Perceptual Efficacy of Electrical Stimulation of Human Retina with a Microelectrode Array during Short-Term Surgical Trials

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Purpose. This work is part of a feasibility assessment of a retinal prosthesis as a means to restore vision to patients with blindness caused by retinitis pigmentosa. The primary goal was to assess the concordance of the form of induced perception and the pattern of electrical stimulation of the retina, and the reproducibility of the responses.

Methods. Five volunteers with severe retinitis pigmentosa and one with normal vision were studied. A companion paper in this issue provides details on demographics, visual function, surgical methods, general stimulation strategy, and data analysis. Volunteers were awake during surgery while a 10-μm-thick, microfabricated electrode array was placed on the retina. The array was connected to extraocular current sources that delivered charges to 50-, 100-, and 400-μm-diameter electrodes. Negative control trials were randomly included. Perceptual quality was judged by the similarity between the form of stimulation and perception (i.e., accuracy) and the reproducibility of responses.

Results. Only 1 of 40 control tests yielded a false-positive result. On average, volunteers 3, 5, and 6 reported percepts that matched the stimulation pattern 48% and 32% of the time for single- and multiple-electrode trials, respectively. Two-point discrimination in the best cases may have been achieved in two blind subjects using (center-to-center) electrode separation of 600 and 1960 μm. Reproducibility was achieved 66% of the time in the blind subjects. By comparison, in the normal-sighted subject, perceptual form was reported accurately 57% of the time, with 82% reproducibility, and two-point discrimination may have been achieved in one trial with 620-μm electrode spacing and in two trials each with 1860- and 2480-μm electrode spacing. In subjects 5 and 6, perceptual size was inconsistently related to the charge, although relatively large differences in charge (median: 0.55 microcoulombs [μC]) between two trials produced differently sized percepts. Longer stimuli did not produce rounder percepts.

Conclusions. Single percepts induced by single-electrode stimulation were relatively small, but the form of percepts, especially after multielectrode stimulation, often did not match the stimulation pattern, even in a normal-sighted volunteer. Reproducible percepts were more easily generated than those that matched the stimulation pattern. (*Invest Ophthalmol Vis Sci.* 2003;44:5362–5369) DOI:10.1167/iovs.02-0817

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Supported by the Keck Foundation, the Wynn Foundation, the Massachusetts Lions Club Eye Research Foundation, Grant C-2726-C from the Department of Veterans Affairs, the Catalyst Foundation, the National Science Foundation, Grant BES-0201861, and the Foundation Fighting Blindness.

Submitted for publication August 13, 2002; revised November 18, 2002, and May 21 and June 26, 2003; accepted June 30, 2003.

Disclosure: **J.F. Rizzo III** (P); **J. Wyatt** (P); **J. Loewenstein**, None; **S. Kelly**, None; **D. Shire** (P)

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Significant progress toward development of a retinal prosthesis has been made by several groups.[1–13] A crucial milestone yet to be achieved is the demonstration that such devices improve the quality of life for blind patients. This psychophysical study is an initial feasibility assessment toward that milestone. Our primary goals were to assess the degree to which the form of induced percepts matches the stimulation pattern and the perceptual effect of various stimulus parameters.

Methods

A companion paper in this issue[14] and an online Appendix (available at *http://www.iovs.org/cgi/content/full/44/12/5355/DC1*) provide additional details about the methods and results and an expanded discussion of our findings and their implications. This study is restricted to the last four experiments, given that the first two produced only meager visual percepts.[14] Table 1 provides an overview of testing protocols. Only symmetrical, charge-balanced pulses delivered through electrode arrays were used (see Ref. 14, Figs. 2, 3). To assess perceptual efficacy, responses were judged by the concordance between the stimulation pattern and the form of the percept, and by the reproducibility of responses. Criteria for the former were that stimulation by one electrode would produce a small (i.e., not larger than a quarter as if viewed at arm's length), single percept and that stimulation of multiple electrodes in a row or column would produce multiple percepts or a line. Reproducibility (i.e., the similarity of form elicited by identical stimuli at different times) was judged by one author (JFR), and another author (JL) performed independent comparative interpretations of 20% of the trials (chosen randomly) that yielded percepts.

The study was conducted in accordance with the provisions of the Declaration of Helsinki.

Results

Overview

Image size is reported as if viewed at arm's length. Electrode spacing is center-to-center separation. The two judges (see online Appendix) classified 83% and 82% of the responses identically for accuracy and reproducibility, respectively.

Hypotheses

Hypothesis 1. Blind subjects will report a single, small percept after stimulation through one electrode at or slightly above threshold.

With a 100- or 400-μm electrode, 185 percepts were elicited from volunteers 3, 5, and 6. A small percept was reported in 1 (6%) of 17, 38 (35%) of 109, and 50 (85%) of 59 trials, respectively (Table 2). On average, the hypothesis was satisfied

TABLE 1. Overview of Stimulation Protocol

Volunteer	Electrode Configuration	Stimulus Frequency (Hz)	Stimulus Duration* (ms)	Pulse Train Duration (sec)
3	Monopolar for all large and most small electrode trials	6 or 30	8	1.5
4	Monopolar	20	2	1.5
5	Monopolar	20	0.25, 1, 4, 16	1.5
6	Mostly monopolar	20	0.25, 1, 4, 16	1.5†

* Duration of the negative phase of a biphasic pulse pair. Biphasic pulse pairs were repeated at a given frequency until a completed "pulse train duration" was reached.

† Occasionally 4.0.

48% of the time. Of responses not consistent with the hypothesis: (1) volunteer 3 mostly reported faint, flashing images and on four occasions a long line; (2) volunteer 5 reported a line 5% of the time and clusters of two or three small images 60% of the time; (3) volunteer 6 reported a line 5% of the time and clusters of two or three small images 10% of the time.

Hypothesis 2. Blind subjects will report percepts that match the pattern of multielectrode stimulation.

Eighty-four trials tested this hypothesis, which for subjects 3, 5, and 6 was satisfied 55%, 21%, and 29% (average 32%) of the time, respectively (Table 2). Given these limited results, only three letter-recognition (T or L) trials were attempted, none of which yielded the anticipated responses.

Hypothesis 3. Two-point discrimination can be achieved in a blind subject by delivering electrical stimulation through two electrodes.

In experiment 3, driving eight large electrodes (600-μm spacing) induced perception of a line of four distinct images or similar percept three of three times. Stimulation of one column of four large electrodes yielded no response, but driving the other four electrodes again induced perception of a line of four images. We illuminated the eye and saw a tilted array, with only one edge contacting the retina, which presumably accounted for the perception of four images, rather than eight (Fig. 1).

In experiment 5, we used large electrodes with monopolar or bipolar stimulation (which produced similar results). Seventeen paired trials were performed by sequentially driving one then two electrodes to determine whether the second electrode would produce an additional percept (Fig. 2; Table 3). Two-point discrimination was not consistently obtained with

TABLE 2. Accuracy and Reproducibility of Responses

	Number of Stimulation Trials	Number (%) of Trials Yielding a Percept	Number (%) of Percepts Matching Expectation*	Number of Trials Testing Reproducibility	Number (%) of Reproducible Responses
Experiment 1	24				
Multiple electrodes on array	24	4 (17)	†	0	—
Experiment 2	42				
Negative control	6	0 (0)			
Single needle electrode	36	7 (19)	‡	‡	‡
Experiment 3	128				
Negative control	8	0 (0)			
Single needle electrode	29	11 (38)	‡	‡	‡
Single electrode on array	50	17 (34)	1 (6)	1	1 (100)
Multiple electrodes on array	40	22 (55)	12 (55)	2	2 (100)
Experiment 4§	66				
Negative control	10	1 (10)			
Single needle electrode	14	8 (57)	‡	‡	‡
Single electrode on array	19	14 (74)	8 (57)	0	—
Multiple electrodes on array	23	21 (91)	9 (43)	11	9 (82)
Experiment 5	246				
Negative control	9	0 (0)			
Single needle electrode	18	9 (50)	‡	‡	‡
Single electrode on array	178	109 (61)	38 (35)	39	16 (41)
Multiple electrodes on array	41	34 (83)	7 (21)	23	19 (83)
Experiment 6	134				
Negative control	7	0 (0)			
Single needle electrode	8	4 (50)	‡	‡	‡
Single electrode on array	88	59 (67)	50 (85)	22	18 (82)
Multiple electrodes on array	31	28 (90)	8 (29)	12	9 (75)

Negative control trials were initiated by an audible tone that was not followed by electrical stimulation.

* See the Methods section for details.

† Responses were generally vague and judgment of whether they met our expectations could not be made.

‡ Responses with the single needle electrode were used only to determine threshold and not to judge whether responses met a reasonable expectation of form or were reproducible. Form perception was assessed only with electrode arrays that contacted the retina.

§ Subject in Experiment 4 had normal vision.

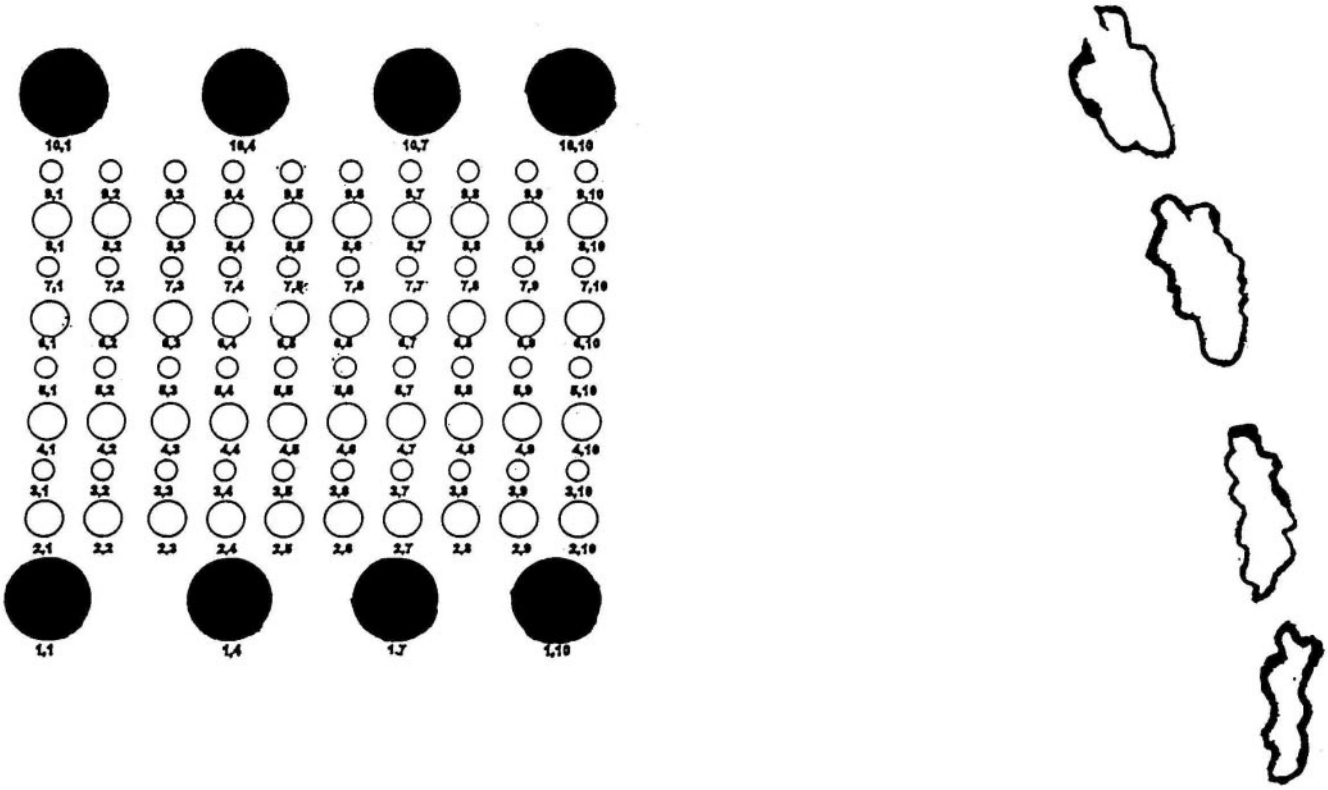

FIGURE 1. Experiment 3: pattern of electrical stimulation delivered through the electrode array (*left*) and the patient's drawing of the induced perception (*right*). The array was in the peripheral retina and was tilted so that only four electrodes along one edge of the array contacted the retina. Stimulation was a 196-μA, 8-ms pulse at 6 Hz. Only the darkened electrodes received current. The orientation of the percepts was appropriate given the orientation of the electrode array on the retina.

any electrode separation. Reports of multiple percepts (see hypothesis 1; Fig. 3) confounded interpretation of the results.

In experiment 6, a persistent effort of 66 trials yielded evidence suggestive of two-point discrimination. Most significantly, six trials driving two electrodes (1860-μm spacing) produced one percept five times and two "objects close together" once. Paired stimulation through one then two electrodes yielded: a brighter percept of a single image twice, a brighter and larger ("dime"-sized) percept once, a larger image once, and "motion" once. A variation used once delivered stimulation through a second end electrode while driving the first, which produced a "pea"-sized image initially and then a doubly bright "dime"-sized image (Fig. 4). No difference was reported with simultaneous stimulation (using identical charge) of two adjacent versus two end electrodes across a row in two of two trials. Three trials using two end electrodes (2480-μm spacing) in a column and two trials using two end diagonal electrodes (3100-μm spacing) all yielded single percepts.

Hypothesis 4. Driving the same electrode(s) with the same stimulus parameters at different times will yield the same percept.

The last three blind subjects reported similar images 3 (100%) of 3, 35 (57%) of 62 and 27 (79%) of 34 times, respectively, when stimulation was unchanged between two trials (average 66%; Table 2).

Hypothesis 5. Accurate percepts can be induced more frequently in normal-sighted than in blind volunteers.

In the single-electrode (100 or 400 μm) trials, the normal subject met our expectation 8 (57%) of 14 times. By this measure, subject 6, legally blind for 15 years, performed better (Table 2). The normal subject reported reproducible percepts 82% (9/11) of the time versus the blind subjects' 66% (hypothesis 4).

In multiple-electrode trials, the normal subject reported "accurate" percepts 43% of the time (versus 32% for blind volunteers: hypothesis 2). A subset of these trials tested two-point discrimination (for one example, see Fig. 5). Across these and other similar trials (n = 14), at best, she distinguished stimulation separated by 620 μm one time, and in two of two cases each she distinguished electrode separation of 1860 and 2480 μm. See hypothesis 3 for comparison to blind patients.

Hypothesis 6. Increasing stimulus charge will increase the size of a percept.

In one analysis, perceptual size was recorded per stimulus charge. There were 52 and 33 trials with single electrodes for the last two subjects, respectively. To permit uniform comparison of charge density, the smaller number of trials with the 100-μm electrode was excluded, leaving 40 and 30 trials, respectively, with the 400-μm electrode. In subject 5, the median charge that yielded a pea- or dime-sized percept was identical (1.4 microcoulombs [μC]). In subject 6, the median charges that produced a pea-, dime-, or quarter-sized percept were 0.4, 0.8, and 1.1 μC, respectively, which is consistent with the hypothesis.

In another analysis, we assessed whether percepts enlarged or shrank in pairs of trials (not necessarily sequential) in which charge was the only variable. Subjects 5 and 6 satisfied the hypothesis only 29% of the time (Table 4). However, trials that satisfied the hypothesis had a median difference in charge of 0.55 μC versus 0.24 μC for those that did not.

Hypothesis 7. Longer stimulus duration will produce rounder percepts.

Only single, round, or elongated percepts induced by stimulation through one electrode were considered; 108 responses (from subjects 4, 5, and 6) met these criteria. Five (100%) of 5 percepts by subject 4, 47 (63%) of 74 by subject 5, and 25 (86%) of 29 by subject 6 were round. Across all durations, a

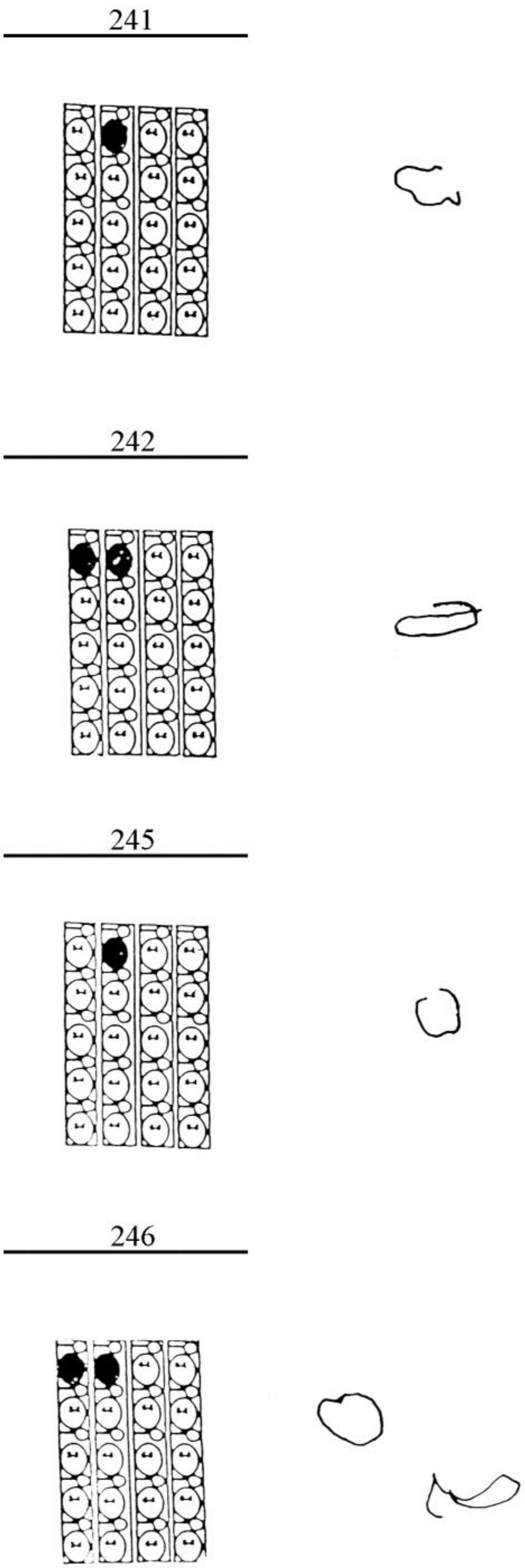

Table 3. Evaluation of Two-Point Discrimination in Experiment 5

Center-to-Center Electrode Spacing (μm)	Trials (*n*)	Trials with Additional Percept(s) (*n*)	Trials with no Additional Percept (*n*)
620	2	1	1
1240	4	2	2
1960	7	5	2
2480	4	1	3

Evaluation was conducted by determining whether sequential stimulation through one and then two 400-μm diameter electrodes yielded additional percept(s). The same slightly suprathreshold charge was used for each electrode and 1.5-second pulse train duration was used for each of the paired stimuli.

round percept was reported 2.5 times more than an elongated percept (Table 5). This hypothesis was rejected.

Hypothesis 8. Perceptual shape will differ with stimulation through electrodes oriented parallel versus orthogonal to retinal ganglion cell axons.

In experiment 5, a "circle" was reported four of four times when columnar electrodes (oriented along axons) were driven, whereas orthogonal stimulation produced multiple percepts (circle and lines) five of five times. In experiment 6, four trials using columnar stimulation yielded an elongated, curved ("banana"-shaped) percept three times and a spot "larger than a quarter" once (Fig. 6), whereas four trials across axons yielded a "round" percept three times and a line of percepts once (all with 250 μA).

Discussion

These experiments were challenging because the volunteers had to endure intraocular surgery, were emotionally involved in the experimental outcome, and were seeing novel percepts. Further, testing was short-term and involved fewer trials than is standard in psychophysical experiments. Nonetheless, given that only 1 of 40 control tests produced a false image and that test–retest trials yielded relatively high reproducibility (66%), we believe our testing provided useful data.

Our hypotheses were designed to address the ability of blind subjects with retinitis pigmentosa to report basic form perception (hypotheses 1–4), perceptual differences between the normal-sighted volunteer and blind subjects (hypothesis 5), and perceptual effects of various stimulus parameters (hypotheses 6–8). Our results are both encouraging and sobering.

Hypothesis 1 tested whether stimulation through one electrode would yield single, small percepts. The hypothesis was satisfied 48% of the time over 185 trials. Percepts that were too large were uncommon errors. Much more commonly (i.e., 60% of the time in volunteer 5), multiple percepts were reported,

Figure 2. Experiment 5: pattern of electric stimulation (*left*) and patient's drawing of the induced perceptions (*right*). Location of the array is shown in Figure 3. Numbers above the schematic of the electrode arrays indicate the stimulation trial. Stimulation 241 was delivered through a single electrode, and the patient reported seeing a "circle." The next stimulation occurred through two adjacent electrodes, and the patient reported seeing a "line." Reproducibility was checked by returning to the single-electrode stimulus three trials later, and again the patient reported seeing a "circle." Stimulation 246 yielded a closely spaced "circle and a line," compared with the "line" reported in the prior identically performed stimulation (242). All stimuli were 350 μA per electrode, 4-ms pulses delivered with a bipolar configuration through the darkened electrodes. Two-point discrimination would seem to be evident in the last trial (246), but in this volunteer two-point discrimination was not consistently obtained with any electrode separation.

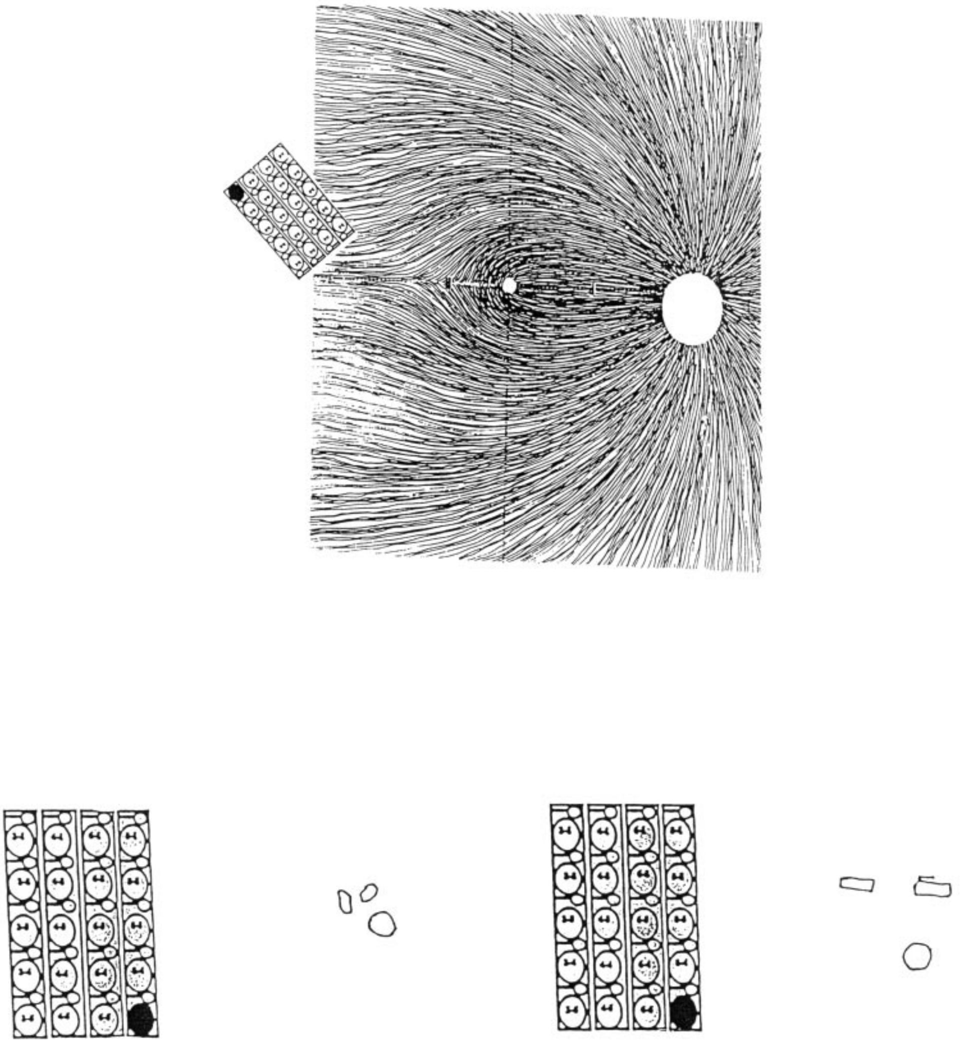

FIGURE 3. Experiment 5. *Top*: schematic of the retina of the right eye to show location of the electrode array in relation to the orientation of retinal ganglion cell axons. The array is scaled to size according to the width of the optic nerve head (*large, open circular region*). *Small, open circular region* to the *left* of the optic nerve head represents the fovea. *Bottom*: pattern of electric stimulation and patient's drawing of the elicited percepts in two trials. Both trials were performed by delivering 250-μA, 4-ms pulses through one 400-μm electrode (*darkened*) in bipolar configuration. The volunteer reported that the induced circular percepts (drawings on the *right* of each electrode array schematic) were equal in size to a pea as if viewed at arm's length. A similar appearing cluster of three percepts was reported for these two trials, which were performed identically. There was one intervening trial (not shown) with the same electrode and duration but using 200 μA, and no perception was reported. (Drawing of retina taken from Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye*: *An Atlas and Textbook*. Philadelphia: WB Saunders; 1971).

the explanation for which is unknown, although a similar phenomenon occurs with visual cortical stimulation.[15,16]

For hypothesis 2, we studied percepts generated by multiple-electrode stimulation. Here, less success (32% vs. 48% for single electrode trials) was achieved in producing percepts that matched the stimulation pattern. Candidate explanations include anatomic and physiological disease of the retina and visual cortex secondary to chronic blindness[17–21]; our ignorance of effective stimulation strategies; interaction of electrical fields from adjacent electrodes; and insufficient learning opportunity for the subjects. Hypothesis 5 eliminates the first consideration because our normal subject performed less well than blind subject 6, which indicates that factors other than blindness hindered our outcomes.

Hypothesis 3 produced the least optimistic results. At best, two-point discrimination may have been achieved by subject 3 with electrode spacing of 600 μm and by subject 5 with electrode spacing of 1960 (but not 2480) μm. Yet, hypothesis 4 revealed relatively good reproducibility. This suggests that seemingly aberrant responses, especially seeing multiple images when one electrode is driven, are not random. Unchanging factors, such as our methods of stimulation or retinal or cortical disease, rather than subjective factors, probably accounted for a substantial fraction of responses that did not match the stimulation pattern.

Hypotheses 6, 7, and 8 explored perceptual effects of various stimulus paradigms. In hypothesis 6, we presumed that higher charges would enlarge the electrical field and hence the percept. Mixed results were obtained. With one analysis, volunteer 6 but not volunteer 5 satisfied the hypothesis. In a second analysis, relatively large differences in charge (median: $\geq$0.55 μC) between two trials yielded larger percepts.

The motivation to test hypothesis 7 derived from Greenberg[22] who reported that longer duration stimuli ($\geq$0.5 ms)

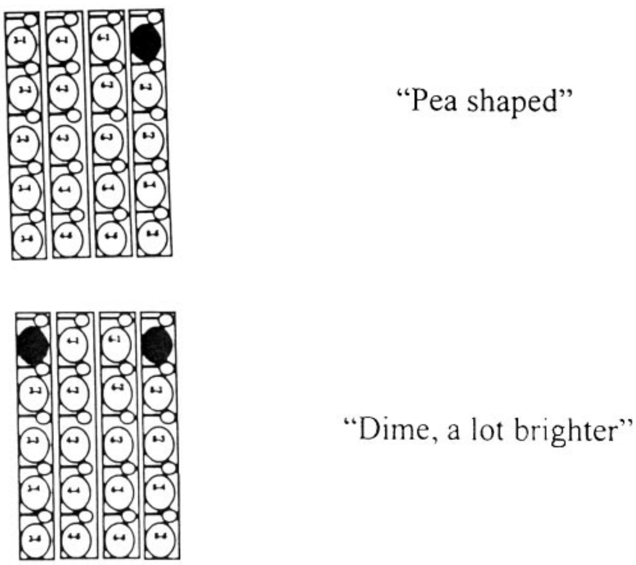

FIGURE 4. Experiment 6. Subject's description of induced perceptions with 250-μA per electrode, 4-ms pulses delivered in monopolar configuration through the darkened electrodes. With an initial stimulus through one electrode (*top*), the subject reported seeing a circle about the size of a pea (if viewed at arm's length). Then, stimulation was added to a second electrode (*bottom*), which produced a larger (and brighter) "dime"-sized image. Location of the array is shown in Figure 6.

preferentially activate bipolar neurons and from Weiland et al.,[9] who suggested that activation of the middle retina produces round percepts. We tested this hypothesis with nearly 100 trials and discovered that round percepts were equally or more frequently reported at durations that were considerably shorter and longer than Greenberg's benchmark (Table 5). Our finding does not discount Greenberg's in vitro observations, for which we have some supportive evidence.[23]

Hypothesis 8 was tested because we assumed that activation of multiple electrodes along axons would be more likely to activate those axons. In experiment 6, this orientation generated elongated percepts, which is consistent with the hypothesis. In experiment 5, the orthogonal orientation generated multiple percepts, which suggests that in this configuration each electrode had a higher probability of producing an individual percept. The differences in outcome between these two patients suggest that stimulation strategies of a prosthesis may have to be customized to achieve desired percepts in individual patients.

By comparison to our results, Humayun et al.[24] reported resolution of 1.5° of visual angle in a patient with light perception vision, despite the variable positioning of electrode(s) that must have occurred with their handheld technique. Moving a needle electrode by hand through the vitreous cavity provides the advantage of being able to survey a wide area of retina for points of low threshold. In five of six experiments, we also used a handheld approach as a screening technique to be

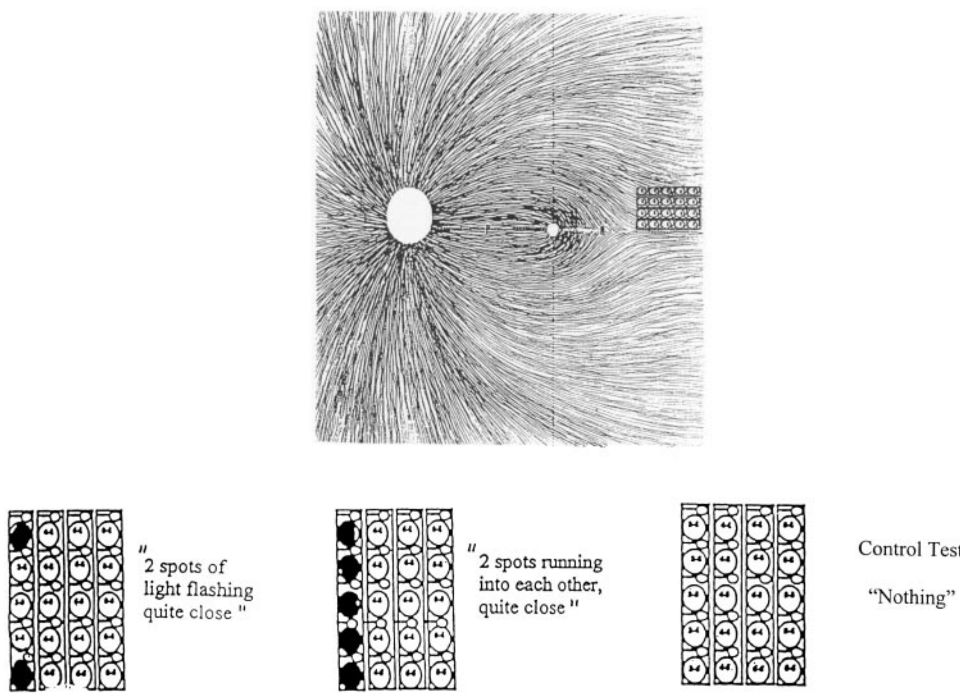

FIGURE 5. Experiment 4. *Top*: schematic of the retina of the left eye to show location of the electrode array in relation to the orientation of retinal ganglion cell axons. The array is scaled to size with respect to the optic nerve head. This experiment was performed on a patient with normal vision. *Bottom*: pattern of electrical stimulation delivered through the electrode array and subject's verbal description of the induced images (in *quotes*) on three consecutive trials. In the first two paradigms (*left*) 250-μA, 2-ms stimulation was delivered through the *darkened* electrodes. Seven of seven trials of either of these two paradigms produced percepts that were judged to be "accurate." In the first example to the *left*, the volunteer reported "two spots" on two of two occasions when the two end electrodes, which had a center-to-center spacing of 2480 μm, were driven. With the middle example, she reported two dots five of five times when all five large electrodes were driven. In two of these cases she stated that the "dots were running into each other," as might be reasonably expected following stimulation through adjacent electrodes. The first result provides an impression of the degree of two-point discrimination obtained by this normal-sighted volunteer. The third paradigm was a control test in which no current was delivered, and the subject reported seeing "nothing." The *large, open circular region* represents the optic nerve head; the *small, open circular region* represents the fovea. (Drawing of retina taken from Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye*: *An Atlas and Textbook*. Philadelphia: WB Saunders; 1971).

Table 4. "Accuracy" of Responses for Paired Trials in which the Second Stimulus of a Pair Used Either an Increase or Decrease in Charge

		Paired Trials Using Increased Charge			Paired Trials Using Decreased Charge			
Subject	**Paired Trials (*n*)**	**(*n*)**	**Median Increase in Charge (μC)**	**% Correct**	**(*n*)**	**Median Decrease in Charge (μC)**	**% Correct**	**Total % Correct**
5	20	12	0.24	8	8	0.25	13	10
6	15	9	0.7	66	6	0.2	33	53

The two stimuli for each paired trial were performed identically, except that the second stimulus of a pair used either an increase or decrease in the amount of charge with respect to the first stimulus. "Accuracy" was defined as reporting (1) an increase in the size of a single percept when the second stimulus of a paired trial used higher charge; or (2) a decrease in the size of a single percept when the second stimulus of a paired trial used lower charge.

certain that volunteers would see percepts in response to electrical stimulation near the retina before the introduction of an electrode array, which required additional surgical steps (see companion paper[14] for more information). At best, we may have achieved resolution of 2.25° to 4.50° with our electrode array in contact with the retina. Further, our patients often did not report percepts that matched the stimulation pattern and frequently described multiple percepts when one electrode was driven, neither of which was reported by Humayun et al.[24] The results from normal volunteers are equally disparate. The two subjects in Weiland et al.[9] reported football-sized, dark percepts every time the normal retina was stimulated near threshold.[9] Over 43 trials, our normal-sighted patient never reported darkness, and all percepts were considerably smaller than a football. Use of different stimulation frequencies and other methodological differences, insofar as they can be gleaned, may account for some differences in outcomes.

In summary, volunteers who have been legally blind for many years can see percepts induced by electrical stimulation of the retina. The single percepts were relatively small, which offers hope of generating a montage of such percepts to create useful images. However, the form of percepts, especially with multielectrode stimulation, often did not match the stimulation pattern. The lack of a better outcome in our normal-sighted patient suggests that retinal degeneration alone does not explain the limited results in our blind patients and emphasizes the need to learn effective stimulation methods. Nonetheless, even simple images, if reproducible, could help severely blind patients.

Acute testing provides useful insights into strategies for creating vision, but probably underestimates what could be achieved with permanently implanted devices, which offer opportunity for learning (by patients and researchers) and neural plasticity. Indeed, Humayun et al.[25] have reported a learning effect for a patient who had received a chronic implant.

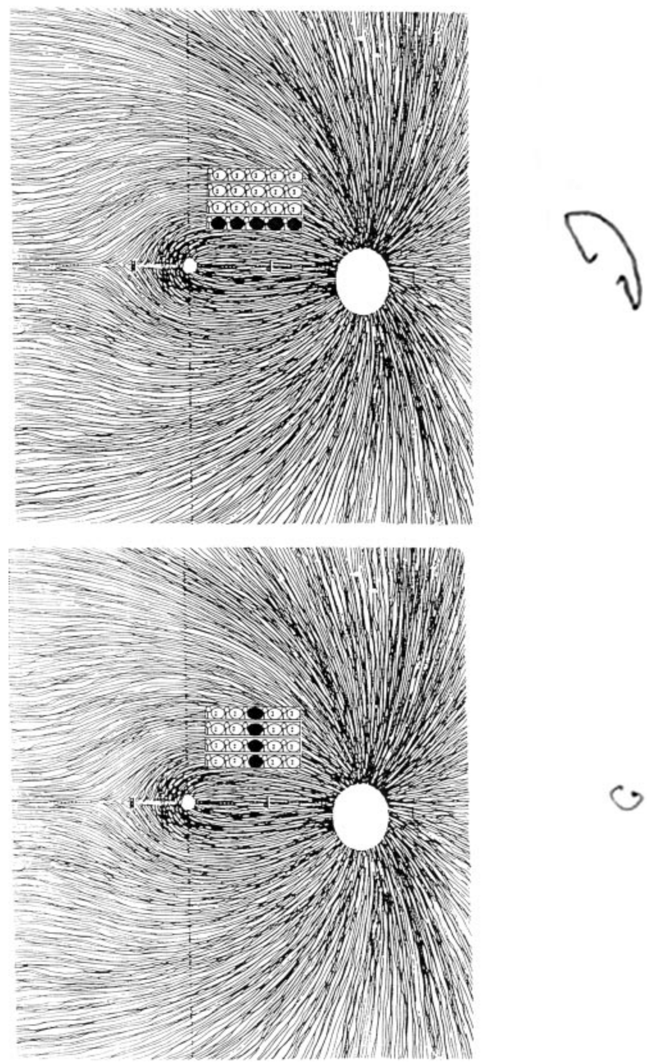

Figure 6. Experiment 6. *Left*: Location of the electrode array with respect to the orientation of retinal ganglion cell axons of the right eye. *Right*: Subject's drawing of the induced perceptions. The first trial (*top*) drove electrodes that were oriented in parallel to the axons, which yielded a banana-shaped percept. The orientation of the banana, with the lower end tilted to the right, matched an expectation based on activation of axons under the array that were extensions of ganglion cell bodies that were distributed along a curved line between the array and the horizontal raphe. The second trial (*bottom*), which drove electrodes that were oriented perpendicular to the axons, yielded a percept of a circular object. All stimuli were performed with 250-μA per electrode, 4-ms pulses delivered in monopolar configuration through the darkened electrodes. The *large, open circular regions* represent the optic nerve head; the *small, open circular regions* represent the fovea. (Drawing of retina taken from Hogan MJ, Alvarado JA, Weddell JE. *Histology of the Human Eye: An Atlas and Textbook.* Philadelphia: WB Saunders; 1971).

Table 5. Perceptual Appearance for Volunteers 4, 5, and 6 in Relation to Stimulus Duration

	0.25 msec	**1 ms**	**2 ms**	**4 ms**	**16 ms**	**Total Trials Across All Durations (*n*)**
Round	4	9	5	49	10	77
Elongated	4	3	0	15	9	31

All stimuli were given through a single electrode on a microfabricated array. Only trials that produced a single percept were considered for this analysis. The numbers in each cell represent the number of trials performed with each stimulus duration. Stimulus duration is for the negative pulse of a biphasic pair.

Acknowledgments

Acknowledgments are as stated in the companion article.

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