



Residual photoreceptors affect the response of a degenerate retina to electrical stimulation

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Photovoltaic subretinal prosthesis can restore central vision in patients blinded by age-related macular degeneration with letter acuity matching its 100 μm pixel size. Improving resolution requires smaller pixels, but to still reach the target neurons, electric field should be less confined. However, wide-spreading field may engage adjacent photoreceptors and alter the visual perception. We studied the effects of residual photoreceptors on retinal responses to electrical stimulation using monopolar and bipolar photovoltaic arrays implanted subretinally in Long Evans rats with local photoreceptor loss, and compared that to RCS rats lacking all photoreceptors. Patterned retinal activation (880 nm, 0.5 to 10 ms) was assessed using visually evoked potentials under scotopic and photopic conditions, with and without the intravitreal injection of neurotransmitter blockers. Results were analyzed using a computational model of photoreceptor activation by various electric field configurations. We observed two mechanisms of photoreceptors engagement in electrical activation of the degenerate retina: 1) Dark-adapted photoreceptors near the implant can be simulated directly by a negative electric potential of the common return electrode along the edge of the array. 2) Light-adapted photoreceptors can reduce the stimulation threshold of bipolar cells within about 100 μm from the implant's edge. Both effects may lead to reduced perceptual uniformity. Bipolar pixels with local return electrodes generate better confined electric fields than monopolar arrays and thus are less affected by the nearby photoreceptors. However, even such implants should be placed a few hundred micrometers from the edge of scotoma to minimize the unintended percepts.

restoration of sight | retinal prosthesis | electrical stimulation | visually evoked potentials | retinal degeneration

Patients afflicted by retinal degenerative diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP), experience loss of vision due to death of photoreceptors (1). Retinal prostheses aim at restoring visual function in such patients by stimulating the remaining interneurons. In patients with AMD, photoreceptors in the central macula, which is responsible for high-resolution vision, are lost, but the inner retinal neurons are largely preserved. Subretinal prostheses provide central vision by stimulating these interneurons, while not affecting the peripheral healthy retina.

One such device, the PRIMA system, provides prosthetic vision to AMD patients with letter acuity up to 20/420, matching the sampling limit of its 100 μm pixels (2). With the current bipolar design of photovoltaic arrays (Fig. 1 *A* and *B*), where active electrodes are surrounded by local returns in each pixel, reducing the pixel size decreases the field penetration into tissue, thus precluding retinal stimulation with much smaller pixels (3). Monopolar arrays (Fig. 1 *C* and *D*) having a global return electrode along the edge of the implant provide deeper penetration of electric field, enabling the use of smaller pixels, down to 20 μm , geometrically corresponding to 20/80 acuity in the human eye (4).

In this study, we explore the effect of the residual photoreceptors outside the implant on its electrical stimulation. For this purpose, we implanted Long-Evans (LE) rats subretinally (between the retina and the retinal pigmented epithelium) with the monopolar and bipolar photovoltaic arrays, which resulted in degeneration of photoreceptors directly above the implant, while being preserved outside the device (5). This condition resembles local retinal degeneration in AMD. To examine the role of photoreceptors in subretinal stimulation, we measured the stimulation thresholds with and without the mGluR6 agonist L-AP4 (L-2-amino-4-phosphonobutyric acid), which blocks the ON pathway from photoreceptors—by far the prevailing pathway in the rod-dominant rat retina (6, 7). We compared these results to similar previous measurements in Royal College of Surgeons (RCS) rats after a complete degeneration of all photoreceptors.

Significance

Photovoltaic subretinal prosthesis can restore form vision in patients blinded by age-related macular degeneration. However, residual photoreceptors surrounding the degenerate area can substantially alter the responses of the inner retinal neurons to electrical stimulation, leading to nonuniform prosthetic vision. Understanding the mechanisms of electrical stimulation of various retinal neurons and their interactions via retinal neural network is critical for providing high quality prosthetic vision in patients blinded by macular degeneration. Our findings provide mechanistic insight into these interactions and establish design principles for next-generation high-resolution retinal implants, including electrode configuration and implant placement strategies, to maximize functional vision while minimizing the unintended perceptual artifacts.

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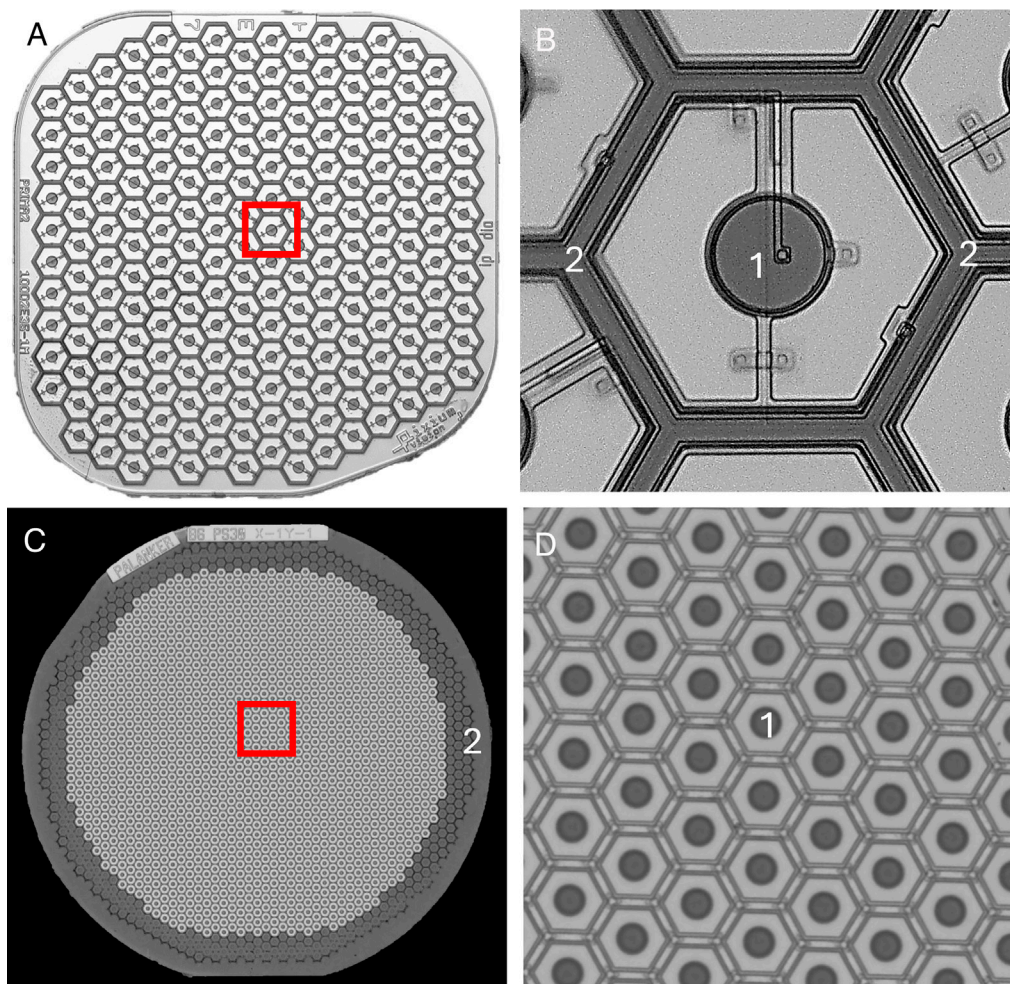


Fig. 1. 1.5 mm wide photovoltaic implants described in this study. (A) Implant with bipolar electrode configuration. (B) Higher magnification view of 100 μm pixels with an active central electrode (1) and a mesh of local returns (2). (C) Monopolar implant with 20 μm pixels with a global surrounding return electrode (2). (D) Higher magnification view illustrating active electrodes exposed to electrolyte (1) and local returns within pixels, connected in a common mesh, but insulated from electrolyte by SiC/SiO₂ coating, except for the exposed ring electrode along the implant's edge (2).

We also modeled both healthy and partially degenerate photoreceptors in the software NEURON to assess their effect on electrical stimulation above and around the devices with global and local returns.

Results

Stimulation Thresholds in LE and RCS Rats. Dependence of the stimulation threshold on pulse duration with monopolar array in Long-Evans (LE) rats under photopic conditions ($n = 4$) is shown in Fig. 2A (black). With 10 ms pulses, stimulation threshold was $0.024 \pm 0.007 \text{ mW/mm}^2$, which is nearly three times lower than the 0.060 mW/mm^2 previously measured in RCS rats (Fig. 2A, magenta) (4). The 3.2 ms chronaxie of the Weiss equation-fitted Strength-Duration (S-D) curve indicates activation of the bipolar cells (BCs) (8, 9), like in RCS rats (3). The 0.024 mW/mm^2 irradiance corresponds to a voltage drop of about 4 mV (obtained from modeled electric fields) across bipolar cells—much lower than in our previous studies in RCS rats, where the threshold at 10 ms was approximately 11 mV (3).

These results suggest that the threshold of bipolar cells may be reduced due to input from adjacent photoreceptors. Additionally, negative potential of the common return electrode along the edge of a monopolar implant may hyperpolarize the adjacent photoreceptors (Fig. 3C) and thereby elicit a visually evoked potential (VEP).

To check the latter, we dark-adapted the animals ($n = 3$) to increase the photoreceptors sensitivity. In the dark, the neurotransmitter release rate of fully depolarized photoreceptors (at around -40 mV) reaches its maximum, so any hyperpolarization results in a graded reduction of the glutamate release (10, 11). The rod-dominated rat retina in dark-adapted conditions can respond to photon flux as low as 1 photon per photoreceptor per second, which corresponds to hyperpolarization by about 1 mV (12, 13). Dark adaptation significantly changed the strength-duration curve (Fig. 2A, red). At 10 ms, the threshold decreased to $0.014 \pm 0.001 \text{ mW/mm}^2$, while at shorter pulses it increased. This new S-D curve did not fit the Weiss' equation typical for other neurons (9), suggesting that different types of cells are activated at different pulse durations. We observed similar behavior in earlier ex-vivo studies using patch clamp recording (9), where photoreceptors dominated the retinal response at pulse durations exceeding 10 ms. This trend is also consistent with previous studies demonstrating that high frequency sinusoidal electrical stimuli (25 and 100 Hz) activate bipolar and ganglion cells, while lower frequency stimuli (5 and 10 Hz) activate photoreceptors (14).

Interestingly, bleaching the photoreceptors with 20,000 lx of white light for 3 min ($n = 4$) reduced the VEP amplitude above the threshold (at 0.2 mW/mm^2 at 10 ms, Fig. 2B)—from the mean SNR of 2.59 ± 0.49 to 1.31 ± 0.25 . This observation is consistent with our previous studies of the interactions between the peripheral retina

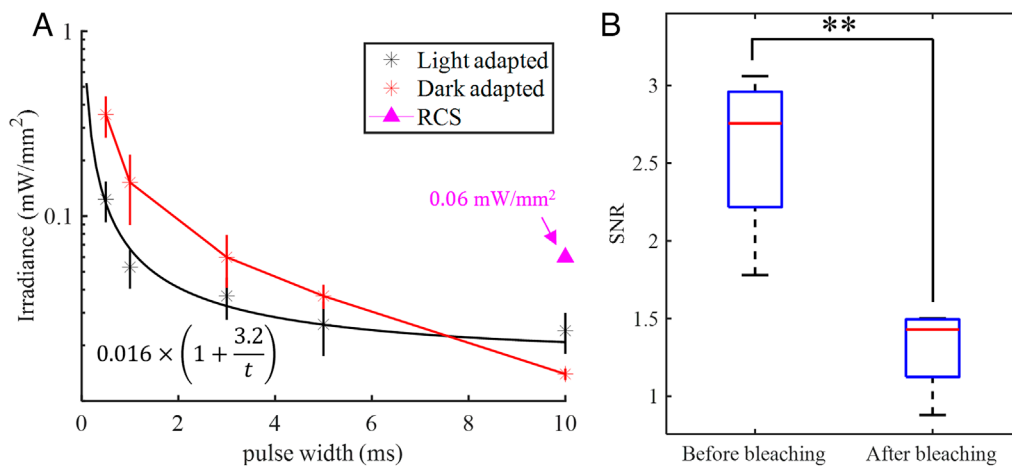


Fig. 2. (A) Strength duration (S-D) curves for monopolar implant with 20 μm pixels: irradiance thresholds as a function of pulse duration in LE rats >16 wk post-op, under different lighting conditions. Under room lighting, the rheobase is 0.016 mW/mm^2 (black), much lower than previously published [4, 6] with RCS rats (magenta), but 3.2 ms chronaxie is still in the range typical for bipolar cells. Dark adaptation changes the S-D curve, no longer fitting the Weiss equation, revealing direct stimulation of photoreceptors (red). (B) Exposure of PRs to 20,000 lx of white light for 3 min reduces the VEP amplitude ($n = 4$, P -value = 0.0069) at suprathreshold stimulation (0.2 mW/mm^2) from 2.59 ± 0.49 before bleaching to 1.31 ± 0.25 after bleaching.

and central prosthetic vision (15, 16). Remarkably, these observations demonstrate two opposite effects of adjacent photoreceptors on electrical stimulation of bipolar cells: at room lighting, they reduced the electrical stimulation threshold compared to the degenerate retina, and yet after strong bleaching, they attenuate the magnitude of electrical response.

With bipolar pixel arrays (PRIMA) (17) illuminated in the center (Fig. 4), stimulation threshold was much higher than with monopolar pixel arrays—0.2 mW/mm^2 at 10 ms pulse duration for both the LE (Fig. 4, black) ($n = 14$) and in RCS rats from a previous study (Fig. 4, magenta) (3). Under dark adaptation ($n = 3$), stimulation thresholds with bipolar pixels did not change compared to photopic conditions (Fig. 4, red). This finding indicates that, unlike monopolar arrays that have strong negative potential along the return electrode at the edge of the implants (Fig. 1C), bipolar implants with an evenly distributed mesh of return electrodes (Fig. 1B) do not stimulate even dark-adapted photoreceptors. This also indicates that since the thresholds are the same in light and dark-adapted conditions, photoreceptors (PRs) do not affect the stimulation thresholds of BCs like in monopolar pixel arrays.

However, when one side of the implant was illuminated ($n = 3$), the threshold in LE rats at room lighting decreased by about a factor of 3 to 0.067 mW/mm^2 (Fig. 4, blue), revealing the influence of photoreceptors near the edge of the implant. In the dark ($n = 4$), the threshold increased slightly (Fig. 4, dashed line). Two effects can happen with the beam shifted to the edge: a) bipolar cells at the edge experience stronger electrical stimulation and their response becomes dominant in the population of cells above the implant. Photoreceptors under ambient lighting depolarize the ON BCs near the edge and reduce their stimulation threshold. b) With one side of the implant illuminated, stronger negative potential builds up on the other (dark) part of the implant, where return electrodes in nonilluminated pixels attract the return current, like the global return electrode in monopolar arrays. This negative potential hyperpolarizes the adjacent photoreceptors and elicits their response with longer pulses (Fig. 4, dashed line), albeit not as strongly as with monopolar implants (Fig. 2A, red line).

Effect of Neurotransmitter Blockers on Stimulation. To further assess involvement of photoreceptors, we recorded VEP after intravitreal injection of L-AP4 ($n = 3$), the mGluR6 glutamate receptor agonist, which blocks the rod and ON cone inputs to

bipolar cells by fully activating the glutamate receptors, which results in hyperpolarized ON bipolar cells (equivalent of dark conditions) (18, 19). With monopolar implants, stimulation threshold at 10 ms increased to $0.067 \pm 0.005 \text{ mW}/\text{mm}^2$ (Fig. 5A, green), closely matching the threshold in RCS rats: 0.060 mW/mm^2 (Fig. 5A, magenta) (4). Fitting the data with the Weiss equation yielded the chronaxie of 2.9 ms—in the range for bipolar cells stimulation [1.8 to 3.5 ms (3, 8)]. This indicates that stimulation with the monopolar implant originates in bipolar cells, and after application of L-AP4, their resting potential is lower (and therefore the threshold is about 4 times higher) than when illuminated photoreceptors outside the implant provide a depolarizing input (Fig. 5A—green vs. black line). Additionally, injection of the cocktail that blocks all synaptic transmission in the retina completely abolished the VEP signal at this irradiance, further indicating that the thresholds are driven by bipolar cells.

Implants with local returns under room lighting exhibited similar thresholds in light and dark conditions (0.24 and 0.23 mW/mm^2 at 10 ms, respectively), as well as with L-AP4 (0.22 mW/mm^2 , Fig. 5B), indicating that, unlike with monopolar arrays, photoreceptors do not affect the bipolar cells threshold with bipolar devices in our illumination settings. This is likely due to nonuniform illumination in our setup which impacts the electric field from bipolar pixels, unlike monopolar arrays which create much more uniform field due to strong crosstalk between neighboring pixels, as shown in Fig. 5C–F. As shown in Fig. 4 (blue vs. black line), the nonuniform illumination resulted in a stimulation threshold decrease by about a factor of 3 when the edge of the bipolar pixels array was illuminated. This measurement demonstrates that the stimulation threshold is defined by bipolar cells in the strongest field area, and when this area is close to the implant's edge, illuminated photoreceptors outside the implant reduce the stimulation threshold by depolarizing the ON bipolar cells under room lighting conditions.

Modeling the Stimulation of Photoreceptors and Bipolar Cells.

To examine the electric potential drop across retinal neurons, we computed the electric field generated by photovoltaic arrays in electrolyte [1,000 Ωcm resistivity (8)] near the implant (Fig. 5C–F). We adopted the “voltmeter approximation,” where the voltage difference between the somatic and the axonal ends of the bipolar cells defines the stimulus strength (8), with

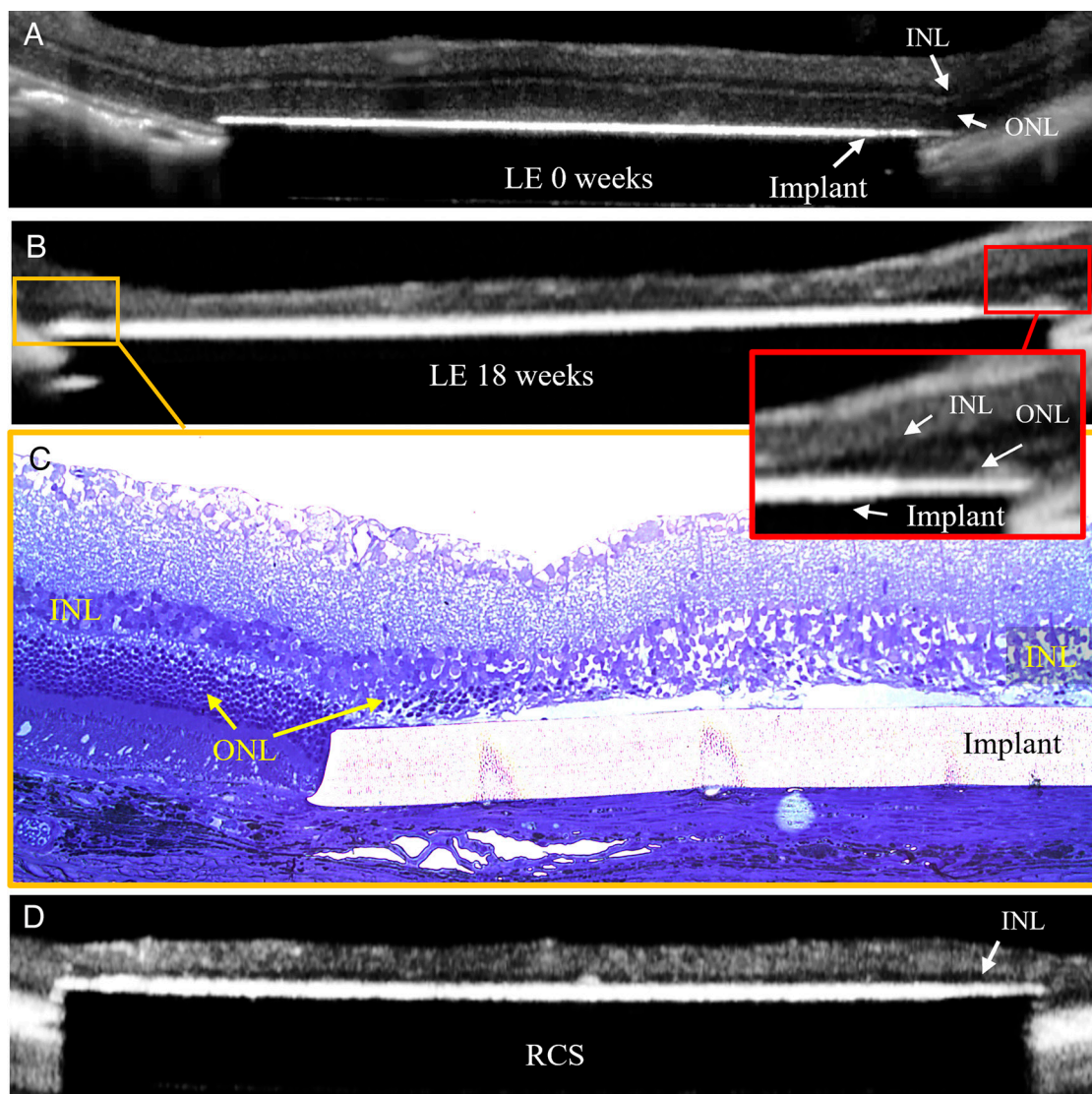


Fig. 3. (A) OCT B-scan of the subretinal implant in LE rat at day 0. (B) ONL above the implant completely disappears after 8 wk. (C) Histology demonstrates remnant photoreceptor nuclei still present above the edge of the implant 18 wk post-op. (D) OCT B-scan of the subretinal implant in RCS rat.

bipolar cells being 50 μm long (3). With monopolar arrays at stimulation threshold of $0.024 \text{ mW}/\text{mm}^2$, the maximum voltage drop across bipolar cells (between 1 and 50 μm above the implant) was 1.7 mV, and with L-AP4 injection ($0.067 \text{ mW}/\text{mm}^2$)–5.1 mV (Fig. 5E). With bipolar arrays, there was no observable difference in the thresholds with and without L-AP4 ($0.24 \text{ mW}/\text{mm}^2$), corresponding to a maximum of 11.8 mV drop across bipolar cells. This is approximately 2.3 times that of monopolar arrays (Fig. 5F). However, the average electric potential drop over the pixel area was 4.7 mV for both monopolar and bipolar arrays, indicating that VEP represents response of a population of cells, rather than just a few neurons located in the strongest field.

In LE rats, photoreceptors are preserved outside the implant, and cell bodies without the outer segments (OS) remain above implant near the edge (Fig. 3B). To assess the photoreceptors' response and the lateral extent of their effect on retinal activation, we computed the electric field around the implant (Fig. 6). Photoreceptors were placed at 20 to 25 μm increments between 500 μm and 1,000 μm from the implant's center (edge of the implant is at 750 μm). Healthy photoreceptors are shown outside the implant while photoreceptor nuclei are preserved above the implant up to 100 μm from its edge (Fig. 6C).

The maximum hyperpolarization of the photoreceptor terminals occurred within the negative potential zone at the edge of the monopolar implant (Fig. 6A). At stimulation threshold of $0.020 \text{ mW}/\text{mm}^2$, this was -1.5 mV in healthy photoreceptors above the implant (Fig. 6B, blue), and by -0.45 mV in degenerate photoreceptors (Fig. 6B, red). This is within the range of hyperpolarization of dark adapted rod photoreceptors in response to single photons per second: $-0.64 \pm 0.48 \text{ mV}$ (13). At $0.02 \text{ mW}/\text{mm}^2$ irradiance and 10 ms pulse width, the maximum voltage drop across the degenerate photoreceptor cell body was -1.6 mV (Fig. 6D). These findings indicate that retinal activation in the dark at threshold ($0.014 \text{ mW}/\text{mm}^2$ at 10 ms) lower than that of direct stimulation of bipolar cells ($0.067 \text{ mW}/\text{mm}^2$) occurs due to residual photoreceptors in the area of negative potential near the peripheral return electrode of monopolar implants (red curve in Fig. 5A). In light-adapted conditions, however, bipolar cells are depolarized due to the influence of photoreceptors outside the implant, and their stimulation threshold decreases to $0.024 \text{ mW}/\text{mm}^2$ at 10 ms (black curve in Fig. 5A). Chronaxie of the S-D curve in light-adapted conditions (3.2 ms) indicates stimulation of bipolar cells rather than direct activation of PRs.

With bipolar photovoltaic arrays, much tighter confinement of electric field caused by return electrodes around each pixel

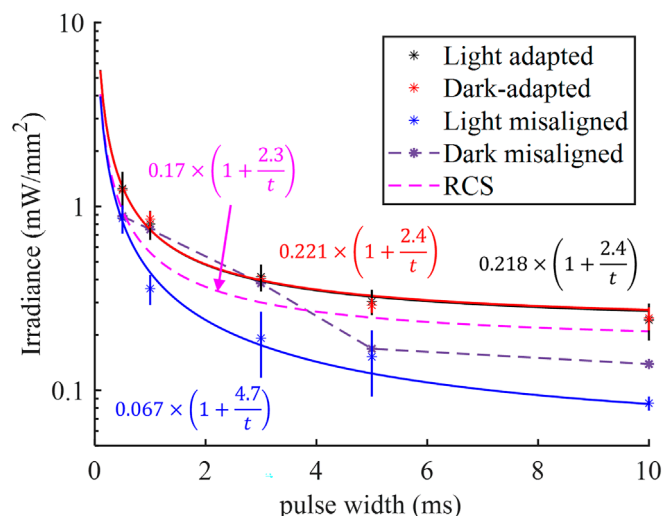


Fig. 4. Strength duration (S-D) curves with PRIMA implants: irradiance thresholds as a function of pulse duration in LE rats >16 wk post-op, under different lighting conditions. The S-D curves did not change between light- (black) and dark-adapted (red) states, with a rheobase of 0.22 mW/mm² and a chronaxie of 2.4 ms. Illuminating the edge of the PRIMA implant in light-adapted retina by misaligning the beam, reduces the rheobase to 0.067 mW/mm² (blue), by a factor of 3 from stimulation at the center (black). Dark-adapted retina under misaligned NIR beam (purple, dashed) exhibits reduced thresholds only at 5 and 10 ms, indicating direct stimulation of photoreceptors at longer pulses by negative potential near the local returns. At shorter pulses (0.5, 1, and 3 ms), stimulation is dominated by BCs, and the thresholds are similar to those in RCS rats (shown from previous publication [3] for comparison, magenta).

(Fig. 1B) resulted in much smaller hyperpolarization of healthy photoreceptors outside the device at stimulation threshold (Fig. 6A, blue dashed)—a maximum of -0.5 mV at 0.20 mW/mm². This is approximately a third of the value observed with monopolar implants at their threshold (0.020 mW/mm²) (Fig. 6A, blue asterisks). Degenerate photoreceptors polarize in the electric field of bipolar arrays even less (Fig. 6A, red dashed). Distributed return electrodes in bipolar arrays provide a tight field confinement which allows avoiding the activation of photoreceptors adjacent to the implant. However, with a very nonuniform illumination (e.g., a beam shifted to the edge), such implant may still induce direct stimulation of photoreceptors in the dark, as shown in Fig. 4 (purple, dashed).

Discussion

Surrounding Photoreceptors Affect the Electrical Stimulation Threshold. One of the challenges with bipolar photovoltaic arrays (PRIMA) is that electric field is so constrained by the local return electrodes that with pixels much smaller than 100 μ m, it cannot reach the bipolar cells in the inner nuclear layer (INL) (3). This issue could be mitigated using an array of monopolar pixels. Such devices provide deeper penetrating electric field, albeit with reduced contrast (20). However, this study identified a potential problem: in the dark, photoreceptors can be stimulated directly with 5 to 10 ms pulses by negative potential around a common return electrode near the edge of the implant. This suggests that if the device is placed at the border of a scotoma (2), healthy photoreceptors, or even partially degenerated photoreceptors that still respond to light due to opsins localized in the ciliary membrane and inner segment (21), may skew the percepts near the implant's edge. Above the implant, photoreceptor nuclei are preserved up to 100 μ m from its edge. Modeling shows (Fig. 6A and B) that they can be electrically activated, and blocking

their synapses with L-AP4 can affect the VEP response, as was experimentally observed (Fig. 5A).

Photovoltaic prosthesis PRIMA, currently used in clinical trials, has bipolar pixels and therefore much smaller negative potential near its edges than that with monopolar arrays (Fig. 5C and D). Therefore, it is not expected to stimulate the adjacent photoreceptors under uniform illumination, and PRIMA patients indeed did not report perceptions of a brighter edge of the implant. Future implant designs should therefore be bipolar, with better penetration of electric field into the retina achieved with 3-D electrodes (22) rather than with the field summation from monopolar pixels (20).

Another effect of the remnant photoreceptors surrounding the implant may influence the threshold of bipolar cells near the edge of the device even with bipolar arrays—depolarization of ON BCs under ambient lighting. To avoid the potential influence of remaining photoreceptors on prosthetic vision, implant should be placed at least 150 μ m from the healthy retina.

The stimulation threshold of photoreceptors drops with increasing pulse width, with no observable saturation in the range of this study—up to 10 ms. Our previous studies demonstrated a similar trend continuing at least to 100 ms (9). Other studies have also reported that subretinal stimulation of degenerate photoreceptors can elicit retinal responses (23). Incredibly low stimulation thresholds of photoreceptors at long exposures may explain the low irradiance thresholds observed with other subretinal optoelectronic implants (24).

Potential Mechanisms of Signal Propagation and Associated Thresholds. Under photopic conditions, the recorded threshold for monopolar implants in LE rats was about 3 to 4 times lower at all pulse widths compared to that with L-AP4 injection (Fig. 5A, black vs. green). Surprisingly, under dark-adapted conditions, stimulation threshold increased for pulse durations <8 ms (Fig. 5A, red) but decreased for longer pulses. It indicates that stimulation in scotopic conditions may be driven by a combination of photoreceptors and bipolar cells. Photoreceptors are the most sensitive in the dark, when they maintain a membrane potential of approximately -40 mV (25), resulting in ON bipolar cells maintaining a membrane potential of -41 mV (26), about 2.5 mV below the synaptic threshold of ON bipolar cells to release glutamate onto ON retinal ganglion cells (RGCs), when calcium channels open at -38.5 mV (27). Similar state occurs with L-AP4 (mGluR6 agonist) injection. Under photopic conditions, the ON bipolar cells are depolarized up to 10 mV by photoreceptors outside the implant and hence exhibit lower electric threshold (black S-D curve in Fig. 5A). Dark-adapted thresholds reflect a transition from bipolar cells-mediated stimulation with shorter pulses (<1 ms) to photoreceptors-mediated response with longer pulses (Fig. 5A, red). L-AP4 injection (green line) reveals the threshold for stimulation of bipolar cells alone, without any contribution from photoreceptors.

Bipolar cells' threshold could be influenced by the remaining photoreceptors surrounding the implant though either the AII amacrine network (28) or through direct input from degenerated PRs (PRs lacking outer segments) above the edge of the device. As rod bipolar cells directly communicate to AII cells, they could laterally transmit signals from outside the implant to bipolar cells above the implant, thereby affecting their threshold (Fig. 7A) within the reach of AII cells (about 100 μ m) (29). Degenerated PRs can also receive signals from adjacent healthy PRs through gap junctions located in the cone pedicles and rod spherules (30, 31), which are still preserved in local degeneration. This way, degenerate PRs can be hyperpolarized by illuminated healthy

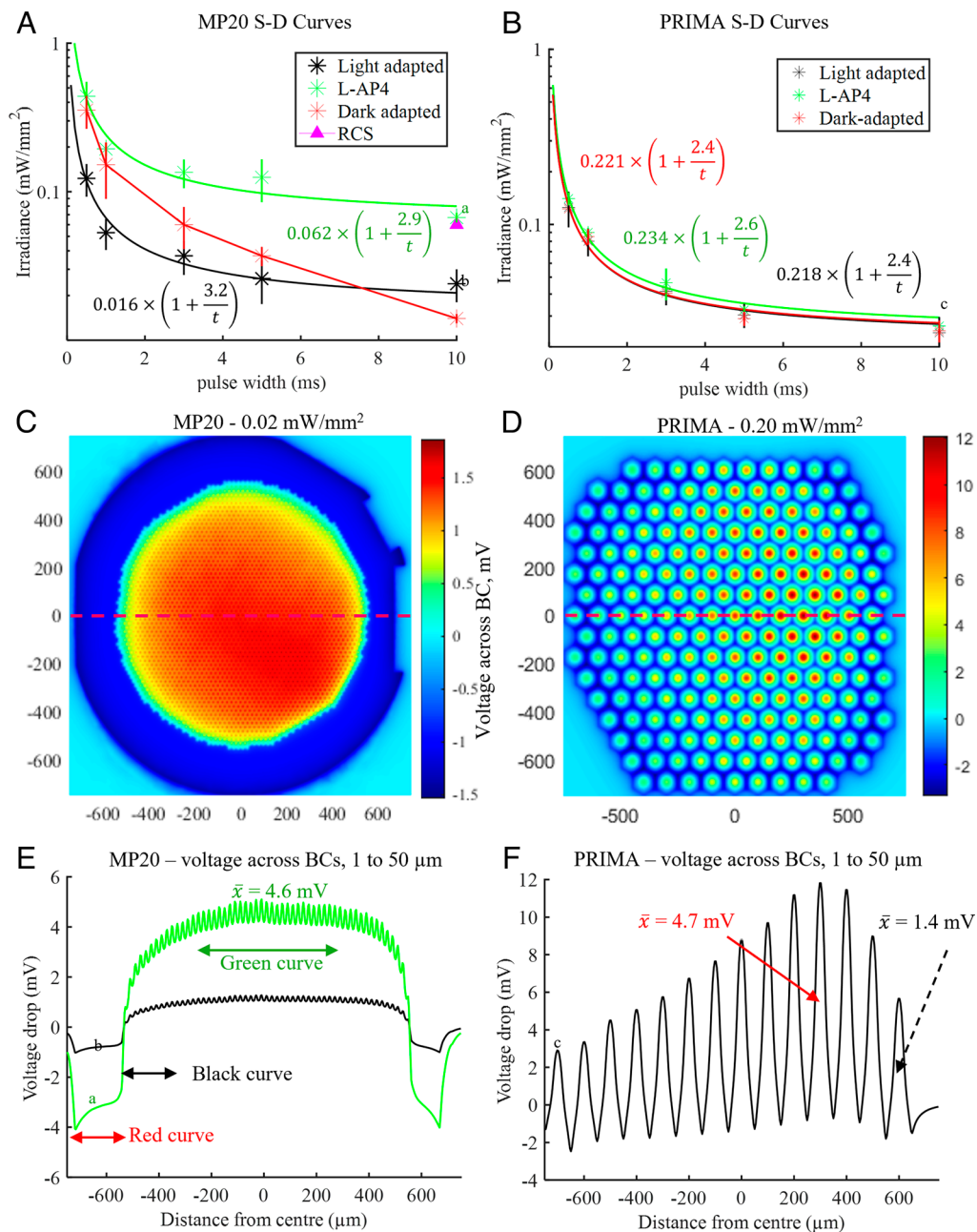


Fig. 5. (A) At room lighting, rheobase with 20 μm monopolar pixel arrays is 0.016 mW/mm² (black). Dark-adaptation changes the shape of S-D curve, no longer fitting Weiss equation and thereby revealing stimulation of PRs (red) by longer pulses. Intravitreal injection of L-AP4 (green) increased the rheobase to 0.06 mW/mm² matching the threshold previously recorded in RCS rats (magenta). (B) With bipolar implants (PRIMA), thresholds with and without PR blocker L-AP4 are the same, indicating that they are not affected by residual PRs outside the implant. Dark adaptation did not change the response either (red). (C) Electric field across bipolar cells at 0.02 mW/mm² (50 μm) under monopolar configuration. Implant diameter is 1.5 mm. (D) Electric potential across bipolar cells at 0.20 mW/mm² (50 μm above the PRIMA implant). (E) Voltage drop across BCs (from 1 to 50 μm) above the implant at 0.06 mW/mm² (green, threshold at 10 ms in A, labeled "a") and 0.02 mW/mm² (black, threshold at 10 ms in A, labeled "b"). Average voltage drop over 100 μm width is 4.6 mV. Arrows show regions responsible for the thresholds in A. (F) Voltage drop across BCs (from 1 to 50 μm) above the implant at 0.20 mW/mm² (black, threshold at 10 ms in B, labeled "c") and the average across a 100 μm pixel (red*). Average voltage drop across 100 μm width is 4.7 mV for a pixel in the center and 1.4 mV for a pixel on the edge of the implant.

photoreceptors and affect the membrane potential of ON BCs near the edge (Fig. 7B) resulting in reduced thresholds. Direct input from healthy PRs to BCs above the implant is unlikely as rod bipolar cells have an average receptive field of 67 μm , and cone bipolars have an average receptive field of 43 μm (32), which is less than the distance from the device edge to its photovoltaic pixels separated by the 250 μm wide common return electrode in monopolar arrays. PRs lacking outer segments (also called dormant) above the implant's edge may also be hyperpolarized in the negative electric field, like healthy photoreceptors outside the implant. If those dormant PRs retained some light sensitivity, they

may also contribute to modulation of retinal response by ambient light, like healthy photoreceptors outside the implant.

Additionally, we found that strong bleaching (overhyperpolarizing) of PRs decreases the VEP amplitude in response to electrical stimulation (Fig. 2B), which is consistent with previous findings (15, 16). Attenuation of the retinal response to electrical stimulation in this case could be due to GABA inhibition of ON ganglion cells via horizontal and amacrine cells. Additionally, PRs strongly hyperpolarized by bleaching cannot be hyperpolarized much further by negative electric field near the common return electrode. Similarly, ON BCs strongly depolarized under bleaching

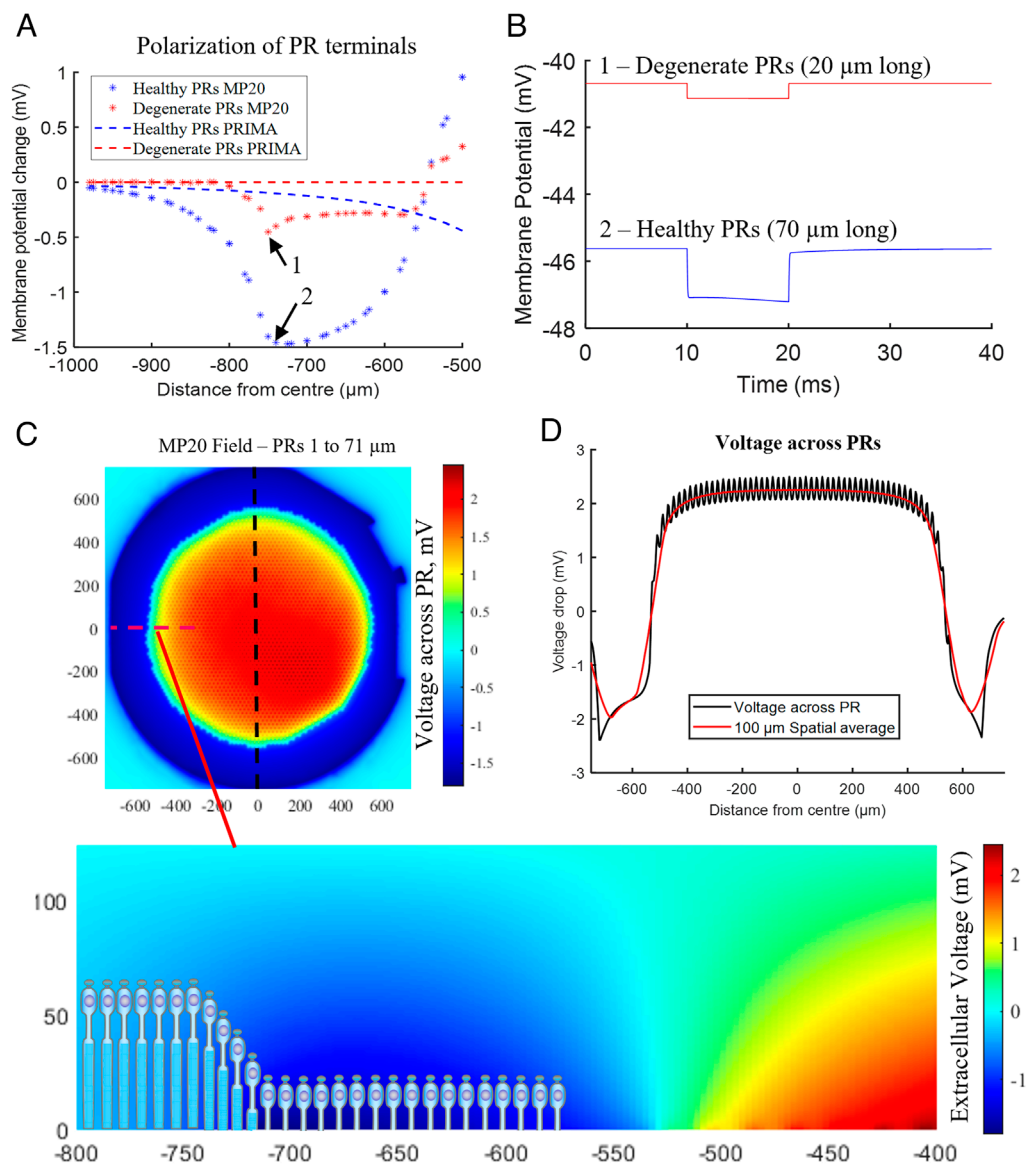


Fig. 6. NEURON model of PR response under monopolar and bipolar electrode configuration. (A) Maximum membrane potential change reveals thresholds for both degenerate PRs (0.5 mV hyperpolarization) and healthy PRs (1.5 mV hyperpolarization). Healthy PRs near bipolar implant do not reach the threshold due to very constrained electric field by local return electrodes. (B) Polarization of the degenerate and healthy photoreceptors at the edge of the implant, where the electric potential change is at the maximum. (C) Electric potential near monopolar implant at 0.02 mW/mm². (D) Voltage drop across PRs (from 1 to 70 μm height) demonstrating maximum hyperpolarization near the edge of the implant (along dashed line in C). Average voltage across five pixels (100 μm) shown in red.

cannot be stimulated much further by positive electric field, thus reducing the VEP response at the same irradiance. This suggests that strong surrounding natural illumination can attenuate prosthetic vision by decreasing the retinal response, while a weak illumination may reduce the stimulation threshold.

Different Thresholds with Monopolar and Bipolar Arrays. Eliminating the effect of photoreceptors by L-AP4 injection in LE rats or using RCS rats, demonstrates a major difference between the stimulation thresholds of bipolar cells with monopolar and bipolar arrays (0.06 mW/mm² vs. 0.20 mW/mm² at 10 ms, Fig. 5A and B). Voltage drop across bipolar cells at their respective thresholds is shown in Fig. 5C–F. As VEP is a population response and RGC response is the weighted sum of their input from BCs above threshold (in this case a weighted sum of the positive step of potential across BCs), we also calculated the average voltage across BCs. For bipolar array, where there are negative areas in

each pixel, only positive voltages (which depolarize BCs) were used to calculate the average. At the threshold irradiances, the average potential drop across BCs over the illuminated monopolar array was 4.6 mV (Fig. 5E, green), very similar to that over bipolar array: 4.7 mV (Fig. 5F, red). The peak voltage with bipolar arrays at 10 ms pulse width was 11.8 mV (Fig. 5F), consistent with our previous findings of approximately 11 mV (3).

A much lower stimulation threshold at photopic conditions than with L-AP4 for monopolar arrays (0.024 mW/mm² vs. 0.067 mW/mm² at 10 ms, Fig. 5A) can be explained by increased resting potential of ON BCs at the edge of the implant due to photoreceptors input (19). As discussed above, the maximum lateral range of photoreceptors' influence on BCs in the rat retina is 90 μm (33), which is equivalent to 4.5 monopolar pixels of 20 μm, or less than one 100 μm bipolar pixel. At this irradiance, BCs directly above the active monopolar pixels on the edge experience an average 1.6 mV drop (Fig. 5E, black), which is sufficient to elicit a

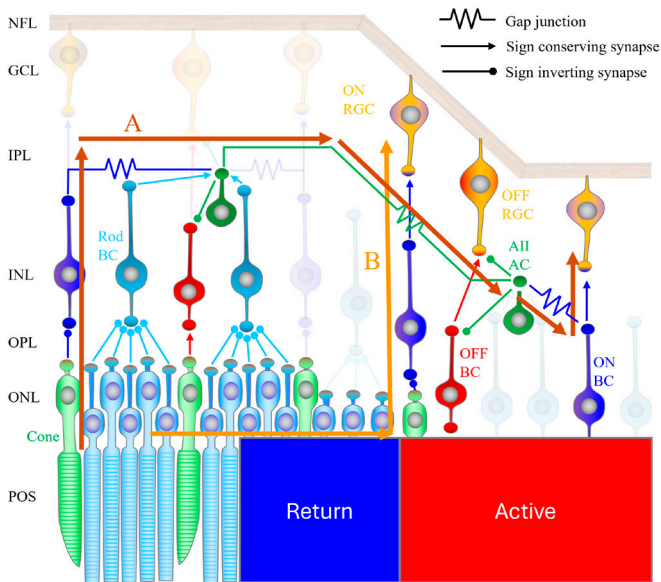


Fig. 7. Possible pathways for dark-adapted photoreceptors around the implant to affect the thresholds above the implant. (A) Rod photoreceptors (light blue) send signals to rod BCs, which then depolarize AII ACs (dark green). Additionally, cones (light green) are connected to ON BCs (dark blue) which are electrically coupled to AII ACs. ACs form a network of coupled cells which spread signals laterally, affecting the membrane potential of BCs and RGCs away from the PRs location. (B) Rod and cone PRs form a network of electrically coupled neurons which can transmit signals laterally, via the degenerate PRs, reducing the threshold of ON BCs. These mechanisms of lateral communication allow remaining PRs to influence the response of BCs above the active electrodes.

response, while a single 100 μm pixel on the edge of the bipolar array at its stimulation threshold (0.20 mW/mm^2) has an average potential drop of 1.4 mV across BCs (Fig. 5F). Although these values are quite similar, at this irradiance, the bipolar cells in the center of the bipolar array experience a much larger drop in electric potential (4.7 mV in bipolar array vs. 1.8 mV in monopolar array).

Decrease of stimulation threshold in photopic conditions was not observed with bipolar arrays (Fig. 5B) because of nonuniformity of illumination in our setup. Electric fields above bipolar arrays replicate the illumination pattern much better than monopolar arrays, which smear and spread it due to strong cross-talk between electrodes (Fig. 5C and E vs. Fig. 5D and F). However, when the NIR illumination beam was shifted to the edge of the bipolar implant (having local returns), stimulation threshold decreased similarly to that with monopolar arrays (Fig. 4, blue).

In the human retina, rod bipolar cells and AII amacrine cells have a dendritic field diameter of $109.2 \pm 68.4 \mu\text{m}$ and $47.3 \pm 25.4 \mu\text{m}$, respectively (34), suggesting that a single rod can affect bipolar cells (rod $\rightarrow$ rod bipolar cell $\rightarrow$ AII amacrine cell $\rightarrow$ ON bipolar cell) at distances of up to $78.3 \pm 46.9 \mu\text{m}$. Therefore, to avoid PRs influence on stimulation threshold requires placing the implant at least 150 μm from the edge of the scotoma.

Modeling also demonstrates that photoreceptors can be stimulated by the large return electrodes of monopolar arrays, but not with bipolar implants (Fig. 6A). Although the peak negative potential above monopolar and bipolar arrays is similar (−1.3 mV vs. −1.5 mV, Fig. 5C and D), higher negative potential is concentrated near the edge of the monopolar implant (Fig. 5C), while in bipolar arrays it is distributed over narrow local returns surrounding each pixel (Fig. 5D). Assuming 70 μm long healthy photoreceptors at the edge, the average voltage drop across PR over a 100 μm wide area is −1.2 mV for monopolar and −0.5 mV for bipolar arrays. As a result, with monopolar arrays, the PR

Table 1. Voltage across various cells at stimulation thresholds for both monopolar (dark-adapted: 0.015, light-adapted: 0.024, and L-AP4: 0.062 mW/mm^2) and PRIMA implants (0.20 mW/mm^2), averaged over 100 μm width: PRs at the edge of the return electrode in monopolar implants (from 1 μm to 70 μm height), BCs on the edge of the active electrode (from 1 to 50 μm), and BCs on the center of the active electrodes

	Irradiance (mW/mm^2)	PRs (mV)	BCs (Edge) (mV)	BCs (Center) (mV)
MP	0.015	−1.2	0.7	1.13
	0.024	−1.6	1.6	1.8
	0.062	−4.2	2.8	4.6
PRIMA	0.20	−0.5	1.4	4.7
Thresholds	–	−1.2	1.6	4.6

Monopolar implants first reach PR threshold of −1.2 mV at 0.015 mW/mm^2 , before reaching PR-affected BC threshold of 1.6 mV at 0.024 mW/mm^2 . Due to lack of PR-driven depolarization, threshold of BCs at the center of the implant is almost three times higher, with 4.6 mV drop across the BC cell at 0.062 mW/mm^2 . PRIMA reaches BC threshold first at 0.2 mW/mm^2 , also unaffected by light adaptation of the PRs. Stimulation thresholds for each cell are shown at the bottom of the table. Voltages at or above thresholds are shown in bold.

threshold is 3 times below that of BCs (0.014 vs. 0.06 mW/mm^2 at 10 ms, Fig. 5A, red vs. green curve), while with bipolar arrays, the BCs threshold (4.7 mV across BCs at 0.2 mW/mm^2) is reached before the PR threshold (−0.5 mV across PRs at 0.2 mW/mm^2 , threshold of −1.2 mV), as summarized in Table 1.

Dominance of the ON Over OFF Pathway. The retinal neural network includes ON and OFF pathways which respond to increase or decrease of light, respectively. Signaling mechanisms, including the effect of dark adaptation and of L-AP4 blocker discussed above, assume that the ON pathway dominates the retinal response to subretinal photovoltaic stimulation, which may explain why patients report only bright phosphenes (35), as opposed to both bright and dark percepts reported with cortical (36, 37) and epiretinal stimulation. For the OFF pathway, shifts of thresholds upon dark adaptation and L-AP4 injection are expected to be the opposite of that observed in this study. ON bipolar cells are hyperpolarized under L-AP4 due to maximum activation of metabotropic glutamate receptors, resulting in an increased threshold, while OFF bipolar cells are not directly influenced by L-AP4. Additionally, hyperpolarization of ON and rod bipolar cells results in the suppression of the amacrine cell network, thereby reducing the glycinergic rectification of the OFF pathway (6). Therefore, dark adaptation or L-AP4 application is expected to reduce the threshold for OFF bipolar cells—opposite of the effect observed in our study.

Dominance of the ON pathway may be explained by several factors. Since rod BCs have only the ON type, rod-dominated rat retina (99%) is naturally dominated by the ON pathway (38). An additional factor could be that much lower spontaneous firing rate in ON than in OFF RGCs in the degenerate retina (39) results in a higher signal-to-noise ratio in ON vs. OFF pathway, making it perceptually dominant. Yet another reason could be the rectification of the OFF pathway by AII amacrine cells (6), resulting in the ON bipolar responses dominating the retinal output (6). Additionally, stimulation threshold of ON BCs may be lower than OFF BCs because ON BCs are depolarized while OFF BCs are hyperpolarized in the degenerate retina due to the absence of glutamate input from PRs. ON BCs are also longer than OFF BCs, resulting in a higher voltage drop across the cell causing more depolarization in ON BCs than OFF BCs (40).

The ON pathway dominance has been previously reported in both subretinal electrical stimulation (41) as well as in BC targeted optogenetics (42). It has been described that blocking glycinergic inhibitory inputs to OFF BCs and OFF RGCs from AII amacrine cells results in 50% reduced rectification (41), suggesting that coupling of the rod BC to AII AC network plays a significant role in causing ON pathway dominance. Additionally, in BC-targeted optogenetic therapies (42), ON responses dominate (68.7% ON vs. 25.7% OFF) in the treated *rd1* mouse retina, which also indicates the role of AII amacrine cells in shaping the ON pathway dominance.

Effect of Synaptic Plasticity on Stimulation Thresholds. Interestingly, thresholds in LE rats (local degeneration) with L-AP4 injection and RCS rats (full degeneration) (4) are the same, even though the baseline membrane potentials should be different (19). L-AP4, as a glutamate agonist (equivalent to maximum glutamate concentration or dark conditions), causes hyperpolarization of ON bipolar cells, while the loss of the glutamate input due to missing photoreceptors in the degenerate RCS retina results in depolarization of ON bipolar cells (equivalent to bleached retina under bright light conditions) (19). It was shown previously that despite the loss of glutamate input to ON BCs, the ON RGCs maintain the same spontaneous firing rate throughout the course of retinal degeneration (39), indicating adaptation of the retina by reducing the ON BC synaptic output (synaptic plasticity) (43).

This reduction in synaptic output to RGCs has been previously reported in *rd1* and *rd10* mouse retina (44). It was shown that although the number of ribbon synapses did not change in retinal degeneration, excitatory postsynaptic potentials (EPSCs) in ON RGCs were reduced in the degenerate retina because of the loss of glutamate input in ON BCs from photoreceptors. As a result, the lack of glutamate input to BCs in RCS rats, and full activation of the glutamate receptor in BCs with L-AP4 in LE rats yield the same threshold for bipolar cell activation. Such “self-calibration” of the inner retina by synaptic plasticity preserves the same perceptual thresholds between healthy and degenerate retina and plays a crucial role in maintaining the same electrical stimulation thresholds.

Limitations. Irradiances in this study are close to stimulation threshold ($<1.2 \text{ mW/mm}^2$), while higher settings are used in clinical trials (3.5 mW/mm^2) [2]. Role of the photoreceptors-mediated stimulation may be less significant at higher settings if response from other neurons is close to saturation. Future modeling work will be needed to quantify the photoreceptors contribution at suprathreshold settings. This is much more complex task since it involves modeling of the whole retinal neural network.

Edge brightening effects, predicted in this study, are not reported in clinical papers. They have been observed occasionally but not quantified due to large variability between stimulation patterns and between patients owing to differences in scotoma size and distance from the implant to the edge of the scotoma.

We did not observe formation of a glial seal above the implant in these experiments, however if it forms in some patients due to retinal injury, it will likely attenuate the stimulation due to increased distance to the target cells and increased impedance of the fibrotic layer.

Conclusions. Some photoreceptors are often retained during retinal degeneration, especially in maculopathies. Our study indicates two different effects by which photoreceptors influence the subretinal electrical stimulation: 1) if exposed to negative electric potential, photoreceptors may respond at significantly lower threshold with longer pulses ($\geq 10 \text{ ms}$) compared to direct stimulation of bipolar cells

above the implant, and 2) bipolar cells near the edge of the implant are more depolarized due to photoreceptor input in photopic conditions, resulting in a reduced threshold. To avoid a bright percept near the edge of the implant, devices should be designed such that they do not generate a negative potential spilling beyond their edges. As such, bipolar arrays, having local return electrodes in each pixel, provide a more promising design for subretinal prosthesis. However, for small bipolar pixels, electric field penetration into the retina with flat arrays is insufficient (45), and 3-D electrodes are required to provide better penetration of electric field into the INL, while retaining good lateral confinement (46). But even with bipolar arrays, to avoid the depolarizing effect of residual photoreceptors on bipolar cells, implants should be placed at least $150 \mu\text{m}$ from the edge of scotoma.

Materials and Methods

All experimental procedures were conducted in accordance with the Statement for the Use of Animals in Ophthalmic and Vision research of the Association for Research in Vision and Ophthalmology (ARVO) and approved by the Stanford Administrative Panel on Laboratory Animal Care (APLAC). Animals were maintained at the Stanford Animal Facility under 12 h light /12 h dark cycles with food and water ad libitum. Animals that required dark adaptation were placed in complete darkness for at least 12 h.

Surgical Procedures. Animals were anesthetized with a mixture of ketamine (75 mg/kg) and xylazine (5 mg/kg) injected intraperitoneally. All rats were implanted with three transcranial screw electrodes: one over each hemisphere of the visual cortex (4 mm lateral from midline, 6 mm caudal to bregma), and a reference electrode (2 mm left of midline and 2 mm anterior to bregma). To ensure stable results, measurements were performed at least 8 wk post implantation (47). Bipolar photovoltaic devices with $100 \mu\text{m}$ pixels and monopolar photovoltaic devices with $20 \mu\text{m}$ pixels of 1.5 mm in diameter and 30 mm in thickness were implanted subretinally, as previously described (4, 48). Retinal implants were placed in the temporal-dorsal region, approximately 1 mm away from the optic nerve. RCS rats were used after age P180, when photoreceptors completely disappeared (49). In LE rats, loss of the outer nuclear layer (ONL) (Fig. 3) by 8 wk was checked with optical coherence tomography (OCT; HRA2-Spectralis; Heidelberg Engineering, Heidelberg, Germany). Histology slices (Fig. 3C) also demonstrate that photoreceptors are not present above the implant. Healthy photoreceptors outside the implant respond to light, thereby regulating the BCs potential near the implant's edge. Some photoreceptor nuclei are present above the implant (up to $100 \mu\text{m}$ from its edge). They do not have inner and outer segments and hence are not light-sensitive, but can still respond to electrical stimulation.

To check efficiency of L-AP4 (0.8 mM) in blocking the photoreceptors, VEP response to full-field green light flashes was recorded in LE rats before and after the intravitreal injection in a control area 1.5 mm nasal from the implant, where photoreceptors are present. The VEP signal was lost and did not reappear for 3 h post injection of the blocker. Additionally, this was also checked for the full cocktail of blockers (0.8 mM L-AP7, 0.8 mM L-AP4, 0.2 mM NBQX, 0.4 mM strychnine, and 0.32 mM picrotoxin) and the signal also did not reappear for 3 h post injection.

Electrophysiological Measurements. Arrays were illuminated with 880 nm NIR laser (M1F-880 nm-400 μm , DILAS, Tucson, AZ) with irradiances from 0.01 to 0.88 mW/mm^2 and pulse durations from 0.5 to 10 ms at 2 Hz repetition rate. Digital micromirror display (DMD; DLP Light Commander, LOGIC PD, Carlsbad, CA) used for a pattern formation and the image projection optical assembly were mounted on a slit lamp for alignment onto the implant in rat eye, as previously described (3, 4).

VEPs were recorded using the Espion E3 system (Diagnosys LLC, Lowell, MA) at a sampling rate of 4 kHz and averaged over 250 trials. For retinal degenerate conditions, VEP measurements were conducted at least 16 wk after subretinal implantation to ensure stabilization of the VEP amplitudes (47) and complete degeneration of photoreceptors above the implant (5, 48). VEP experiments with degenerate retinas were conducted in photopic conditions (room lighting) using experimental setup as previously described (3, 4). For experiments in scotopic conditions, animals were dark adapted for 12 h.

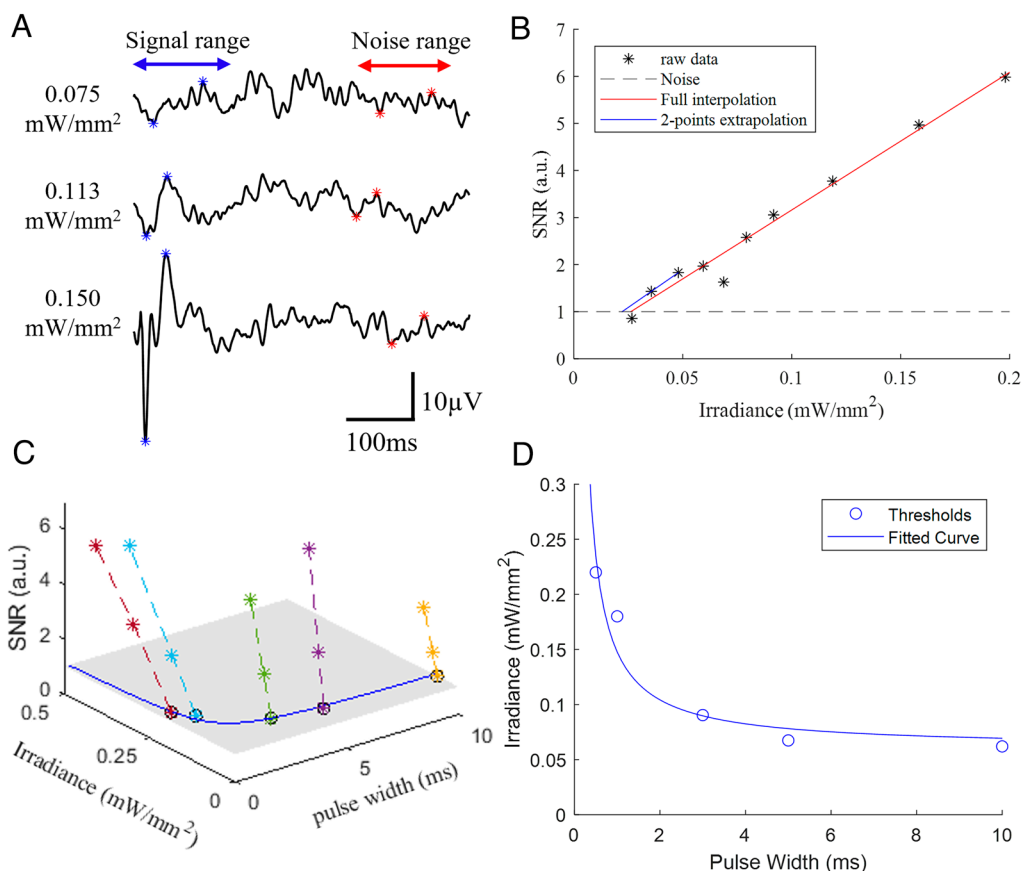


Fig. 8. (A) Example VEP waveforms demonstrating an increase in VEP signal with increasing irradiance. The signal peaks are shown as blue asterisks (*) while the noise is shown as red asterisks (*). (B) Extrapolation to the threshold (blue) is calculated by taking two points above the noise level. Close to the threshold, the signal-to-noise ratio (SNR) scales linearly with irradiance (red). (C) Extrapolation of the strength duration (S-D) curve based on thresholds at multiple pulse durations. (D) An example of an S-D curve fitted to Weiss' equation.

Typical VEP waveforms are shown in Fig. 8A. Peak-to-peak VEP amplitude was calculated as a difference between the first trough in the signal within 120 ms of the stimulus onset and the peak within 100 ms after the trough (Fig. 8A). Noise was determined in a similar fashion, 320 ms after the stimulus onset. Stimulation threshold was defined as the irradiance required to obtain a signal-to-noise ratio (SNR) of 1 through linear extrapolation of two points with an SNR > 1 (Fig. 8B). The threshold was checked by ensuring that at irradiance below the extrapolated threshold, no signal was detected (SNR < 1). Error from linear extrapolation of the lowest two points with an SNR > 1 was less than 15% in comparison to using 10 points. To determine the strength-duration curve of retinal stimulation, the thresholds $I(t)$ were measured at pulse durations t ranging from 0.5 to 10 ms and fitted with the Weiss equation: $I(t) = I_R \left(1 + \frac{T}{t}\right)$, where I_R is a rheobase and T is a chronaxie (50) (Fig. 8C and D). The VEP data were analyzed using custom code in MATLAB available at <https://zenodo.org/records/17982537> (51).

Modeling of Neural Stimulation. Electric field in the retina was calculated using Retinal Prosthesis Simulator (RPSim)—a software package that models electric current generated by a photovoltaic array under patterned illumination and calculates electric potential in electrolyte by combining a finite-element method-based physics engine (COMSOL) with an electrical circuit solver (20, 52). Here, a degenerate rat retina was modeled as a 126 μm thick layer of 1,000 $\Omega\cdot\text{cm}$ resistivity (20), with the microelectrode array placed immediately below the inner nuclear layer (while for healthy retina, placed below the PR outer segments). Thickness of the healthy rat retina was assumed to be 200 μm based on OCT

imaging. Stimuli consisted of a single rectangular pulse with magnitudes defined by RPSim, reproducing the experimental conditions.

Healthy photoreceptors were modeled as 70 μm long cells which include a soma of 8 μm in diameter, inner segment, and outer segment. Partially degenerated photoreceptors were modeled as containing only the soma, which corresponds to the ONL observed at the edge of the implant in OCT and in histology (external limiting membrane is not visible), estimated to be 20 μm in length. Ion channels of the photoreceptor were based on previously published models (27, 53), modified to include multiple compartments (35 for healthy, 10 for degenerate) to improve sensitivity to extracellular electric field. Photoreceptors were placed into electric field between 500 μm and 1,000 μm from the center of the implant at 20 to 25 μm increments.

Data, Materials, and Software Availability. Code data have been deposited in Zenodo/Github (10.5281/zenodo.17982536) (51).

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