# Visual Sensations Mediated By Subretinal Microelectrode Arrays Implanted Into Blind Retinitis Pigmentosa Patients

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## Abstract

Eight patients have received subretinal implants, powered and controlled via a subdermal cable that enters the body retroauricularly and ends in a thin intraocular foil, placed transsclerally between the retinal pigment epithelium and the neuroretina. The tip of this foil carries two distinct arrays, a Multiphotodiode Array (MPDA) with 1500 electrodes, each electrode being controlled by an adjacent photodiode and an amplifier within a 3x3x0.1 mm chip, as well as a second one with 16 electrodes on a 1.2 x 1.2mm array, for direct stimulation (DS) directly controlled from outside. Safety of the approach has been investigated by means of angiography, OCT and fundus photography. Efficacy has been investigated in terms of threshold voltages to elicit phosphenes and the ability to perceive visual information mediated by the MPDA. Patients were tested for 4 weeks and spatial as well as temporal characteristics of repetitive multielectrode-stimulation were investigated.

The implant was well tolerated in all eight patients. OCT and angiography showed minor changes which were transient in most cases. Comparison of fundus photographs showed good subretinal stability of the implant without significant movement of the implants in relation to retinal structures. Threshold values have been determined for different spatial and temporal stimulation settings and were within safety margins. We were able to analyze the dependency of thresholds on pulse form (biphasic vs monophasic voltage controlled pulses), pulse duration, pulse repetition frequency, number of pulses in a pulse series, and on the pattern of electrode activation in several blind subjects. It was demonstrated that the subretinal MPDA yields visual percepts in a light dependent fashion and the minimum illumination level to elicit these percepts was determined.

## 1 Introduction

Several concepts have been developed how to restore vision in blind persons by implanting electronic devices to evoke useful visual sensations. Since 1995, our consortium has developed a so-called “active” subretinal microphotodiode array (MPDA), based on in vitro measurements (Stett et al. 2000) and in various animal models (Zrenner et al, 1999, Schwahn et al. 2001). These *in vitro experiments revealed* that:
(1) charge injections of about 1 nC per electrode are sufficient to excite post-receptoral retinal neurons;
(2) electrode separation distances of 50-150 µm in the outer retina can be resolved in ganglion cell recordings;
(3) retinae with completely degenerated photoreceptors (RCS rats, 160 days and older) can be excited by subretinally in a proper spatially organized manner;
(4) surface coating of MPDAs as e.g. with laminins can improve cell adhesion and biocompatibility (Guenther et al, 1999).
*In vivo experiments* revealed that:
(1) inner retinal layers are well preserved in the central retina, as shown by comparative histological studies of human and animal forms of degenerative retinal disorders (see Zrenner et al., 1997);
(2) A safe introduction of the devices via a scleral flap near the limbus through the subretinal space (like in a tunnel) to the back of the eye is possible (Sachs et al. 2005 and ARVO 1999, Shinoda et al. ARVO 2004);
(3) inner retinal layers are well preserved after subretinal long term implantation (28 months) in pigs;
(4) MPDAs remain fixated at stable subretinal positions as investigated in both rabbit and pig;
(5) Adequate coating has been developed to protect MPDAs from damage tested for 12 months.
(6) Cortical recordings with multielectrodes and optical recording from the visual cortex of cat revealed a spatial resolution for electrical subretinal stimulation of at least 1 degree (Eckhorn et al. 2006).
Based on these findings a subretinal implant was developed that is suited for implantation into the human eye.
Presently a *clinical study* is ongoing, where wire-bound MPDAs are being implanted for four weeks into one eye of 8 blind RP patients. Within a subretinal layer of 1/10 mm there are photodiodes, amplifiers and circuits that adapt the electrical signal to the nerve cell to the strength of the brightness of the object to be seen and its surroundings. This is the first active subretinal chip ever implanted in patients (see Zrenner et al., ARVO 2006, 2007 and Gekeler et al. ARVO 2008).

# 2. Methods

## 2.1 The Subretinal Implant

The active implant consists of approximately 1500 light-sensitive cells on a surface of 3x3 mm (each cell containing an amplifier and a TiN electrode of 50x50µm, spaced 70µm) as well as a 4x4 array of identical electrodes, spaced 280µm, for direct stimulation (DS), chronically implanted next to the foveal rim in 6 patients. MPDA (so-called chip) and DS array are positioned on a small subretinal polyimide foil powered via a subretinal transchoroidal, retroauricular transdermal line that provides power and control signals to the chip and stimulation currents to the DS electrode array. Stimulation parameters for each DS electrode and chip activity and sensitivity can be controlled independently by a software tool that allows to transform the orientation of the visual space to the orientation of the electrode field and to set individual stimulation parameters in the stimulation box via a wireless transmitter. Moreover, all stimulation parameters and patient's "yes" or "no" responses to each parameter are recorded automatically by a particular software. (Sailer, ARVO 2005). For selection of patients, corneal DTL-electrodes and an alternative forced choice method was used to determine electrical excitability of the retina and of optic nerve transmission in normals and patients with degenerative retinal disease; determination of phosphene threshold with corneal electrodes has turned out to provide an important criterion for the suitability of patients for electrical retinal prostheses (Gekeler et al. 2006).

## 2.2 Study design

In the present study, wire-bound MPDAs were implanted for four weeks into one eye of 8 blind RP patients who had no useful vision for more than 5 years and a visual acuity earlier in life > 20/200. They perceived corneally elicited electrical phosphenes and had no other serious eye or general diseases.
The implant safely stored in a trocar was guided from a retrauricular skin incision to the region of the upper lid; from there it was fed via a silastic tube into the intraorbital space. After vitrectomy and a small peripheral retinal detachment it was then fed via a flap in the sclera and a transchoroidal access along a guiding foil into the subretial space and then gently pushed into a final parafoveal position, as developed in pigs previously); radiodiathermy and a specially designed implantation instrument were used to penetrate the choroid without causing bleeding; silicone oil was used as a tamponade (Sachs et al. ARVO 2005, 2006, 2007). This transchoroidal procedure was applied in 8 patients without adverse events such as retinal detachment, bleeding, infection etc. (Sachs et al. ARVO 2008).

## 2.3 Stimulation procedures

A battery of computerized, standardized tests for patients with visual prostheses was developed to quantify the functional outcome (Zrenner et al. ARVO 2004, Wilke et al. ARVO 2006, 2007). Visual perception of brightness elicited by applying biphasic voltage impulses to DS electrodes from 1 to 2,5V (t = 0.5 to 6 ms) was assessed using a scale from 5 (very strong) to 0 (none); additionally double impulses with differences up to 0.8V between two stimuli (10 s interval) as well as pulse trains were applied.

# 3. Results

## 3.1 Direct stimulation of the DS-Array

Electrical stimulation of rows, columns and blocks of 4 electrodes allowed some patients to clearly distinguish horizontal from vertical lines and positions, respectively. Under optimal conditions, dot alignment (vertical vs horizontal up to 86% correct) and direction of dot movement (4 AFC, up to 91% correct) was properly recognized, if three or four neighbouring electrodes were switched on simultaneously or sequentially at 1 s intervals (Zrenner et al. ARVO 2007). Brightness perception of spots varied from scale 0 to 5 in a linear manner if voltages between 1.5 and 2.5 were applied (randomly 6 times) to a square of 4 electrodes. This corresponds to a charge increase of approximately 0.23 $mC/cm^2$ for each of the 5 steps. A difference in brightness between two consecutive pulses was discerned, if a difference in charge of at least 16 $\mu C/cm^2$ was applied. If equal charges were applied to both conditions, the second flash always was perceived slightly dimmer irrespective of the stimulation level. Subjective brightness amplification phenomena were observed at medium stimulation levels with pulse trains and at certain frequencies. The subjective size of spot perception upon stimulation of a square of 4 electrodes increased from 1 to 5 mm at arm´s length, if the voltage was increased from 1,5 to 2,5 V. Interestingly at the offset of current, the spot disappeared in a quick sequence of individual very small pixels.

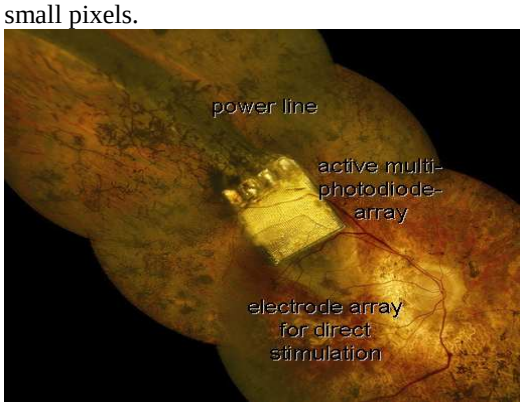


**Fig. 1** DS-Array, MPDA and powerline in the subretinal space of a patient suffering from retinitis pigmentosa

### 3.2 Light stimulation of the MPDA

Four of eight patients perceived the light projected onto the MPDA. In SLO microperimetry of the MPDA, single light spots down to 100 to 400 µm in diameter were detected. Via the MPDA patients were able to correctly localize a white plate on a black table cloth or a window when freely moving ín a room (Zrenner et al. ARVO 2007). In 2 of the devices there were problems with cable contact stability or encapsulation, in two other cases the retina of patients was degenerated too extensively (blindness > 15y). Nevertheless subretinal electrical multielectrode stimulation can provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters.

### 3.3 Life Quality

The brief symptom inventory (BSI) by Derogatis, a validated 53-item questionnaire was used for the assessment of variations in psychological stress of the patients before and during the four week study. The sum score total Global Severity Index (tGSI) was used for evaluation (Peters et al ARVO 2007). At screening all subjects (mean 50.33, SD 12.17) were in the normal range of the tGSI. The difference at close out visit compared to screening (t-test: mean diff 6.17, SD 8.95; p=0.08) showed a tendency to lower values in a sense of better emotional balance at the end of trial participation.

## 4. Discussion

Active, power driven subretinal implants presented here are able to provide useful visual information; passive elements (Chow et al. 2004) cannot provide sufficient energy for electrical neural stimulation. Subretinal active stimulation always yielded spatially confined retinotopic perceptions in form of round whitish or yellowish dots. Spatial dimensions of percepts elicited by single electrodes could be determined to be approximately one degree of visual angle. The size and brightness of such percepts can be modulated with stimulation strength. However, percepts from multiple-electrode stimulation, although still strictly retinotopic, are somewhat more complex than the mere spatial composite of single electrode stimulation. Depending on electrode array density, this effect hampers spatial resolution or even two-point discrimination, as seen in all published results with electrical stimulation so far. Several mechanisms leading to this effect will be discussed. Among them, neuronal reorganization (Marc et al. 2003) seems to play a minor role, given the size of retinal area stimulated by individual electrodes and the fact that lateral displacement of neuronal structures does rarely exceed 100 micrometer (Strettoi, pers. comm.). Temporal characteristics of subretinally elicited percepts depend on numerous factors such as pulse amplitude, characteristics of proceeding stimuli, as well as size of retinal area stimulated. These investigations in patients show a window for safety and efficacy of multielectrode stimulation of the retina on the one hand and the necessity of individual adaptation for feasible approaches on the other.

## 5. Conclusion

Subretinal electrical multielectrode stimulation can provide a useful range of localized brightness perceptions in blind patients within a limited range of temporal, spatial and electrical parameters. However, it is still not clear what type of image a patient will be able to see after prolonged use of such devices. It is expected, that like in cochlear implants, the brain can learn to interpret images from their features, like in learning to interpret art sketches in normal vision.

## 6. Literature

(other than ARVO abstracts quoted in the text;
for ARVO abstracts see www.arvo.org )


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