

Functional Outcome in Subretinal Electronic Implants Depends on Foveal Eccentricity

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PURPOSE. An active microelectronic subretinal implant, developed to replace the photoreceptive function in hereditary degenerations of the outer retina, has been applied in a pilot and clinical study in patients with end-stage retinal degeneration.

METHODS. The study population comprised 20 blind patients, all of whom lost vision as result of a hereditary retinal disease. An active visual implant was placed surgically within the subretinal space of each patient: subfoveal placement in eight patients (group 1) and parafoveal placement in 12 (group 2). Standardized low-vision tests, including light perception, light localization, movement detection, grating acuity, and visual acuity by Landolt C-rings, were used under masked, randomized implant-OFF and implant-ON conditions. For the chip-mediated vision functional results of both subject groups were compared.

RESULTS. Three of 20 patients were excluded from analysis because of surgical or technical implant issues. Among patients with nonfoveal placement of the implant, 80% could perceive light, 10% recognized location, and 10% correctly distinguished stripe patterns up to a resolution of 0.33 cycles/degree. No nonfoveal placement patient passed the motion or Landolt C-ring tests. When the implant was placed subfoveally, 100% of patients could perceive light and determine light localization, 75% could resolve motion up to 35°/s, 88% correctly distinguished stripe patterns up to a resolution of 3.3 cycles/degree, and 38% passed a Landolt C-ring test with a decimal visual acuity of up to 20/546 (logMAR 1.43).

CONCLUSIONS. Subfoveal placement of active subretinal visual implants allows superior measurable outcomes compared to para- or nonfoveal placement locations. (ClinicalTrials.gov numbers, NCT01024803, NCT00515814.)

Keywords: neuroprosthetics, artificial vision, subretinal visual implant, retinitis pigmentosa

For restoration of visual function in hereditary degenerative photoreceptor disease, a number of approaches, including gene-therapy,¹⁻³ stem-cell therapy,⁴⁻⁶ electrostimulation,⁷ and electronic visual implants, are being investigated.⁸⁻¹⁴ Visual implants, designed to restore visual function by stimulating visual pathway neurons, are divided classically into subretinal,^{8-10,12} epiretinal,^{11,13,14} suprachoroidal,^{15,16} cortical,^{17,18} and optic nerve cuff¹⁹ categories.

The subretinal visual implant,^{8,9,20} alpha IMS (Retina Implant AG, Reutlingen, Germany), was designed to mimic the functions of outer retinal photoreceptors and is intended for use in end-stage photoreceptor degenerative disease. The photoreceptive part of the implant, the subretinal chip, comprises 1500 microphotodiode-amplifier-electrode units that absorb photons and convert them into a retinotopically correct, graded electrical signal for the bipolar cell layer.²¹

The Alpha IMS implant covers approximately 15° of the visual field and, thus, is comparable to other retinal implants that currently are used in blind human subject trials.^{11,13} To our knowledge, the influence of implant eccentricity (i.e., position of the implant in relation to the fovea) on functional outcomes has not yet been studied. In the case of end-stage retinitis

pigmentosa (RP), where most of the photoreceptors are degenerated, such an implant, in theory, can be placed successfully anywhere under the retina to function. Because of differences in retinal structures throughout the entire inner retinal network, we hypothesized that the subretinal implant will have differing effects contingent upon its retinal placement.

In a central subfoveal location, there is an inner retinal network along with the central visual pathway, which is specialized for high resolution and feature perception. The fovea, however, differs in structure from the rest of the retina. In the human eye, the very center of the fovea, that is, the 350 μm wide foveola, is composed entirely of cone cell bodies, which are longer and thinner than the more peripheral cones, and specialized to detect details of the visual image.^{22,23} Furthermore, within this central 1 mm² area of the fovea, the plexiform, inner nuclear (INL), and ganglion cell layers are displaced to one side to allow light to pass unimpeded to the cones.^{22,23} Consequently, no synapses between cones and bipolar cells are found in the foveola, as all of these cells are shifted slightly to the perifoveal area. If a subretinal electronic implant is placed in such an area, to replace the function of the

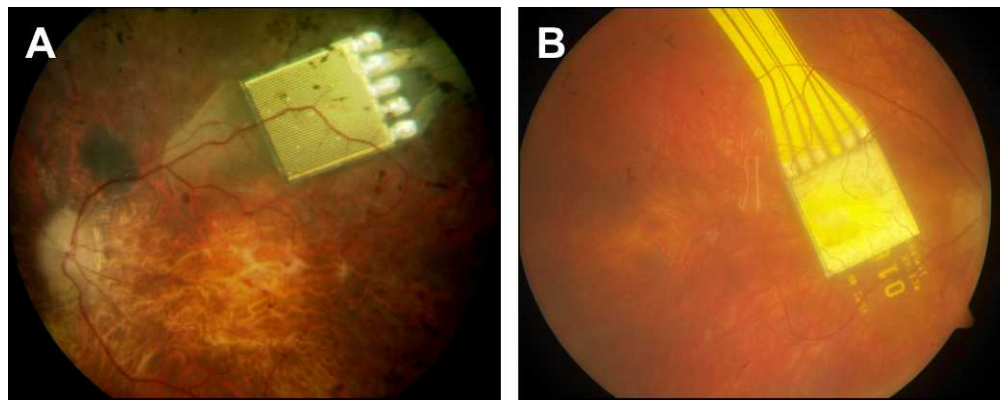


FIGURE 1. Fundus view of a (A) noncentral and (B) central placement of subretinal implant.

degenerated cones, it theoretically could cause a central scotoma, or at least distort the retinotopy. As our results show, however, this did not present a major problem.

If placing a subretinal implant parafoveally, that is, on the posterior eye pole, but not under the foveola, such a problem is anticipated. However, from a 5° eccentricity, the best possible visual resolution falls to half of the central resolution, while from a 10° eccentricity, the best resolvable angle decreases dramatically. Moreover, approximately 50% of the cortical visual area in the central visual cortex is devoted to the central 5° of the visual field, and most of this area is occupied by 2.5° central vision.²⁴ These facts may represent disadvantages of a parafoveal placement of the subretinal visual implant. Placement of a visual implant in an extremely peripheral location would lead to improper implant function, based on the impossibility of light falling onto the chip through the pupil as well as improper eye movement conditions.

We compared results of quantitatively assessed visual functions of patients who received a subfoveally placed subretinal implant versus those who received a nonfoveally placed implant. Detailed reports of visual functions via the subretinal visual implant (Retina Implant AG) have been published previously.^{8,9,20,25}

METHODS

Patients

Initially, 24 patients were screened; 12 in a pilot trial (patients P1-P12) and 12 in a clinical trial (patients C1-12). All patients suffered from some form of end-stage hereditary retinal degeneration: RP ($n = 21$; patients P1-P6, P8-P12, and C1-C10), cone-rod dystrophy ($n = 2$; patients P7 and C12), and chorioideremia ($n = 1$; patient P11). Patients P3 and C11 withdrew their consent after formal inclusion, and patients C3 and C4 did not fulfill inclusion criteria after complete screening. Thus, each of 20 patients (15 men, 5 women; ages, 45.95 ± 7.9 years) received an active visual subretinal implant in one eye. Visual function before the trial was light perception or worse, or defective light source localization resulting from retinal degeneration. No subject suffered from any other eye disease that could affect retinal layers or other parts of the visual pathway.

Written informed consent, in accordance with the Code of Ethics of the World Medical Association (according to the tenets of the Declaration of Helsinki) was obtained from all patients before study participation. The study was approved by the local ethics committee.

Subretinal Implant

The subretinal implant device has a microphotodiode array (MPDA, the actual microchip) measuring $3.0 \text{ mm} \times 3.1 \text{ mm} \times 70 \mu\text{m}$. Each microchip consists of 1500 pixels ($70 \mu\text{m} \times 70 \mu\text{m}$) of photodiode-amplifier-electrode units, which convert light into electrical pulses. Pulses are delivered locally to overlying retinal neurons via microelectrodes. For a power supply, the chip is bonded onto an approximately $20\text{-}\mu\text{m}$ thick subretinal polyimide foil, which exits the eye through the choroid and sclera at the equator.

Following vitrectomy, the device was implanted into the subretinal space via a transscleral, transchoroidal approach.^{26,27} An extraocular cable then was run through a loop in the orbit, exiting under the skin at the orbital rim under the temporal muscle to the back of the ear. In patients P1 to P12, the cable exited the skin behind the ear and was connected to a battery-driven stimulus generator, where the examiner also could adapt control parameters, such as contrast sensitivity and brightness gain.⁸ For patients C1 to C12, a subdermal coil was fixed onto the skull bone, and an external power supply was provided via electromagnetic induction (subretinal implant Alpha IMS; Retina Implant AG).⁹ In this wireless version of the power supply, patients are able to contrast sensitivity and brightness gain manually, using two knobs located on the power supply box.

A subretinal implant was placed parafoveally (i.e., the fovea was not within the area of the chip) in patients P1 to P11, C1, and C6 (Fig. 1A), and subfoveally (i.e., the fovea was within the area of the chip) in patients P12, C2, C5, and C7 to C10, (Fig. 1B). In patient C12, the chip was implanted first parafoveally, but was repositioned surgically afterwards to a subfoveal location. The chip location has been planned before implantation according to retinal morphometry.²⁸

Pilot and Clinical Trials

The pilot trial^{8,25} was conducted from 2005 to 2009, in the Center for Ophthalmology of the University of Tübingen (Tübingen, Germany). Because of the wire-bound power supply with its retroauricular connection, implants could be activated only in a hospital setting, with an obligatory explantation after a maximum of 3 months. A multicenter clinical trial currently is running in a number of locations; the single center phase was performed from 2010 to 2011 in the Center for Ophthalmology of the University of Tübingen. The study period was 12 months. When using the wireless power supply in the clinical trial, an explantation was no longer required. The pilot and clinical trials are registered at www.

TABLE. Best-Achieved Functional Outcomes for Parafoveal and Subfoveal Placements of the Subretinal Implant

	Light	Location	Motion	Grating	Landolt
Parafoveal					
P4	No	No	No	No	N.D.
P5	No	No	No	No	N.D.
P6	Yes	No	No	No	N.D.
P7	Yes	No	No	No	N.D.
P8	Yes	No	No	No	N.D.
P9	Yes	No	No	No	N.D.
P10	Yes	N.D.	N.D.	No	No
P11	Yes	No	No	No	No
C6	Yes	No	No	No	N.D.
C12	Yes	Yes	No	0.33 cpd	No
Subfoveal					
P12	Yes	Yes	1.1°/s	0.46 cpd	0.021
C2	Yes	Yes	No	No	No
C5	Yes	Yes	3°/s	0.33 cpd	No
C7	Yes	Yes	No	0.30 cpd	0.01
C8	Yes	Yes	7°/s	0.33 cpd	No
C9	Yes	Yes	35°/s	3.33 cpd	0.037
C10	Yes	Yes	5°/s	0.50 cpd	N.D.
C12	Yes	Yes	5°/s	1.00 cpd	No

For motion detection, grating, and visual acuities, the best results obtained for each subject are presented. Yes, passing the test successfully; No, failing the test; N.D., the test was not done; cpd, cycles per degree.

clinicaltrials.gov (NCT01024803 and NCT00515814, respectively).

Functional Tests

For determining visual function, standardized tests were run sequentially, from the easiest to the most challenging. If an easier test could not be performed successfully, it was not necessary to apply the more challenging ones.²⁹

For the first functional assessment, a battery of very low-vision tests in the form of a screen task, that is, Basic Assessment of Light and Motion (BaLM), was conducted.³⁰ The following subtests, all as two- or four-alternative forced-choice tests, were used: light perception, location detection, and motion perception. The BaLM test was followed by assessment of grating acuity (spatial resolution) and standard visual acuity

with Landolt C-rings, also as screen tasks, either as semi-automated assessments, that is, the Basic Grating Acuity (BaGA) and Freiburg Visual Acuity Test (FrACT), or as manually presented slides.^{29,31} For patient C7, who had difficulties with the screen tasks, a stripe pattern and paper Landolt C-rings in reverse contrast tests were given, both in daylight, on a table with corresponding resolutions as measured for the observation distance.

All tests were performed under two conditions: implant “ON” and “OFF.” Subjects were masked to the condition. Two independent test runs conducted in random order were carried out with the power supply switched on or off. Tests were performed repeatedly during follow-up visits (up to 18 visits). The best results obtained via the implant-mediated vision for each subject during the trial period date are presented and compared between the two groups.

Foveal Thickness

Severe foveal thinning in end-stage retina degeneration could imply secondary bipolar cell loss in this region. To examine whether foveal thickness presents an additional prediction parameter of the visual function, we correlated the foveal thickness before implantation with the best achieved grid resolution in patients of the subfoveal group.

RESULTS

Ex-post technical analysis of the device revealed a technical defect in its functioning after explantation from patients P1 and P2. For patient C1, a surgical problem resulted in failure of light perception via the chip. Therefore, these three patients were excluded from comparative analyses, as a reason other than implant localization caused failure in the test performances.

Functional outcomes of the subretinal implant for both groups are summarized in the Table and Figure 2.

Parafoveal Region Placement

Ten patients (P4–P11, C6, and C12 before implant repositioning) with nonfoveal placement of the subretinal chip are included in the results. Eight (80%) patients were able to perceive light with the implant. One (10%) patient (C12) was able to recognize location. No (0%) patient was able to resolve motion in standardized tests. One (10%) patient (C12) was able to distinguish stripe patterns correctly up to a resolution of 0.33 cycles/degree. Additionally, P10 was able to recognize

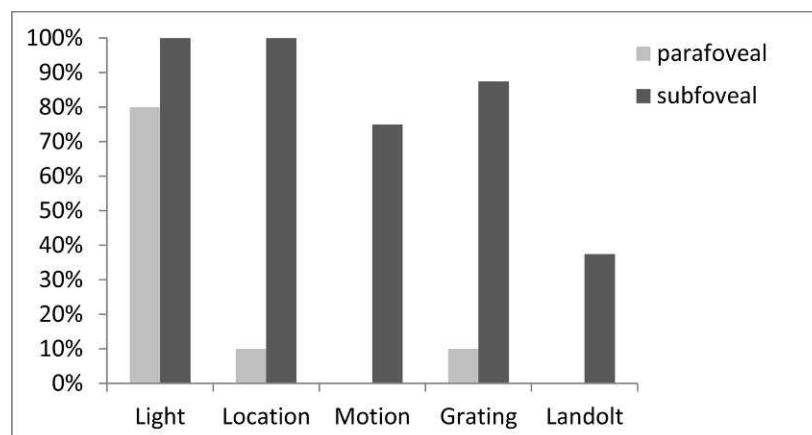


FIGURE 2. Percentages of patients (both groups) who were able to perform the test correctly.

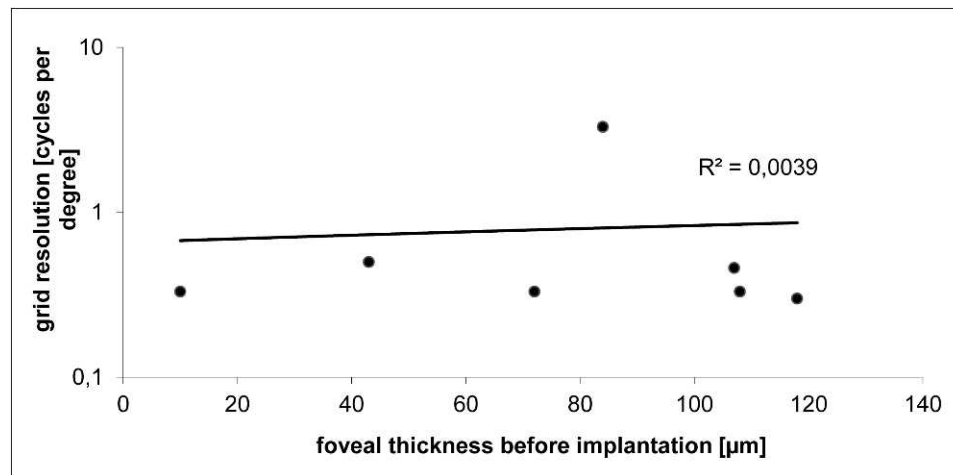


FIGURE 3. Thickness of the fovea and the best achieved grid resolution in patients with subfoveal placement of the chip do not correlate significantly ($R^2 = 0.0039$).

stripe patterns if projected with infrared light, recognizable by the chip, via a scanning laser ophthalmoscope aimed at the chip.⁸ As this latter is not a standardized test, this performance is not included in our results. No (0%) patient passed the Landolt C-ring test.

Subfoveal Region Placement

Eight patients (P12, C2, C5, C7-C10, and C12 after implant repositioning) with subfoveal placement of the subretinal chip are included in the results. With the implant, all eight (100%) patients were able to perceive light and recognize location. Six (75%) patients were able to resolve motion, with a maximal speed range of 1.1°/s to 35°/s. Seven (88%) patients were able to distinguish stripe patterns correctly up to a resolution of 3.3 cpd. Three (38%) patients passed the Landolt C-ring test, with a decimal visual acuity of up to 20/546.

There was no correlation between the thickness of the fovea and the best achieved grid resolution in patients with subfoveal placement of the chip ($R^2 = 0.0039$, Fig. 3).

DISCUSSION

Active microelectronic subretinal visual implants restore parts of neuronal visual functions by electrically activating the inner retina, and are used under conditions of degenerated photoreceptors. This approach is in current use in a clinical trial with patients who have lost vision as result of an outer retinal degenerative disease. We compared standardized functional test results from patients who received a subretinal implant in a central retinal location to those who received an implant in a paracentral location. We found that placement of the subretinal implant in a manner that includes the foveola (subfoveal placement) in the active portion of the implant consistently leads to better results than those achieved with nonfoveal placement. There are several possible reasons to explain this. First of all, the central retina has a special role in visual processing, and its structural composition differs from that of the remaining retina. In addition, brain processing is disproportionately higher for the central visual field than for other regions. Both conditions contribute to the fact that (in the healthy eye) the foveola is the best preconditioned area for high visual resolution and recognition ability.

Morphology of the Human Fovea Centralis

The 350 μm central retina of healthy human eyes comprises only cone cell bodies, which are longer and thinner than the more peripheral cones.^{22,23} Each cone has a “private” bipolar cell that directly combines the cone’s input to a midget ganglion cell.³² In the peripheral retina, groups of cones and rods converge on a parasol ganglion cell, resulting in poorer visual resolution.^{23,32} Moreover, beyond an eccentricity of 5°, the number of cones decreases dramatically. The middle peripheral retina is dominated by rods, whose maximum density is at a 20° eccentricity.

Physiologically, there are no synapses between cones and bipolar cells within the central 1 mm² area. Here, all synapses are slightly perifoveolar and, thus, the very centrally positioned cone-bipolar cell synapses actually are somewhat retinotopically incorrect. This suggests that, theoretically, central placement of a subretinal implant is disadvantageous, since the so-displaced bipolar cell synapses would give rise to a central scotoma following subretinal electrical stimulation. However, the central portion of the retina, the 350-μm diameter foveola, actually covers only a few pixels of the chip. Since these are placed at 70-μm intervals, <80 pixels from 1500 corresponds to the foveolar area, that means approximately <6%. Thus, perception of this minor central part of the chip’s visual area could give rise to small scotomas. In reality, however, this was not a significant problem. Patients perceived the visual field afforded by the chip as continuous and homogeneous. Earlier experiments using direct subretinal stimulation in blind RP patients showed that perception elicited by a single subretinal electrode had a size of approximately 280 μm.³³ Such overlapping of electrode fields could explain the continuous perception observed by our patients. Additionally, perceptual filling-in of an active visual adaptation neural process³⁴ might have had a role. One exception was patient C10 who, reported a missing central part of the perception, but had a visibly enlarged foveal avascular zone, revealed by postimplantation angiography (Fig. 4B). In this case, a superimposed ischemic condition of the macula might have been responsible for the continuously reported “central hole” in the square-shaped visual area imparted by the implant, rather than any of the above-mentioned hypotheses.

In earlier histological studies, mean cell count of retinal layers in RP was established (Fig. 5),^{35,36} and it was shown that,

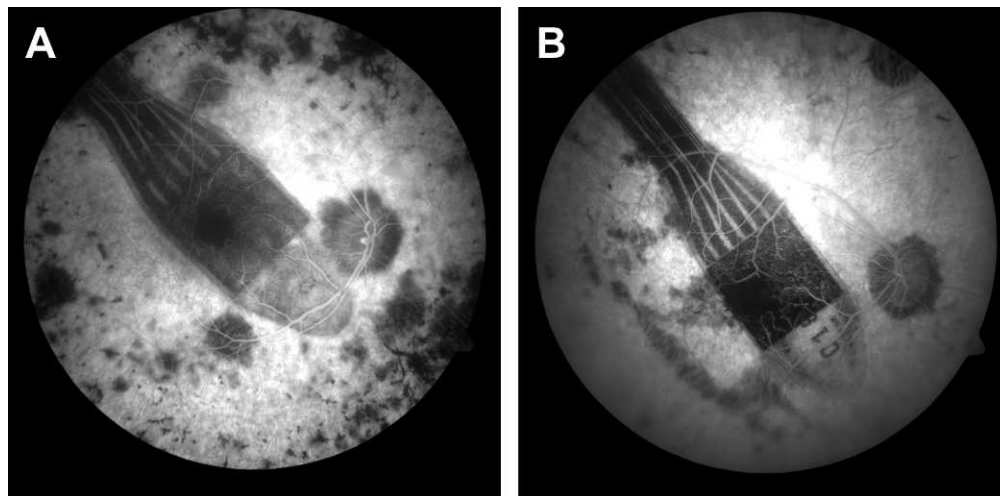


FIGURE 4. (A) Fundus view during fluorescein angiography of a subretinal implant with subfoveal positioning. (B) The central avascular zone becomes visible on the surface via angiography of subject C10. The central avascular zone of the fovea is increased and the perifoveolar microvascular network attenuated.

in RP, the decrease in the number of bipolar cells is not as profound as the loss of ganglion cells, even in donor eyes from older persons with severe long-standing RP.³⁶ Especially in the central 5°-region, the INL in RP does not differ substantially from that of healthy control subjects.^{36,37} For ganglion cells, cell loss seems to be more profound in RP, differing significantly according to severity of disease.^{35,36}

Histologic examination of the 700- to 1500- μm paracentral retina revealed a mean cell count of the INL to be 33.3 ± 9.7 in severe RP patients.³⁶ In the mouse model of retinal degeneration, bipolar cells and horizontal cells do alter their morphology, and retract and redirect dendrites after photoreceptor degeneration, but they do not exhibit a significant loss in cell count.³⁸ However, as horizontal cells lie parallel with the subretinally

placed microchip and the stimulation current flows predominantly vertically, the horizontal cells are much less stimulated by the electrodes than the bipolar cells; moreover, as triad synapses probably have been lost completely in most cases, horizontal cell influence on bipolar cell layer should be minimal. Additionally, the density of horizontal cells in the retina is approximately 30 times smaller than that of bipolar cells.³⁹ Thus, in the INL we consider only the bipolar cells to be stimulated by the subretinal chip. As can be seen in Figure 5, the regions up to 1500 μm eccentricity in severe RP patients have the highest number of bipolar cells. Since microscopic cell counts were made on a 100- μm \times 100- μm square, a corresponding number of bipolar cells for one sensor of our chip (which is 70 μm \times 70 μm) is approximately 16. Similarly,

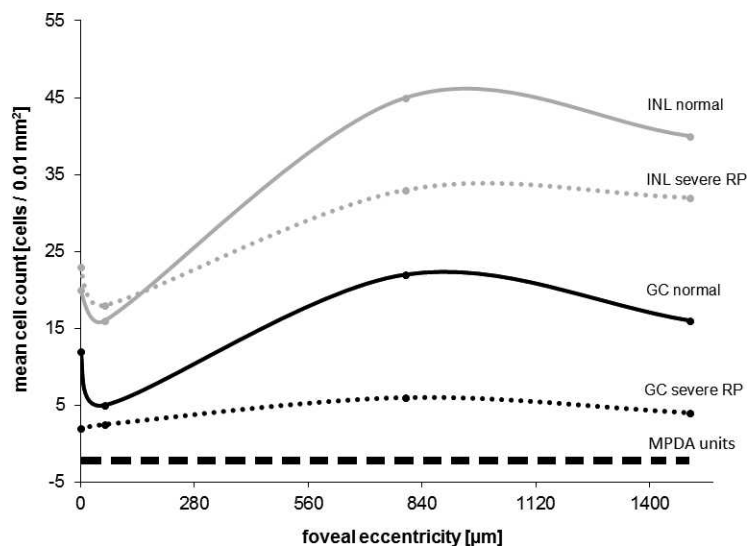


FIGURE 5. Averaged cell count, according to retinal eccentricity, for INL and ganglion cells (GC) for severe RP and controls (figure adapted from studies of Wilke R, Gabel VP, Sachs S, et al. Spatial resolution and perception of patterns mediated by a subretinal 16-electrode array in patients blinded by hereditary retinal dystrophies. *Invest Ophthalmol Vis Sci.* 2011;52:5995–6003³³; Stone JL, Barlow WE, Humayun MS, de Juan E Jr, Milam AH. Morphometric analysis of macular photoreceptors and ganglion cells in retinas with retinitis pigmentosa. *Arch Ophthalmol.* 1992;110:1634–1639³⁵; and Santos A, Humayun MS, de Juan E Jr, et al. Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. *Arch Ophthalmol.* 1997;115:511–515.³⁶ The 70- μm -wide fields of microphotodiode-amplifier-electrode units form a regular subretinal pattern. Intervals of black dashed line correspond to the retinal distance covered by one unit.

coverage can be calculated for ganglion cells, although these cells are not stimulated directly by the subretinal implant. Following such calculations a single microphotodiode-electrode unit, therefore, should address at least 2 to 3 ganglion cells directly via bipolar cells and a few more indirectly via amacrine cell connection in the inner plexiform layer. In severe RP, 5.7 ± 4.1 ganglion cells are in the above-mentioned region.³⁶

Foveal thickness as a measure of bipolar cells loss does not correlate with the achieved visual function via the chip (Fig. 3), although the number of remaining bipolar cells must be crucial for the visual function via a subretinal implant. As can be assumed from empirical observations in the ongoing part of the clinical trial, a possible predictor for outcome of visual acuity is not the foveal thickness per se, but the preservation of inner retinal layering visible in high resolution OCT before implantation at the posterior pole. Due to the small number of data of the patient cohort presented here, this empirical observation at present cannot be proven statistically.

Although the subretinal electrode nonselectively stimulates ON as well as OFF bipolar and ganglion cells, patients do have meaningful visual perceptions. This seeming paradox can be explained in several ways. If photoreceptors are lost to degeneration, the invaginating (sign-inverting) synapses between photoreceptors and bipolar cells no longer exist. It also can be hypothesized that injection of current via metal electrodes depolarizes and hyperpolarizes the membrane of ON and OFF cells in an equal manner. For instance, if ON and OFF bipolar cells are depolarized by the current pulse, all ganglion cells connected to these bipolar cells, including those that have been OFF ganglion cells, would respond with depolarization and produce action potentials, thus, mediating an ON-signal. Furthermore, long ON bipolar cells in degenerated retinas are best addressed by monopolar electrodes and a pulse duration of $>150 \mu\text{s}$,⁴⁰ corresponding to the monophasic pulse of 1 ms generated by the chip. In complete congenital stationary night blindness (CSNB) no ON bipolar cells exist. Although affected patients usually have a reduced visual acuity of approximately 20/40, they also can have full vision. Therefore, while the push-and-pull action of the ON/OFF system improves contrast vision, it is not essential for spatial resolution.

Subretinally applied anodic pulses can stimulate photoreceptors with similar thresholds as bipolar cells, as could be shown in *ex vivo* rabbit retinae.²¹ However, the electric stimulation threshold of remnant photoreceptor somata in end-stage degeneration may be higher in the outer retina, because their morphology changes from a cylinder-like to a spheroid shape.²¹ These altered photoreceptors, found in the central retina, could be reactivated in another therapeutic approach, the optogenetics.⁴¹ In the pilot trial, no high resolution OCT was available, but it is possible that their density is lower parafoveally due to the centripetal nature of the degeneration. Thus, it cannot be excluded that the stimulation of residual cone inner segments contributes to the visual function in some patients with a centrally placed microchip.

Central Nervous System Processing and the Human Fovea

In addition to the influences bestowed by foveal histology, central nervous system processing of foveal input itself also may explain why subfoveal placement of a visual implant is favorable. In the fovea, there is a high density of ganglion cells, and the number of optic nerve fibers in this area is almost equal to the number of cones.²² In addition, the central visual pathway is devoted primarily to the central visual area. Approximately 50% of the cortical visual area is occupied by

the central 5° of the visual field, with the greater part belonging to the 2.5° area of central vision.²⁴

Animal experiments have shown that the size of the retinal receptive fields in the cortex increases with eccentricity, the so-called "cortical magnification factor."^{42,43} In the primate visual cortex, approximately 1° of foveal vision is represented by approximately 20 mm of cortex. In contrast, at 10° peripheral vision, 1° is represented by only approximately 1.5 mm.⁴³

Even more specialized tasks are processed by the primary visual cortex, thanks to the enlarged area that is devoted to the central retinal field. For example, for every receptive field, there exists ocular dominance and orientation preference columns⁴⁴ that already are decoding for direction of motion, spatial frequency, and orientation input from the retinal field. The primary visual cortex also contributes to the processing of size, binocular vision, and depth perception.^{23,45,46}

In human vision, poor resolution, poor recognition, and poor interpretation of noncentral vision are phenomena that are demonstrated easily by the phenomenon of "crowding" in peripheral vision.^{47,48} Crowding appears to be independent of peripheral stimulus size, and depends only on eccentricity. Reading experiments have shown that crowding may start at 5° visual periphery.⁴⁹ Thus, the explanation cannot lie solely in the increased cortical magnification factor; there must be an additional central nervous difference in quality of visual perception between central and peripheral vision.⁴⁷ It may be noted that the 5° visual angle corresponds to a retinal distance of approximately 1200 μm , a distance that is nearly one-third of the rim-size of our implant. This suggests that a slightly paracentral location may exert a great effect on failure of object recognition via the chip.

Taken together, processing from foveal input is highly specialized and detailed, thus, affording optimum performance of a number of tasks that require combining information across different scales.

Alternative explanations as to why the central retina is able to mediate visual functions better via a subretinally placed implant versus a parafoveally placed implant also must be addressed. Significant among these may be the amount of time that has elapsed since final photoreceptor degeneration in a particular retinal location. Typically, in RP, degeneration of the photoreceptors begins in the periphery and proceeds (over years) into the central area. In end-stage disease, however, although the foveal photoreceptors also are degenerated, the time elapsed after the last photoreceptor has degenerated is much shorter, the shortest of the entire retina, in fact. Also, in RP, it is known that remodeling of the inner retinal layers occurs after photoreceptor degeneration.^{23,50} What happens to the inner retina following photoreceptor degeneration has not been clarified completely to our knowledge. It has been reported that bipolar cells retract their dendrites or create new axon-like structures, glutamate receptors of the ON bipolar cells change to the receptors of the OFF bipolar cells, and many neurons of the inner layer die along with the degenerating photoreceptors.^{23,50,51} There also is a marked loss of ganglion, but not bipolar, cells in end-stage RP.^{36,52}

If the missing input to the inner retina leads to neuronal disorganization, the amount of time elapsed after photoreceptor degeneration may have an impact on the best possible functioning of the inner retinal layer.

In patients (P12, C5, C8) who experienced very good functional results, 15 to 25 years have passed since they last were able to read. Furthermore, patient C12, who suffered from cone-rod dystrophy, first received the implant in a paracentral location; in a second surgery, the implant was repositioned to a subfoveal location. If the time elapsed from local photoreceptor degeneration had had a role, this patient's

functional results would have worsened, since, in cone-rod degeneration, the central cones are the first to degenerate. However, after the repositioning, the patient reported subjective improvement, which was verified by his improved results in standardized tests. While this represents only one case, and a training-effect over time might have had a role as well, it also might indicate the retinal and central advantages of central location placement for subretinal visual implants.

CONCLUSIONS

Using several standardized visual function tasks, we showed that subfoveal placement of a subretinal visual implant chip allowed better visual outcomes compared to parafoveal or nonfoveal placement.

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