Spatial Resolution and Perception of Patterns Mediated by a Subretinal 16-Electrode Array in Patients Blinded by Hereditary Retinal Dystrophies

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PURPOSE. The perception of 11 persons blinded by hereditary retinal degeneration elicited by a subretinally implanted 16-electrode array used for light-independent direct stimulation of the retina is described. This device is part of the Tübingen retina implant, which also employs a light-sensitive, multiphotodiode array (MPDA). The ability to reliably recognize complex spatial percepts was investigated.

METHODS. Eleven blind volunteers received implants and participated in standardized psychophysical tests investigating the size and shape of perceptions elicited by single-electrode activation, multiple-electrode activation, and activation of compound patterns such as simplified letters.

RESULTS. Visual percepts were elicited reliably in 8 of 11 patients. On single-electrode activation, percepts were generally described as round spots of light of distinguishable localization in the visual field. On activation of a pattern of electrodes, percepts matched that pattern when electrodes were activated sequentially. Patterns such as horizontal or vertical bars were identified reliably; the most recent participant was able to recognize simplified letters presented on the 16-electrode array. The smallest distance between sites of concurrent retinal stimulation still yielding discernible spots of light was assessed to be 280 µm, corresponding to a logMAR of 1.78.

CONCLUSIONS. Subretinal electric stimulation can yield reliable, predictable percepts. Patterned perception is feasible, enabling blind persons to recognize shapes and discriminate different letters. Stimulation paradigms must be optimized, to further increase spatial resolution, demanding a better understanding of physical and biological effects of single versus repetitive stimulation (ClinicalTrials.gov number, NCT00515814). (Invest Ophthalmol Vis Sci. 2011;52:5995–6003) DOI:10.1167/iovs.10-6946

Retinal implants can elicit visual percepts by electrical stimulation of retinal neurons in patients blinded by degenerative retinal diseases, including retinitis pigmentosa (RP), in which outer retinal cells deteriorate, whereas inner retinal cells remain intact for a prolonged period.1–4 Two principally different approaches are currently pursued to interface with remaining retinal neurons using microelectrode arrays5–23: (1) implantation of electrode arrays at the epiretinal site in proximity to the retinal ganglion cells and their axons,8,10,11,24,25 and (2) implantation of electrode arrays or microchips containing light-sensitive multiphotodiode arrays (MPDAs) in the subretinal space which are in proximity to the outer plexiform layer.20,26–28

The latter approach is intended to replace degenerated photoreceptors and to use the remaining signal processing of the inner retina, whereas epiretinal implants interface with ganglion cell bodies directly. However, with currently available stimulation paradigms and electrode arrays, neither approach is yet fully able to selectively stimulate either bipolar or ganglion cells. Both approaches are likely to stimulate much more than only targeted cells and their somata; axons and, for example, amacrine cells may also respond. Employment of an MPDA renders external image processing redundant and enables a large number of electrodes to be positioned subretinally.

On the basis of in vitro and in vivo studies29–31 considering the relevant issues of biocompatibility, biostability, transscleral surgical techniques, thresholds of stimulation, and the limits of spatial resolution,32–36 our consortium has developed and tested a subretinally implanted MPDA that transforms visual scenes into corresponding spatial patterns of electrical stimuli.57 The implant consists of two functional entities: (1) the MPDA with 1500 independent elements, each of which senses incident light using a photodiode, amplifies the signal,
and applies a constant-voltage signal at the respective micro-electrode.38,39; and (2) an additional electrode array of 16 hard-wired electrodes for light-independent direct-stimulation experiments (DS array).

The additional DS array permits direct stimulation of the retina with precise control over electrical stimulus parameters and allows for arbitrary spatial patterns of stimulation to be tested that deserve thorough assessment on their own. We tested that deserve thorough assessment on their own. We

and allows for arbitrary spatial patterns of stimulation to be tested with precise control over electrical stimulus parameters and permits direct stimulation of the retina. This array was modified during the course of the study to increase the safe charge injection capacity of the electrodes: In first-generation implants 50 μm2 (50 μm)2 hardwired microelectrodes (titanium nitride, TiN) in a rectangular grid with a spacing of 280 μm (Fig. 1a) is used for light-independent direct-stimulation experiments (DS array).

The study was approved by the university’s ethics committee, which granted a study period of 4 weeks (S1–S8), and, according to an amended protocol, 4 months (S9–S12), respectively.

**Implanted Device**

The implant consists of the MPDA on a polyimide foil that also contains the DS array and wire connections for percutaneous power supply and is implanted in the subretinal space40,41 (Figs. 1a, 1e). The DS array of 4 × 4 hardwaried microelectrodes (titanium nitride, TiN) in a rectangular grid with a spacing of 280 μm (Fig. 1a) is used for light-independent, direct stimulation of the retina. This array was modified during the course of the study to increase the safe charge injection capacity of the electrodes: In first-generation implants 50 × 50-μm electrodes (S1–S8; Fig. 1b) were used and in second-generation implants, 100 × 100-μm electrodes (one electrode consisting of four 50-μm electrodes close together owing to the production process; S9–12, compare Fig. 1c). The electrodes are driven monophasically, with one large return electrode subcutaneously placed near the orbital rim. The implant is connected to a battery-driven stimulus generator via a percutaneous cable (Fig. 1d). It employs a single constant voltage source that can route one stimulation voltage to an arbitrary combination of electrodes. Therefore, in concurrent stimulation of multiple electrodes, differences in thresholds between electrodes could not be accounted for. Amplitude (0–2.3 V), pulse duration (0.5–6 ms), and pulse shape (square-wave anodic or cathodic first, biphasic, or monophasic) can be adjusted. Each electrode is grounded after stimulation, to allow for charge balance.

**Implantation Procedure**

The implantation procedure is described elsewhere in detail.26–45 Briefly, after implantation of the percutaneous cable under the tempo-

### Table 1. Characteristics of Patients with End-Stage Hereditary Retinal Dystrophies

<table>
<thead>
<tr>
<th>Patient identifier</th>
<th>Diagnosis and visual function</th>
<th>Electrode size</th>
<th>Perception of phosphenes upon single electrode activation</th>
<th>Nr. of electrodes</th>
<th>Type of perception</th>
<th>Perception of phosphenes upon multiple electrode activation</th>
<th>Perception of pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>a.d. cone-rod dystrophy</td>
<td>(50 μm)²</td>
<td>✓</td>
<td>14/16</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S2</td>
<td>early onset retinitis pigmentosa</td>
<td>(50 μm)²</td>
<td>x</td>
<td>10/16</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S3</td>
<td>LP</td>
<td>(50 μm)²</td>
<td>x</td>
<td>5/16</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S4</td>
<td>early onset retinitis pigmentosa, simplex</td>
<td>(50 μm)²</td>
<td>x</td>
<td>16/16</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S5</td>
<td>a.d. retinitis pigmentosa</td>
<td>(50 μm)²</td>
<td>x</td>
<td>15/16</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S6</td>
<td>cone-rod dystrophy</td>
<td>(100 μm)²</td>
<td>✓</td>
<td>15/16</td>
<td>n.d.</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S7</td>
<td>syndromic retinitis pigmentosa</td>
<td>(100 μm)²</td>
<td>x</td>
<td>n.d.</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S8</td>
<td>cone-rod dystrophy</td>
<td>(100 μm)²</td>
<td>x</td>
<td>n.d.</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S9</td>
<td>a.r. retinitis pigmentosa</td>
<td>(100 μm)²</td>
<td>x</td>
<td>n.d.</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S10</td>
<td>Choroideremia</td>
<td>(100 μm)²</td>
<td>x</td>
<td>n.d.</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S11</td>
<td>retinitis pigmentosa, simplex</td>
<td>(100 μm)²</td>
<td>x</td>
<td>n.d.</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>S12</td>
<td></td>
<td>(100 μm)²</td>
<td>x</td>
<td>n.d.</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Six of the 11 participants had reliable perception of phosphenes when only a single electrode was activated. The number of electrodes for single electrode perception indicates the number of electrodes from which thresholds could be obtained. This number could vary during the implantation period. Type of perception: S2 always reported seeing elongated, arclike phosphenes. S11 did so when higher stimulation levels were used. All other subjects reported single phosphenes as round, yellowish spots. Two more patients saw phosphenes when more than one electrode was activated concurrently. Five of them could reliably discern different patterns like lines or simple letters. Ad, autosomal dominant; Ar, autosomal recessive; LP, light perception; n.d., not done.
eral muscle, the implant tip is positioned in the orbit, and a scleral flap is prepared behind the limbus. After vitrectomy and induction of a flat local retinal detachment, the polyimide foil carrying the MPDA and DS array is inserted subretinally at the site of the scleral flap and advanced to the desired location at the posterior pole, according to preoperative planning (Kusnyerik A, et al. IOVS 2010;51:ARVO E-Abstract 3024; Kusnyerik A, et al. IOVS 2008;49:ARVO E-Abstract 3025).

Stimulation Paradigm
Before psychophysical testing, the perceptual threshold for each electrode was determined in a standardized staircase procedure, increasing stimulation until the safety limit or perception was reached three times. Single pulses of 0.5- to 6-ms duration and the four pulse forms were tested in separate sessions. Generally, single biphasic pulses with a duration of 2 to 3 ms yielded the best reproducible thresholds. Transferred charge at threshold was typically in the range of 20 to 60 nC per phase.26

The stimulation parameters were tested only for influence on thresholds (Wilke R, et al. IOVS 2010;51:ARVO E-Abstract 2026), not for the perception of patterns. All psychophysical tests were performed by using the stimulation setting with the lowest thresholds, and single-pulse stimulation was applied, so that the participants saw a certain pattern only once for a brief time.

Psychophysical Tests and Statistics
After an initial phase for finding the optimal stimulation parameter and a brief learning phase, all psychophysical tests were performed employing an alternative forced-choice scheme.44 Reported results include the chance rate and the P value calculated from the binomial function. Although the chance rate depends only on the number of choices given, the P value also depends on the number of trials and indicates the probability of obtaining the respective hit rate or a higher one by guessing. Results with P < 0.05 were considered to be significant. The sequence within individual tests was randomized. Results are summed from tests of multiple sessions.

Tasks for Discriminating Orientation and Motion. These tasks were performed only in participants who repeatedly reported the perception of a line on activation of four electrodes in a row. In the orientation task, they were instructed to discriminate between two or four orientations, and in the motion task, to report the direction of sequential activation of four electrodes. Orientation was reported against their subjective horizontal. When participants reported the angle under which the electrode array was implanted (usually <30° against the horizontal), they were asked to use this angle as the relative horizontal.

Tasks for Discriminating Pattern. After each participant was allowed to describe the perceptions freely, pattern recognition was tested in an alternative forced-choice (AFC) approach. When concurrent stimulation was used, those tasks included the differentiation of simplified letters (Z, U, H, A, P, X, L, and T), of the orientation of parallel lines, or of the orientation of two lines that formed an angle (Fig. 3b). When sequential stimulation was used, each electrode of a certain pattern was activated in a predefined way, to form a contiguous pattern (e.g., L). The ability to distinguish between one or two lines, a
geometric arrangement resembling a triangle or a square, and three different sets of four letters (Z, L, C, T, V, I, and O) was tested (Fig. 4b). Each electrode was activated only once in this sequence, by single-pulse stimulation.

Results

All 11 volunteers received the implant successfully and underwent explantation after termination of the study without complications. One patient refused to have the device explanted after completion of the study. He has retained the implant for 5 years; however, the percutaneous cable connection was removed after 1 year.

In some participants, transient retinal edema and episodes of slight intraretinal bleeding have been observed after implantation that resolved within several days. During the course of the study, no serious adverse events (SAEs) were observed.

Thresholds and Single-Electrode Stimulation

Thresholds for single-electrode activation were tested for all 16 electrodes in each participant. Only in S10 could thresholds for all 16 electrodes be obtained (Table 1). All participants except S4, S5, and S9 had visual sensations on activation of the DS electrodes. Those subjects never had any reproduceable visual sensations (Table 1). Clinical examination by fluorescein angiography revealed absent retinal perfusion in participants S4 and S9 at the site of implantation. It is likely that the advanced retinal degeneration in those participants prohibited successful stimulation. In subject S9, technical hardware checks suggested early failure of the implanted device which was verified after explantation.

All eight remaining participants had visual perception on activation of one or more electrodes, and only they are further described here. Three of the five participants who had received the smaller first-generation DS electrodes (S1, S7, and S8) and all provided with the larger DS electrodes (S10, S11, and S12) had reliable, reproduceable perception of bright light spots on activation of single electrodes. Six participants described these percepts as round spots of light with a yellowish appearance. S2, who described visual sensations only when more than one electrode was activated, reported consistently seeing an arc or movement, S11 described his percepts at higher stimulation levels, often as short lines, semicircles, or circles (Table 1). Notably, all patients had initially difficulties in discerning electrically evoked phosphenes from spontaneous phosphenes, which were particularly apparent in S7 and S11. We observed that most of the participants (S1, S7, S8, S10, S11, and S12) readily discriminated percepts by their location in the visual field and correctly described the relative position of two phosphenes presented sequentially. This achievement was evaluated systematically only in S6. Figure 2 shows that he could correctly indicate the location of the second phosphene in relation to the first one in up to 83% of the trials.

Multiple Electrode Stimulation: Concurrent Activation

On concurrent activation of electrodes, all eight participants had reliable and reproduceable percepts (Table 1). In S12, concurrent stimulation could not be tested systematically because of limitations in experimentation time (see Fig. 3); however, he repeatedly reported reproduceable phosphenes when more than one electrode was activated simultaneously (compare Table 1). Five (S1, S6, S8, S10, and S11) of the remaining seven tested participants reported spontaneously and repeatedly seeing a straight line when four electrodes in a row were activated concurrently. S1 described small indentations along this line, others sometimes a line of varying thickness along its length. Those five participants were given an AFC test to discern orientation of the lines. Depending on the number of available electrodes, the test was 2- or 4AFC (Fig. 3a). Only participant S2 could not reliably detect the orientation of lines, and in subject S6, results did not reach statistical significance, although they were clearly above chance level. Further, when electrodes forming compound patterns like T, L, or O were activated, we encouraged those participants to describe their percepts independently, before we informed them of the activated electrode pattern. None of them was able to spontaneously describe the perceived pattern in a way that resembled the pattern of activation of the electrodes. Moreover, in various forced-choice approaches, none of them was able to discriminate between those patterns (Fig. 3b). It was observed later (from S10 on) that sequential stimulation of electrodes allowed correctly recognition of such letters. Therefore, it cannot be concluded whether the participants tested earlier would have seen the letters if the electrodes had been activated sequentially.

Multiple Electrode Stimulation: Sequential Activation

Electrodes were activated sequentially (with intervals varying between 10 and 200 ms) in a row or column, to test the perception of movement in four participants (S1, S6, S10, and S12). Because of the restrictions in time available for testing, the effect of the time interval on structured perception could not be tested systematically. All four tested subjects were able to correctly identify the direction of movement (Fig. 4a). This sequential approach also resulted in correct perception of more complex patterns. We observed that the three most recent participants in whom we could test sequential stimulation more extensively recognized novel patterns readily and instantly. Only S11 had difficulty with this task, obviously because phosphenes from single electrodes were not round but were arc- or semicircle-shaped. Perception of the orientation of a pattern resembling the letter C was tested systematically in those three participants. S10 and S12 reliably discerned four orientations of the object (Fig. 4a), but S11 failed to do so. Only if sequential stimulation was applied was S10 able to correctly solve this task. In participant S10 only, we further tested the discrimination between single and double lines, and
between the presentation of a square and a triangle, both comprising four electrodes (Fig. 4b). She described the geometric forms correctly. Participant S12 was able to recognize different letters and could clearly discriminate three different sets of four letters (e.g., C, O, I, and L) in a 4AFC test. He also reported that he saw the letters “as learned in school,” which clearly points to recognition of the letters. Single letters of the subset C, I, L, and O were more reliably discriminated than letters of the subset C, I, L, and Z (Fig. 4c). Although this systematic testing was not performed in S10 and S11 due to time constraints in this pilot trial, S10 was clearly able to distinguish between the letters I and U and between a triangle and a square (Fig. 4a, 4b).

Assessment of Single Spot Size, Object Size, and Spatial Resolution

When asked to imagine seeing a phosphene as if it were an object presented at a distance of approximately one arm’s length, its size was generally compared to the size of a pea. S1 (first generation implant, smaller electrodes) described the percept generated by four adjacent electrodes as a line in which indentations were visible, delineating the four percepts elicited by the individual electrodes (Fig. 5a). Consequently, the diameter of a single spot percept can be estimated in the range of the grid spacing, extending 280 μm on the retina or ~60 arc min of visual angle. This description matches that by S10 (second-generation implant, larger electrodes) who was asked to estimate the size of the dark area between two dots generated by two electrodes of variable distances. From these results, the size of a percept elicited by a single electrode can be estimated to be approximately 280 μm (Fig. 5b).

Taken together, these findings suggest that minimum angle of resolution with the present type of subretinal array corresponds to a retinal distance of approximately 280 μm or 60 arc min of visual angle. This outcome equates to a visual acuity for two-point discrimination of logMAR 1.78. In previous in vitro experiments using fine-needle electrodes (tip size 1 μm), however, a minimum separable of logMAR 1.32 (retinal distance 100 μm) was determined. It cannot be concluded at this stage whether the effects of electric cross-talk or of the particular state of retinal degeneration and remodeling contributed to the lower visual acuity found in this human study.

Those values are derived from near threshold stimulation; they can provide only an estimate of the size of single percepts as size increased with stimulation amplitude, a fact that is supported in an epiretinal study. S6 was asked to indicate the size of a percept while stimulation voltages were varied (Fig. 6). An increase in stimulation voltage from its threshold value of 1.7 to 2.2V increased the reported percept size in this experiment by roughly 50%.
Notably, with the two types of electrodes used in this study, the applied voltage rather than the electrode size determines the size of the percept.

**DISCUSSION**

Multiple groups are pursuing similar approaches, a few are already conducting clinical trials (Humayun M, et al. *IOVS* 2009;50:ARVO E-Abstract 4744; Walter P, et al. *IOVS* 2008;49:ARVO E-Abstract 3023; Richard G, et al. *IOVS* 2009;50:ARVO E-Abstract 4580; Richard G, et al. *IOVS* 2008;49:ARVO E-Abstract 1786.5,10,50–52) For epiretinal stimulation Humayun et al. (*IOVS* 2009;50:ARVO E-Abstract 4744) reported one participant who received a 16-electrode array and was able to see spots of light and to recognize simple shapes by head scanning. Nanduri et al. (*IOVS* 2009;50:ARVO E-Abstract 4582)51 reported that different electrodes elicited different shapes of percepts, including curved lines, wedges, and round contours. The shape of percepts changed with stimulation amplitude and with activation of one or more electrodes. Those findings seem to be in contrast to ours, where subretinal stimulation by single electrodes led, in most cases, to perception of well-defined, round spots of light, independent of stimulation voltage. In only one case (S11) did we observe a change in phosphene shape at higher stimulus amplitudes. We observed that activation of two to four electrodes generally did not notably influence the shape of individual dots.

Our findings of percepts of invariant color may be a consequence of the particular localization that favors stimulation of bipolar cell layers.36 As 50- to 100-µm electrodes certainly stimulate a large group of bipolar cells rather homogenously, the inputs to the various types of color opponent cells are relatively balanced and thereby may lead to perceptions close to the neutral point in the color space, resulting in the perception of very desaturated, whitish colors. Also, generally no perception of movement or particular color has been reported that would equate with that perceived by direct activation of individual ganglion cells. Only S2 reported consistently seeing motion and changing percepts on single-pulse stimulation. This result is in contrast to the other 10 implantees and may indicate an involvement of directionally selective cells or temporally inhomogeneous charge distribution and stimulation.

Richard et al. (*IOVS* 2008;49:ARVO E-Abstract 1786) reported on four patients provided with a 49-electrode epiretinal prosthesis who were able to discern simple patterns like horizontal and vertical bars and a cross. McMahon et al. (*IOVS* 2007;48:ARVO E-Abstract 4443) reported perception of simplified grating patterns with epiretinal stimulation. Yanai et al.8 reported three patients who received a 16-electrode epiretinal prosthesis. All of them could detect motion; two of them could...
detect orientation of lines in a 4 AFC test and discriminate the orientation of L in a 4 AFC test. Besides the epiretinal location of these electrodes, the size and spacing of the electrodes used (i.e., platinum electrodes 800-μm spacing and 520- and 260-μm diameter) is a major difference from those used in our study.

We found that in some participants the smaller first-generation electrodes were not sufficient to yield percepts. By grouping two or more electrodes (typically 2 × 2 electrodes) together in first-generation arrays, nearly all participants were able to perceive light spots on activation. The same phenomenon was observed in a study by Yanai et al.,8 who also described grouping four electrodes.

To overcome the charge transfer capacity limitations of the small electrodes, the geometric surface of electrodes was increased fourfold after S8. All participants who received this new implant type (except S9) had perceptions on single-electrode activation. Notably, the size of percepts evoked by single-electrode activation did not seem to be significantly influenced by the enlargement of electrode size. Phosphene sizes in S1 (first generation implant) and in S10 (second generation implant) both were estimated to be 280 μm, significantly larger than those elicited by single electrodes (50 × 50 and 120 × 120 μm, respectively). Assuming that two overlapping pointspread functions are produced by each of two neighboring electrodes and considering that S1 was able to see indentations between two neighboring percepts elicited by 280-μm distance, it can be expected that the minimum angle of resolution achievable by electric stimulation is near 60 arc min (logMAR 1.78). However, this value would be expected to vary considerably interindividually, given the retinal situation at the implantation site.

Three participants (S4, S5, and S9) in the present study never had any perception. In S9, early technical failure of the implant impeded stimulation. In participants S4 and S5 who had been blind for 15 to 20 years, retinal degeneration was at a very advanced stage, with central retinal thickness of ~100 μm and heavily impaired retinal perfusion at the site of implantation. The extent of impaired perfusion is only noticeable in fluorescence angiography after implantation, because the chip serves as a barrier to block choroidal fluorescence, rendering retinal microvasculature visible on top of the chip. It must also be determined to what extent retinal remodeling and creation of fibrous subretinal layers in advanced stages contribute to the inability to elicit phosphene in patients with longstanding retinal degeneration.53 Certainly, many factors, including onset of disease, specific mutation, and consequent pathophysiological changes, contribute to the ability to electrically stimulate remaining retinal tissue. Owing to the very individual course of hereditary retinal degeneration duration, of blindness alone, may not be a good predictive factor, as S12 was able to recognize electrically evoked letters, despite reporting onset of difficulty in reading approximately 15 years ago and being unable to see letters for the past 6 years. We expect that measuring retinal thickness by OCT at the implantation site and

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**Figure 5.** Assessment of percept size and spatial resolution. (a) Estimation of overlap of single dots. S1 was asked to describe the spatial relation between single phosphene when four electrodes in a line were activated. He was given four black circles to arrange in such a way that they just touched each other. Given a grid spacing between electrodes of 280 μm, a percept elicited by single-electrode activation can be estimated to cover a retinal area 280 μm diameter. (b) Estimation of gap size between two phosphene. S10 was asked to estimate the black gap between phosphene that was visible when two electrodes of various distances were activated concurrently. She estimated the gap size with the help of a sliding caliper. Mean values and SD (n = 18) are plotted versus retinal distance of the two activated electrodes. Linear regression (dotted line) estimates the distance between two electrodes at which the phosphene would just touch each other (gap size, 0 mm) as 282 μm.

**Figure 6.** Increase in percept diameter with increasing stimulation voltage. S6 was asked to assess the size of a percept with the help of a sliding caliper. The electrodes were activated with different voltages presented in random order. In this participant, 1.5 V was just below threshold (only 2 tests of 18 yielded a percept). Mean values and ±1 SD (n = 50) are shown. Linear regression reveals a slope of 3.0 mm/V, meaning that an increase from 1.7 to 2.2 V roughly increases the diameter of the percept by 50%.
careful investigation of retinal perfusion and thresholds for corneally elicited phosphophines will be the crucial in selecting patients suited for implantation.

Percepts elicited by single subretinal electrodes can combine to form simple patterns such as lines. Figure 3 illustrates the basic approach that was taken when planning and initiating the study. The study protocol initially included only concurrent stimulation. It was surprising and disappointing to find that, even though individual electrodes could be perceived clearly by S1, only simple shapes like straight lines were recognized (Fig. 3a). Compound patterns could neither be described nor discriminated correctly (Fig. 3b). Motivated by the observation that S1 could easily follow a line of sequentially activated electrodes (Fig. 4a), we amended the study protocol and hard-and software to be more flexible in trying sequential stimulation with successive participants. Only for the three most recent implantees was this fully implemented and testable. Because of time constraints in this first pilot study, we could not perform all tests in all participants. We found that S10 could describe and discriminate patterns resembling the letters I, U, and C; a triangle; and a square, whereas S11 could not. Only in S12 could we test letter recognition using sequential stimulation systematically. This clearly is an exploratory study, and conclusions from it must be regarded as hypothesis until further evidence from theoretical, in vitro, or in vivo approaches is available.

Two phenomena may contribute to an explanation of why concurrent stimulation may result in poor spatial resolution:

1. Single electrodes exhibit distinct perceptual thresholds. With the current implant design, concurrently activated electrodes must be addressed with the same voltage. Considering the effect of voltage on dot size, dots that form a shape will appear in different sizes, rendering objects more difficult to recognize.

2. Current spread in the retina. When multiple electrodes inject currents concurrently, summation effects of those currents will lead to electric cross-talk and loss of spatial confinement of stimulation (Khallili Moghaddam G, et al. IOVS 2011;52:ARVO E-Abstract 429). The effect must be assumed to be particularly detrimental on spatial resolution when single inactive electrodes are surrounded by numerous electrodes passing current, as is the case with the letters O and X. Its effect should be less noticeable when only electrodes in a line or a row are activated.

These considerations and our initial observations in two patients indicate that sequential activation may overcome some of those problems. Using this approach, participants 10 and 12 were able to describe precisely the pattern of activated electrodes, discern the orientation of the letter C, and read other simplified letters (Fig. 4).

Notably, interstimulus intervals of >100 ms were necessary to yield precise patterns of perception (compare Fig. 2). This requirement is very likely linked to the observation that consecutive stimulation fails to trigger ganglion cell responses and perception (Wilke R, et al. IOVS 2011;52:ARVO E-Abstract 458) when presented too fast and imposes a challenge for sequential and repetitive simulation. This difference between the MPDA results and DS stimulation is one of the most important. Probably owing to the fact that microsaccades allow permanent scanning of letters and objects and thereby continuously refresh the percept through projection on different retinal areas, as lined out in the electronic supplement by Zrenner et al., perceptual fading using the MPDA is less of a problem. In contrast, repetitive DS stimulation addresses continuously the same retinal area and leads to effects of perceptual fading (Wilke R, et al. IOVS 2011;52:ARVO E-Abstract 458; Zrenner, et al. IOVS 2010;51:ARVO E-Abstract 4319; Wilke R, et al. IOVS 2009;50:ARVO E-Abstract 4595).

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References


