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Subretinal Visual Implant Alpha IMS – Clinical trial interim report

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ABSTRACT

A subretinal visual implant (Alpha IMS, Retina Implant AG, Reutlingen, Germany) was implanted in 29 blind participants with outer retinal degeneration in an international multicenter clinical trial. Primary efficacy endpoints of the study protocol were a significant improvement of activities of daily living and mobility to be assessed by activities of daily living tasks, recognition tasks, mobility, or a combination thereof. Secondary efficacy endpoints were a significant improvement of visual acuity/light perception and/or object recognition (clinicaltrials.gov, NCT01024803).

During up to 12 months observation time twenty-one participants (72%) reached the primary endpoints, of which thirteen participants (45%) reported restoration of visual function which they use in daily life. Additionally, detection, localization, and identification of objects were significantly better with the implant power switched on in the first 3 months.

Twenty-five participants (86%) reached the secondary endpoints. Measurable grating acuity was up to 3.3 cycles per degree, visual acuities using standardized Landolt C-rings were 20/2000, 20/2000, 20/606 and 20/546. Maximal correct motion perception ranged from 3 to 35 degrees per second. These results show that subretinal implants can restore very-low-vision or low vision in blind (light perception or less) patients with end-stage hereditary retinal degenerations.

1. Introduction

Hereditary retinal degenerations (e.g. retinitis pigmentosa, RP) are characterised by progressive loss of rod and/or cone function over years or decades, frequently leading to blindness in middle age. Several therapeutic approaches are under development for hereditary degeneration of the outer retina, including gene-therapy (Bainbridge et al., 2008; Busskamp et al., 2012; Maguire et al., 2009), electrostimulation (Schatz et al., 2011) and microelectronic visual implants (Humayun et al., 2012; Stingl et al., 2013b; Stingl & Zrenner, 2013b; Zrenner et al., 2011).

Many of the attempts are in preclinical stage; some are in clinical trials. Their applicability depends on various factors: early stages of photoreceptor degenerations may benefit from gene therapy or neuroprotection. Gene replacement therapy has been successfully applied in several gene mutations causing hereditary

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photoreceptor degenerations (Bainbridge et al., 2008; Maguire et al., 2009), where not only rescue of the remaining vision, but also an improvement in several patients in a 3-years follow-up has been reported (Testa et al., 2013). Neuroprotective effects via release of endogenous growth factors have been demonstrated by transcorneal electrostimulation (Schatz et al., 2011) or intraocularly applied growth factors (Sieving et al., 2006), however their degree of efficacy has not yet been finally evaluated. In late stages of hereditary retinal degenerations rods and cones are almost completely lost. Treatment options considered in such cases are "optogenetics" where inner retina cells are made light sensitive by means of channel rhodopsins, or stem cells, all applied so far not yet in clinical studies. At present only electronic implants are available for patients blind from hereditary retinal degenerations.

Several types of electronic retinal implants have either been approved as commercial products such as Argus II, (Second Sight, Sylmar, CA, see Humayun et al., 2012) and Alpha IMS (Retina Implant AG, Reutlingen, Germany, see Stingl et al., 2013b) or are under development (Ayton et al., 2014; Guenther, Lovell, & Suaning, 2012; Luo & da Cruz, 2014; Menzel-Severing et al., 2012; Stingl & Zrenner, 2013; Zrenner, 2013) for the treatment of hereditary retinal degenerations. Their aim is to restore some vision in end-stage disease for patients who are completely blind or who have light perception without light localization. All of these implants consist of a light-capturing unit (an external camera or an intraocular photodiode array) and an electrode array for stimulation of retinal neurons, mostly those in the inner retina. By electrically stimulating the remaining neurons, the implants initiate a visual percept, replacing to some extent the lost photoreceptor function with artificial vision.

The two types of implants available commercially, the subretinal implant Alpha IMS (Retina Implant AG; Reutlingen, Germany) and the epiretinal implant Argus II (Second Sight, Sylmar, CA) differ in their function in two major aspects: the epiretinal implant has an external head mounted camera and stimulates the ganglion cells of the retina, the third visual pathway neuron whose axons build the optic nerve. The number of stimulation electrodes reaches currently up to 60 and the signal is processed in an external computer and decoded via an epibulbar device that drives the 60 electrodes via transocular wires for an optimal stimulation of the ganglion cells at the retinal output. In contrast, the subretinal implant has a light sensitive 1500 photodiode-array positioned in the layer of the degenerated photoreceptors (subretinally) and stimulates the bipolar cells layer at the retinal input (the second visual pathway neuron, which is connected to the photoreceptors in a healthy eye) and thereby uses the processing power of the neuronal network of the inner retina. The photodiodes are coupled via 1500 amplifiers directly to the stimulation electrodes in an array of independent 1500 "pixels".

A consortium led by the University of Tübingen has been developing various types of active subretinal visual implants since the 1990s (Zrenner, 2002; Zrenner et al., 1999). After preclinical biocompatibility, safety, and biostability tests (Gekeler et al., 2007; Guenther et al., 1999; Kohler et al., 2001; Schwahn et al., 2001), a first wire-bound version of the subretinal implant with 1500 pixels was tested in a pilot study in 11 blind volunteers, where a retroauricular transdermal cable connected the visual implant with an external battery supply. Surprising functional outcomes in three of the subjects, allowing for recognition of unknown objects and even reading large letters, including the detection of spelling errors, were published (Stingl et al., 2013c; Zrenner et al., 2011). Subsequently, a version with wireless transmission of power and signals (transdermally via coils in the retroauricular region, see Figs. 1 and 2), the subretinal implant Alpha IMS of Retina Implant AG, Reutlingen, Germany was implanted in further 29 eyes of 29 blind participants with degeneration of the outer retina in an ongoing clinical trial that consists of module 1 (a single centre study in Tübingen) and module 2 (a multicentre trial at authors' sites). Primary efficacy endpoints were a significant improvement of activities of daily living and mobility shown via activities of daily living tasks, recognition tasks, mobility, or a combination thereof. Secondary efficacy endpoints were a significant improvement of visual acuity/light perception and/or object recognition (clinicaltrials.gov, NCT01024803). Results from the nine participants in module 1 have been published (Stingl et al., 2012, 2013b,c). This manuscript describes the results obtained in the multicentre trial, with a combined analysis of the original nine module-1-participants and the additional 20 participants recruited in module 2.

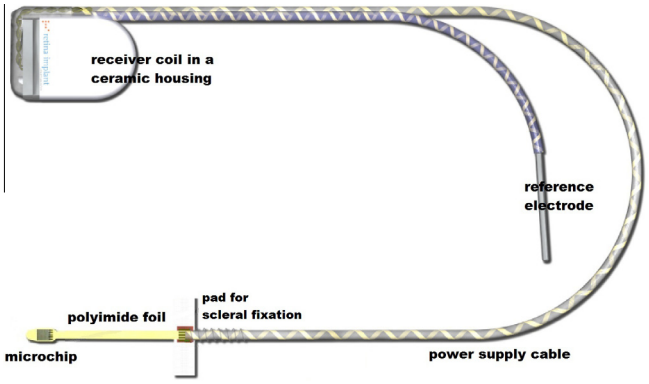

Fig. 1. Retina Implant Alpha IMS: detail on the device. The Retina Implant Alpha IMS consists of the vision chip (multiphotodiodes array) on a polyimide foil (both placed subretinally), a power supply cable connecting the microchip with the receiver coil in a ceramic housing and the reference electrode placed subdermally at the temple and retroauricular region.

2. Material and methods

2.1. Participants

Twenty-nine participants (13 females, 16 males) with a mean age (±standard deviation) of 53.8 ± 8.2 years (range 35–71 years) were enrolled in the clinical trial (www.clinicaltrials.gov, NCT01024803) and received the implant in one eye. Visual function prior to implantation was light perception without projection (20 participants) or no light perception (9 participants) as tested by the ophthalmologist using the standard flashlight test manually by direct illumination of the eye from 5 directions. The loss of vision was caused by hereditary degenerations of the photoreceptors (25 participants had retinitis pigmentosa, 4 had cone-rod dystrophy). None of the participants had other eye diseases that might have affected the visual pathway. Written informed consent was obtained from all participants and the trial was conducted in accordance with the declaration of Helsinki. Research ethics committee approval was obtained for all 7 sites.

2.2. Subretinal Implant Alpha IMS

The Retina Implant Alpha IMS (Fig. 1) consists of a subretinal microphotodiode-array (MPDA, the "microchip") on a polyimide foil and a cable for power supply and signal control, ending in a receiver coil, housed together with electronic circuits in a small subdermal box behind the ear, similar to technology used in cochlear implants (Fig. 2). A separate short cable connects the return electrode to the subdermal box. The MPDA consists of 1500 independent photodiode-amplifier-electrode units, each of which transforms the local luminance information into an electrical current that is amplified for the stimulation of the adjacent

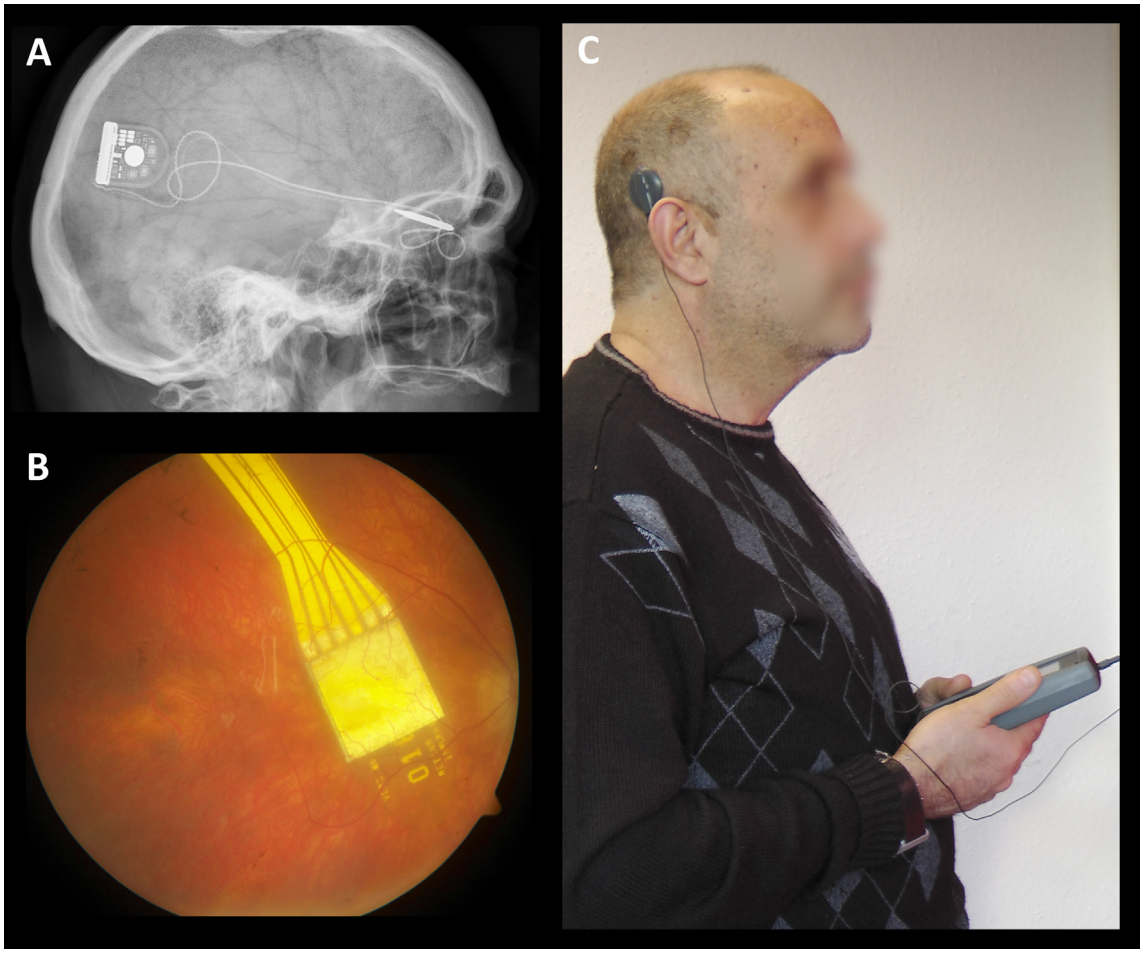

Fig. 2. Retina Implant Alpha IMS: clinical setting. (A) Illustration of the placement of the receiver coil and the power supply cable in an X-ray image. (B) Image of the Retina Implant Alpha IMS on the eye fundus. (C) Handling of the hand held unit: for activation of the visual chip the transmitter coil has to be put on top of the receiver coil and is kept in place magnetically behind the ear. The coils provide a wireless inductive transfer of energy and control signals. The participant can switch on or off the device on the hand held unit, as well as adjust contrast sensitivity and brightness manually via two knobs (adapted from Stingl et al., 2013b).

bipolar cells (Eickenscheidt et al., 2012; Stett et al., 2000) via a 50×50 μm titanium nitride electrode. Thus, a point-by-point electrical image of the luminance information is forwarded to bipolar cells and processed in the inner retina and the afferent visual pathway. Each electrode of the chip typically releases 1 ms pulses in a defined frequency, usually 5 Hz, creating a slightly flickering perception consisting of up to 9 grey levels (Zrenner et al., 2011). As each photodiode-electrode unit theoretically works independently from the neighbouring ones (although in vitro experiments point out that there might be interferences of the electric fields of each electrode), the image reported by the patients reminds of a blurred screen of a black-and white television set allowing for shape perception up to a theoretical two-point resolution of 0.25° of visual angle.

An external battery-driven power supply equipped with a transmitter coil permits an inductive transfer of energy and control signals (Fig. 2). A special feature of the subretinal implant is that the light-to-voltage conversion of the luminance information falling onto the retina, used for electric stimulation of the retinal bipolar cells (Eickenscheidt et al., 2012; Stett et al., 2000), maintains retinotopy in the moving eye. On the external device Retina Implant Alpha IMS has manual adjustment of contrast and brightness for defining the transfer characteristic output curve allowing optimal contrast vision in different luminance conditions. Further technical details have been published earlier (Stingl et al., 2013b; Zrenner et al., 2011, including electronic data supplements).

2.3. Surgical implantation

The subretinal implant was surgically implanted into one eye, under general anesthesia. As depicted in Fig. 2, the polyimide foil that carries the microchip leads subretinally toward the retinal periphery, where it exits the intraocular space through the choroid and sclera. By means of a sealed ceramic connector piece, sutured onto the sclera, the gold wires printed on the foil connect to the round cable that makes a loop within the orbital space (to allow for free eye movement) before it leads to the retroauricular electronic box. Further details on surgical technique have been published (Besch et al., 2008; Sachs et al., 2010).

2.4. Study procedures

Primary efficacy endpoints of the study protocol were a significant improvement of activities of daily living and mobility to be assessed by activities of daily living tasks, recognition tasks, mobility, or a combination thereof. Secondary efficacy endpoints were a significant improvement of visual acuity/light perception and/or object recognition (clinicaltrials.gov, NCT01024803).

Protocol-mandated follow-up extended to 1 year, and included serial retinal imaging with multiple tests of visual function, and adverse event reporting (Stingl et al., 2013a). It was not possible to simulate sham surgery, hence participants served as their own internal controls, comparing the visual function with the implant

power switched on or off. The status of the chip power ON or OFF was not indicated to the patient. Additionally, in most of the patients, tests were performed using light levels that were not visible via the remaining photoreceptors in the eye, if those photoreceptors had retained light perception. The following tests (Stingl et al., 2013a; Zrenner et al., 2011) were repeated in up to 7 follow-up visits during the year of observation.

2.4.1. Basic visual functions ("screen tasks")

Light threshold perception, light source localization, and motion detection of dot patterns were tested on a 60 cm distant screen as 2- or 4-alternatives forced-choice (AFC) tests (Basic Light and Motion – BaLM test) in 8 or 12 trials each. The methodology of the BaLM test that is now mentioned by the FDA as one of the possible tests for electronic implants has been described in detail (Bach et al., 2010, Food and Drug Administration. Investigational Device Exemption Guidance for Retinal Prostheses, 2013) and was used here to measure the secondary endpoints of the study.

The participant was asked whether he/she has seen a flash of light (2AFC, light threshold perception), to localize the illuminated part of the screen (4AFC, light source localization) and to determine the movement direction of a dot pattern (4AFC, motion detection). The first speed tested was 3.3 degrees per second (dps) as the default value set in BaLM. If the participant passed the motion detection, the speed was increased to 5 dps, 7 dps or higher values according to the examiners' consideration. The participant responded via a keyboard or verbally. Due to simplicity of the screen tasks there were no training procedures.

At least 75% (in 2-AFC) or 62.5% (in 4-AFC) correct responses were required to pass the test (defined by the inflection point of the sigmoid psychometric curve). Feedback was given after completion of each test.

2.4.2. Spatial resolution

Grating acuity and visual acuity (VA) with standardized Landolt C-rings in contrast reversal (white ring on black background), the secondary endpoints of the study, were tested on a 60 cm distant screen as 2- or 4-alternatives forced-choice tests in 8 or 12 trials per resolution level. The participant was asked to tell the orientation of the grating and the direction of the C-ring gap respectively. The participants responded via a keyboard or verbally without time limitations. In most of the patients a short training was performed prior to the very first test by showing and explaining the vertical grating pattern and/or the C-Ring in the middle of the screen. At least 75% (in 2-AFC) or 62.5% (in 4-AFC) correct responses were required to pass the test. Feedback was given after completion of each test.

2.4.3. Activities of daily living and recognition tasks

Recognition tasks and activities of daily living (ADL) tasks, the primary endpoints of the study, were performed on a black table using white objects. A short training procedure preceded the tests, except "grey scales", to make the volunteer acquainted with the objects visually and by touch. After completion of each test trial, feedback about correctness of the responses was given. The luminance of the white objects on the table was usually around 200–600 cd/m^2, that of the black table cloth usually below 30 cd/m^2.

2.4.3.1. Geometric shapes. Four objects of about 5° visual angle each were placed in front of the participant, who was not informed about the number of the objects. The participant had to report how many objects were present, point to their position, and describe what they were (shape description and localization) with a timeout of 4 min. Correct responses were documented as scores (from 0 to 4 for each of the three questions; for example, if the patient reported 'I can see three shapes: a circle (points toward the crescent), a triangle (points toward the triangle) and a square (points toward the square)', the documented scores are identification 3, recognition 2 and localization 3).

2.4.3.2. Table setup. Four dining objects (such as cups and cutlery) were placed around a white large plate in front of the participant, who was not informed about the number of the objects. The participant had to report how many objects were present around the plate, localize them, and identify them (shape description) with a timeout of 4 min. Correct responses were documented as scores (from 0 to 4 for each of the three questions).

2.4.3.3. Clock task. White clock hands were placed at angles of 0°, 90° or 180° to each other indicating a clock time. This therefore presented a 16-alternative forced choice test; a response rate above 53% was taken as a pass. The participant was asked to "tell the time" with a timeout of 2 min. During each test (one per study visit) the participant had to read a randomly set clock, 12 times.

2.4.3.4. Letters. Participants were asked to read white letters on a black background (26-alternative forced choice test; a response rate above 52% was taken as a pass). The letter size subtended a visual angle of up to 10°. Timeout of each letter reading was 2 min.

2.4.3.5. Grey levels. The aim of this test was to define the number of grey levels which can be distinguished within the luminance transfer function. An intermediate grey color was presented on one half of a screen with one of six different levels of grey on the other half of the screen: three brighter levels (Michelson contrast in comparison to the intermediate grey 0.29, 0.52 and 0.63) and three darker levels (Michelson contrast in comparison to the intermediate grey 0.96, 0.56 and 0.33). Each of the six combinations was presented three times in random order. Participants were asked which side of the monitor was brighter. Combinations of different grey levels which were distinguished correctly at least twice were documented as recognized. Number of recognized grey scales was the endpoint result of the test. A full screen at the intermediate grey level served as control. There was no timeout for the responses.

The light levels for the screen tests were usually adapted individually to interfere as little as possible with eventually present remaining light perception and light sensitivity of the MPDA was set such that the dark areas of the screen evoked minimum currents and the light areas evoked maximum currents; the bright light level of the screen tasks was usually between 100 and 2500 cd/m^2 and of the black areas approx. 0.1–50 cd/m^2, respectively.

2.4.3.6. Patients' reports. Additionally, patients used the implant at their homes and in daily living and reported subjectively their visual experiences. These reports were documented to analyze improvements in orientation and mobility in daily lives of the participants (one of the primary endpoints of the study).

3. Results

Twenty-one participants (72%) reached the primary efficacy endpoints as set in the study protocol ("significant improvement of activities of daily living and mobility shown via activities of daily living tasks, recognition tasks, mobility, or a combination thereof"). Twenty-five participants (86%) reached the secondary endpoints ("significant improvement of visual acuity/light perception and/or object recognition"). The following paragraphs give details on the performance for the particular tests. For summary of results with the implant switched on for each patient see Table 1.

Table 1
Table shows the best achieved results for each participant in the function tests with the implant power on. In AFC tests (Light perception, Light source localization, clock task, reading letters) " + " indicates the participant passed the test, "–" indicates he/she failed. Motion perception results show the highest speed where the participant was able to distinguish the motion direction correctly ("dps" means degrees per second). Grating acuity results is documented in cycles per degree ("cpd"), the visual acuity as tested by Landolt C-rings in the Snellen fraction. For grey levels the number of correctly distinguished shades of grey is shown. For the categorization of daily life experiences please see the text.

	Light	Location	Motion [dps]	Grating acuity [cpd]	Landolt C VA	Grey levels	Clock	Letters	Daily life experiences
TU-01	–	na	na	na	na	na	–	na	None
TU-02	+	+	–	–	–	na	+	+	Useful
TU-05	+	+	3	0,33	–	na	–	–	Useful
TU-06	+	–	–	–	na	na	–	na	Little
TU-07	+	+	na	0,3	20/2000	na	–	–	Useful
TU-08	+	+	7	0,3	–	3	na	+	Useful
TU-09	+	+	35	3,3	20/546	na	+	+	Useful
TU-10	+	+	5	0,5	–	4	na	–	Little
TU-12	+	+	5	1	–	3	+	+	Little
TU-14	+	+	na	–	na	5	na	na	None
TU-15	+	+	–	1	na	1	–	na	Little
BU-01	–	–	–	–	–	–	–	–	None
BU-02	+	–	–	–	na	4	–	–	Useful
DD-01	+	+	–	–	na	na	na	na	Useful
DD-03	+	–	na	na	na	–	–	–	None
LO-01	+	–	3,3	0,33	na	2	–	na	Useful
LO-07	+	+	–	0,1	na	na	–	+	Useful
LO-08	+	+	–	–	na	na	na	na	None
LO-16	+	+	–	–	na	2	na	na	Little
OX-01	+	–	–	–	–	3	–	–	Little
OX-02	+	+	–	0,33	na	5	–	–	Useful
OX-03	+	–	–	0,33	na	4	–	–	Useful
OX-04	+	+	–	1	–	4	–	–	Useful
OX-05	+	+	–	0,33	–	4	+	–	Little
OX-06	+	+	–	1	20/2000	6	+	–	Useful
SI-01	–	–	–	na	na	na	na	na	None
SI-02	+	–	–	–	–	–	–	–	Little
HK-01	+	–	–	na	20/606	6	–	–	None
HK-02	–	–	–	–	–	–	–	na	None
% passed	86%	59%	21%	48%	14%	52%	17%	14%	45%

"na" means not assessable; the visual function of the patient did not allow to perform the test.

3.1. Primary endpoints

3.1.1. Activities of daily living and recognition tasks

3.1.1.1. ADL: geometric shapes. Scores with implants on and off were compared pair-wise with a non-parametric (Wilcoxon) test. Detection, localization, and recognition of geometric shapes in a good contrast was significantly better with the implant power on compared to off during the first three months (Fig. 3). From the month 6 visits and beyond, the statistical significance decreased ($p > 0.05$) for most of the on–off comparisons, (Fig. 3). This might be due to fewer data, as well as to a slight increase in the performance with the implant power off, as discussed below.

3.1.1.2. ADL: table setup. Scores with the implant on and off were compared pair-wise using all available data and the Wilcoxon test. Detection, localization, and recognition of table objects in a good contrast was significantly better with the implant on compared to off during the first three months (Fig. 3). From the month 6 visits and beyond, the statistical significance decreased ($p > 0.05$) for most of the on–off comparisons (Fig. 3). This might also be due to fewer data and a slight increase in the performance with the implant power off.

3.1.1.3. Clock task. Using the non-parametric (Wilcoxon) test the performance over all subjects was not statistically significantly better with implant on vs. off for the clock task (Fig. 4A). Five participants passed the test at least once during the trial visits and could read the clock hands and tell the time (Table 1). One participant passed the clock task once with the implant turned off.

3.1.1.4. Letters. Using the non-parametric (Wilcoxon) test the performance over all subjects was not statistically significantly better with implant on vs. off for the clock task (Fig. 4B). Four participants passed the test at least once during the trial visits and could read letters (Table 1). Additionally, one participant (TU-12) passed the test with the implant turned on as well as off at the end of the study (month 9), probably using a peripheral residual field with widened pupils, whereas the patient could not read letters at the time of screening; this positive development may be due to beneficial effects described for electrical stimulation treatment (see Section 4).

3.1.1.5. Grey levels. Using the non-parametric (Wilcoxon) test the performance over all subjects was significantly better ($p < 0.05$) with implant on vs. off for grey levels recognition in months 1, 2 and 12 (Fig. 4C).

Fifteen participants (52%) were able to recognize at least one grey level, ranging up to six (only six levels were tested in the present study), compared to an intermediate grey level. The number of grey levels correctly distinguished is illustrated in Table 1. Eight participants (28%) recognized up to three grey levels with the implant off.

3.1.2. Daily life experiences

Participants used the visual implant during their daily life, at home, outdoors, or at work, usually up to 2–3 h daily. The type of vision experienced was described as a blurred image, consisting of shapes of different grey levels, slightly flickering (due to the working frequency of the implant, typically 5 Hz), in a square-shaped visual field of up to 15° diagonally (Stingl et al., 2012, 2013b). Several participants spontaneously reported a slight improvement of the remaining light perception with the implant off during the course of the study; however, none of them could see objects without the implant power being switched on.

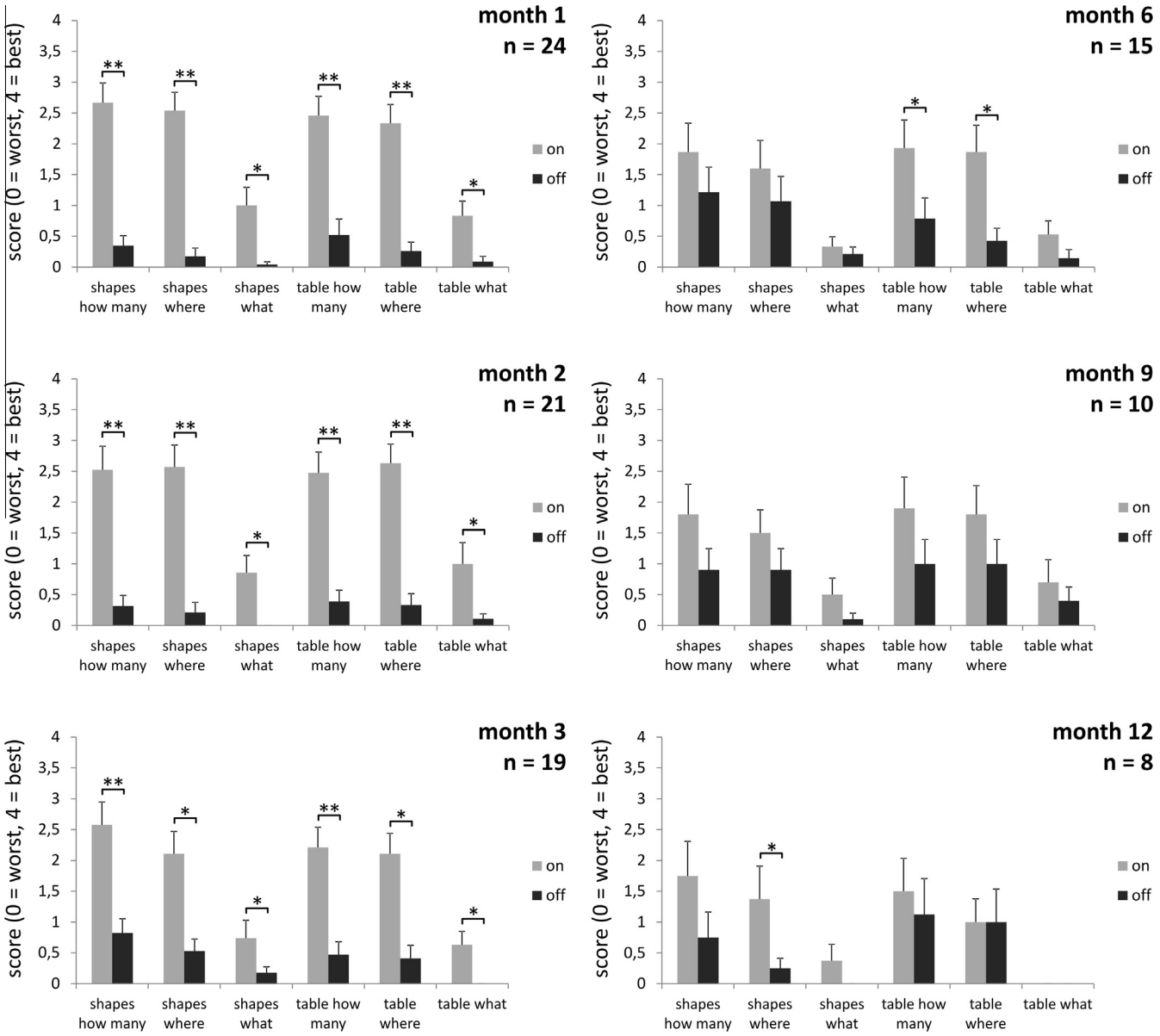

Fig. 3. ADL tasks. ADL tasks for shapes and table setups (see Section 2.4.3). Nonparametric testing showed significant differences between the scores achieved with the implant power switched on vs. off for all test questions in the first three months (see Sections 3.1.1.1 and 3.1.1.2). "*n*" indicates number of participants with available data for the particular visit; * and ** indicate statistic significances of $p < 0.05$ and $p < 0.001$ resp. The value for "table what" score at month 12 is zero.

Eight participants (28%, including the four who did not have any light perception via the implant) did not benefit in daily life. A further eight participants (28%) could localize objects with a good contrast in their daily life, but could not recognize shapes or details (Fig. 5). Thirteen participants (45%) reported useful new daily life experiences with the implant, being able to see shapes and/or details of objects in grey scales (Table 1, Fig. 5). Some of their visual experiences match the criteria of improving independence and social connectedness as proposed recently for the endpoints of visual prostheses (see The Lasker/IRRF Initiative for Innovation in Vision Science, 2014a, chap. 3). The following visual experiences were described with the implant power on (examples).

3.1.2.1. Facial and other personal features. Participants reported seeing the shape of another person's head, mouth, glasses, a baby in a white dress, scarf around the neck, and other features.

3.1.2.2. Buildings. For example, house outlines, windows, town-hall silhouette, and curtain stripes.

3.1.2.3. Outdoors. Street lamps at night showing the direction of the street, pavement lines, arches of a viaduct, landmarks, and others.

3.1.2.4. Vehicles. Car lights moving at night, car reflexions, recognizing different types of buses.

3.1.2.5. Nature. Sunflower stalk, river on the horizon, dog-tail wagging, garden table, moon, and others.

3.1.2.6. Own body. Hand, head silhouette in the mirror, striped jacket in the mirror.

3.1.2.7. Indoors. Such as picture frame on the wall, fluorescent tubes, kitchen objects, plates in a good contrast, bottles, cup handle, washbasin, and bottles on shelves.

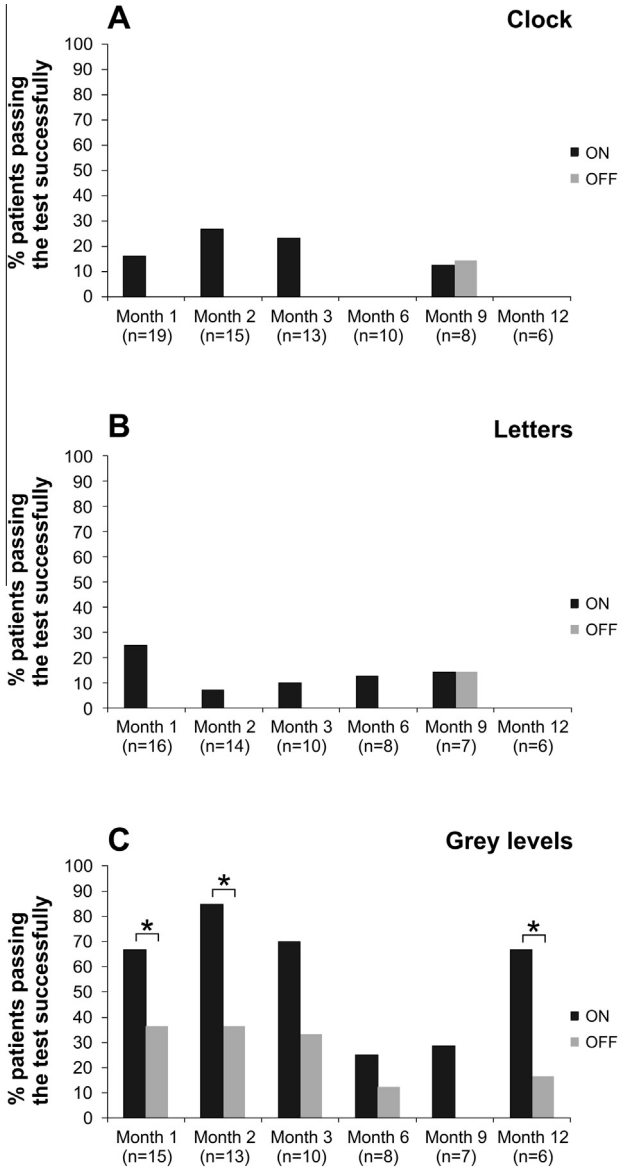

Fig. 4. Recognition tasks. Recognition tasks: (A) clock task, (B) reading letters, (C) recognition of grey levels (for setup see Sections 2.4.3.3–2.4.3.5). The bars depict percentages of patients who passed successfully the particular AFC tasks with the implant power switched on (black bars) and off (grey bars) in all study visits (for details see Sections 3.1.1.3–3.1.1.5). *Above the bars indicate statistical significance ($p < 0.05$) if compared on vs. off in a non-parametric (Wilcoxon) test. "*n*" describes the number of subjects who performed the particular test in the visits.

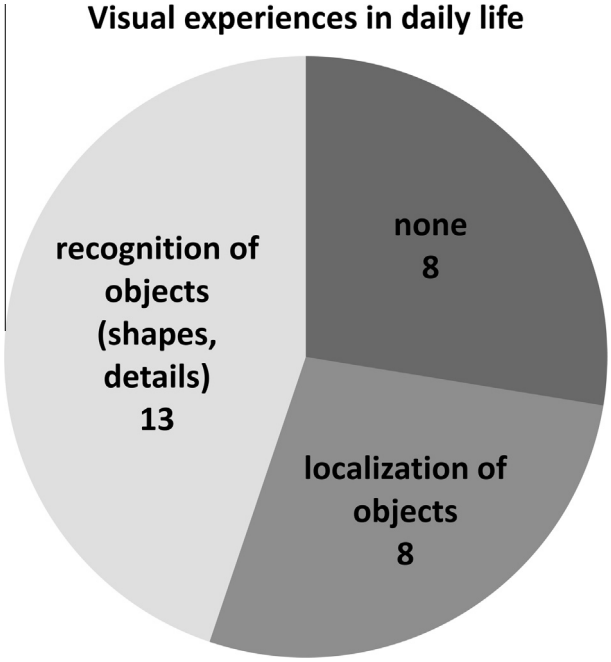

Fig. 5. Daily life experiences. Numbers of participants grouped according to their reports of visual experiences in daily life. Eight participants did not benefit from the visual implant in daily life. Further eight participants could only localize objects. 13 participants reported regained visual experiences with descriptions of shapes or details in scales of grey. For details of the descriptions see Section 3.1.2.

3.2. Secondary endpoints

3.2.1. Basic visual functions

Of 29 participants, four could not perceive any light using the subretinal implant. The most probable reasons in these cases were: (1) intraoperative touch of the optic nerve during device insertion, with subsequent optic disc swelling interrupting MPDA signal propagation by the ganglion cells; (2) retinal edema after implant repositioning; (3) suspected retinal perfusion problems overlying the MPDA; and (4) technical failure of the implant. The remaining 25 participants (86%) were able to perceive light via the subretinal implant tested in a 2 alternative forced choice mode.

Using the non-parametric (Wilcoxon) test the performance over all subjects was significantly better ($p < 0.05$) with implant on vs. off for light perception in all visits and for light localization in months 1, 2, 3 and 6 (Fig. 6A–C).

The highest speed for which the direction was correctly recognized with the implant switched on ranged from 3 to 35 degrees per second (Table 1). With the implant power off, one patient passed the motion task (3.3 degrees per second) in a 4-AFC task once by reaching 62.5% correct responses (Fig. 6C), but volunteered that this was by guessing.

3.2.2. Spatial resolution

Using the non-parametric (Wilcoxon) test the performance over all subjects was significantly better ($p < 0.05$) with implant on vs. off for the grating acuity in months 1, 2 and 3 (Fig. 7).

The grating acuity resolutions with implant power on ranged from 0.1 to 3.3 cycles per degree (Table 1). Five participants passed a 2 alternative forced choice grating acuity task once by reaching 75% correct responses despite chip power being switched off; four of them indicated that it was done by guessing (Fig. 7A), whereas in all five patients the grating acuity with implant power switched off was lower than with the implant power on. Four participants successfully completed standardized visual acuity (VA) testing using contrast reversal Landolt C-rings, with VAs of 20/2000, 20/2000, 20/606 and 20/546 (Table 1).

3.3. Safety

Two serious adverse events (SAEs) were reported during the trial: an increase of intraocular pressure up to 46 mmHg that was successfully treated and resolved without sequelae; and retinal detachment immediately after explantation of the device, treated surgically with laser coagulation and silicone oil, which resolved but with local retinal fibrotic changes.

Safety analyzes of the first, monocentric part of the trial (module 1, see Section 1) have been published recently (Kitiratschky et al., 2014). A detailed description of the whole cohort of the clinical trial safety data, including the non-serious adverse events (AEs) will be presented in another publication. The adverse events

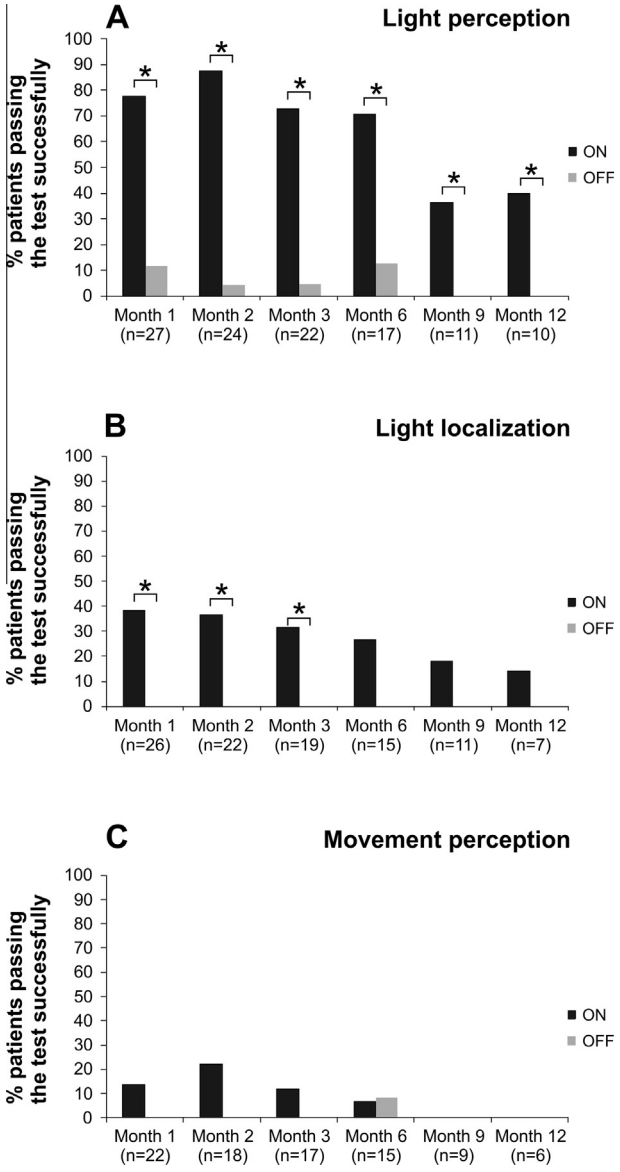

Fig. 6. Basic visual functions ("screen tasks"). Basic visual functions as assessed by the BaLM test: (A) light perception, (B) light localization, (C) movement detections (for setup see Section 2.4.1). The bars depict percentages of patients who passed successfully the particular AFC tasks with the implant power switched on (black bars) and off (grey bars) in all study visits (for details see Section 3.2.1). *Above the bars indicate statistical significance ($p < 0.05$) if compared on vs. off in a non-parametric (Wilcoxon) test. "*n*" describes the number of subjects who performed the particular test in the visits.

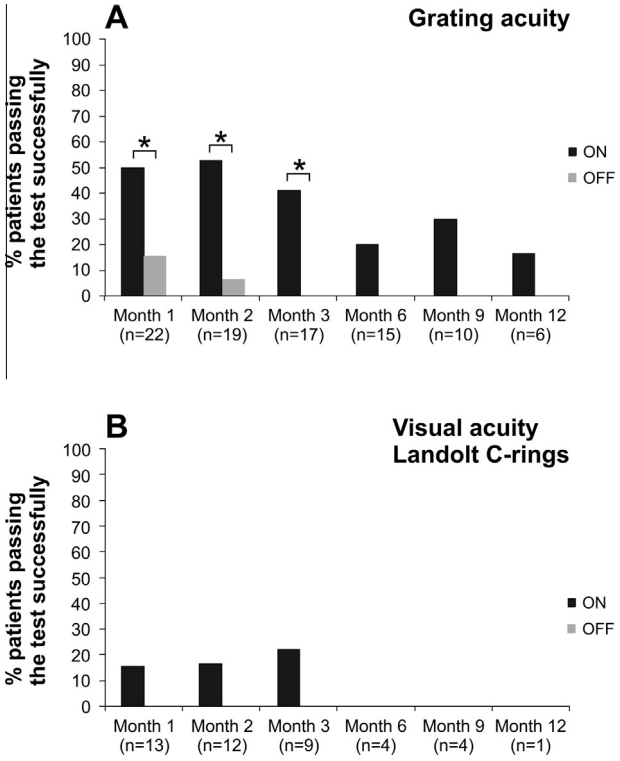

Fig. 7. Spatial resolution. Measures of spatial resolution: (A) grating acuity, (B) visual acuity measured with Landoldt C-rings (for setup see Section 2.4.2). The bars depict percentages of patients who passed successfully the particular AFC tasks with the implant power switched on (black bars) and off (grey bars) in all study visits (for details see Section 3.2.2). *Above the bars indicate statistical significance ($p < 0.05$) if compared on vs. off in a non-parametric (Wilcoxon) test. "*n*" describes the number of subjects who performed the particular test in the visits.

were almost all transient, were treated where possible and did not cause persistent or significant health impairments. Two serious adverse events occuring during module 1 phase could be treated (Kitiratschky et al., 2014).

4. Discussion

These results provide proof of principle that a subretinal implant can restore reliably measurable visual function and potentially useful vision in low-vision or very low-vision range in selected patients with end-stage degenerations of the outer retina such as RP.

Vision with a subretinal implant differs from natural vision in a healthy eye in several ways. Firstly, there is limited spatial resolution. The distance between the light-sensitive photodiodes is 70 μm in a square-shaped-array, allowing for a theoretical maximum VA of approximately 20/250. Preclinical work (Stett et al., 2000) indicates that a distance of less than 50 μm between the single planar electrodes does not improve spatial resolution without additional measures, due to the dissipation of electrical currents within the retinal tissue. Grating acuity and VA results from some of our participants show that the measured VA comes close to this theoretical limit; one participant achieved a grating acuity of 3.3 cycles per degree, corresponding to 20/200. Optotype and grating acuity, however, should not be directly compared (Katz & Sireteanu, 1989), because grating acuity relies on cues derived from angles of lines across a large visual field (even when lines are interrupted), whereas optotype VA depends on the recognition of single optotype features in a very small visual field. The best Landolt C-rings acuity of the same participant was 20/546.

Secondly, electronic implants with planar electrodes do not replicate normal color perception. The images perceived with the subretinal implant are composed of grey levels, as the photodiodes transform the luminance information into an electrical current that, for each electrode, stimulates all color coding bipolar cell types beneath the electrode. Most of the patients are able to distinguish several levels of grey. With a subretinal implant stimulating an end-stage degenerated retina, the 70 μm × 70 μm pixels cover approximately 16 bipolar cells (Stingl et al., 2013c), a number that also depends on the degree of retinal degeneration, with approximately 80% of bipolar cells still present after many years of blindness (Santos et al., 1997). To date, it is not possible to stimulate the cellular connections established earlier in life for green, red and blue selectively and thereby restore natural color vision.

Thirdly, the visual field is limited to the area of the photodiode array. The square of the submacular implant measures

3 mm × 3 mm, which results in a square-shaped visual field of up to 15° of visual angle diagonally. This is sufficient for orientation, given that RP patients can quite well navigate with fields of this size, but it still far more constricted than a normal visual field.

Fourthly, contrast perception and brightness must be adjusted manually in response to ambient illumination and patient preference. On the hand-held battery unit, there are two knobs for manual adjustment of both parameters. With visual training, patients learn to adjust the transmission characteristics of the implant during the first days or weeks after implantation. The procedure is reminiscent of optimizing the image in older black-and-white television sets with two separate knobs for brightness and contrast. The working range of the implant is relatively broad, with luminance from 1 to 100,000 cd/m^2.

Lastly, the perceived image has a blinking character based on the working frequency of the implant. Typically, this is set to 5 Hz, leading to a relatively constant image, but several participants preferred a lower frequency in order to prevent image fading, other reached 20 Hz repetition rate. The origin of these differences in temporal resolution without fading is not clear; there are indications that the ability to use the involuntary microsaccades that allow refreshing the images may play a role and that utilization of such microsaccades may improve over time or that an intrinsic characteristic of the degenerated retina leads to different temporal resolution capability.

Interestingly, the time necessary for re-learning vision is relatively short. Localization of dots and direction of lines was possible usually from the first days, improving within days to weeks to the best possible vision of the particular individual. An evidence for this authors' observation can be taken from the figures Figs. 3, 4, 6 and 7, showing that the results from the "month 1" visit are comparable to visit "month 2", followed by a slight decrease of the functional results from the third month on (caused by technical difficulties as described below).

Activities of daily living as well as real-life visual experiences show that this type of subretinal multi-photodiode array can stimulate the inner retina to obtain a useful perception. The increase in visual function from blindness to a low-vision or very-low vision range can provide significant help for participants who became blind from a chronically progressive degeneration of the retina. The majority of the participants could at least localize objects with a good contrast within their own environments. Almost half of the participants gained useful visual experiences by being able to recognize the details of objects or shapes in real life. The ADL laboratory tests were performed with high contrast (white objects on a black table) and showed a significant improvement of the detection, localization, and identification of objects in the near-vision range, compared to the results with the implant off during the first three months.

The improved vision seen in some participants after several months with the implant power being switched off might possibly be explained by the well-known release of growth factors that occurs after electrical stimulation. Both pre-clinical (Morimoto et al., 2012; Schmid et al., 2009) and clinical studies (Schatz et al., 2011) suggest that this can in turn improve visual function. Indeed, a few participants spontaneously reported an improved light perception with the implant off, especially at the end of the study. Such observations of improvement of remaining vision have been made also in previous attempts to restore vision by subretinal implants in RP patients (Chow et al., 2004). Although those implants – due to very peripheral position and lack of electronic amplification – did not provide vision restoration, central vision in such patients improved considerably, probably due to effects of growth factors (Pardue et al., 2005). We assume that the functional improvements seen in our patients during the course of the study also with non-activated implants may be due to such well established treatment effects after continued electrical stimulation in patients that had still light perception preoperatively.

Additionally, in almost all tests a decrease of function over time with the implant power switched on was observed in a number of participants (Figs. 3, 4, 6 and 7). There are no indications that this phenomenon is caused by biological reasons such as retinal structure changes or local adverse events. Rather, the decrease of the functional performance after implantation was caused by technical failures of the implants occurring in some cases already after 3–12 months after implantation, which is also one of the reasons why the number of participants performing the tests in the later visits decreases. In some patients breaks in the intraorbital cable part caused by the mechanical stress from eye movements occurred (Kernstock et al., 2011). This problem has meanwhile been successfully solved by a surgical technique leading the intraorbital part of the cable in a parabulbar loop minimizing the mechanical stress onto the cable during eye movements, so that this problem did not occur beyond the seventh participant of the trial. Other modes of technical failures have been solved by improving encapsulation of the electronic chip which in laboratory tests showed a considerably prolonged lifetime, currently assessed also in the ongoing clinical trial.

The reaction time was limited to 4 min in the ADL tasks and to 2 min in the recognition tasks. In the screen tasks there were mostly no timeout as usually the responses took several seconds only; however, some participants wanted the pattern presented up to several minutes. The authors learned that this measure is more an expression of the patient's personality than a functionality parameter; some patients report their first impression immediately, whereas many patients try check more times or have difficulties to make a decision in an AFC test, prolonging thus the reaction time although they commented afterwards that their first impression did not change much.

As we published previously, the best visual function is obtained if the chip is located in a subfoveal position (Stingl et al., 2013c; Zrenner et al., 2011). Before surgery, the desired subfoveal position is determined (Kusnyerik et al., 2012). However, due to adhesions, foveal thinning, the curvature of the eye, and the length and flexibility of the polyimide foil, it is not always possible to precisely position the chip. Among the 29 participants, the foveola was on the MPDA in 11 cases, on the chip but close to the MPDA border in 12 cases, and not on the MPDA in 6 cases (usually with a parafoveal position, but up to 3.8 mm away from the nearest chip border). An evaluation of best achieved functional measures for each individual shows also in this cohort, that a parafoveal position most likely limits the best possible spatial resolution (Fig. 6); grating acuity and visual acuity with Landolt C-rings are achievable in more participants and of higher value if the fovea is on the microchip surface (Fig. 8A and B). However, the fovea placement in relation to the microchip does not seem to play a big role for most daily life experiences or the number of distinguishable grey scales (Fig. 8C and D). This might be explained by the low level of vision (low-vision or very-low-vision) that the implant can restore, which is biologically achievable in the whole macular region. Also the amount of distinguishable grey levels is not a direct capability of the fovea alone.

We do not see any direct effect of age or disease duration on the functional outcome. However, the authors have an impression that a kind of ability and motivation to learn a "new perception" and understand the principal function and technical possibilities of the implant might be advantageous, but this is not a measure which could be objectively documented.

Worldwide, currently subretinal, epiretinal, suprachoroidal, cortical and optic nerve implant are under development (Brelén et al., 2010; Humayun et al., 2012; Schmidt et al., 1996; Weiland, Cho, & Humayun, 2011; Zrenner, 2002, 2012, 2013). At present,

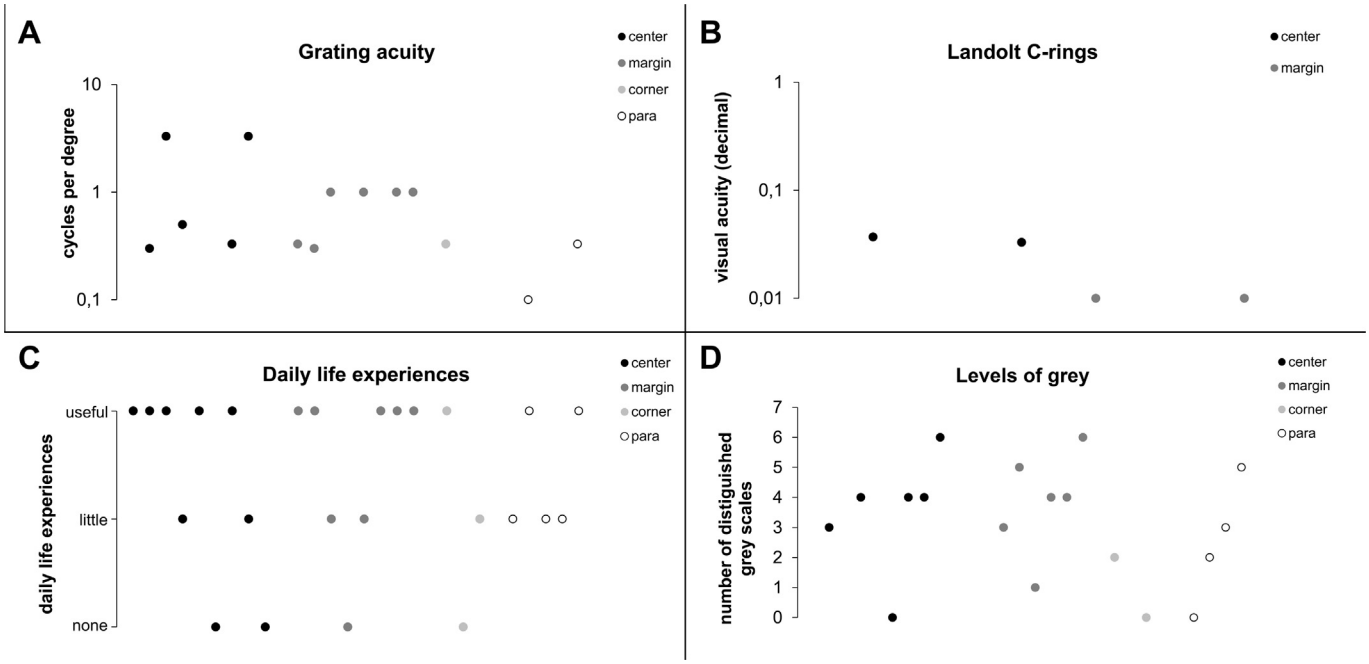

Fig. 8. Effect of the position of the fovea to the subretinal microchip. The color-coded dots represent participants, for whom the results of grating acuity (A), visual acuity (B), daily life reports (C) and number of correctly documented grey scales (D) were available. The colors of the dots represent where the fovea was placed in relation on to the microchip in the particular participant: para (chip was parafoveally, thus the fovea was not on the chip surface), corner (fovea was in the region of the chip corner), margin (fovea was close to the chip border) and centre (fovea was on the microchip surface, not in the proximity of the border). (A) Grating acuity and (B) visual acuity with Landolt C-rings were better and more often measureable if the fovea was stimulated by the chip (chip not parafoveally). (C) Daily life experiences and (D) number of distinguishable grey levels do not show such a tendency.

only the epiretinal Argus II (Second Sight Medical Products Inc. Sylmar USA) prosthesis with the FDA approval and the subretinal Alpha IMS (Retina Implant AG, Reutlingen Germany) implant, both having received the CE mark for use in Europe, have been the subjects of long-term clinical studies in blind patients with hereditary retinal degenerations. Recently also a small number of patients with a suprachoroidal implant have been reported (Ayton et al., 2014). Moreover, there are earlier reports on human patients with a passive subretinal implant (Chow et al., 2010) and EPIRET3, another epiretinal prosthesis (Menzel-Severing et al., 2012) who did not report on daily life experiences, mediated regularly by electronic implant devices.

Both subretinal implant Alpha IMS and the epiretinal implant Argus II could show improvement of the vision in end-stage retinitis pigmentosa patients. However, there are several differences in both systems. The epiretinal prosthesis uses an external camera affixed to spectacles and stimulates directly the ganglion cells with a transformed signal via 60 electrodes, and thus does not primarily involve the bipolar and amacrine cells. This might be an advantage in cases where the bipolar cells layer has degenerated profoundly and ganglion cell system being intact which is rarely the case; to our opinion, including the bipolar cell and amacrine cell circuitry in the visual processing is an enormous advantage for a more natural perception and fast restoration. Inner retina circuitry carries out a number of important processes such as contrast enhancement or movement perception and enable – in contrary to the long ganglion cells axons – a good retinotopy of the image. Moreover, histological work show that the bipolar cell layer usually – despite some reorganization – is present in most patients after years of blindness (Santos et al., 1997) and does not degenerate profoundly even in end-stage disease. Further, the use of an external camera eliminates the chance of utilizing natural eye movements which are important not only for visual search but also serve to prevent image fading on the retina by small involuntary eye movements that refresh images during visual perception and maintain image position stability by the efference copy transmission to the brain, for which the utilization of the extraocular muscle system is instrumental.

Indeed, patients with Subretinal Implant Alpha IMS move their eyes in order to find and localize the objects. In the screen tasks, once they have found the object on the area of the microchip, most patients can see the spatial characteristics and shape without using gaze or head movements. For outdoor use or during scanning larger areas such as table, head movements are necessary, too. Patients wearing a subretinal implant also perform microsaccades with their eyes, refreshing thus the image on the retina (Hafed et al., publication in progress).

Nevertheless an external camera and image pre-processing as necessary for the epiretinal approach brings additional advantages. Accommodation and magnification by zooming in the camera system can improve perception of details (Humayun et al., 2012) and preprocessing of images might enable some additional encoding of information, although such technical measures cannot improve visual acuity, as assessed in proper ophthalmological terms. Moreover, optical magnifying devices for low vision such as lenses can be applied with subretinal implants as well.

Another advantage of the epiretinal approach is an easier surgical insertion – the median implant surgery time is 4 h (Humayun et al., 2012) compared to six to eight hours in the case of the subretinal implantation. The epiretinal system has also shown longer observation times the follow-up of patients wearing the epiretinal prosthesis reaches up to 2.7 years (Humayun et al., 2012) and meanwhile longer (>5 years).

On the other hand, the Alpha IMS with 1500 electrodes has shown better visual results so far, compared to the Argus II with 60 electrodes. The best result of grating visual acuity mediated by Argus II to date is 20/1262 (Humayun et al., 2012) (decimal 0.016), visual acuity measured by standardized Landolt C-ring tests with an epiretinal prosthesis was not reported so far. Also the range of daily life reports of patients wearing Alpha IMS is broader

and its technical stability, shown in laboratory tests, has improved several fold, presently assessed in clinical trials.

Microelectronic visual implants are designed for completely blind persons with retinal degenerations. However, especially for low vision and very low vision patients a number of non-invasive visual rehabilitation tools have been developed to allow for an improved functional performance and visual rehabilitation. Optical and electronic magnifying devices are available on the market for many years, enabling a regular or contrast-reversal magnification of up to 70-times. Mobile digital devices based on video goggles can zoom, autofocus, and adapt to ambient luminance in an enlarged visual field, but most of the devices have a bulky appearance which is socially not easily acceptable. An alternative approach is the tongue stimulator, a non-invasive device which transfers the visual image into a vibrating pattern on the tongue. With the tongue stimulator "Brainport" blind individuals can pass the light perception, time resolution and grating acuity task in a screen module similar to the setup described in the present manuscript (Nau, Bach, & Fisher, 2013). Also conversion of the image into acoustical signals is used for orientation and mobility, letter recognition and other visual tasks, as was published for congenitally blind individuals (Striem-Amit et al., 2012). For recent advances see also The Lasker/IRRF Initiative for Innovation in Vision Science, (2014b, chap. 9).

5. Conclusions

The results of our study show that a subretinal implant is able to restore rudimentary but potentially useful vision in patients blind from hereditary degenerations of the photoreceptors. Almost half of the participants could recognize object shapes and detail in daily life and almost three-quarters could localize high-contrast objects. The implant received a CE mark granting marketing authorization within the European Community in July 2013 and for some centers in Germany public health insurance negotiations for reimbursement have been positive. Nevertheless it is of utmost importance that interested patients are properly informed about the present limitations of electronic implants and that the maximum achievable visual restoration is corresponding only to very low vision of a kind that patients may have experienced just before becoming blind. Moreover, despite well maintained retinal layering, assessed by OCT, it cannot be predicted at present, which patients after implantation may have very useful object perception in daily life and which patients may have only improved light perception and how long the restoration of very-low-vision abilities will be maintained.

Conflicts of interest

Katarina Stingl: Employed by University of Tübingen by means provided by Retina Implant AG, Reutlingen for the clinical trial, travel support. Eberhart Zrenner, Florian Gekeler: Stock ownership in Retina Implant AG, Reutlingen, paid consultant, holder of patents as inventor/developer, travel support from Retina Implant AG, Reutlingen. Helmut Sachs: Stock ownership in Retina Implant AG, Reutlingen, paid consultants.

Karl Ulrich Bartz-Schmidt, Dorothea Besch, Assen Koitschev, Akos Kusnyerik, Janos Nemeth, Robert E MacLaren, Caroline Chee, Mohamed Adheem Naser Naeem, Mandeep S. Singh, Markus Groppe, Timothy L. Jackson, Charles L. Cottriall, James Neffendorf, James D. Ramsden, Andrew Simpson, David Wong: No financial conflicts of interest.

Tobias Peters, Barbara Wilhelm: CRO of the trial on behalf of Retina Implant AG, Reutlingen.

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