Report

Current Biology

Cortical Interactions between Prosthetic and Natural Vision

Highlights

- Prosthetic and natural responses to non-patterned retinal stimuli summed linearly in the cortex
- Natural visual flankers inhibit responses to prosthetic targets
- This inhibitory effect was not observed when a GABAa inhibitor was administered
- Basic cortical interactions between prosthetic and natural retinal responses are preserved

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In Brief

Retinal prosthesis in AMD patients provides electrical stimulation to the central retina , whereas the peripheral healthy retina responds naturally to light. Arens-Arad et al. characterize the cortical interactions between prosthetic and natural vision and find many similarities to natural visual processesing.

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Current Biology
Report

Cortical Interactions between Prosthetic and Natural Vision

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SUMMARY

Outer retinal degenerative diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), are among the leading causes of incurable blindness in the Western world [1]. Retinal prostheses have been shown to restore some useful vision by electrically stimulating the remaining retinal neurons [2]. In contrast to inherited retinal degenerative diseases (e.g., RP), typically leading to a complete loss of the visual field, in AMD patients the disease is localized to the macula, leaving the peripheral vision intact. Implanting a retinal prosthesis in the central macula in AMD patients [3, 4] leads to an intriguing situation where the patient's central retina is stimulated electrically, whereas the peripheral healthy retina responds to natural light stimulation. An important question is whether the visual cortex responds to these two concurrent stimuli similarly to the interaction between two adjacent natural light stimuli projected onto healthy retina. Here, we investigated the cortical interactions between prosthetic and natural vision based on visually evoked potentials (VEPs) recorded in rats implanted with photovoltaic subretinal implants. Using this model, where prosthetic and natural vision information are combined in the visual cortex, we observed striking similarities in the interactions of natural and prosthetic vision, including similar effect of background illumination, linear summation of non-patterned stimuli, and lateral inhibition with spatial patterns [5], which increased with target contrast. These results support the idea of combined prosthetic and natural vision in restoration of sight for AMD patients.

RESULTS

This work focuses on the interactions between natural and prosthetic vision. We have previously shown that the subretinal implant results in local degeneration of photoreceptors above the implant, while leaving the inner retina intact and the surrounding retina unaffected [6] (Figure 1B). Therefore, this model offers an opportunity to investigate the interactions between prosthetic vision induced by near-IR (NIR) illumination of the photovoltaic implant and natural visual responses of the surrounding intact retina elicited simultaneously.

Effect of Background Illumination on Cortical Responses to Prosthetic and Natural Vision Flash Stimuli

As a first step, we studied the effect of visible light background on cortical responses to prosthetic retinal activation and compared it with natural visual stimulus of a similar shape presented to normally sighted animals (Figure 1A). To this end, visible flashes with varying intensities were projected onto healthy rat retina at three background illumination levels. Stimulus size, pulse duration, and repetition rate were comparable to those used for activating the retinal prosthesis. As shown in Figure 1C, cortical responses to pulsed visible stimuli decreased with increasing background illumination similarly to prosthetic visual responses (Figure 1D). The effect of the background illumination on prosthetic visually evoked potential (VEP) amplitude was found to be statistically significant (one-way ANOVA; $p < 0.005$) for NIR irradiance exceeding 0.25 mW/mm^2. This result indicates similarities between the cortical processing of pulsed natural and prosthetic stimuli on top of background illumination and are in agreement with previous reports about such interactions for natural [7] or combined natural and prosthetic vision [8].

Interactions of Cortical Responses to Combined Prosthetic and Natural Vision Non-patterned Stimuli

The next step was investigating the interactions induced by spatially uniform pulsed stimuli: flashes or contrast steps. Thus, flash stimuli consisting of the 1-mm central disk and a 3.5-mm peripheral annulus (Figures 2A and 2B) were presented at a repetition rate of 2 Hz. In rats with an implant, a central disk was presented using NIR, whereas in normally sighted controls, it was presented using visible light with similar temporal parameters. The response to the combined stimulus was compared to the linear summation (LS) of the waveforms induced by the NIR and visible stimuli presented separately (Figures 2C and 2D).

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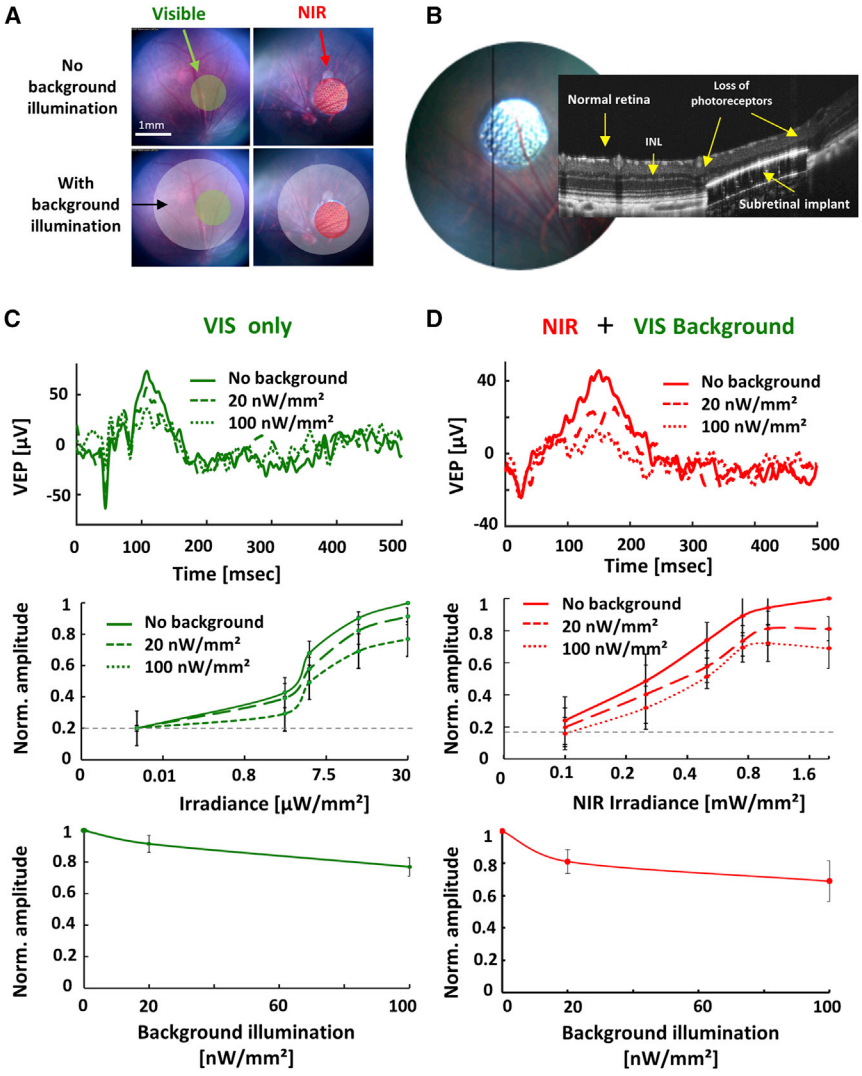

Figure 1. Effect of Background Illumination on Cortical Responses to NIR and Visible Flash Stimuli

(A) Fundus image of a rat with an illustrated 1-mm-diameter disk projected onto the retina using green light-emitting diode (LED) (top left) or onto a subretinal implant using NIR light (top right). Bottom row: the same experiment with a uniform white background illumination is shown.

(B) Fundus photo and optical coherence tomography (OCT) image of a normal retina implanted with subretinal prosthesis, which induced local loss of photoreceptors above the implant.

(C) Natural vision. Top: representative cortical signals in response to a visible flash stimulus without the background (solid line) and with a light background at two luminance levels (dashed and dotted lines) are shown. Middle: normalized average VEP amplitudes in response to visible flash stimuli at various luminance levels, without the background (solid line), and for two levels of light background luminance (dashed and dotted lines) are shown. The horizontal dashed line represents the noise level. Bottom: normalized VEP amplitude as a function of the background illumination for a constant flash irradiance is shown. Error bars represent the SEM.

(D) Prosthetic vision. Top: representative VEP signals in response to NIR flash without the background (solid line) and with the background at two luminance levels (dashed and dotted lines) are shown. Middle: normalized average VEP amplitude in response to NIR flash stimuli for varying irradiance levels without the background (solid line) and with the background at two luminance levels (dashed and dotted lines) is shown. The horizontal dashed line represents the noise level. Bottom: normalized VEP amplitude as a function of the background illumination for constant NIR flash irradiance is shown. Error bars represent the SEM.

The deviation from linear summation, termed the "second order" response, was calculated by subtracting the linear summation from the response to the combined stimuli, similar to [5].

As shown in Figures 2E and 2F, the amplitude of the cortical responses to combined stimuli was similar to the linear summation of the separate responses to natural vision and prosthetic stimuli ($p > 0.5$; one-way ANOVA) for both prosthetic-visible and visible-visible control. The "second order" (Figures 2C and 2D, right lower plot) did not exceed the noise level, suggesting that neither facilitation nor inhibition occurred between the responses to the central prosthetic and the surrounding natural stimuli. These results are in agreement with previous studies of such interactions in natural vision [8] and demonstrate the similarity of these interactions in combined natural and prosthetic vision.

To investigate visual interactions for luminance steps, we projected solid stimuli of approximately 10 mm^2 diameter in the periphery and 1 mm^2 in the center, alternating between two levels of irradiance. The VEP signals in response to an increase and decrease in irradiance represent the "ON" and "OFF" responses of the visual system, respectively [9]. The irradiance levels of the projected pair of stimuli were chosen to achieve luminance steps of 100%, 50%, 25%, and 12.5% (Figures S3A and S3B), as described in STAR Methods. As expected, a higher luminance step resulted in an increase in the VEP amplitude for both natural (Figure S3C) and prosthetic stimuli, with the latter saturating at a lower step (Figure S3D) for "ON" and "OFF" responses. OFF responses were significantly smaller than ON responses for both prosthetic and natural vision (Figures S3E and S3F). Furthermore, the prosthetic response was significantly lower than the response to the natural-light luminance step. The ON response step threshold was 25% and 6% for prosthetic and natural vison, respectively, revealing the significantly lower luminance step sensitivity of prosthetic vision. Further analysis of the interactions thus focused on the ON responses to luminance steps of 25%, 50%, and 100%. Figures 3C and 3D shows representative VEP signals in response to stimuli with visible center, surrounding annulus, calculated linear summation, and the "second order"—the difference between the combined response and LS of its components. Figure 3D shows the same for the NIR stimulus in the center. Signal amplitude in response to the combined center

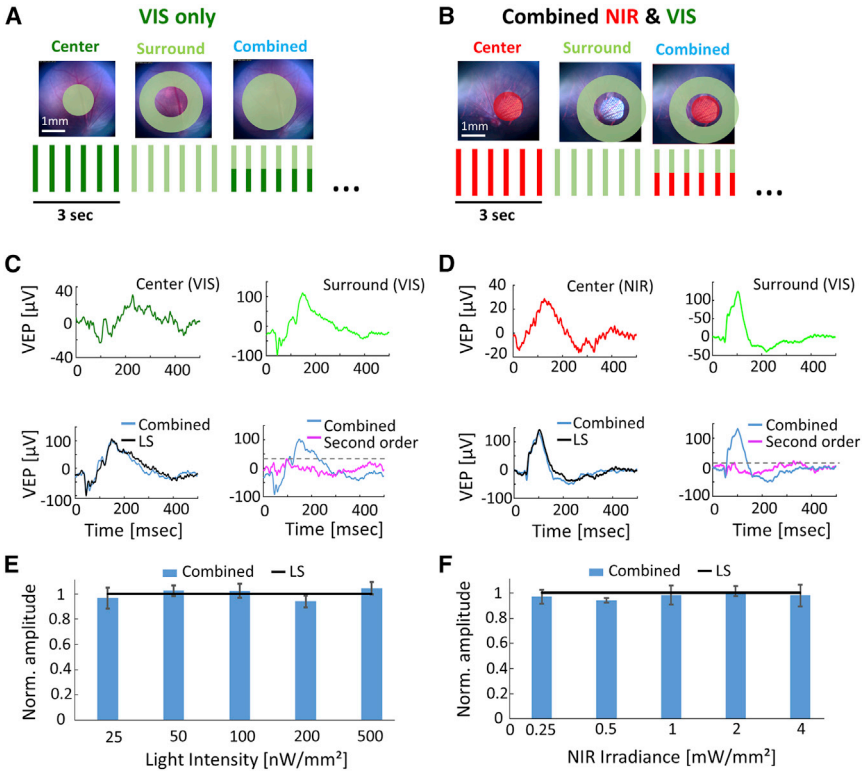

Figure 2. Interaction of Cortical Responses to Combined Natural and Prosthetic Flash Stimuli

(A) Green light stimulation sequence consisting of 6 pulses (10 ms, 2 Hz) for a 1-mm disk, a surrounding annulus, and two of them combined.

(B) A similar sequence with the disk illuminated by NIR flashes.

(C) Representative VEP signals in response to 3 visible stimuli, as well as linear summation of the two cortical responses and the "second order"—the difference between the responses to the combined stimulus and linear summation (LS) of its components. The horizontal dashed line represents the noise level.

(D) Representative VEP signals in response to NIR and visible flashes, to their combination, a LS of the two cortical responses, and the second order. The horizontal dashed line represents the noise level.

(E) Average VEP amplitude as a function of the center stimulus intensity at a constant intensity of the surrounding annulus (10 $\mu W/mm^2$), relative to their LS. Error bars represent the SEM.

(F) Average VEP amplitude as a function of the NIR flash intensity, with a constant intensity of the surrounding visible annulus (10 $\mu W/mm^2$), relative to the amplitude of their linear summation (black line). Error bars represent the SEM.

and surround stimuli was found to be similar ($p > 0.5$; one-way ANOVA) to linear summation of the responses to such stimuli presented separately for both visible (Figure 3E) and combined prosthetic and visible stimuli (Figure 3F). As with flash stimuli (Figures 2E and 2F), this result indicates the lack of lateral facilitation or inhibition for either natural or prosthetic targets in the center.

Interaction of Cortical Responses to Combined Prosthetic and Natural Vision Patterned Stimuli

To investigate interactions between prosthetic and natural visual responses to more complex stimuli, we applied alternating grid patterns (Figures 4A and 4B; see STAR Methods). Such patterns are used to evaluate visual acuity in non-communicating subjects [10–12]. Using these patterns in rodents, we have recently demonstrated that grating acuity matched the 70-μm pixel pitch of the photovoltaic arrays [9]. We also observed that prosthetic vision with subretinal implants preserves many features of natural retinal signal processing, including center-surround antagonism [13] and non-linear summation of sub-units in receptive fields of the ganglion cells [14].

We studied the interactions between the 1-mm-diameter target and 1-mm-wide square flankers stimuli consisting of gratings (Figures 4A and 4B), as described in [15] and [5]. Spatial contrast of the target pattern varied from 6% to 100%, whereas contrast of the flankers was always maintained at 100%.

To serve as a comparison basis, we first studied the interaction between target and flankers in normally sighted animals in response to natural light stimuli. Representative cortical signals obtained with 100% target contrast and flankers, simultaneously and apart, as well as their linear summation are shown in Figures 4C and 4D. As shown in Figure 4C for the natural stimuli, the combined stimulus elicited a significantly smaller response than did the linear summation of the responses to target and to flankers separately. This apparent deviation from linear summation increased with the target contrast, as shown in Figure 4E (trend analysis $p < 0.001$). Thus, at the 100% target contrast level, the deviation from the linear summation was 35% ± 10% and it gradually decreased with decreasing target contrast level (7% ± 3% for the 6% contrast).

A similar trend was observed with prosthetic vision in the target (Figure 4D). The presumed lateral inhibition increased with increasing target contrast, reaching 40% ± 3% deviation from linear summation at the 100% contrast level (Figure 4F). The deviation from linear summation was statistically significant ($p < 0.05$) for contrast levels exceeding 50%, and the deviation gradually increased with increasing target contrast (p for trend < 0.05). Comparison of the non-normalized response amplitudes of prosthetic to natural stimuli showed smaller prosthetic responses to the combined target and flicker stimuli (Figure S4); the difference, however, was not statistically significant (one-way ANOVA; $p > 0.5$) due to inter-animal variation.

These striking similarities between cortical responses to complex prosthetic and natural stimuli strongly suggest that basic interactions between prosthetic and natural vision are preserved in the cortex.

The observed summation effect was not dependent on the orientation (orthogonal or collinear) of the target and flankers (Figures S1A and S1B). Lateral inhibition was observed to the same extent with both orientations for both natural and prosthetic targets. These results further illustrate the similarity of cortical interactions between natural and prosthetic vision to that observed with natural vision alone [16].

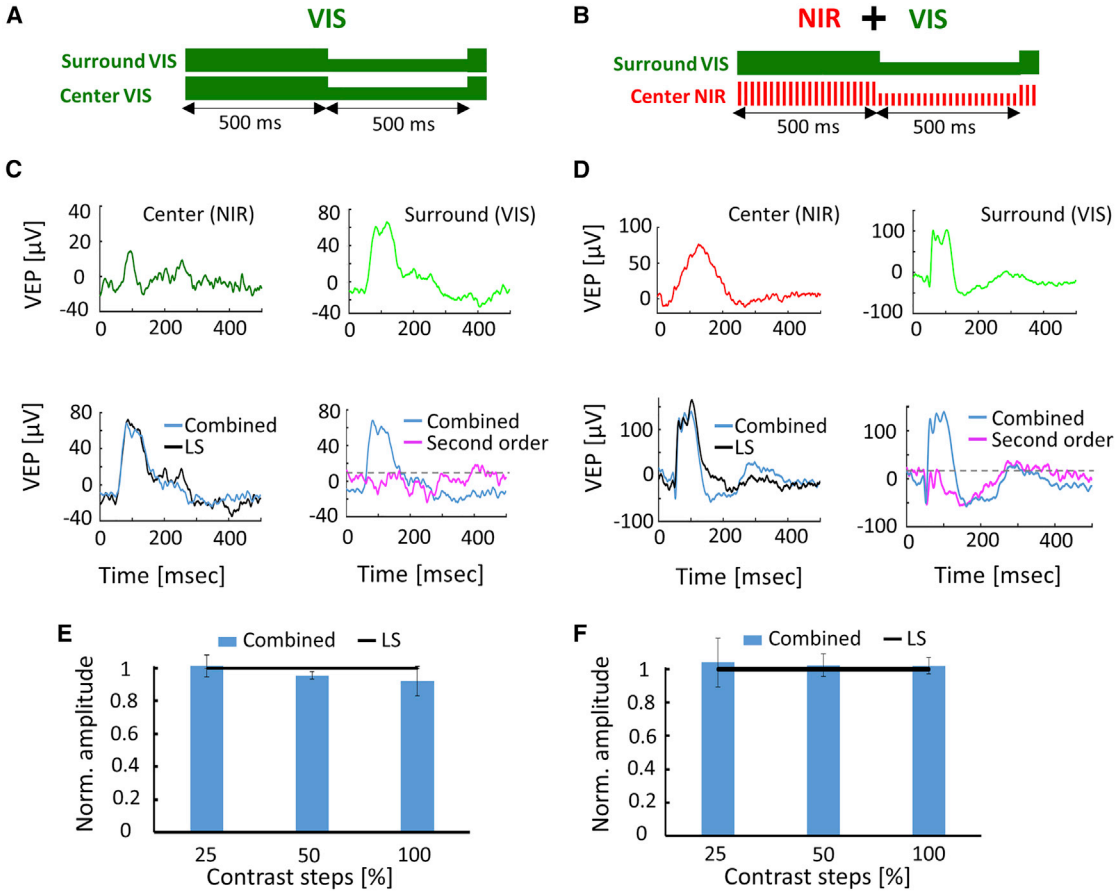

Figure 3. Interaction of Cortical Responses to Combined Natural and Prosthetic Luminance Steps

(A and B) Illustration of the combined center and surround luminance step stimuli, with visible (A) or NIR (B) center.

(C) Representative VEP signals in response to visible stimuli: 1 mm center, surrounding annulus, calculated linear summation (LS), and the second order—the difference between the combined response and LS of its components. The horizontal dashed line represents the noise level.

(D) Same for the NIR stimulus in the center. The horizontal dashed line represents the noise level.

(E) Average VEP amplitude for various luminance steps (25%, 50%, and 100%), relative to the linear summation (black line).

(F) Same for prosthetic stimulus in the center. Error bars represent the SEM.

See also Figure S3.

The Effect of a $GABA_A$ Antagonist on Lateral Interactions

To validate our hypothesis that the mechanism underlying the differences between the combined response and the linear summation for the target and flankers' stimuli is lateral inhibition mediated by $GABA_A$ [17, 18], we compared the VEP signals before and after injecting bicuculline, a $GABA_A$ antagonist. As shown in Figures S2A and S2B for natural vision and in Figure S2C for combined prosthetic and natural vision, the inhibition was eliminated following the injection, suggesting that $GABA_A$ is involved in the underlying mechanism. 72 h later, the same experiment was performed after the complete drug washout, showing that the extent of inhibition was similar to the one observed prior to applying the blocker for both natural (Figures S2A and S2B) and combined vision (Figure S2C).

DISCUSSION

Restoration of central vision in age-related macular degeneration (AMD) patients through electronic retinal prostheses [19], optogenetics [20], or photo-switches [21] requires the visual cortex to process the visual information arising from two very different sources: the natural healthy retina in the periphery and prosthetic vision in the center. Despite the preservation of some of the features of retinal signal processing with subretinal stimulation, such as flicker fusion [9], adaptation to static images, antagonistic center-surround organization [13], and the non-linear summation of sub-units in receptive fields [22], prosthetic retinal signaling is far from normal due to indiscriminate stimulation of various cell types in the inner nuclear layer (INL). Encouraging is the fact that, with partial cochlear implants, the auditory cortex successfully integrates the prosthetic input from the high-pitch areas and natural signals coming from the low-pitch part of the cochlea [23]. In this study, we utilized a unique animal model of local retinal degeneration to investigate the cortical summation of the prosthetic and natural retinal signals.

Our results show that cortical responses to both natural and prosthetic flash stimuli decreased similarly with increasing

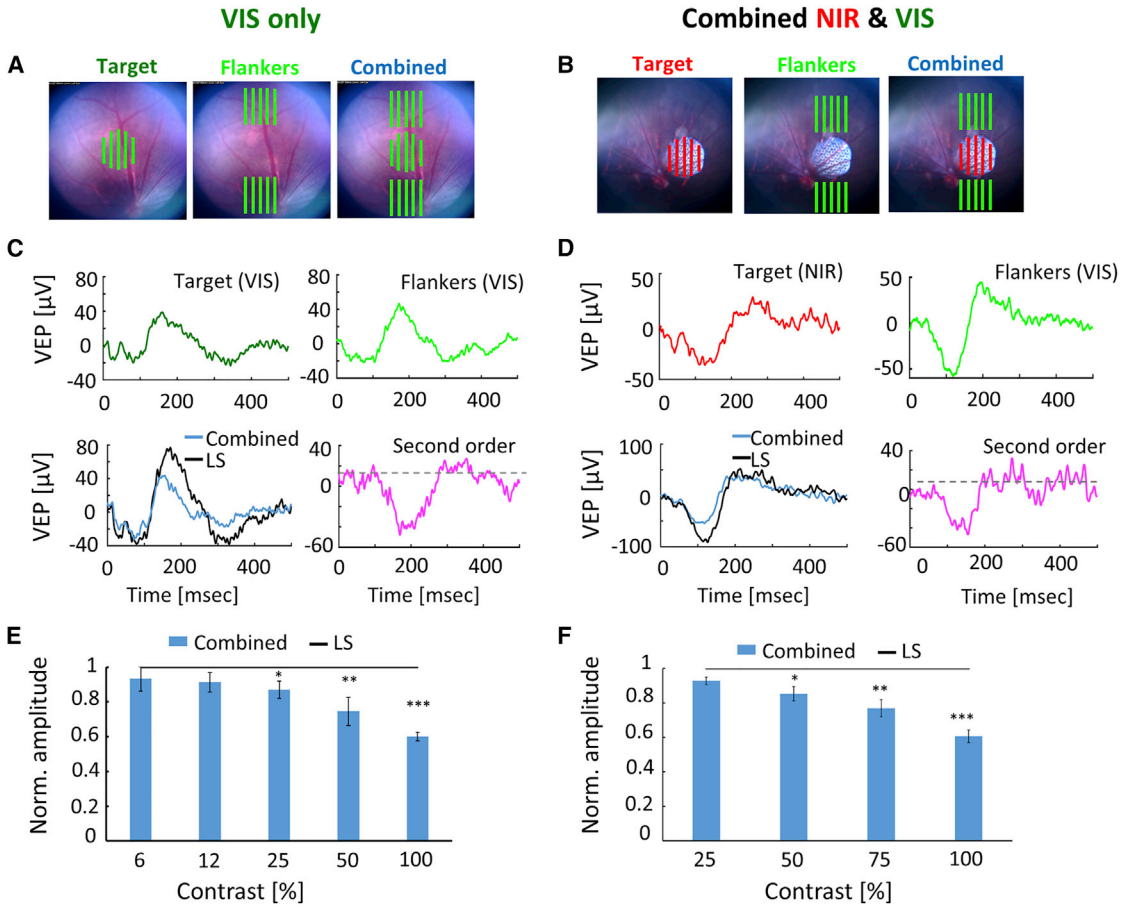

Figure 4. Lateral Inhibition in Natural and Prosthetic Vision

(A and B) Target with varying contrast and flankers with a 100% contrast presented either separately or simultaneously for natural vision (A) and for combined natural and prosthetic vision (B).

(C and D) Representative VEP signals with a target contrast of 100% in response to visible (C) or combined NIR and visible (D) stimuli: target, flankers, combined target and flankers, calculated LS, and the second order.

(E and F) VEP amplitude in response to combined stimulation as a function of the target contrast, relative to the calculated LS, for normal vision (E) and for combined normal and prosthetic vision (F). The horizontal dashed line represents the noise level. Error bars represent the SEM.

See also Figures S1, S2, and S4.

natural background illumination. In natural vision, such a decrease is expected due to adaptation processes arising from the photoreceptors and horizontal cells [7, 24] or due to cortical processes associated with reduced contrast between the local stimulus and the surroundings [25]. A similar decrease (up to 30%) observed in the prosthetic response in the presence of background illumination suggests that AMD patients with a retinal prosthesis are likely to be affected by the background illumination, and hence, the ambient lighting conditions should be balanced with the brightness of prosthetic vision.

VEP amplitudes also increased similarly in response to increasing luminance steps for both natural (Figure S3E) and prosthetic (Figure S3F) stimuli, albeit with a higher luminance step threshold (25%) for prosthetic than for natural vison (6%). In the earlier behavioral measurements, however, the thresholds were about twice lower: 12% and 2.3%, respectively [26].

With simple non-patterned prosthetic and natural visual stimuli (flashes or contrast steps), the response to the combined stimulus was well approximated by linear summation of the responses to the two different stimuli presented separately, as also noted earlier by Lorach et al. [8].

With patterned prosthetic and natural vision stimuli, however, the response to a combined (target and flankers) stimulus was significantly smaller than the linear summation of the responses to each stimulus presented separately (Figure 4). This result indicates the involvement of lateral inhibition, which was enhanced with higher target contrast. Both of these observations exhibit remarkable similarities in the cortical integration of the responses originating from adjacent areas on the retina, elicited either naturally or by combined natural and prosthetic stimuli.

Numerous studies have already reported the non-linear interactions between the target and flankers in humans [27–30], primates [5, 31], and rats [16, 32, 33] for natural vision. Our results, demonstrating the inhibition of the retinal response to a central target when natural flankers are introduced, are in agreement with the behavioral studies in rats [16, 32, 33]. We show here, for the first time, the same interactions with the central target

representing prosthetic vision, suggesting that cortical aspects of prosthetic vision utilize, at least partially, similar visual processing. For both natural vision and combined natural-prosthetic stimuli, the inhibitory effect increased with the target contrast, in agreement with previous reports in humans [27], cats [34], primates [5], and rats [16, 32, 33].

Our results showing that, for both prosthetic and natural vision, the inhibitory effect of the flankers was not orientation selective are in agreement with Kurylo [16] and in line with the lack of structured orientation-selective columns in rodents [35–37]. This is in contrast with observations in humans [15], cats [38], and primates [31]. Interestingly, recent behavioral studies with rats [32, 33] did report the orientation-dependent inhibitory effect of the flankers, thus calling for further research on the underlying neural circuits.

Our observations that injection of the $GABA_A$ antagonist, bicuculline, brought the response to pattern stimuli to a similar level to that of the linear summation confirmed that the mechanism underlying the lateral inhibition is mediated by $GABA_A$ receptors. Such interactions in normal vision have been observed earlier in the visual cortex of rats [17, 18, 36]. Nevertheless, because the $GABA_A$ antagonist was administered systemically in our study rather than locally to the cortex, the reduced inhibition could arise from the retina or subcortical areas [39].

Our study has several limitations. First, VEP measurements in anesthetized animals, used in our study, have lower sensitivity than in behavioral experiments [40]. Future studies should focus on behaving animals using mobile projection systems (e.g., [41]). Second, the VEP signals reflect the cumulative activity of the visual cortex induced by retinal stimulation and they lack the specificity of the individual cell responses, which is important for understanding the underlying visual processing. Another potential limitation is the use of stimuli in the linear range response, which is not always the case in visual scenes. Future studies should focus on responses to complex and natural stimuli at a higher resolution, based on optical or multi-unit electrical recordings.

In conclusion, cortical summation of the signals arising from different areas on the retina exhibits striking similarities between the responses to natural vision and combined prosthetic-natural stimuli. Our results suggest that, despite the marked differences in the retinal encoding of prosthetic signals compared to natural vision, some of the basic interactions in the cortex are preserved and enable integration of the visual information arising from the prosthetic retina and the adjacent normal retina. These observations support the feasibility of restoring central vision in patients with age-related macular degeneration, where central prosthetic and peripheral natural vision should co-exist.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.cub.2019.11.028.

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AUTHOR CONTRIBUTIONS

Conceptualization, T.A.-A., D.P., and Y.M.; Methodology, T.A.-A., N.F., and Y.M.; Conducted Experiments, T.A.-A., R.L., and A.M.; Resources, T.F. and D.P.; Writing – Original Draft, T.A.-A., N.F., R.L., and Y.M.; Writing – Review & Editing, Y.M., T.F., and D.P.; Visualization, T.A.-A. and N.F.; Supervision and Funding, Y.M.

DECLARATION OF INTERESTS

D.P. is the author of the patents owned by Stanford University and licensed to Pixium Vision for commercial development of the photovoltaic retinal prosthesis. He also serves as a consultant to Pixium Vision.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, Peptides, and Recombinant Proteins		
Bicuculline methiodide	TOCRIS BIOSCIENSE	Cat# 2503
Experimental Models: Organisms/Strains		
Long Evans rats	Bar Ilan institutional animal facility	HsdBlu:LE
Software and Algorithms		
MATLAB v2017a/b, 2018a	MathWorks	https://www.mathworks.com/

LEAD CONTACT AND MATERIALS AVAILABILITY

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Yossi Mandel (Yossi.Mandel@biu.ac.il). This study did not generate new unique reagents.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Subjects and surgery

All animal experiments and procedures were approved by the Bar Ilan University animal care committee and are in accordance with the ARVO guidelines for animal research. Experiments were conducted on Long Evans rats (n = 5), males, age 4-8 months.

Photovoltaic implants, 1 mm in diameter, composed of 140μm pixels were fabricated at Stanford University, as described previously [42]. The implants were inserted into the subretinal space following a protocol reported earlier by our group [43]. Experiments were performed at least 4 weeks following implantation of the photovoltaic implant. For the recording of the cortical responses, screw electrodes were implanted into the scull above V1, as described in [43].

METHOD DETAILS

Stimulation system

Natural and prosthetic visual stimulation were performed using a customized projection system integrated with a fundus camera (Phoenix Research Laboratories, Micron IV system). This system enables the imaging of the retina and the implant, as well as direct the projection of the stimulus pattern onto the desired location on the retina. The projection system engine (Texas Instruments LightCrafter 4500 DLP Platform) is based on a Digital Micromirror Device with a display resolution of 912 × 1140 and a 10.8 μm micromirror pitch. This system includes both visible (green LED 525nm) and NIR light (910nm diode laser) sources, and provides full control of the shape, duration, and intensity of the patterned stimuli projected onto rat retina.

The effect of background luminance on cortical responses to natural or prosthetic flashed stimuli

To investigate the effect of background luminance on responses of the visual cortex, 10ms flashes were projected at 2Hz either on the subretinal photovoltaic implant using a NIR laser (0.25-4mW/mm^2) or onto normal retina using a green LED (0.05-30μW/mm^2) (Figure 1A). The retinal spot size for both stimuli was 1 mm in diameter. Background illumination was provided by uniform white light covering 50 degrees of the retinal plane at either 20 or 100nW/mm^2, which was projected through the same imaging system continuously (Figure 1A). Cortical responses to NIR or green flashes with varying background illuminations (0, 20, and 100 nW/mm^2) were then compared.

Cortical interaction between natural and prosthetic flash stimuli

Three types of the flash stimuli were applied to investigate the interactions of cortical responses to natural and prosthetic visual stimulation: a 1mm central prosthetic stimulus, (910nm, 4mW/mm^2, 10ms, 2Hz), a peripheral visible stimulus (525nm, 250nW/mm^2, 10ms, 2Hz), and a combined visible and prosthetic stimulus (Figure 2B). In order to neutralize the effect of the physiological state of the animal (e.g., the depth of anesthesia, body temperature), stimuli were projected at 2Hz in a random sequence, with a total of 300 repetitions. The average cortical response to each stimulus type was then calculated. The response to the combined central prosthetic with a peripheral natural stimulus was compared to a similar natural pattern composed of a central 1mm disk, encircled by a peripheral ring (Figure 2A).

Natural and prosthetic responses to contrast steps

To study the response to luminance steps with natural or prosthetic stimuli, irradiance was modulated to generate a 100, 50, 25, 12.5, 6, and 3 percent luminance change. This was calculated according to the Michelson contrast formula: (Imax - Imin)/ (Imax + Imin) (1), where Imax is the highest intensity (4mW/mm^2 for NIR and 0.25μW/mm^2 for visible light) and Imin is the lowest (Figures S3A and S3B). Irradiance was modulated every 500ms in a sequence of 300 repetitions, while recording cortical responses to both the increase (''ON response'') and the decrease (''OFF response'') of the light intensity, similar to [9].

To investigate the interaction between cortical responses to natural and prosthetic luminance steps, we used the same central disk and peripheral annulus, as in flash stimuli (Figures 2A and 2B). Irradiance was modulated every 500ms in a sequence of 300 repetitions, with luminance steps of 100, 50, and 25% (Figures 3A and 3B). Cortical responses for increasing luminance (''ON response'') were analyzed.

Lateral interactions between the target and flankers in natural vision

To study the characteristic cortical interactions between the central target and peripheral flankers in the rodent visual system, experiments were first performed on normally sighted rats with no implant. The alternating grid stimuli (2 cycles per mm (CPM), 10ms pulses at 41Hz with pattern alteration at 2Hz, similar to [14]) projected using the green light were composed of a central 1mm diameter disk and two collinear flankers of the same size and spatial frequency, located above and below the target (Figure 4A), similar to the stimulus described in [5]. The stimuli in each experiment consisted of either the target, flankers, or a combined stimulus (target and flankers). These stimuli were projected in a sequence with a total of 300 repetitions for each type. The contrast level of the targets was set to 25, 50, 75, or 100%, whereas the flankers' contrast was maintained at 100%.

Lateral interaction between prosthetic target and natural flankers

The same procedure as described above was performed on wild-type rats implanted subretinally with a photovoltaic array (1mm diameter) (Figure 4B). Experiments were performed 4 weeks post implantation, after the photoreceptors above the implant have completely degenerated, as we previously reported [43], whereas the surrounding retina remains normal, as shown in Figure 1B.

The projected image sequence was composed of: target - alternating patterned activation of the implant by NIR illumination (2 CPM, corresponding to 3-4 pixels); flankers – alternating collinear patterned flankers activation of the region of the natural retina above and below the target with 532nm light, and a combined prosthetic target with natural collinear flankers (Figure 4B). The contrast level of the target was set to 25, 50, 75, or 100%, whereas the flankers' contrast was maintained at 100%.

Pharmacological intervention

To identify the mechanisms underlying lateral interaction, which we hypothesize is mediated by $GABA_A$, we performed the same experimental paradigm described above (flankers and target) before and after administering the known $GABA_A$ antagonist - Bicuculline. It was administered intraperitoneally (0.35mg/kg) [44], and the effect on the cortical responses was investigated for both natural vision and for combined prosthetic and natural stimuli (Figure S2). The same experiments were also performed following a 72hr washout of Bicuculline.

QUANTIFICATION AND STATISTICAL ANALYSIS

VEP recording and analysis

Visual cortex activity induced by the various visual, prosthetic, or combined stimuli described above was acquired through the cranially implanted screws [43] and recorded using AlphaSnR (Alpha Omega, Ltd.) with a sampling rate of 1375Hz, using x20 amplification, and 4-200Hz LFP filters. The acquired signals were then analyzed offline using a custom MATLAB program (The Mathworks, Waltham, MA, USA). The visual evoked potential (VEP) signal was the average 300 repetitions for each stimulus type. Each experiment consisted of several different stimulus types projected sequentially, with each single stimulus type repeated 6 times. To study the interactions between target and flankers, the average response to each stimulus type excluded the responses to the first two repetitions of each stimulus type in order to mitigate the effect of adaptation to a new type of stimulus. A linear summation of the prosthetic and natural responses was calculated through a simple algebraic summation of the corresponding waveforms induced by the NIR and visible stimuli presented separately. The linear summation was then compared to the signal obtained with the actual combined stimulus (NIR + visible projected simultaneously). The noise level of the recorded signals was calculated from the data segments where no stimulus was presented.

DATA AND CODE AVAILABILITY

The data supporting the current study have not been deposited in a public repository because it was generated by a customized software in a non-standard format. The data is available from the lead contact (yossi.mandel@biu.ac.il) on request.