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# Visual perception in a blind subject with a chronic microelectronic retinal prosthesis

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**Abstract**

A retinal prosthesis was permanently implanted in the eye of a completely blind test subject. This report details the results from the first 10 weeks of testing with the implant subject. The implanted device included an extraocular case to hold electronics, an intraocular electrode array (platinum disks, 4×4 arrangement) designed to interface with the retina, and a cable to connect the electronics case to the electrode array. The subject was able to see perceptions of light (spots) on all 16 electrodes of the array. In addition, the subject was able to use a camera to detect the presence or absence of ambient light, to detect motion, and to recognize simple shapes.


## 1. Introduction

Millions of people worldwide lose their photoreceptors either due to retinal degenerations (e.g. retinitis pigmentosa (RP) or age-related macular degeneration (AMD)) (Heckenlively, Boughman, & Friedman, 1988; Klein, Klein, Jensen, & Meuer, 1997; Klein, Klein, & Linton, 1992). The feasibility of an implantable retinal prosthesis that would partially restore vision by direct electrical stimulation of retinal neurons is supported by several studies. Morphometric analyses in post-mortem eyes with almost complete photoreceptor loss either due to RP or AMD have shown as many as 90% of the inner retinal neurons remain histologically intact (Humayun et al., 1999; Kim, Sadda, Humayun, et al., 2002; Kim, Sadda, Pearlman, et al., 2002; Santos et al., 1997). In tests where electrical stimulating devices were temporarily positioned on the retina, blind subjects reported seeing percepts that corresponded in time and location to the electrical stimulus (Humayun et al., 1996; Humayun, de Juan, et al., 1999). Several research groups have investigated various aspects of retinal prostheses, ranging from electrical stimulation of retinal neurons to surgical implantation methods (Chow & Chow, 1997; Eckmiller, 1997; Humayun, 2001; Rizzo & Wyatt, 1997; Zrenner et al., 1997). Two distinct retinal prosthesis efforts have materialized depending on the position of the stimulating electrode array. In the first, the electrodes are positioned on the ganglion cell side of the retina (epiretinal approach) (Eckmiller, 1997; Humayun, 2001; Rizzo & Wyatt, 1997), whereas in the second the electrodes and most of the electronics are placed between the retina and the retinal pigment epithelium (subretinal approach) (Chow & Chow, 1997; Zrenner et al., 1997). Both approaches have advantages and disadvantages (Zrenner, 2002). The device developed for this study has a 16 electrode stimulating array positioned on the epiretinal surface, an electronic implant positioned outside the eye to generate stimulation pulses, and an external system for image acquisition, processing, and wireless communication (to the implanted unit; Fig. 1). Herein, we report on the results of our first human

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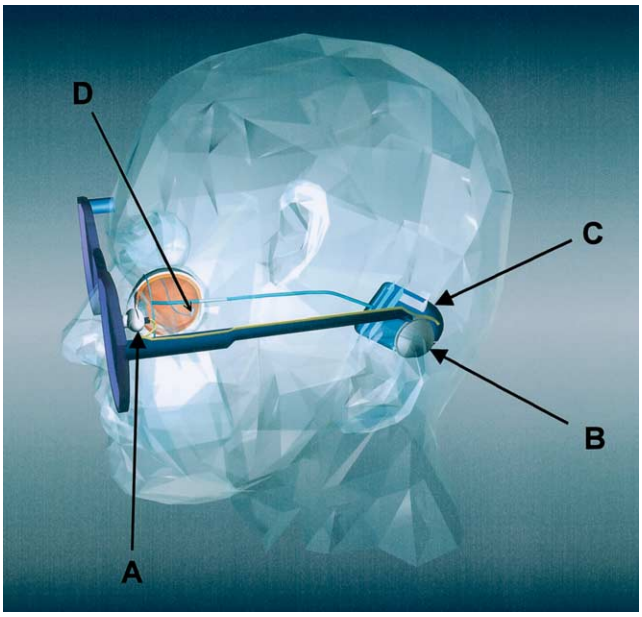



Fig. 1. Schematic showing the concept of the retinal prosthesis. (A) Camera in the glass frame; (B) wireless transmitter; (C) extraocular electronic case (receiver) and (D) intraocular implant (electrodes array).

epiretinal implant in a blind subject with retinitis pigmentosa.

## 2. Material and methods

### 2.1. Subject selection

After obtaining FDA approval and institutional review board approval from the University of Southern California to conduct an investigational study, subjects with bare or no light perception secondary to photoreceptor loss were considered for enrollment in the study. Subjects with visual loss due to all other causes were excluded. Informed consent was obtained, which explicitly stated the investigational nature of both the device and surgery and also emphasized that the subject should not expect any short or long-term benefit. Once consented, standard electrophysiological tests and psychophysical tests designed to assess very low levels of vision were used to determine whether the subject's visual function met the qualifications for a test subject (i.e. bare light perception or worse vision in at least one eye). These tests included dark-adapted flash detection/discrimination; static and kinetic perimetry; electroretinogram (ERG); visually evoked potential (VEP); scanning laser ophthalmoscopy (SLO); and electrically evoked response (EER). Baseline anatomical condition was documented with fundus photography, fluorescein angiography, and optical coherence tomography.

### 2.2. Electronic implant

The electronic device implanted was developed by our group in conjunction with Second Sight, LLC$^{TM}$ (Valencia, CA). As shown in Fig. 1, it consists of an implanted and an external unit. The external unit consists of a small camera worn in the glasses that connects to a belt-worn visual processing unit (VPU)$^{TM}$ (VPU$^{TM}$ not shown in figure). The VPU$^{TM}$ encodes visual information acquired from the camera and transfers electrical stimulation commands to the implanted unit. The data transfer is accomplished via a wireless link using an external antenna that is magnetically stabilized over the electronic implant. Personal computer based custom software was also used to actively control the electrical stimulation command through the VPU. The implanted unit consists of an extraocular (electronic case) and an intraocular component (electrode array). The extraocular unit is surgically attached to the temporal area of the skull. A subcutaneous cable connected to this extraocular electronic case is used to conduct electrical current across the eye wall to an intraocular electrode array placed on the retinal surface. The electrode array consists of 16 disc shaped platinum electrodes in a square $4\times4$ layout. Each electrode was (520) μm in diameter. Edge-to-edge separation between two adjacent electrodes was 200 μm.

### 2.3. Surgical procedure

About two weeks prior to the surgery botulinum toxin (BOTOX®, Allergan, Inc., Irvine, CA) was injected in the superior, inferior, medial and lateral rectus muscles of the test subject, due to the concern that the subject's eye movement might break the cable connecting the intraocular electrode array to the extraocular electronic case. Under general anesthesia, the electronic implant was placed in a recessed well created in the temporal skull as is done for cochlear implants (Webb, Pyman, Franz, & Clark, 1990). To secure and protect the cable, a shallow groove was created along the temporal skull. The cable was then placed in the groove and delivered through a lateral canthotomy into the periocular space. The cable and electrode array were passed subconjunctivally under each of the four recti muscles and introduced into the eye through a 5 mm circumferential scleral incision placed 3 mm posterior to the limbus. Prior to introduction of the implant, the majority of the vitreous gel was removed. The electrode array was then positioned just temporal to the fovea and a single retinal tack (second sight retinal tack) was inserted through the electrode array and into the sclera. At the end of the implant procedure, the device was tested electrically to assure that all wires were intact. The subject was examined on post-operative day 1 and then three times a week for the next 2.5 months.

### 2.4. Electrical stimulation tests

Subject testing was conducted in three ways: double masked, subject masked, or subject training. Double masked tests were designed as forced choice tests during which both the tester and subject were masked as to the actual stimulus and the subject was trained to describe the perception in a limited number of ways. Subject masked tests were designed to allow the subject to provide detailed descriptions of the percepts. The tester, who was aware of the stimulus conditions, would ask questions such as "Do you see anything?" followed by, for example, "Where did you see the spot?" False positive testing (i.e. no stimulus presented) was included in the subject-masked tests to verify the responses. Subject training experiments were designed to teach the subject to discriminate patterns of stimulation. Subject training was usually followed by double masked testing. Double masked testing was used to evaluate the subject's ability to spatially discriminate and locate two or more electrodes. Subject masked testing was used to determine stimulus thresholds and investigate properties of single percepts. Most testing was conducted with a computer supplying the test pattern, but in a limited number of tests a camera was used to detect high contrast images. Testing was limited to 4 h/day, 2–3 days/week. Electrode impedance was typically measured twice a day. The subject's left (unoperated) eye was patched during testing. The implant was only activated in the clinic. An electrically evoked potential was recorded using scalp electrode positioned in a standard visual evoked potential configuration.

## 3. Results

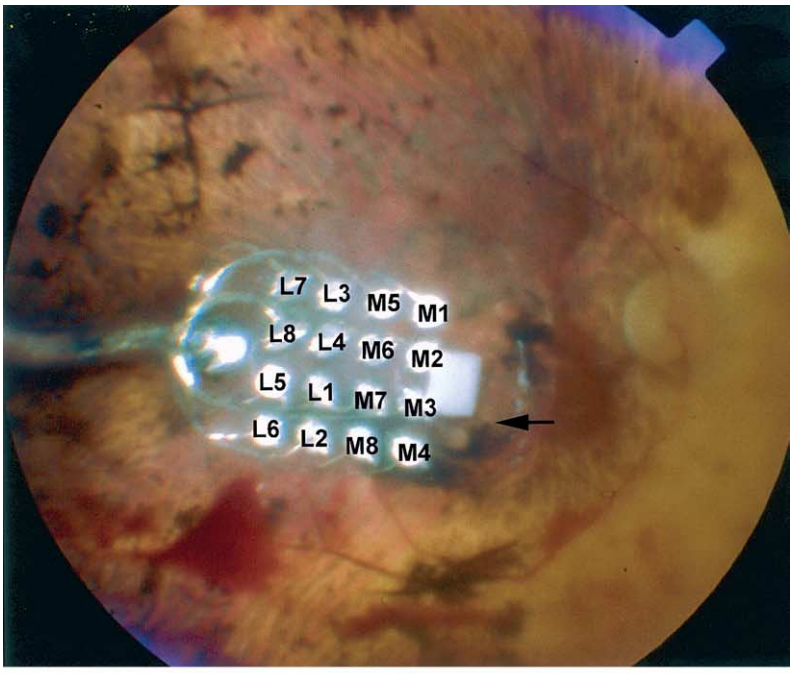
On the basis of the results of tests listed under subject selection section, we identified a 74 year old male with X-linked retinitis pigmentosa. The subject had no light perception in his right eye and bare light perception in his left eye. In fact, we had tested this subject over the last 10 years to confirm the level of vision in each eye. The subject reported not seeing from his right eye for more than 50 years. This eye was selected for implantation of our first electronic device, as it had no vision at all. The surgical implantation was without any complications (Fig. 2).

Threshold current to elicit a visual response was found for all 16 electrodes. A statistical analysis of the threshold current versus time showed that three electrodes showed a significant decrease in current, 10 electrodes had no significant change in threshold current, and three electrode showed a statistically significant increase in current (increase or decrease determined by slope of line from regression analysis of threshold stimulus current performed with MS Excel data analysis tool, $p < 0.05$ for significance of slope). The thresholds ranged from 39 μA to 1.3 mA during the first days of testing, and from 50 to 500 uA at 10 weeks after the surgery. The timing of the pulse was typically a biphasic current pulse, 1 ms/phase with a 1 ms intraphase delay. These numbers were chosen based on prior studies that suggest a stimulus impulse longer than 0.5 ms can target bipolar cells (Fig. 3). The threshold level of electrical stimulus charge remained below 0.35 mC/cm$^2$ electrodes on 13 electrodes of the 16 (81.25%) electrodes (0.35 mC/cm$^2$ is an established long-term safety limit for platinum when pulses of at least 0.6 ms are used) (Greenberg, 1998). The threshold stimulus for each electrode position is shown on first day of stimulation and then 2.5 months later in Fig. 4A, B. The most dramatic decrease in threshold was seen at the electrodes furthest away from the fovea (i.e. at the perimeter of the electrode array). Electrode impedances ranged from 4 to 55 kOhms (at 1 KHz, average, 23 kOhms) over 2.5 months of testing (Fig. 5).

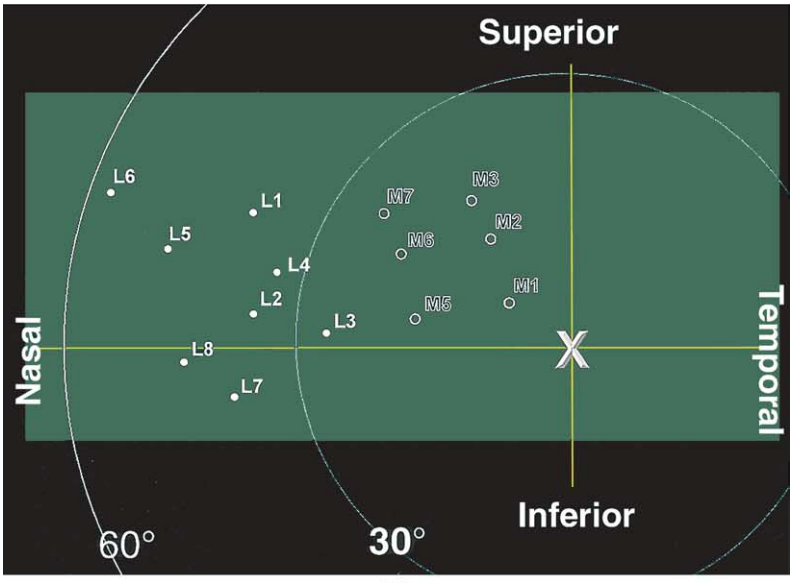
Visual perceptions elicited by electrical stimulation of the retina with a single electrode produced a single spot described in one of two general different forms. Most percepts were described as round spots of light. Less frequently reported was a lighted center with a black surrounding ring. This dark ring was described as a "halo", darker than the background. The halo was typically seen at stimulus currents near perception threshold. Four different colors were reported. The lighted spots were usually described as either yellow or white and occasionally as red-orange. Blue colored percepts were noted when high frequency stimulation was extinguished (i.e. the blue percept was an "off-response"). When asked to describe the size of visual percepts at an arm's length, the subject reported spots ranging from a match head to a quarter. The subject drew these percepts as small as 0.25 cm in diameter on a drawing board positioned in his lap (approximately 30 cm away from his eye). In general, the size of the phosphenes increased with higher stimulation current (Table 1).

The subject reported the location of the perception that in general matched the location of the active stimulating electrode. The subject could distinguish between two adjacent electrodes of the array with center-to-center separation of 720 μm. The subject was asked to describe the location of each electrode as it was activated. All the electrodes were positioned temporal to the fovea of the right eye and all the elicited perceptions were described in the subject's nasal visual field (Fig. 2). In general, the reported position of the electrode corresponded with the location of the electrode on the retina. Fig. 2B shows a map describing the location of the percepts reported by the subject.

The subject demonstrated the ability to describe the relative location of percepts generated by selected




(A)




(B)

Fig. 2. (A) Fundus photo taken 2 weeks after surgery showing electrode position on the retina (black arrow indicate a reference point in the pigmentary change). (B) Schematic showing the position of the percepts in the subject's visual field. These are perceptions as viewed from the subject's viewpoint (i.e. as the subject was looking out). In general, electrodes superiorly located induce percepts inferiorly located. This map is already correct for the horizontal orientation (electrodes temporally located induce percepts nasally located). Not all electrodes are included because the threshold current to elicit a response with those electrodes were relatively high at that time.

electrodes. For these tests, a training period preceded double masked testing. In the first set of two-alternative forced choice tests, the subject was told that one of two electrodes would be activated and was instructed to identify the active electrode. Using various pairs of vertically or horizontally aligned electrodes in five separate trials, the subject was asked to describe the stimulus as "up" versus "down" (vertically aligned pair) or "left" versus "right" (horizontally aligned pair). Subject scored 10/12, 12/12, 6/8, 8/8, and 8/8 (correct responses/total responses, chance = 50% correct; Table 2). In the second set of tests, two electrodes were activated in succession (within 3 s) and the subject was asked to describe the order in which the electrodes were activated based on the location of the percepts. Four trials of this type were run. In one trial, the subject was asked to

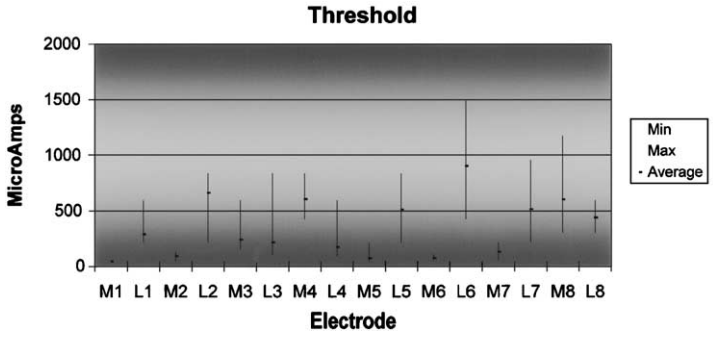



Fig. 3. Graph showing the threshold current to elicit a response for all 16 electrodes over 2.5 months of testing (range, average). Clinical units are related logarithmically to microamperes, e.g. 100 CU = 14 μA, 150 CU = 77 μA, 200 CU = 400 μA.

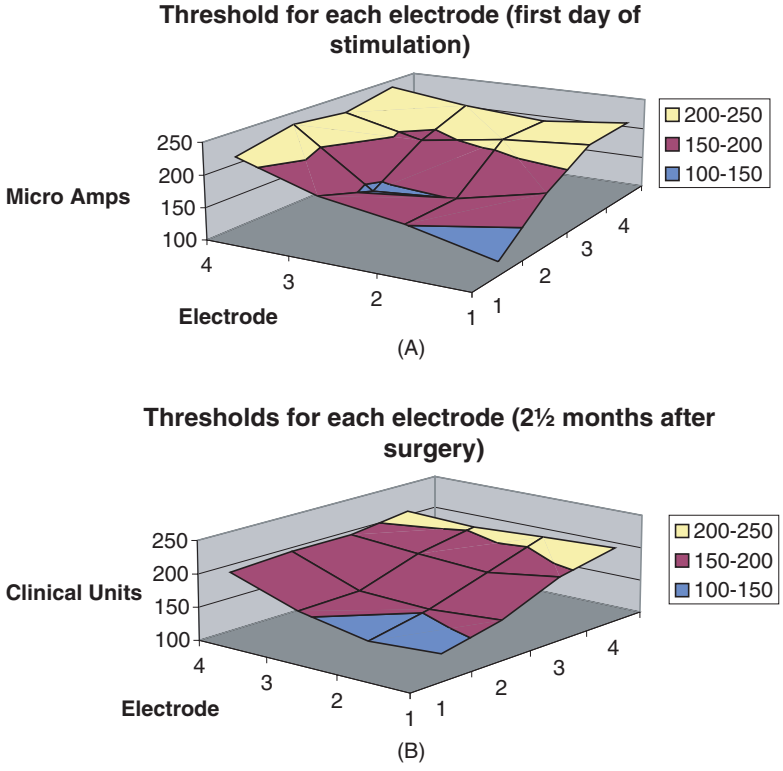



Fig. 4. (A) Electrode mapping of threshold current to elicit a response at first day of stimulation (1 week after surgery). (B) Electrode mapping of threshold current 2.5 months after surgery. Each intersection on the grid corresponds to an electrode position. Location 1,1 on grid corresponds to electrode closest to fovea. Clinical units are related logarithmically to microamperes, e.g. 100 CU = 14 μA, 150 CU = 77 μA, 200 CU = 400 μA.

describe the pattern as either "up–down" or "down–up"; subject score 7/8 (chance = 50% correct). In one trial, the subject was asked to describe the pattern as "left–right" or "right–left"; subject score 8/8 (chance = 50% correct). In two trials, the subject was asked to describe the pattern in one of four ways: "up–down", "down–up", "left–right", or "right–left"; subject scores 6/8 and 6/8 (chance = 25% correct; Table 2).

Brightness tests revealed that with increasing or decreasing current the visual perception got brighter or dimmer, respectively. For each of the 12 electrodes tested the current was decreased 12 times and increased eight times by 6–12% each transition (20 transitions per electrode). On average, the subject identified the transition correctly more than 74% of the time (chance = 50% correct). The subject was given an arbitrary scale of 0–10 with 10 being the brightest and 0 representing no perception. During the course of the 2.5 months, the subject identified all 10 levels of brightness on all tested electrodes. However, in general the percepts produced by the electrodes nearer the fovea demonstrated a more consistent correlation between brightness and stimulus current. In contrast, the percepts generated by peripheral electrodes in general were less responsive

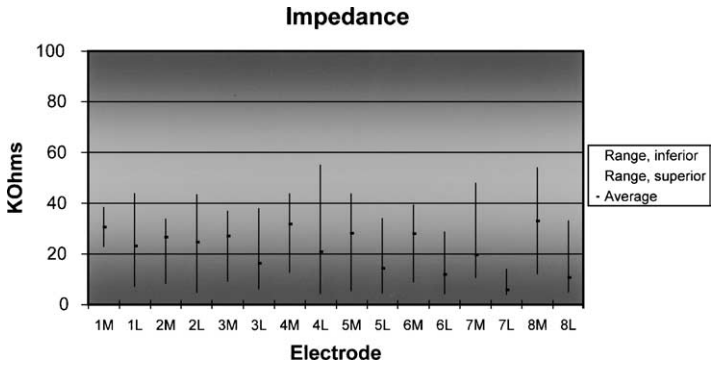



Fig. 5. Graph showing impedances of all 16 electrodes over 21/2 months of testing (range, average).

Table 1
Visual percepts

| | |
|---|---|
| Forms | Mostly perceived as round spots of light. Less frequently reported as a lighted center with a black surrounding ring |
| Size | Spots size ranging from a "match head" to a "quarter" |
| Location | The location of the perception in general matched the location of the active stimulating electrode |
| Resolution | 120 arc min (2°) or 20/2400 |
| Brightness | At least 10 levels of brightness on all tested electrodes |
| Color | The lighted spots were mostly described as either yellow or white and occasionally as red-orange or blue |
| Duration | Most visual percepts had the duration of the electrical stimulation (about 0.1 s) |

to increases in stimulus current and tended to remain dim.

The subject demonstrated the ability to use the VPU$^{TM}$ to detect ambient light and to distinguish the direction of motion of objects. With the camera initially covered (i.e., no light), the subject was asked to determine if the camera remained covered or if the camera was exposed to light. In a double masked trial, the subject scored 10/10 (chance = 50% correct; Table 2). In a darkened room, the subject could locate a flashlight carried by a person who was 200 cm away in 10/10 trials on three different days (Table 2). In another test, the subject could locate a dark object under normal room light conditions (a 15 cm square black box at 60 cm away). Also, a 15 cm square book with a black cover was held 5 cm away from the camera in normal lighted room conditions. The book was moved up or down out of the field of the camera. In 4/5 trials, the subject correctly and immediately identified the direction the book was moved (chance = 50% correct).

Cortical evoked potential were elicited by electrical stimulation of the retina with the implant. N1–P1 amplitude was 4.29 μV, and the N1 and P1 latencies were 23.2 and 52 ms, respectively (Fig. 6). The cortical signal was repeatable over several trials, suggesting the evoked potential was correlated to the stimulus despite the poor signal to noise ratio. VEPs could not be recorded from either eye pre or post-operatively. Even though the left eye had bare light perception, the perception of light could only be evoked with a photographic flash, which is more intense than the standard bright flash used for VEP recording. Even the perception of the photographic flash was transient, so that only the first few in a series of flashes could be detected.

Serial photographs were obtained of the implant both preoperatively and on scheduled post-operative dates (Fig. 7). The photographs reveal minimal if any movement of the device. A comparison of pre operative and post-operative fluorescein angiograms showed no changes in the vasculature of the retina and choroid.

## 4. Discussion

Retinitis pigmentosa afflicts 1/4000 and a large number of these patients become legally blind in their fifth decade (Heckenlively et al., 1988). An even greater number of people lose vision due to photoreceptor loss in age related macular degeneration (AMD) (Klein et al., 1997; Klein et al., 1992). Although some treatments to slow the progression of AMD are available, no treatment exists that can replace the function of lost photoreceptors. We have summarized our results from the first 10 weeks of testing an electronic device implanted in an RP subject who has a history of being completely blind in the implanted eye for more than 50 years due to photoreceptor loss. Electrical stimulation results in the subject seeing spots of light (phosphenes) that are both reliable and reproducible with respect to the spatial location of the stimulating electrodes on the retina and the stimulating electrical current. The threshold currents to elicit the responses are consider-

Table 2
Testing results

| Test type | Test description | Chances of randomly correct | Number of trials | Correct answers |
|---|---|---|---|---|
| Pair of vertically aligned electrodes | "Up" versus "down" | 50% | 2 | 10/12 (83.3%) and 12/12/ (100%) |
| Pair of horizontally aligned electrodes | "Left" versus "right" | 50% | 3 | 6/8 (75%), 8/8 (100%), and 8/8 (100%) |
| Sequential activation of a pair of electrodes | "Up–down" versus "down–up" | 50% | 1 | 7/8 (87.5%) |
| | "Left–right" versus "right–left" | 50% | 1 | 8/8 (100%) |
| | "Up–down" or "down–up" or "left–right" or "right–left" | 25% | 2 | 6/8 (75%) and 6/8 (75%) |
| Camera testing | On–off light in front of camera | 50% | 1 | 10/10 (100%) |
| | Locating a flash light in movement in a darkened room | N/A | 3 | 10/10 (100%); 10/10 (100%) and 10/10 (100%) |
| | Detecting motion of a black box moved in front of the camera | 50% | 1 | 4/5 (80%) |

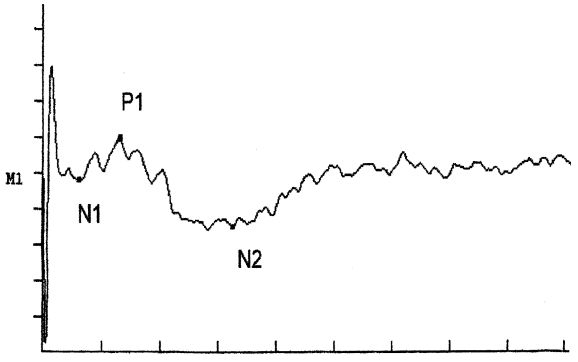



Fig. 6. Electrically evoked response (EER) was recorded using eight stimulation electrodes in parallel: M1, M5, L3, L7, M2, M6, L4, and L8 at threshold. Figure shows shorter latency and distinct N1 and P1 responses compared to visual evoked responses (VEPs). N1–P1 amplitude was 4.29 μV, and the N1 and P1 latencies were 23.2 and 52 ms, respectively. VEPs could not be recorded from either eye. (Scale: $Y$ axis = 4.88 μV/division; $X$ axis = 40 ms/division.) Although only half of the array was used during stimulation, which corresponds to a $1.2 \times 2.6$ mm area of retina directly under the array, N1–P1 peak is at least twice the peak to peak noise.

ably lower than previously reported short-term tests (Humayun et al., 1996; Humayun, de Juan, et al., 1999). Over time, the thresholds also appear to stay the same or decrease for a number of the electrodes. Most of the threshold currents are within safe limits for long-term electrical stimulation of neurons using platinum electrodes. This has significant, positive implications for the success of a retinal implant because lower threshold currents mean less power required by the electronics and therefore less heat dissipated in the eye. The electrode size for this prototype was based on safely supplying a stimulus current of 700 μA for 1 ms. This corresponds to charge density less than 0.35 mC/cm$^2$. Since the actual current needed is in many cases lower, electrodes can be made smaller yet still support the same current. Thus, lower current requirements may lead to the use of a smaller, more densely packed electrode array that would put hundreds of individual percepts in the macula, possibly increasing the resolution afforded by the implant (Robblee & Rose, 1990).

The location of the percept corresponded to the electrode that was stimulated. The size and brightness of the percept were dependant upon the stimulus parameters.The elicited percept size was calculated from the drawings of the subject. The closest electrode separation we could test due to the electrode array design was resolved by the subject. We have not yet tested the subject to evaluate independent mobility and this functionality remains to be proven for the electronic implant.

One suggested disadvantage of epiretinal stimulation is that it would produce percepts not spatially consistent with the electrode location because the axons of ganglion cells from many areas of the retina pass immediately under the electrode. If these axons were stimulated in addition to the bipolar and ganglion cell soma, then the reported perceptions may no longer be retinotopically correct (i.e. correspond to the electrode position on the retina). The fact that the subject reported perceptions of round spots in locations consistent with the electrode supports experimental and modeling studies suggesting that deeper retinal cells can be targeted without stimulating the superficial ganglion cell axons (Greenberg, 1998; Greenberg, Velte, Humayun, Scarlatis, & de Juan, 1999). The relationship between brightness and stimulus level is also important, since this suggests that information on relative intensity of light can also be

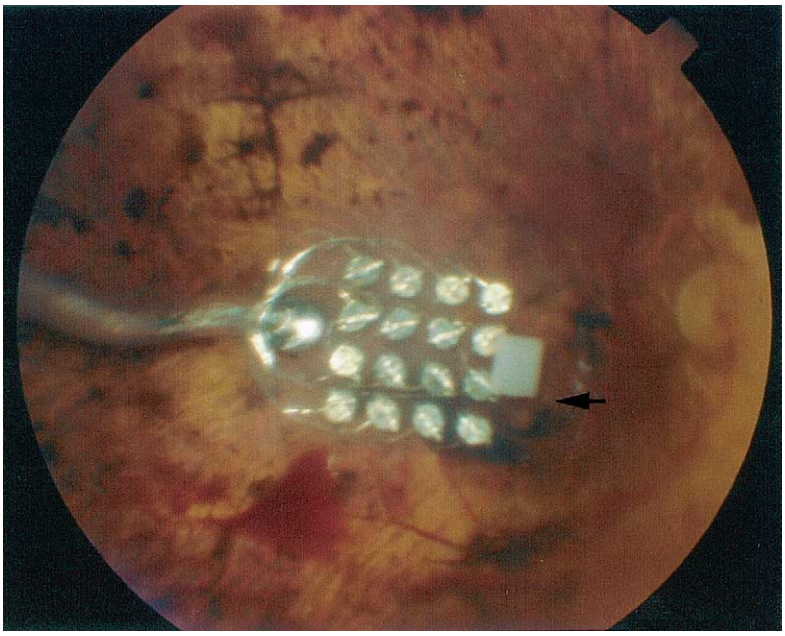


Fig. 7. Fundus photograph taken 2 months after surgery showing the relative stable positioning of the electrode array over 6 weeks. Electrode array does not move relative to the pigmentary changes of the retina (black arrow indicates same pigmentary changes shown in Fig. 2A as reference).

partially restored. This ability would allow a continuum of contrast to be presented to the subject rather than a binary (''on/off'') representation of an image. Colorful perceptions had also been described by our subjects who had undergone short-term tests (Humayun et al., 1996; Humayun, de Juan, et al., 1999; Humayun & de, 1998). Yellow is the predominant color of most of the percepts reported. Given that we have far more red and green sensitive cones, one explanation for the yellow color could be that a mix of the neural circuits that normally subserve these two color pathways is being stimulated. At this time, it is not clear how to reliably elicit the other reported red-orange and blue colors.

Using pattern electrical stimulation of the retina, the subject was able to repeatedly report the order in which different electrodes were activated based on the location of the electrodes. Individual percepts were used in combination and the subject was able to distinguish a ''direction'' that corresponded to the order of electrode activation. This is a first step towards providing information about direction as well as edges and shapes so the subject can possibly attain unaided mobility or read large print. We can successfully get the subject to see 2 spots in sequence and thus convey the sensation of direction. Probably the most important information from this testing is that in this short period of testing we also observed that his ability to locate the phosphene in a retinotopically correct visual field increased with use.

A similar learning effect was seen with increased use of the camera. These tests are more realistic than the computer controlled tests and more closely approximate vision in a daily environment. The first day the subject used a video camera to control the electrical stimulation pattern, he was able to locate a spot of light on a wall located 120 cm away. The subject could also locate a flash light carried by a person located 200 cm away in a darkened room. With increased use of the camera, the subject was able to do more complex tasks. Under normal room lighting, the subject could locate and detect the direction of motion of a dark object. This could parallel the training period that many cochlear implant subjects need (Tyler, Parkinson, Woodworth, Lowder, & Gantz, 1997). Longer-term investigation would be required to clarify and characterize this potentially beneficial effect.

In summary, the subject can reliably and reproducibly report spots of light elicited by activation of individual electrodes positioned on the retina. Currently, the subject can determine some directional movement. Further training and testing will be necessary to determine the maximum effectiveness of this type of treatment for restoring vision that would allow mobility and recognition of simple forms. The next generation electronic retinal prosthesis is expected to provide higher number of electrodes and more complex stimulation control capability.

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