholds rise with electrode height at a rate consistent with predictions that thresholds should rise with the square of the distance between the electrode and the retinal surface.

We did not find that thresholds decreased with electrode size. The thresholds of S3 (250-μm electrodes) were not significantly lower than those of S2b (500-μm electrodes). This was somewhat surprising, given that both modeling and electrophysiological data from retina suggest that threshold charge generally decreases with electrode area [21], [22]. For example, a recent study compared stimulus thresholds for rabbit retinal ganglion cells using electrodes of 500 versus 125 μm and found an inverse relationship between threshold charge and electrode area [21]. Other studies show no correlation between electrode area and current threshold [6], [23]–[25], suggesting a complex interaction that is not completely predictable by electric field theory. One possibility is that uneven distribution of current around the edges of our large electrodes reduced local differences in current density as a function of electrode size. Alternatively, the height of our electrodes from the retinal surface may have reduced electrode size effects. It seems plausible that with smaller electrodes closer to the electrode surface we might have seen the expected relationship between electrode size and threshold.

V. Conclusion

Subjects chronically implanted with prototype retinal prostheses have perceptual thresholds lower than those obtained during acute studies. Proximity to the retina plays a role in determining the threshold and impedance, but only for electrodes that are greater than 0.5 mm from the retina. Within this distance, perception thresholds and impedances do not seem to be strongly dependent on the proximity of the electrode to the retina. Thresholds did not seem to depend on the diameter of the electrode.

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Manjunatha Mahadevappa received the Ph.D. degree from the Indian Institute of Technology, Bombay.

He was a Research Fellow with the Doheny Eye Institute, Los Angeles, CA, from 2001 to 2003. He is currently a Research Fellow with the University of Kentucky, Lexington.

James D. Weiland received the B.S. degree, M.S. degree in biomedical engineering, M.S. degree in electrical engineering, and the Ph.D. degree in biomedical engineering from the University of Michigan, Ann Arbor, in 1988, 1993, 1995, and 1997, respectively.

After receiving the B.S. degree, he spent four years in industry with Pratt & Whitney Aircraft Engines, West Palm Beach, FL. He joined the Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, MD, in 1997 as a Postdoctoral Fellow and, in 1999, became an Assistant Professor of ophthalmology. He joined the Doheny Eye Institute, Los Angeles, CA, in 2001 as part of a larger group of faculty that collectively founded the Doheny Retina Institute, Los Angeles. Currently, he is the Director of the Intraocular Retinal Prosthesis Laboratory, Doheny Retina Institute, an Assistant Professor of Ophthalmology with the Keck School of Medicine, University of Southern California (USC), Los Angeles, and an Assistant Professor of biomedical engineering at USC. His research interests include retinal prostheses, neural prostheses, electrode technology, visual evoked responses, and implantable electrical systems.

Dr. Weiland is a member of the IEEE Engineering in Medicing and Biology Society, the Biomedical Engineering Society, and the Association for Research in Vision and Ophthalmology.

Douglas Yanai received the M.D. degree from the Federal University of Parana, Parana, Brazil.

He was a Research Fellow with the Doheny Eye Institute, Los Angeles, CA, from 2002 to 2003. He is a retina specialist currently practicing ophthalmology in Sinope, Brazil.

Ione Fine received the undergraduate degree from Oxford University, Oxford, U.K., and the Ph.D. degree from the University of Rochester, Rochester, NY.

She carried out postdoctoral research at the University of California, San Diego. Her research examines perceptual learning and plasticity with an emphasis on the effects of visual deprivation. Her current research includes measuring performance in patients who have been implanted with electrode retinal prostheses and examining the effects of long-term visual deprivation.

Robert J. Greenberg received the B.S. degree in electrical and biomedical engineering from Duke University, Durham, NC, in 1990, the degree in technical electronics from the Nassau Technical Institute, in 1985, the M.D. degree from The Johns Hopkins School of Medicine, Baltimore, MD, in 1997, and the Ph.D. degree from the Biomedical Engineering Department, The Johns Hopkins University, Baltimore, in 1998.

He co-founded Second Sight, Sylmar, CA, and has served as its President and CEO since its inception early 1999. During that time, he has also held an Adjunct Faculty position at the University of California, Los Angeles (UCLA), has been Associate Director of the Alfred E. Mann Institute, the University of Southern California (USC), Los Angeles, and currently sits on the Board of Directors of the Southern California Biomedical Council (SCBC)—a nonprofit association dedicated to the fostering of the bio-medical industry in the Los Angeles Metropolitan area. Prior to the formation of Second Sight, he was a Co-Director of the Alfred E. Mann Foundation. He has also served as a Medical Officer and Lead Reviewer of investigational device exemptions (IDEs) and 510(k)s at the Neurological Devices Division, Office of Device Evaluation, U.S. Food and Drug Administration (FDA). From 1991 to 1997, he conducted animal and human trials demonstrating the feasibility of retinal electrical stimulation in patients with Retinitis Pigmentosa at the Wilmer Eye Institute, The Johns Hopkins Hospital, Baltimore. He also has biosensor and microsensor fabrication experience. He has received many awards, patents, and publications in various technical fields. In addition to Second Sight, he has also started several other companies including Campus Security, where he designed, manufactured, and marketed an electronic intercom security system called TELEKEY. These intercoms are currently in use in every dormitory at Princeton University, Duke University, and several other universities across the United States.

Mark S. Humayun received the B.S. degree from Georgetown University, Washington, DC, the M.D. degree from Duke University, Durham, NC, and the Ph.D. degree from the University of North Carolina, Chapel Hill, in 1984, 1989, and 1994, respectively.

He is currently Professor of Ophthalmology and Biomedical Engineering at the University of Southern California, Los Angeles, and the Associate Director of Research at the Doheny Retina Institute at the same university. His research interests include retinal prosthesis, implantable microelectronics, and ophthalmic surgical instrumentation.

Dr. Humayun is a Member of the IEEE Engineering in Medicine and Biology Society (EMBS), the Biomedical Engineering Society, the Association for Research in Vision and Ophthalmology, the Vitreous Society, and the Retina Society.