Cortical Activation Via an Implanted Wireless Retinal Prosthesis

Peter Walter,[1] *Zoltán F. Kisvárday,*[2,3] *Michael Görtz,*[4,5] *Nils Alteheld,*[1] *Gernot Rossler,*[1] *Thomas Stieglitz,*[6,7] *and Ulf T. Eysel*[2]

Purpose. To demonstrate local cortical activations in the primary visual cortex of the cat as a result of retinal electrical stimulation by means of a completely wireless-controlled, implantable retinal prosthesis in a series of acute experiments.

Methods. The transfer of energy to drive the device and signals to activate any combination of 25 retinal electrodes was achieved completely wirelessly by an external transmitter positioned in front of the eye. Individually configured electrical stimuli were applied via any combination of 25 electrodes, on sending the necessary pulse parameters to the implant. Placement of the implant onto the retinal surface was achieved after lensectomy and vitrectomy in the cat. Fixation was performed with a retinal tack. Cortical activation patterns were recorded by means of optical imaging of intrinsic signals.

Results. Implantation and fixation were successfully performed in three cats. Wireless activation of the implant by radiofrequency was demonstrated by recording of stimulus artifacts from the sclera. Local activation of the visual cortex measured by optical imaging of intrinsic signals revealed a shift of cortical response that was well correlated with a change in the position of the activated retinal electrodes.

Conclusions. The results demonstrate the retinotopic activation of the visual cortex using a completely wireless, remote-controlled retinal implant. (*Invest Ophthalmol Vis Sci.* 2005; 46:1780–1785) DOI:10.1167/iovs.04-0924

Electrical stimulation of the retina has been considered a possible new treatment in cases of blindness associated with retinitis pigmentosa (RP) or other progressive degenerations of the retina. Even though experiments using electrical stimulation of the retina to study its function were performed more than 50 years ago[1–3] and the first reports on retinal stimulation related to a possible treatment were published more than 30 years ago,[4,5] a remotely controlled implantable medical device for human application is still not available. Histopathological studies demonstrated that in progressive retinal degeneration such as occurs in RP, despite the near complete loss of photoreceptors, even in advanced cases, second- and third-order retinal neurons can be found, mainly in the macular area.[6–8] Furthermore, direct electrical stimulation of the inner retinal surface in subjects with long-standing blindness from RP yielded visual sensations in these patients, described as circumscribed visual percepts.[9] These studies encouraged several research groups to start or continue work on therapeutic retinal stimulation for the blind. After considerable progress in the fabrication of microsystems based on flexible substrates and further developments in the integration of many electrical functions in very small microchips, the construction of such a device seems now to be possible. Devices for electrical stimulation of the retina have already been implanted in humans with RP-related blindness. Chow et al.[10] used light-driven microphotodiodes, which they implanted in the subretinal space, whereas Humayun et al.[11] implanted epiretinal microcontact devices that were connected with a cable to a receiver element outside the eye. In both studies, patients reported some visual sensation.[10,11] In 1995, a German research team (EPI-RET) launched a program to develop a completely wireless device for the electrical stimulation of the inner retinal surface. The system consists of extraocular components for image capturing, signal processing, energy, and signal transmission, and it also consists of an intraocular electrode array and an interface to receive energy and signals to generate current pulses for retinal stimulation.[12,13] The general design of the system is shown in Figure 1. The purpose of our study was to answer three questions: Is it possible to implant such a device in the vertebrate eye? Does the device function after the implantation procedure? Is it possible to activate the visual cortex using the device?

Methods

Preparation of Animals

The retinal prosthesis was implanted in anesthetized and paralyzed normal adult cats followed by electrophysiological recordings from the cornea and optical imaging of intrinsic signals from the visual cortex. The experimental procedures were performed according to the guidelines of the German Animal Welfare Act and conformed to the legal requirements of the National Academy of Sciences USA (Guide for the Care and Use of Laboratory Animals, 1996) and according to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. For initial anesthesia, the animals received a mixture of intramuscular ketamine (7 mg/kg; Ketanest; Pfizer, Berlin, Germany) and xylazine (1 mg/kg; Rompun, Bayer Belgium, Sint-Truiden, Belgium). After the pupils were dilated with atropine sulfate (1%, Atropin-POS) and the nictitating membranes retracted with phenylephrinhydrochloride (5%, Neosynephrin-POS; both from Ursapharm, Saarbrücken, Germany), the eyes of the animal were thoroughly inspected with an ophthalmoscope. During initial surgery the eyes were protected against dehydration with neutral contact lenses. The femoral artery was cannulated and a tracheotomy was performed. All wounds and pressure points

From the [1]Department of Ophthalmology and the [5]Institute of Materials in Electrical Engineering, RWTH Aachen University, Aachen, Germany; the [2]Department of Neurophysiology, Ruhr-Universität Bochum, Bochum, Germany; the [3]Department of Anatomy, Histology, and Embryology, University of Debrecen, Debrecen, Hungary; the [4]Fraunhofer Institute for Microsystems and Electronics, Duisburg, Germany; the [6]Neural Prosthetics Group, Fraunhofer Institute for Biomedical Engineering, St. Ingbert, Germany; and the [7]Institute of Microsystems, University of Freiburg, Freiburg, Germany.

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Corresponding author: Peter Walter, Department of Ophthalmology, RWTH Aachen University, Pauwelsstrasse 30, 52074 Aachen, Germany; pwalter@ukaachen.de.

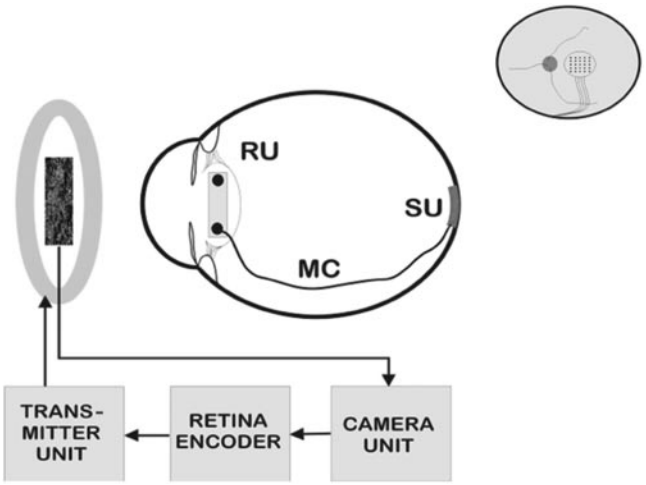

FIGURE 1. The general concept of the epiretinal retina implant approach. The camera unit captures a scene that is analyzed by a retina encoder, which is a tiny computer, to calculate the stimulation sequences from the incoming picture signal. This signal is transferred to a transmitter unit that sends the energy to drive the implant, together with the signal encoding the stimulation pulse parameters for each of 25 retinal electrodes by means of radio frequency that reaches the intraocular implant by magnetic coupling. The extraocular components are integrated into the frame of spectacles. *Right*, *top*: diagram shows the stimulator unit placed on the retinal surface. RU, receiver unit, which captures the incoming data and energy; MC, microcable, which connects receiver and stimulator unit; SU, stimulator unit (microelectrode array), which acts as a flexible microcontact foil adherent to the retinal surface.

were also treated with a local anesthetic (Xylocain gel; Astra Chemicals, Wedel/Holstein, Germany). Prolonged anesthesia was maintained with halothane (Halothan Eurim; Eurim-Pharm, Piding, Germany) during eye surgery (0.6%–1.0%) and recordings (0.4%–0.6%), and breathing was sustained by artificial ventilation with a mixture of N_2O/O_2 (70%:30%). For muscle relaxation, alcuronium chloride (0.15 mg/kg per hour, Alloferin; Hoffman-LaRoche, Grenzach–Whylen, Germany) was perfused with glucose (24 mg/kg per hour; Glokosteril) and Ringer solution (Ringerlösung; both from Fresenius, Bad-Homburg, Germany) through the femoral cannula. During surgery and recording, the vital physiological parameters such as end-tidal CO_2 (3.8%–4.5%), blood pressure (90–140 mm Hg), heart rate, and body temperature (37.5–38°C) were continuously monitored. The animal was positioned in a stereotactic frame, and the head was fixed. During eye surgery, the animal was kept in an upright position so that the eyes faced upward. For the stimulation and recording experiments the animal were in a horizontal position. All experiments were performed as acute experiments.

Eye Surgery

The conjunctiva was opened along the temporal limbus. A 2.8-mm corneal incision was made, and a viscoelastic gel (Healon; Pharmacia, Erlangen, Germany) was injected, to maintain the depth of the anterior chamber and to protect the corneal endothelium. A capsulorrhexis was performed, and the clear lens was removed with a standard phacoemulsification procedure. Remnants of lens cortex were removed with the phaco tip. An infusion cannula was placed in the anterior chamber and sutured to the limbus. The posterior leaf of the capsula was opened at the inferior edge with the ocutome inserted through the corneal incision. Through this opening, the central vitreous was removed and the globe was filled with perfluordecalin (PFD; Acrideca; Acritec, Glienecke, Germany). Next, the incision was enlarged to 10 mm, the anterior chamber filled again with the viscoelastic gel (Healon; Pharmacia), and the receiver unit of the prosthesis was carefully inserted in the capsular bag. With a few sutures, the corneal incision was narrowed, and the stimulator was pushed into the anterior chamber through the remaining opening. The remaining gap of the incision was closed, except for a small opening, for the following manipulations. With a small hook, the stimulator was pushed through the opening of the posterior capsula and placed on the PFD surface. The central aperture of the receiver unit allowed visual inspection of the retina, so that manipulations in the posterior segment were possible with the receiver already in place. The PFD was then carefully removed and exchanged with physiologic saline (BSS; Alcon, Freiburg, Germany) and, simultaneously, the stimulator was placed onto the retinal surface in the region of the area centralis (AC). Finally, the stimulator was fixated with a titanium retinal tack (Geuder, Heidelberg, Germany), the remaining corneal openings were closed with nylon sutures, and the infusion was removed.

Transmitter and Prosthesis

The stimulating pattern was generated with custom-made software and a personal computer. The stimulation software was synchronized with the recording of intrinsic cortical activity by optical imaging. The transmitter was fed with the stimulus parameters through a standard parallel computer interface, and the data were received in the interior of the eye by an inductive link modulating the carrier frequency with an amplitude shift keying (ASK). The prosthesis was powered by the energy of the external radiofrequency (RF) field through magnetic coupling. After energy and data signals were separated from the RF field, the decoded information was transferred via a microcable to the stimulating unit, which can drive up to 25 electrodes, with bipolar current pulses that are adjustable to pulses from 0 to 1130 μs with currents from 0 to 100 μA. A pulse rate up to 500 Hz was possible. As a standard stimulation paradigm biphasic pulse series were applied with a pulse of 250 μs for each phase (negative phase first) and a stimulation amplitude of 100 μA for each phase (negative phase first). Each stimulation event consisted of a train of eight biphasic pulses with a stimulus frequency of 145 Hz. Each train was repeated 16 times with a frequency of 20 Hz leading to a total stimulation cycle of 800 ms.

Recording of Stimulation Artifacts

To test the electrical function of the prosthesis after the implantation, recordings were performed with one silver electrode placed episclerally at the implanted eye and an indifferent electrode at the forehead. The signal was differentially amplified with a low-noise, battery-operated amplifier (DAM-50; WPI, Sarasota, FL) and recorded with a standard digital oscilloscope.

Optical Imaging of the Visual Cortex

The spatial distribution of cortical neuronal activity in response to stimulation with the retinal implant was monitored by the method of optical imaging of intrinsic signals.[14] Herein, only a brief description of the imaging and data acquisition procedures is provided. A craniotomy was made over the central representation of the primary visual cortex (between the Horsley-Clarke coordinates AP −4 and +9 mm and ML 0.5 and 6 mm) in the hemisphere ipsilateral to the retinal implant. A round metal chamber was then cemented (Paladur; Heraeus Kulzer, Wehrheim, Germany) onto the surrounding bone, the dura mater was removed, and the chamber was filled with silicone oil (50 cSt; Aldrich, Milwaukee, WI) and sealed with a glass cover. Optical imaging was then performed (Imager 2001, running VDAQ-NT data acquisition software; Optical Imaging, Mountainside, NJ). Activity images were collected with a charge-coupled device (CCD) camera focused 750 μm below the pial surface. Two different stimulation protocols were used. For control, monocular (in the nonsurgical eye) visual stimuli composed of full-field luminance gratings of four orientations were used that resulted in characteristic patchy activity patterns, called iso-orientation maps.[15] In the test protocol, the activity pattern of the cortex was recorded before, during, and after activation of the retinal implant without visual stimulation (both eyes occluded). In each protocol,

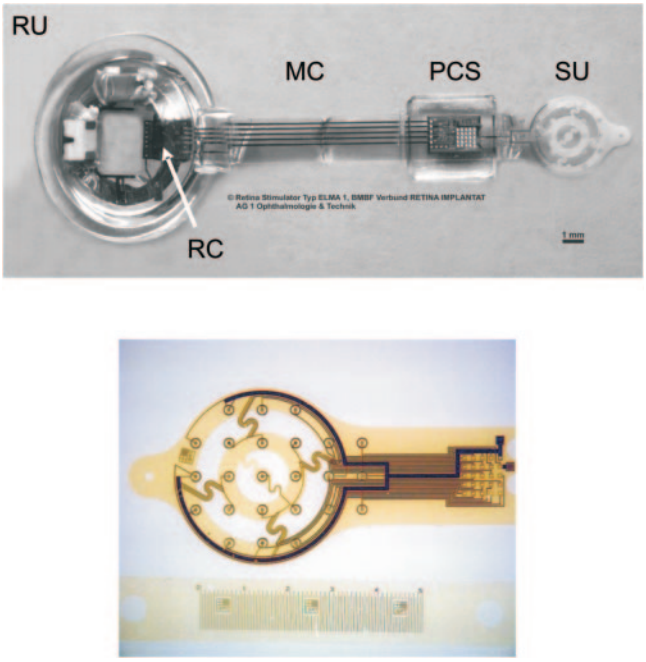

FIGURE 2. *Top*: photograph of the EPI-RET intraocular device. At *left* is the artificial lens (made of polydimethylsiloxane; PDMS) with the receiver unit (RU) for data and energy transfer and the receiver microchip (RC). At *right* is the stimulator unit (SU) consisting of a microchip integrating 25 individually programable current sources (PCSs) and a polyimide matrix with 25 microelectrodes connected with the receiver unit via a microcable (MC). *Bottom*: photograph of implant substrate with the electrode array before assembly of the stimulator chip (pad array on the *right*). For electrical stimulation, different inner electrode dots can be used as cathode and anode, or an inner dot and outer ring can be used as the electrode pair, respectively. Electrode diameter (*inner dot*), 70 μm; electrode distance, 750 μm.

video frames were collected for 4.5 seconds commencing 1 second after stimulus onset (visual or implant-induced).

RESULTS

Remotely Controlled Retinal Stimulator

The intraocular device, shown in Figure 2, is designed as a hybrid microsystem mounted on a tiny and flexible foil carrying and connecting the microchips to the electrode array. The foil is made of polyimide as a carrier and for insulation. It has a thickness of 15 μm and is produced with a technique that fulfills the requirements for neural microimplants.[16] The electrode array, the microcable, and the electronic circuits were monolithically integrated to reduce the size and to increase functional reliability. The electrodes were made of platinum and had a diameter of 70 μm and an interelectrode distance of 750 μm. The substrate containing the individual electrodes comprised three rings with S-shaped connections to ensure good three-dimensional flexibility and to adapt to the shape of the eye after implantation (Fig. 2, bottom). We chose a combination of hybrid and monolithic integration technologies to implement a complex system that matches the size restrictions of the eye.[17] A wire coil, a capacitor and a diode were mounted by means of a surface mounting technology (SMT). The receiver and the stimulator electronics were fabricated as application-specific integrated circuits (ASICs), using silicon technology. They were assembled on the substrate with the microflex interconnection (MFI) technique,[18] which reaches the integration density of flip-chip assembling without the use of solder or any additional material except gold. For the final electrical insulation, the entire implant except the electrodes was coated with poly-*para*-xylylene parylene C, by a vapor deposition polymerization process. This material prevents short circuits and is noncytotoxic, according to the international standard ISO 10993-12.[19] Finally, the receiver and stimulator parts of the implant were molded into silicone. The receiver was designed in the shape of an artificial intraocular lens with a central 2-mm^2 aperture (Fig. 2, top). In this way, already existing implantation techniques could be adopted and the vitreoretinal surgical procedures could be visually monitored.

Surgery

The surgical procedure consisted of modified standard techniques of human ophthalmic surgery and proved feasible. In all three cats operated on, the lens and the vitreous were removed without any complications. However, the correct placement of the receiver part of the implant in the capsular bag was difficult. Rather, it was easier to place the receiver unit, which is embedded in a disclike artificial intraocular lens, so that its edges were placed behind the iris in the sulcus ciliaris so that the artificial, as that left more space underneath the receiver unit, allowing further management with instruments in the posterior segment. The placement of the stimulator head (encapsulated electrode array) of the implant onto the retinal surface was achieved in all cases (Fig. 3), although it was difficult to reach exactly the position of the AC. In one case, the implant was placed directly onto the AC, whereas in the other cases, the position was approximately 1 to 2 disc diameters superior to the AC. A direct contact between the electrodes and the retinal surface was initially seen in all cases. However, a permanent fixation of the stimulator to the retinal surface with a retinal tack was achieved in only two cases; in the third case, a tack could not be inserted, and the stimulator lost contact with the retinal surface. In this case, perfluordecalin, a high-density, high-surface-tension liquid, was also injected, to press the stimulator onto the retinal surface.

After implantation of the intraocular device, recordings of stimulus artifacts with episcleral electrodes showed that the implant remained functional in all three cases. A programmed stimulus waveform sent to the implant by the transmitter coil (Fig. 3) was correctly received, decoded, and the decoded pulse waveforms were released at the stimulus electrodes, as shown by recordings of stimulus artifacts from episcleral electrodes. With this method, we were able to verify continuously the function of the complete system including software, transceiver, and prosthesis, throughout the optical imaging experiments.

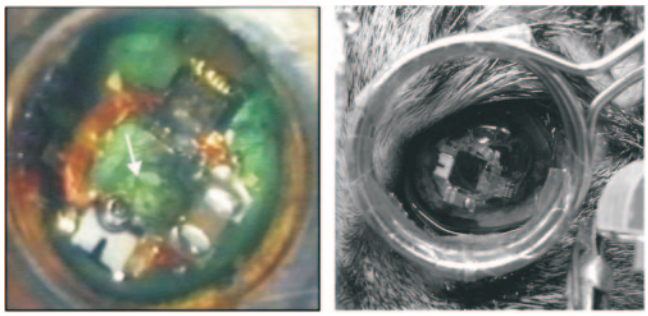

FIGURE 3. *Left*: the receiver unit is shown in the anterior segment and the microelectrode array placed on the retinal surface (*arrow*). *Right*: view of the transmitter coil in front of the surgical eye and the intraocular receiver unit.

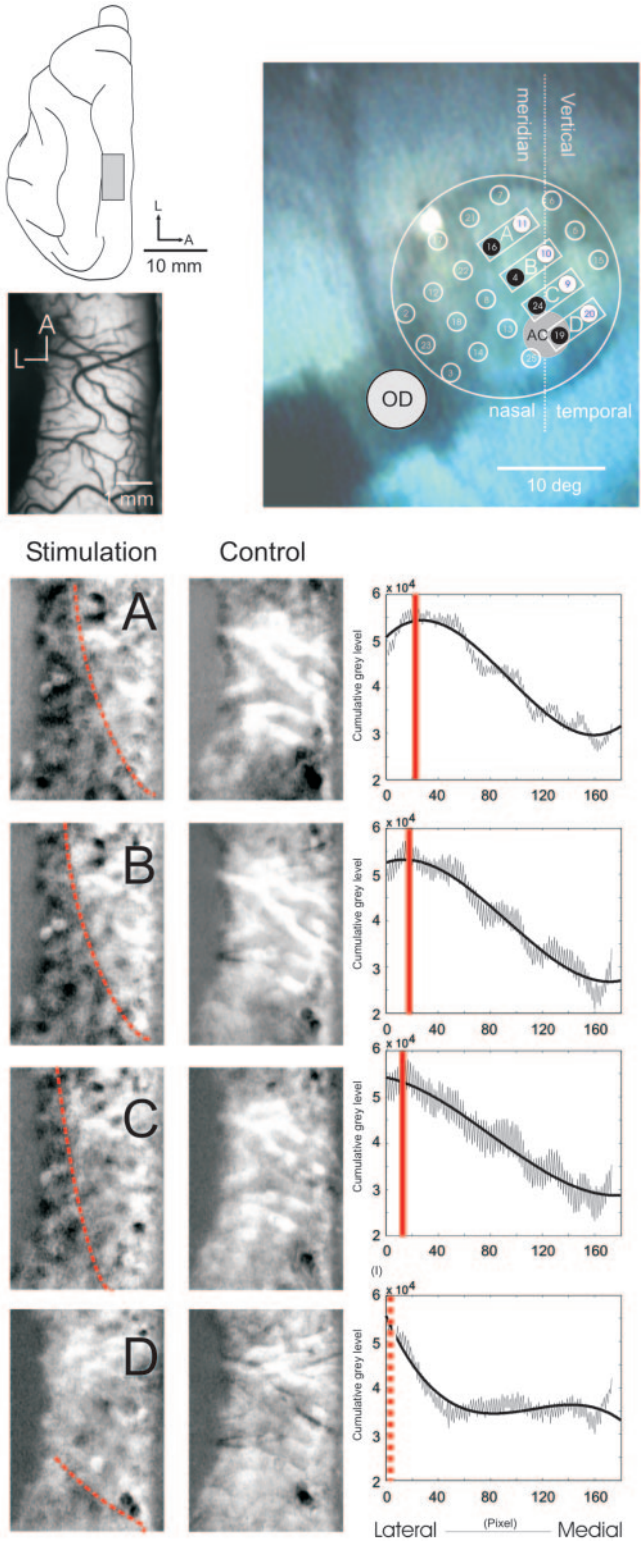

FIGURE 4. Optical imaging of the visual cortex after electrical stimulation of the inner retina with a completely implanted retinal prosthesis. *Top left*: drawing and light micrograph outlining the left hemisphere with the region exposed for optical imaging. *Bottom right*: a schema of the electrodes overlying a fundus image taken directly after implantation of the telemetric device. The electrode array (dimly visible in the background) was positioned mainly in the upper nasal hemiretina across the AC. Individual electrodes are numbered. The positions of the four electrode pairs used for stimulation are marked A, B, C, and D (*black*: anodal poles; *white*: cathodal poles). Activation of the electrode pairs resulted in cortical activation as shown, respectively (**A–D**). *Dark areas*: strongly active regions; *light zones*: less-active regions. *Left*: cortical activation appeared in a patchy fashion mainly in the left part of the imaged cortical region. Furthermore, the border between active and less active regions shifted according to the retinal stimulation site, in line with the visuotopic organization of the cortex. As the stimulation site moved farther lateral and downward in the retina, the activated cortical regions became more lateral and posterior. For a better comparison, *broken black lines* denote the gradual shift of the border between active and less active regions. It is noteworthy that electrode pair D induced activation only in the most caudal part of the imaged region (**D**). *Middle*: results of control recordings that were interleaved with the test conditions. In control experiments, optical images were acquired without electrical stimulation. *Right*: cumulative gray-level distributions of image pixels summed along the anterior–posterior axis of activity images shown in (**A–D**). *Thick lines* represent polynomial fits to the row data. Clearly, the position of peaks (*red bars*) along the latero-medial (LM) axis gradually shifted from medial to lateral as the activation site moved from A to D. For electrode pair D, the retinotopic region was chiefly outside (posterior to) the imaged window; therefore, for the most part of the image only a weak response can be seen. Nevertheless, the corresponding peak (*stippled red line*) of the response field lies most laterally of all conditions. OD, optic disc; A, anterior; L, lateral.

Optical Imaging of the Primary Visual Cortex

A crucial test of the functional efficacy of the implanted electrodes was to detect cortical activation on telemetric stimulation. To this end, optical imaging of intrinsic signals was used because this technique can reveal neuronal activity changes, both subthreshold and spike-related, two-dimensionally and at high spatial resolution across large cortical regions.[20] We found that telemetric stimulation of a single electrode pair gave rise to an increased activation of the visual cortex, extending several millimeters parallel to the cortical surface (Fig. 4). Activation of a neighboring electrode pair caused a predictable positional shift of the activated cortical zone. This phenomenon is illustrated in Figure 4 showing a case in which four electrode positions (pairs) of the implant were tested. The four positions were along a line at an oblique angle with the vertical meridian occupying mainly the upper nasal retinal quadrant and the neighborhood of the vertical meridian. The corresponding cortical activity (Figs. 4A–D, dark regions) displayed a shift along both the anteroposterior and the mediolateral axis, in agreement with the known retinotopic arrangement of the electrodes and the visuotopic organization of this part of the visual cortex.[15] A gray-scale analysis of the activity maps confirmed our qualitative observations, by showing a shift of the darkest zones (most active) from medial to lateral and from rostral to caudal (A–D), when progressively more ventral electrode pairs were activated. Another noteworthy feature was the patchy activity pattern, due to telemetric stimulation, which strongly resembles the pattern and typical interpatch distances of iso-orientation domains observed in previous reports of orientation maps.[21] It is noteworthy that such a "simple" stimulation paradigm was able to elicit coherent activity of remote cortical columns.

DISCUSSION

We have shown that cortical regions can be activated by stimulation with individually programmed and remotely controlled electrical pulses released from electrodes of a wireless and batteryless retinal prosthesis. The experiments proved that a complex device for electrical stimulation of the inner retinal surface can be fabricated with the use of cutting-edge technologies from different engineering fields. Laboratory tests of the function of each implant were performed after each process

step, ensuring the functionality of each assembled component and the final implant. The main challenges in fabricating such a wireless device were the realization of a stable signal and energy transfer using an 11-MHz carrier signal generated by the transmitter with the stimulus waveform parameters at each electrode superimposed on this signal; the realization of an extremely small receiver for rectifying of the supply voltage, for clock extraction, demodulation, and decoding of the waveform signals; the packaging of all electronic components within a very small implant; the hermetic sealing of all electronic components with parylene C; and the fabrication of stimulation electrodes with efficient charge delivery capacities. Such devices can be implanted in the vertebrate eye. Although the morphology of the cat's eye differs considerably from that of the human, the cat was chosen for a functional test of the prosthesis because the functional anatomy of the visual system of the cat is relatively well understood. In fact, the surgical challenge of implanting a complex telemetric device consisting of a receiver and a stimulator is thought to be more difficult in the cat than in the human eye. Whereas in the human eye vitrectomy and instrumental manipulation can be performed very safely through the pars plana, in the cat the same approach could cause severe bleeding or retinal detachment when instruments are inserted through the sclera. Therefore, in the cat, implantation had to be approached through the cornea. Tack fixation was an effective technique for stabilizing retinal stimulators on the retinal surface.[22,23] In the experiments described herein, bleeding in the tack area occurred in one case only. For future experiments and in human implantation tests, we recommend that the tack not be placed directly in the area of the stimulating electrodes, but at some distance away. The results demonstrate that the implant is mechanically robust and will survive the surgeon's manipulations and remain completely functional afterward, an important prerequisite for future applications in humans.

Most important is that the retinal prosthesis we have described elicited cortical activation that had been expected on the basis of previous investigations with cable-bound electrodes and hand-held devices.[24,25] As far as we know, our data represent the first successful experiments in which local cortical activation has been generated by a retinal prosthesis that is completely implanted in the eye without any cable connection passing through the eye wall and is driven by a transponder system for energy and signal transmission. The cortical activation was achieved in the expected and retinotopically correct cortical area. The border of cortical activity shifted by 2 mm toward the posterior when the retinal activation shifted from electrode pair A to pair C (Fig. 4; top right). According to the magnification factors derived for area 18 of the cat[15] this corresponds to approximately 5.3° of visual angle. Because the distance between the electrode pairs A and C along the vertical meridian is 1.1 mm (4.8° of visual angle), in the eye, there is a good agreement between the sites of retinal stimulation and cortical activation. Similarly, the lateromedial shift of the peak of cortical activation was in line with the spatial separation of the retinal electrodes and the cortical magnification factor along this region. The comparatively large area of cortical activation can be explained by local excitation of the retinal network, additional activation of fibers of passage, and the possible uneven efficacy of the different electrodes. Because of the larger magnification factors in human subjects, a better spatial resolution can be expected with the same device when applied in blind patients.

One bottleneck of the current implant version is that it does not allow a read-out of the functional parameters of the implant itself. The communication between the transmitter outside the eye and the implant is unidirectional in sending data and energy to the implant. A bidirectional data stream is desirable (e.g., to transmit impedance data between electrodes or other information on the internal state of the implant to the external device to modify its action, perhaps by adapting stimulus currents).

Future experiments are planned with more complex spatiotemporal stimulus patterns and chronic implants, to test long-term biocompatibility of materials, signal and energy transfer, and stability of long-term electrical stimulation in terms of stimulation thresholds and retinotopy. These experiments and also attempts to integrate higher numbers of electrodes in a pattern resembling ganglion cell density, the fabrication of three-dimensional structured stimulation electrodes to optimize charge transfer to the tissue, bidirectional interaction between the external and internal parts of the prosthesis, and improved fixation techniques are necessary before implantation in humans should be considered.

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Appendix

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