Stimulation with a Wireless Intraocular Epiretinal Implant Elicits Visual Percepts in Blind Humans

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Purpose. Electrical stimulation of retinal neurons has been shown to be a feasible way to elicit visual percepts in patients blind from retinal degenerations. The EPIRET3 retinal implant is the first completely wireless intraocular implant for epiretinal stimulation. Stimulation tests have been performed during a clinical trial that was carried out at the eye clinics of Aachen and Essen to evaluate the safety and the efficacy of the implant.

Methods. Six legally blind retinitis pigmentosa patients were included in the study. In accordance with the regulations laid down in the study protocol, three 1-hour perceptual tests for each subject were performed within 4 weeks of surgery. Stimuli were charge-balanced square current pulses of various durations and current amplitudes.

Results. All subjects reported visual percepts as a result of electrical stimulation by the implant. Thresholds for eliciting visual percepts varied between them but were below the safety limits of electrical stimulation. Stimulation success depended stronger on pulse duration than on current amplitude or total charge delivered. Subjects were able to discriminate between stimulation patterns of different orientations or at different locations of the electrode array.

Conclusions. The EPIRET3 system is suitable to elicit visual percepts in blind retinitis pigmentosa patients. (*Invest Ophthalmol Vis Sci.* 2011;52:449–455) DOI:10.1167/iovs.09-4410

Electrical stimulation of intact neurons in the visual system is considered a promising approach for restoring vision in blind subjects.[1–6] Several approaches are being pursued to investigate the use of implantable devices for the electrical stimulation of the retina,[7–12] the optic nerve,[13,14] the lateral geniculate nucleus,[15] and the visual cortex.[16–19] In blind subjects with retinitis pigmentosa (RP), phosphenes can be elicited using electrical stimulation of the retina, either epiretinally,[20,21] (see also Richard G, et al. *IOVS* 2009;50:ARVO E-Abstract 4580), subretinally,[22,23] or transretinally.[24]

All previously tested retinal prostheses, however, have in common that the device is controlled from outside the eye. Typically, power supply and stimulation signals are transferred by cables into the eyeball. In contrast to these prostheses, the epiretinal stimulation system EPIRET3 is the first remotely controlled wireless device implanted completely within the eye.[25] No cable connections crossing the eye's wall are required to transfer energy and data, which are provided through an inductive link by a transmitter placed in front of the eye.

The safety and efficacy of the EPIRET3 system was evaluated in a prospective clinical trial in six legally blind RP patients. Results on safety have been reported in a previous paper by Roessler et al.[26] Here, we report on the stimulation procedure and the results of stimulation tests evaluating the efficacy of the EPIRET3 system.

Methods

Technology

The EPIRET3 system consists of an extraocular part and a fully implantable intraocular part (Fig. 1). A computer system and a transmitter unit, including a transmitter coil placed in front of the eye, form the extraocular part. The intraocular device is based on a polyimide foil that carries a receiver coil, electronics for signal processing and generation of stimulation currents, and 25 stimulation electrodes manufactured from gold covered with iridium oxide.[27,28] Electrodes measure 100 μm in diameter and are arranged in a hexagonal array (Fig. 2A) with a center-to-center distance of 500 μm. Stimulation data and energy are sent to the implant by way of a wireless radio frequency link. The receiver coil picks up the electromagnetic signals and passes them to a receiver microchip. A custom-made stimulator chip generates stimulation pulses and activates the selected electrodes. Further details about the device technology have been described in previous publications.[25–28]

Implantation

The receiver module of the EPIRET3 device was positioned in place of the lens, and the electrode array was attached to the epiretinal tissue in the region of the macula using two retinal tacks.[26] The size of the implanted electrode array corresponded to approximately 10° in the upper half of the visual field.

Study Design

The primary goal of the clinical trial was to demonstrate that visual sensations could be elicited by electrical stimulation with the EPIRET3 implant and to monitor potential adverse events during a limited implantation time. The study protocol was approved by the appropriate ethics committee and was registered by the German Regulatory Authorities under Trial Number DE/CA21/A/07/Dr.SchmidtIOL/EPIRETIII. The study was performed according to GCP guidelines, the German Medical Product Law, and the Declaration of Helsinki. Activation of the implant to record visual sensations was performed during three sessions around postoperative days 7, 14, and 27, respectively. According to the experimental protocol, at day 28 the implant was removed.

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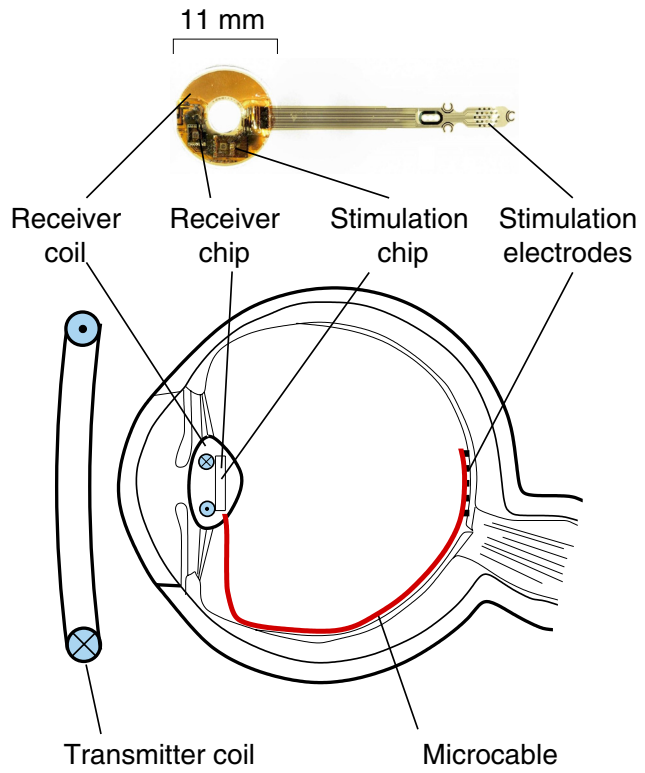

FIGURE 1. Schematic representation of an eye with a retinal implant. A receiver coil within the eye picks up the electromagnetic signals sent by the transmitter coil outside the eye and passes them to a receiver microchip. A custom-made stimulator chip generates the stimulation pulses and activates the selected electrodes placed on the epiretinal surface.

Stimulation Software

For stimulation, a custom-made software read stimulation commands from prepared files on disc and controlled transmission to the implant. In addition, a custom-made interface recorded button presses by which subjects reported the occurrences of visual percepts. All commands sent to the implant and all button press events were recorded with microsecond time precision for off-line analysis.

Subjects

Six patients, four women and two men, ranging in age from 40 to 69 years, participated in the study. Patients had been legally blind from RP for 2 to 8 years. Written informed consent was obtained from each patient. For details on the clinical examinations on each patients, we refer the reader to the reports in the paper by Roesler et al.[26]

Stimulation Procedure

Subjects were trained preoperatively with tactile stimuli to describe percepts verbally and to report the occurrence of percepts by button presses. According to the study protocol, for each subject, three stimulation sessions of 1-hour duration were permitted to determine the perceptual consequences of retinal stimulation with the EPIRET3 system. In each session, subjects sat comfortably in a chair in a dimly lit room, wearing a headset that held the transmitter coil in place at approximately 2 cm in front of the study eye. A DTL electrode[29] was placed in the lower fornix of the study eye to record stimulation artifacts for verification of the stimulation. The nonoperated eye was patched during stimulation tests, and the ambient light level was reduced to exclude a potential influence by light caused by residual light perception.[26] Initially, the correct functioning of the system was tested by delivering charge-balanced pulses of 52 μA and 446 μs corresponding to 0.29 millicoulomb per square centimeter (mC/cm^2), and recording the induced voltage changes at the DTL electrode. The subjects were then encouraged to report verbally all visual percepts and to describe their appearance. In addition, subjects were instructed to press a hand-held button whenever they perceived a visual sensation. Stimulation artifacts were monitored continuously throughout the sessions, and only those trials in which stimulation was confirmed in this way were considered for further analysis.

Stimuli consisted of series of charge-balanced biphasic square current pulses (Fig. 2B). A cathodic pulse was followed by an anodic pulse with the same current amplitude and duration. The charge balance of the biphasic pulses had been verified by current measurements in tests of the stimulation devices preceding the clinical study. Current amplitude, pulse duration, pulse frequency, and number of pulses per stimulus, as well as the electrodes to which the pulses were delivered, could be varied. Parameter ranges used in this clinical trial were chosen on the basis of stimulation tests in cats as an animal model with a previous version of the EPIRET retina implant.[30,31] Stimulation currents were in the range from 3.2 μA to 100 μA, and pulse durations were in the range from 27 μs to 878 μs (Pulse duration always refers to duration per phase). These parameter ranges were divided into 10 and 16 steps, respectively, in roughly equidistant intervals on a logarithmic scale. Stimulus duration was 1.5 seconds, with pulse train frequencies of 20 Hz or 100 Hz. For each pulse train of five charge-balanced pulses, 2 of 25 electrodes of the implant were selected through which the current was delivered—that is, we performed bipolar stimulation between two electrodes of the same size. To construct more complex spatial stimulation patterns, several electrode pairs were activated successively, separated by a delay that corresponded to the temporal distance resulting from pulse train frequency. For example, the stimulation onset delay between electrode pairs was 10 ms when pulses delivered to one electrode pair were repeated at 100 Hz. Stimulation started with a delay in the range of 500 to 3000 ms introduced by the controlling software, and subjects were unaware of when a stimulation began or ended. Similarly, subjects had no information about which stimuli were used or which stimulus parameters were varied. Whenever a subject reported a visual percept, verbally or by pressing a button, the response was classified as "yes" for this trial; otherwise the response was classified as "no." During one stimulation session, 113 stimulus trials per subject could be performed on average.

In a subset of trials, different values for pulse amplitude and duration were used to determine for each subject the stimulation strengths required to elicit visual sensations. Because of the limited time for

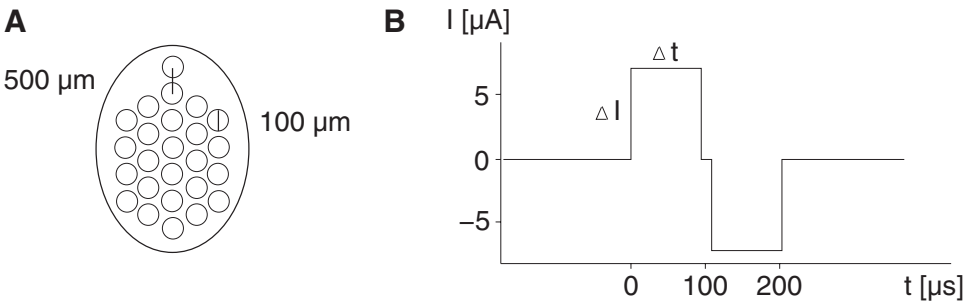

FIGURE 2. Properties of retinal stimulation. (**A**) Geometry of the electrode array. Electrode diameter (100 μm) and spacing (500 μm center-to-center) are not drawn to scale. The electrode array subtended approximately 10° in the visual field. (**B**) Time course of a biphasic stimulation current pulse of 6.5-μA amplitude and 94.5-μs duration per phase.

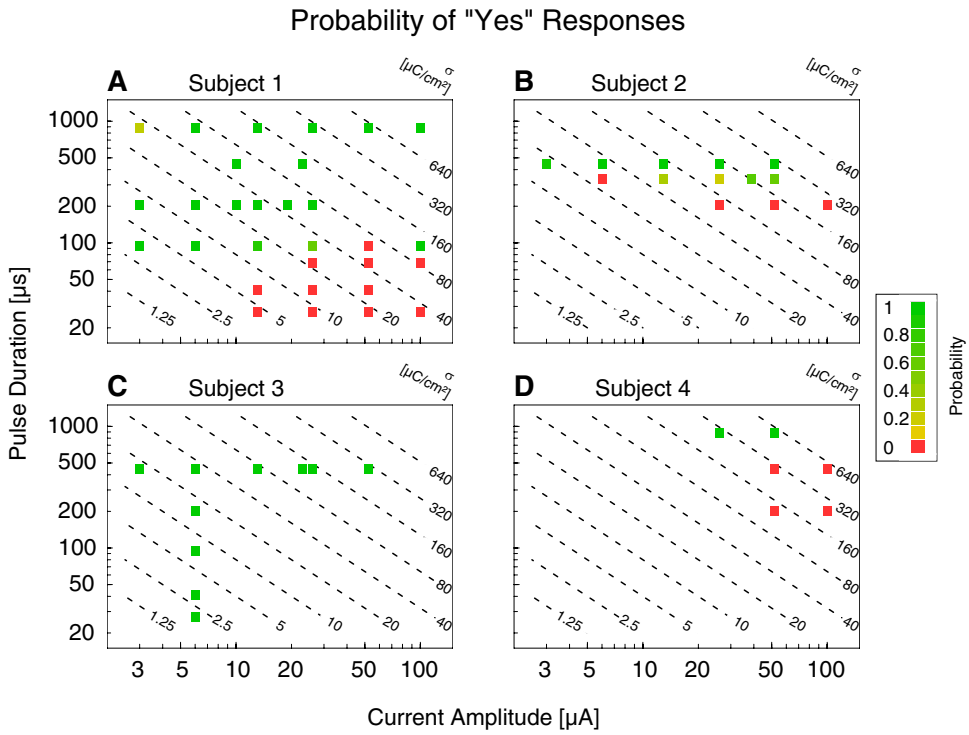

FIGURE 3. Dependence of stimulation success on stimulus parameters. Frequency of "yes" responses to stimuli with different current amplitudes and pulse durations. Each data point represents between 1 and 5 responses; totals are 58 (**A**), 62 (**B**), 15 (**C**), and 20 trials (**D**). Color coding shows the percentage of "yes" responses. *Oblique dashed lines*: Stimuli of equal charge density. For subjects 1, 2, and 4, stimulation success depended mainly on pulse duration, not on charge density.

stimulation tests, we did not determine thresholds for single electrode pairs. Instead we activated all electrodes in each trial, delivering pulses to several electrode pairs successively in random order. In further tests we aimed to determine how the spatial properties of stimuli matched the geometry of the visual percepts.

In addition to the stimulus currents in the ranges given, in approximately 10% of the trials the current was set to zero (catch trials). Thus, in these trials, stimulation commands were sent to the implant as in other trials, but no current was applied. The catch trials served to estimate the probability of the subjects' responding "yes" without stimulation (false positives).

RESULTS

In all six subjects, visual percepts could be elicited by electrical stimulation of the retina with the EPIRET3 system. Four of the subjects spontaneously reported visual percepts in response to the very first stimulation pulses, whereas correct functioning of the system was tested by delivering current pulses of 52 μA and 446 μs. At this point, subjects did not expect to have visual sensations, and they responded very cautiously, such as "Is it possible that I saw a burning match?" ("Kann es sein, dass ich ein brennendes Streichholz gesehen habe?"). In stimulation tests, reports of appearance and disappearance percepts correlated with the beginning and end of stimulations, respectively, although the stimulations were controlled by the software without any signs detectable by the subjects. The false-positive rate estimated from the catch trials was below 6% on average.

General Findings

Subjects 1, 2, 5, and 6 reported visual sensations in all stimulation sessions. In subjects 3 and 4, visual percepts could be elicited in only 1 of 3 stimulation sessions even though induced voltage changes at the DTL electrode could be recorded during all sessions.

Descriptions of visual percepts varied strongly between subjects. Three subjects reported colors described as red, green, blue, and yellow. Visual sensations were typically described as bright, but two of the subjects additionally reported seeing dark or black patterns. Thus, although the same stimulation patterns were used in all patients, the verbal reports indicated that interindividually they elicited different sensations.

Threshold Measurement

Quantitative measurement of stimulation thresholds was performed in subjects 1, 2, 3, and 4. Different values for pulse amplitude and duration, ranging from 3.2 μA $\times$ 27 μs to 100 μA $\times$ 878 μs, were used to determine for each subject the stimulation strength required to elicit visual sensation. In each trial, all electrodes were activated in random order by delivering trains of five current pulses to different electrode pairs successively. The delay separating activation of different electrode pairs was 10 ms (subjects 1, 3, and 4) and 50 ms (subject 2), respectively. Approximately 10% of the trials were catch trials. Figure 3 shows the responses given by subjects 1, 2, 3, and 4 to stimuli of different current amplitudes and pulse durations. Each data point represents 1 to 5 responses. Our results indicate that stimulation success depended strongly on pulse duration. If pulse duration was above an individual critical value, current amplitude, and thus charge density, necessary to elicit visual percepts dropped to very low values. These results differ markedly from typical strength-duration curves[20,32–35] and indicate that charge density may not be an adequate measure of stimulus strength for epiretinal stimulation.

Critical values of pulse duration differed between subjects. Subject 1 responded "yes" to 33 of 40 stimuli with pulse durations at or above 95 μs and to 0 of 18 stimuli with durations at or below 68 μs. However, 95-μs pulses led reliably to visual percepts with current amplitudes down to 6.5 μA (7.8 μC/cm^2), whereas 68-μs pulses were not successful even with 100 μA (86 μC/cm^2). Subject 2 responded "yes" to 37 of 38 stimuli with pulse durations of 446 μs or longer and to 7 of 24 stimuli with durations of 338 μs or shorter. When pulses of

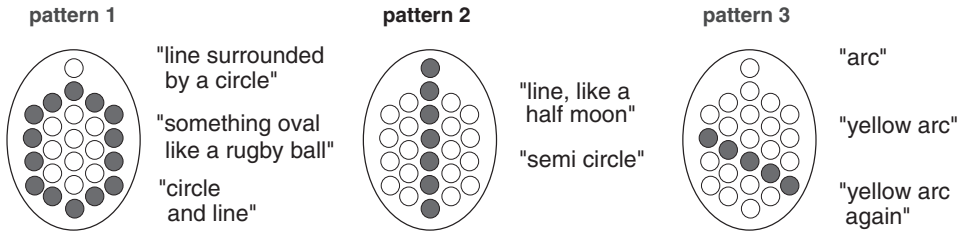

FIGURE 4. Stimulation of spatial patterns. Examples of spatial stimulation patterns (*filled symbols*) and corresponding verbal descriptions of subject 3 after repeated presentations. Stimuli are shown with respect to the visual fields of the subjects. Stimuli delivered to different electrodes elicited percepts with different perceptual properties, depending on the spatial stimulus profile.

446 μs were delivered, positive responses of the subject were reported for current amplitudes as low as 3 μA, corresponding to a charge density of 18.3 μC/cm^2. When pulse duration was 203 μs, stimulation did not elicit visual percepts even with current amplitudes of 100 μA, corresponding to a charge density of 257.9 μC/cm^2. For subject 4, despite the low number of trials (total 20), results were qualitatively similar, as for the other subjects, with a pulse duration threshold of 878 μs. For subject 3, critical pulse duration was below the lowest duration applied in the stimulation tests. This subject reported "yes" to 15 of 15 stimuli at or above 27-μs duration. Percepts were elicited successfully even when current amplitudes were decreased to 6 μA, corresponding to a charge density of 2.2 μC/cm^2. In summary, these results show that stimulation with the implant is efficacious and that stimulation success is not uniquely determined by charge density. For a given charge density, whether a current pulse elicits a percept depends strongly on pulse duration.

Qualitative Observations Supporting the Effectiveness of Stimulation

Subjects indicated the appearance of visual sensations by pressing a handheld button. In addition, verbal descriptions of the percepts were analyzed offline using a video protocol. Because of the time constraints during stimulation sessions, these tests were not sufficient to systematically analyze the relationship between stimulation parameters and qualitative percepts. Nevertheless, the observations presented below, concerning spatial patterns and retinal location of stimulation, further support the finding that stimulation was efficacious and that percepts of specific spatial patterns can be elicited with the EPIRET3 system.

Spatial Patterns

In subject 3, stimuli with the same stimulus parameters delivered to different electrodes elicited percepts with different geometric properties. When different patterns were presented repeatedly, subject 3 always reported that visual percepts ceased when stimulation ended, although beginnings and ends of stimulation were randomized and unknown to the subjects. Stimuli were delivered to electrodes forming specific spatial patterns on the electrode array, whereas current amplitude and pulse duration were kept constant at 13 μA and 94 μs, respectively. Separated by a delay of 10 ms, neighboring electrode pairs were activated successively using single current pulses. When a stimulus pattern forming an ellipse was applied, subject 3 reported seeing a circular or an oval pattern. For a pattern that defined a vertical line, a line ("roter Strich") or a semicircle ("Halbkreis") was reported, respectively. A pattern forming an oblique line was described as an oblique arc ("Bogen") (Fig. 4). Given that there could be only few repetitions, these results are not suitable to strictly prove a correlation between stimulation patterns and geometry of visual percepts, but they confirm that stimulation with the implant elicited visual percepts. Furthermore, the results suggest that subjects were able to differentiate between various stimulation patterns.

Retinal Location of Stimulation

The electrode arrays were positioned on the retinas at the lower temporal quadrants of the left eyes in subjects 1 and 6 and at the lower nasal quadrants of the right eyes of subjects 2 and 3. Accordingly, the positions of the electrode arrays corresponded to the upper right or upper left quadrants of the visual field, respectively. For simplicity, we report all relative positions and directions on the electrode array with respect to the visual fields of the patients. The size of each array corresponded to approximately 10° in the visual field, with the array center at an eccentricity between 5° and 8°. Each ellipse in Figure 5 shows the geometry of the electrode array approximately as seen by the patients. When two stimuli were applied to electrode pairs 900 μm apart on the electrode array resulting in stimulation in the right-left direction in the right visual field, subject 1 reported seeing the second stimulus pattern more nasally ("ein bisschen weiter nach der Nase zu") (Fig. 5A). Subject 2 described her percept resulting from stimulation of a pair of electrodes at the lower left and the upper right to appear above ("höher") the percept elicited by an electrode pair located at the lower edge of the electrode array (Fig. 5A). When a pair of electrodes with a retinal distance of 3000 μm was activated, subject 6 reported seeing two single points, one below the other, and estimated their vertical distance to correspond to 10 cm, as viewed at arm's length ("Zwei einzelne Punkte untereinander. So 10 cm Abstand bei ausgestrecktem Arm"). The retinal distance corresponding to this estimate is in very good agreement with the distance of the stimulation electrodes. Our data show that subjects were able to differentiate between stimulation sites on the electrode array. Although these findings are only exemplary, they may support the conclusion that stimulation with the implant is efficacious.

When electrodes that defined lines with different orientations on the electrode array were activated, subjects reported different orientations. In subjects 1 and 3, one electrode pair was activated during one trial, respectively. In subject 2 adjacent electrode pairs were activated, separated by a delay of 50 ms. Subjects 1, 2, and 3 discriminated oriented stimulus patterns, such as lines including angles of 20° and 60° (Fig. 5B), which again indicates that stimulation with the retinal implant was successful.

DISCUSSION

The clinical trial to test the EPIRET3 system aimed to show that the completely wireless retinal implant is safe and efficacious. The results on safety have been reported by Roessler et al.[26] In six RP patients, implantation and explantation were successful, and severe adverse events were not observed. Charge densities to elicit visual sensations in our subjects were below the electrochemical charge injection limit for iridium oxide electrodes[36] and within the range of charge densities for iridium oxide electrodes that have been found not to induce damage to cortical neurons in the cat.[37] The results reported in the present paper demonstrate that in this clinical trial, visual sensations could be elicited reliably with electrical pulses de-

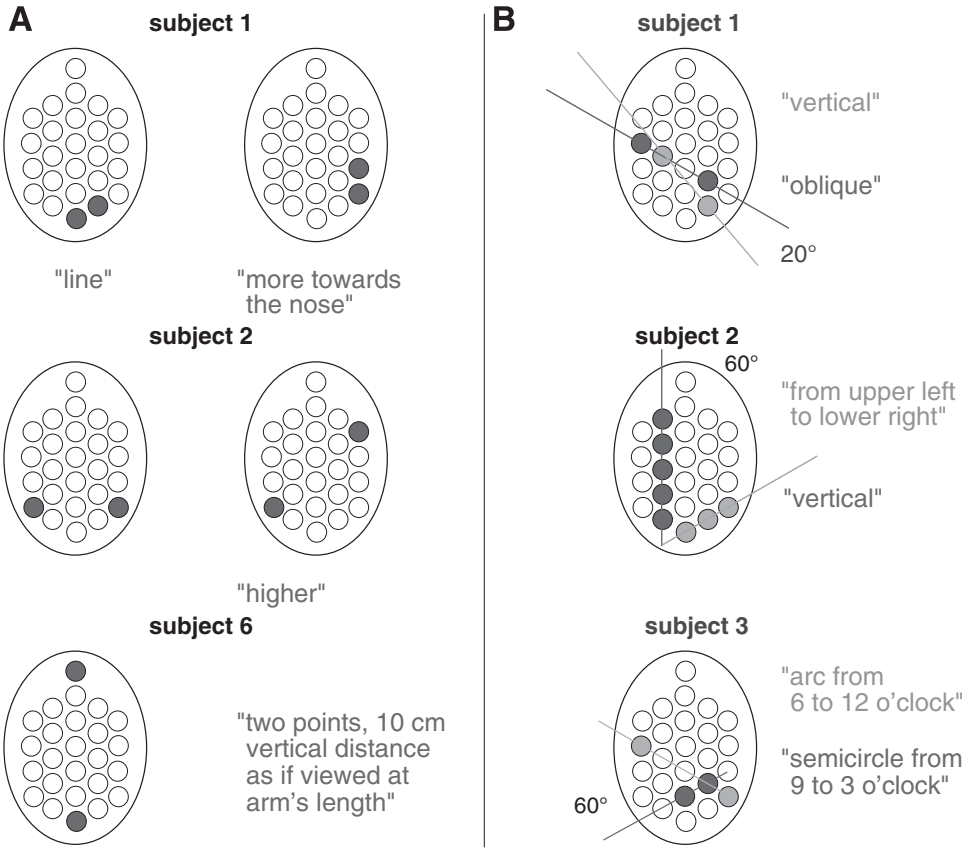

FIGURE 5. Discrimination of spatial pattern. (**A**) Discrimination of spatial positions. Sample verbal responses of subjects 1, 2, and 6 (*top to bottom*) to different stimulation patterns. Stimuli are shown with respect to the visual fields of the subjects. Stimulation by electrodes at different locations on the electrode array elicited located visual percepts. (**B**) Discrimination of orientation. Stimulus patterns on the electrode array and subjects' responses. Subject 1 discriminated oriented stimulus patterns that included an angle of 20°; subjects 2 and 3 discriminated orientations of 60°.

livered by the remotely controlled electrode array. Threshold measurements were performed in four subjects, and in five subjects tests demonstrated the ability to differentiate between different spatiotemporal stimulation patterns.

The EPIRET3 system is the first epiretinal implant that uses completely wireless technology to transfer data and energy to the implant, thus reducing the possibility of infections or long-term effects of mechanical stress. Chow et al. used a wireless subretinal microphotodiode implant powered solely by incident light.[22] Observed improvements in visual functions affected retinal areas distant from the implant, possibly because of neurotrophic effects of electrical stimulation on the retina. Other retinal implants that are currently evaluated in clinical trials make use of wireless technology partially, but, to our knowledge, all require wire connections to the implanted retinal stimulator.[21,23,24,38,39]

Thresholds

Visual sensations were elicited with currents as low as 3.2 μA and charge densities as low as 2.2 μC/cm^2 in single subjects, but thresholds varied strongly across subjects. Previous clinical trials with epiretinal implants showed similar variability in stimulation thresholds[20,40–42] (see also Richard G, et al. *IOVS* 2005;46:ARVO E-Abstract 1143). De Balthasar et al.[38] reported that thresholds decreased across subject implantations and concluded this to be caused by increasing experience in implanting the device. In our study, thresholds were low in the very first subjects implanted, and such a systematic dependence was not observed. Our study protocol restricted observation time to 28 days; therefore, changes in threshold over a period of several months, as reported by de Balthasar et al.,[38] could not be obtained. However, our results during this limited period do not confirm an initial period of instability lasting a couple of weeks, as reported by Mahadevappa et al.[42] Another possible reason for the wide range of thresholds is the variation of the distance between electrodes and ganglion cells.[43,44] De Balthasar et al.[38] measured, for 975-μs pulses, current thresholds as a function of this distance. Their data show, for this pulse duration, a correlation between electrode distance and threshold current, with current thresholds above 100 μA for distances above 300 μm. In our present study, information about electrode distances was not available.

Pulse polarity has been discussed to influence stimulation threshold. However, with bipolar stimulation as used in this study, the electrodes see opposite polarity phases in each stimulus. When the cathodic phase of a biphasic current pulse is delivered to one of the electrodes of an electrode pair, an anodic phase is delivered to the other electrode, and vice versa. Regarding a dependence of threshold on polarity, results from in vitro, in vivo, and perceptual studies are inconclusive: maximum charge injection limit with respect to the electrode material (iridium oxide) is twice as high for anodic first pulses as it is for cathodic first pulses.[36] For this reason, in our study the charge per phase was limited to the lower value. Results from animal physiology have shown higher thresholds for stimuli with the anodic phase leading.[34,35,45] However, in a recent study on human cochlear implant users, it was shown that the anodic phase of stimulation was more effective than the cathodic phase of stimulation.[46] In our study, both polarities were present in each stimulus because symmetric biphasic current pulses had been applied to electrodes of the same size (bipolar mode). Thus, there was no functional difference between stimulation electrode and return electrode.

The rather low stimulation thresholds measured in clinical trials are comparable to those reported from in vitro studies in the mammalian retina,[32] indicating that this approach is suitable to permit long-term stimulation without damage to the retinal tissue.

In two of our subjects, the reliability of eliciting visual sensations was low. Taking into account that in other studies stimulation thresholds above the maximal stimulus strengths used in our study had been observed, we cannot exclude the possibility that stimuli of longer duration and higher amplitude would have led reliably to visual sensations in these subjects. Because of the relatively small electrode surface, however, it was not possible to apply longer pulses or higher current amplitudes to not exceed the safety limits of electrical stimulation.

Dependence of Threshold Current on Pulse Duration

Our data show that stimulation success was not determined uniquely by charge density. When stimuli with the same charge density, but different combinations of current amplitude and pulse duration, were used, stimulation success depended strongly on pulse duration (Fig. 3). Stimulations of rabbit retinal ganglion cells in vitro with extracellular electrodes have found a dependence of threshold current and charge on pulse duration as expected from the physiology of neurons.[32–34] With increasing pulse duration, the current necessary to elicit a response in a retinal ganglion cell decreases gradually and asymptotically approaches the rheobase. Correspondingly, the charge necessary for stimulation increases. Similar relations have been found in RP patients with epiretinal stimulation using handheld electrode arrays[20] and with suprachoroidal transretinal stimulation.[24] Our results with an implanted electrode array differ considerably from previously reported findings. We found a strong dependence of stimulation success on pulse duration even for constant total charge. Consequently, the charge density required to elicit percepts was much lower for stimuli of long pulse duration than for stimuli of short pulse duration (Fig. 3), nearly independently of current amplitude. This dependence would correspond to a strength-duration relationship that shows a strong decrease in threshold current when pulse duration is lowered below the critical value (Fig. 3). Similarly, the charge-versus-duration function would show a strong decrease. This is quite different from what would be expected from the results of in vitro stimulation experiments,[32–35] which typically show an inverse relationship between current and duration at threshold. Our studies differ from these experiments in that we tested the perceptual effects of retinal stimulation. However, for the results to be explained by this difference, we would have to assume that postretinal processing imposes a strong dependence of perceptual threshold on stimulus duration. To our knowledge, such dependence has never been observed in psychophysical experiments. On the contrary, there are reports of dependence of perceptual thresholds on charge density in clinical trials.[20,24] Other clinical studies using epiretinal stimulation electrodes have used stimulation pulses of relatively long durations, typically around 1 ms,[38,39] and did not investigate the dependence of thresholds on pulse duration. Perceptual data obtained from cochlear implant users typically show an approximately constant amount of charge at threshold for biphasic pulses shorter than 500- to 800-μs/phase, though for longer pulse durations, charge at threshold as a function of pulse duration decreases. This indicates that charge at threshold is not a constant over a wider range of pulse durations.[47–49] Our findings suggest that to keep current or charge density as low as possible, current pulses of several hundred microseconds or more should be used for epiretinal stimulation.

Spatiotemporal Stimulation Patterns

Despite the limited amount of data, our results indicate that subjects were able to differentiate between different stimulation patterns. This confirms estimates of spatial resolution based on animal experiments,[31,50–52] suggesting that visual tasks such as discrimination of shapes and detection of movement are achievable using a wireless intraocular epiretinal implant. Caspi et al.[53] reported that one subject drew two lines, including an angle of approximately 90°, in response to a stimulus consisting of two orthogonal rows of electrodes.[53] In other clinical studies with retinal prostheses, including the present one, it was observed that visual percepts did sometimes match the stimulation patterns but sometimes did not[54,55] (see also Richard G, et al. *IOVS* 2008;49:ARVO E-Abstract 1786; Zrenner E, et al. *IOVS* 2008;49:ARVO E-Abstract 659). Cottaris and Elfar[52,56] hypothesized this finding to result from the widespread cortical response after activation of retinal ganglion cells and their axons, whereas excitation of bipolar cells produced more focal responses in the cat primary visual cortex.[34,57,58]

Some of the observations reported here are only qualitative because of the limited testing time granted by the study protocol, which did not allow more than three stimulation sessions of 1-hour duration in each subject within a 4-week period. Nevertheless, our results confirm that visual percepts were elicited by electrical stimulation with the EPIRET3 device. Obviously, longer testing periods in humans are necessary to further investigate the influence of stimulation parameters and to determine changes in thresholds over time.

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