

Visual resolution with retinal implants estimated from recordings in cat visual cortex

Reinhard Eckhorn^{a,*}, Marcus Wilms^a, Thomas Schanze^a, Marcus Eger^a, Lutz Hesse^{a,b}, Ulf T. Eysel^c, Zoltán F. Kisvárdy^{c,1}, Eberhart Zrenner^d, Florian Gekeler^d, Helmut Schwahn^d, Keisuke Shinoda^d, Helmut Sachs^e, Peter Walter^f

^a Department of Physics, Neurophysics Group, Philipps-University Marburg, Germany

^b Eye Clinic, Philipps-University Marburg, Germany

^c Department of Neurophysiology, Medical Faculty, Ruhr-University Bochum, Germany

^d University Eye Hospital, Medical Faculty, University of Tübingen, Germany

^e University Eye Hospital, Medical Faculty, University of Regensburg, Germany

^f University Eye Hospital, Medical Faculty, University of Aachen, Germany

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Abstract

We investigated cortical responses to electrical stimulation of the retina using epi- and sub-retinal electrodes of 20–100 μm diameter. Temporal and spatial resolutions were assessed by recordings from the visual cortex with arrays of microelectrodes and optical imaging. The estimated resolutions were ~ 40 ms and $\sim 1^\circ$ of visual angle. This temporal resolution of 25 frames per second and spatial resolution of about 0.8 cm at about 1 m and correspondingly 8 cm at 10 m distance seems sufficient for useful object recognition and visuo-motor behavior in many in- and out-door situations of daily life.

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1. Introduction

Retinal photoreceptors transform visual stimuli into electrical signals in normal vision. These signals are processed by intraretinal neural networks and the resulting visual information is submitted by retinal ganglion cells to subsequent visual centers. This is not so in the case of diseases of the outer retina, including macula degeneration and retinitis pigmentosa. They lead to a progressive and finally total loss of the photoreceptors. However, a large

percentage of inner retinal neurons remain histologically intact (Santos et al., 1997). In particular, a large number of the retinal ganglion cells stay functionally alive and can transmit action potentials via the optic tract. Apart from the substitution of retinal function by replacing deteriorated outer retinal cells with intact sub-retinal transplants (Seiler, Aramant, & Ball, 1999), most current concepts for restituting retinal functions are based on the electrical stimulation of the remaining intact visual neurons. Electrical stimuli are meant to coarsely mimic visual inputs to subsequent visual processing.

1.1. Previous work

In recent years, two main types of retinal implants have been developed using either sub-retinal or epi-retinal

* Corresponding author. Fax: +49 6421 282 70 34.

E-mail addresses: eckhorn@staff.uni-marburg.de, reinhard.eckhorn@physik.uni-marb (R. Eckhorn).

¹ Present address: University of Debrecen, Department of Anatomy, Histology and Embryology, Hungary.

electrode arrays (e.g., Chow & Chow, 1997; Chow et al., 2001; Eckmiller, 1997; Eger, Wilms, Eckhorn, & Schanze, 2005; Humayun et al., 1996, 1999, 2003; Peyman et al., 1998; Rizzo & Wyatt, 1997; Schanze, Wilms, Eger, Hesse, & Eckhorn, 2002; Schwahn et al., 2001; Wilms, Eger, Schanze, & Eckhorn, 2003; Zrenner et al., 1997, 1999; Zrenner, 2002).

The sub-retinal devices are implanted between the pigment epithelial layer and the outer layers of the retina. Electrical stimulation with such devices directly activates the overlying retinal tissue, for example the outer plexiform layer and bipolar cells in the case of photoreceptor degeneration. The stimulation parameters can partly be determined by the electronics of the implant, and local stimulation is triggered by the light falling onto a micro-photo-diode (or—transistor) array. Stett, Barth, Weiss, Haemmerle, and Zrenner (2000) have shown in *in vitro* experiments in normal and degenerated rat retinae, stimulated by multi-electrode arrays, that spatial resolution at retinal level, as determined by ganglion cell recordings, is at least 70 μm corresponding to $1/3^\circ$ visual angle. Chow and colleagues (2001; Chow et al. 2002) have reported implantation of a passive sub-retinal device (without external energy supply) into the eye of patients, using the method of Peyman (1998). This study was designed to examine biocompatibility of their sub-retinal devices but not their function. After a very short initial phase of diffuse phosphene perception at the site of the device no further light perception was reported by the patients. However, some improvement of still functioning retinal areas, probably due to the release of growth factors induced by the surgery, the result of subthreshold electrical stimulation or the presence of the device itself, have been reported by some of the patients.

Epi-retinal implants are placed from the vitreous side onto the ganglion cell and nerve fiber layer of the retina. In response to visual stimulation through an external image sensor-array, combined with a real-time retina-processor (e.g., see Eckmiller, 1997), the epi-retinal implant evokes action potentials in retinal ganglion cells and their fibers. Finally, both types of implants send visual information in the form of spike patterns of the ganglion cells via the optic nerve to central visual structures.

In recent experiments, the retina of blind patients was electrically stimulated and they reported sensations of light spots in response to focal electrical stimulation of the inner retina (Humayun et al., 1996, 1999, 2003; Rizzo & Wyatt, 1997). These experiments clearly demonstrated the feasibility of generating perception of light patterns in blind people by retinal stimulation. Presently, no final conclusion can be drawn from the first experiments with patients about how close retinal implants meet the below given estimates of minimal requirements for useful artificial vision.

Some principal technical and biophysical problems have been solved for visual prostheses in recent years (Chow & Chow, 1997; Eckmiller, 1997; Hesse, Schanze, Wilms, & Eger, 2000; Humayun, Probst, Juan, McCormick, & Hickingbotham, 1994; Humayun et al., 1996, 1999, 2003; Normann, Maynard, Guillory, & Warren, 1996; Normann,

Maynard, Rousche, & Warren, 1999; Rizzo et al., 1999; Schanze et al., 2002; Stett et al., 2000; Wilms et al., 2003; Wyatt & Rizzo, 1996; Zrenner et al., 1997, 1999; Zrenner, 2002). However, one crucial question remains regarding the type of neural responses evoked in the visual cortex by stimulation with retinal implants. To be potentially useful for visual perception, spatial, temporal, and intensity resolutions must be sufficient to discriminate objects in a static environment and to perceive motion in the dynamic scenes of everyday life.

1.2. Minimal requirements for useful artificial vision

Object recognition relies mainly on spatial resolution. A resolution better than 0.5° of visual angle corresponds to a visual acuity of 1/35 where clinically vision testing starts. 0.5° visual angle is therefore the ultimate goal in the development of retina implants. 2° resolution will lead to *improvement of performance in daily life*, like the recognition of objects that are important for taking meals, for washing, and dressing. Finally, 10° resolution might be sufficient for *mobility and orientation*, allowing subjects to perceive the presence of large objects and their movement directions (e.g., Legge, Ahn, Klitz, & Luebker, 1997). However, gaining at least some improvement of performance in daily life would be highly valuable for blind people and even regaining some mobility and orientation could improve their quality of life considerably. In normal visual processing, spatial resolution can be estimated at any stage of the visual system from the size of the classical receptive fields (CRFs) of its neurons. Inversely, spatial resolution can also be estimated from the spread of neural activation in the primary visual cortex in response to focal retinal stimulation as is done with small visual stimuli and electrical impulses in this investigation.

Minimal requirements for useful artificial vision can be estimated by psychophysical methods (e.g., Cha, Horch, & Normann, 1992a; Legge et al., 1997; Sommerhalder et al., 2003). Near perfect reading at central retinal projection sites requires at least 300 sampling points of the text to be read within about 5° retinal eccentricity. If safe navigation in dynamic out-door environments is also required, stimulation should include eccentricities of $10\text{--}15^\circ$ (Cha et al., 1992a; Geruschat, Turano, & Stahl, 1998) where spatial resolution for navigational purposes can be lower. About 200 additional sampling points are sufficient within this outer “navigational belt.” The number of required sampling points and their spatial distance define the required number and spacing of stimulation electrodes in a retinal implant. With the above psychophysical estimates, a total of about 500 electrodes would be necessary for useful artificial vision.

1.3. Intensity and time resolution

Retinal ganglion cells transmit retinal visual information to higher visual centers—in normal vision and with retinal

implants (independent of epi- or sub-retinal stimulation). Single ganglion cells code, to a first approximation, temporal sequences of local contrasts (intensities) within their receptive fields by spike rate modulations, based on the synaptic preprocessing in the network of inner and outer retinal neurons. This means that the coding resolutions of intensity/contrast and time are intimately related. As the maximal spike rate of a ganglion cell is limited, the number of different successive intensity values that can be transmitted in the absence of noise in terms of Shannon information (Eckhorn & Pöpel, 1975, 1981; Eckhorn, Grüsser, Kröllner, Pellnitz, & Pöpel, 1976; Eger et al., 2005; Rieke, Warland, de Ruyter van Steveninck, & Bialek, 1998; Shannon, 1948) is mainly determined by the amount of time available for transmitting a single contrast value. For example, if a neuron can discharge maximally 32 action potentials during 333 ms (average duration of ocular fixation) it can theoretically code one out of 32 different intensity values within each of the 3 fixation intervals per second (or 5 bit of information in 333 ms which equals 15 bit/s). This resolution seems sufficient for most visual fixation tasks in which spatial details and high resolution of contrasts play a prominent role. If, on the other hand, a pedestrian wants to cross a road in heavy traffic, local contrast resolution is of minor importance, and may be reduced to only 4 different values (resembling 2 bit). However, in such a situation temporal resolution is of vital importance, and needs to be markedly increased to enable effective coding. Our example neuron can at best signal 2 bit by 1–4 spikes per time window of 41.7 ms. Hence, within one second it can transmit 24 times 2 bit equal to 48 bit/s (again assuming the absence of noise). This example demonstrates that a reduction in intensity resolution (from 5 bit to 2 bit per sample or frame) results in a concomitant increase of temporal resolution (from 3 to 24 samples per second) and an overall increase in the rate of information from 15 bit/s to 48 bit/s. It is important to keep in mind that the signals carrying the information are in first approximation spike densities (rates) that can be read out by the succeeding stages of the visual system at quite different speeds (integration window) with the consequence that an increase in temporal resolution reduces the contrast resolution while overall rates of information can increase. It is probable that the visual centers adaptively change the temporal resolution (Agmon-Snir & Segev, 1993) according to the current visual situation which, in turn, affects the available contrast resolution. Retina implants have to generate spike density coding so that the visual centers can use their flexible strategy in which the trade-off between intensity and time resolution is continuously optimized.

1.4. Estimates of spatial and temporal resolutions from anesthetized cats

Before extensive investigations of perceptual resolution with retina implants are carried out in blind humans, we considered it ethically appropriate to test and optimize stimulation with retinal implants in animal models. Based on the

existing broad knowledge about the visual systems of cats (e.g., Gilbert, 1993; Hubel & Wiesel, 1962; Tusa, Palmer, & Rosenquist, 1978; overview: Orban, 1984), we used this species to estimate the achievable resolution in human visual perception with sub- and epi-retinal implants. Most importantly, for identical visual stimuli, human visual perception has been shown to correlate with the receptive field properties of visual cortical neurons in lightly anaesthetized monkeys and cats. Correlations were demonstrated for a variety of perceptual and neural thresholds of visual cortical neurons, including those for luminance and color contrast, flicker frequency, movement direction, and velocity (e.g., Gilbert & Wiesel, 1990; Grind van de, Grüsser, & Lunkenheimer, 1973; Heydt von der & Peterhans, 1989; Knierim & van Essen, 1992; Salzman, Britten, & Newsome, 1990; Wachtler, Sejnowski, & Albright, 2003; overview: Tovee, 1996). From these observations and retinal lesion experiments in primary visual cortex, one can conclude that perception of visual details requires the activation of neurons in this area (e.g., Darian-Smith & Gilbert, 1995). From the time course of their activations by a focal retinal stimulus estimates of perceptual temporal resolution should be possible (Dinse & Krüger, 1994; Grüsser & Creutzfeld, 1957; Rager & Singer, 1998; review in: Bullier, Hupe, James, & Girard, 2001). In addition, the spatial extent of the cortical activations to such stimuli can give conservative estimates of spatial visual resolution. This is possible because the lower visual cortical areas (particularly area 17/V1) are retinotopically well organized so that spatial profiles of cortical activations can directly be related to retinal and visual space (Adams & Horton, 2003; Angelucci, Levitt, Walton, Hupé, & Bullier, 2002; Tusa et al., 1978). These measures were verified in our investigation by light stimulation of the retina before implantation of electrodes combined with recordings of cortical activities from the identical positions used during electrical stimulation.

2. Methods

Stimulation experiments with cortical electrode recordings were performed in 9 adult cats in 13 sessions, and with optical cortical recordings in 4 adult cats (3–5 kg). All experiments were done in accordance to the guidelines of the European Communities Council Directive (86/609/EEC) and were approved by official German Animal Care and Use Committees following the NIH Principles of Laboratory Animal Care (Publication 86–23, revised 1985) and the ARVO guidelines.

2.1. Preparations

Preparations for cortical microelectrode and optical recordings were similar as reported in detail elsewhere (Kisvarday, Buzas, & Eysel, 2001; Schanze et al., 2002; Wilms et al., 2003). Briefly, adult cats received an initial anesthesia with ketamine hydrochloride (Ketanest, 10 mg/kg) and xylazine hydrochloride (Rompun, 1 mg/kg) that was about 2 h later maintained by a mixture of N₂O/O₂ (70%/30%) and halothane (0.3–0.8%, optical imaging experiments) or isoflurane (0.5–1.5%, microelectrode recording experiments) using oro-tracheal intubation for artificial respiration. Eye movements were minimized by i.v. infusion of alcuronium chloride (0.1 mg/(kg h)). End-tidal CO₂ (3–4%), blood pressure (100–140 mmHg), and body temperature (38–39 °C) were monitored continuously.

Semi-chronic preparations for cortical microelectrode recordings were made with initial surgery and anesthesia (induced and prolonged) corresponding to the acute preparations except for the use of oro-tracheal intubation instead of tracheal cannulation for artificial ventilation. For head fixation and the attachment of a recording chamber over the craniotomy at V1/V2 positions, two bolts were implanted in cavities of the forehead. In some cases, an optically controlled laser coagulation of the peripheral retina was performed to reduce the risk of a retinal detachment due to vitreal tractions after insertion of stimulation electrodes.

The refraction of the non-implanted eye was corrected for the viewing distance of the visual stimulation screen at 1.3 m in front of the eyes.

2.2. Insertion of electrodes for epi-retinal stimulation

After lateral canthotomy at one eye the conjunctiva was incised (~1 mm), and a sclerostomy performed behind the limbus, sufficient for insertion of the epi-retinal fibre-microelectrode stimulation arrays. Alternatively, epi-retinal foil electrode arrays (polyimide-platinum thin-film electrodes) were implanted after lensectomy and vitrectomy through corneal incisions and placed on the retinal surface adjacent to the fovea centralis. The position of the foil electrode array was stabilized with Perfluorodecalin.

Insertion of fiber- and thin-film electrodes for epi-retinal stimulation was made as described in detail by Schanze et al. (2002). Briefly, the fiber electrodes (80 μm shaft diameter; Reitböck, 1983) were ground to expose a metal (PtW) cone tip (~20 μm diameter, ~30 μm height) allowing safe charge delivery of up to 20 nC per impulse. The fiber electrodes were axially positioned singly under visual control using a computer driven, adapted fiber electrode manipulator (Eckhorn & Thomas, 1993; 1 mm concentric bundle of 3 or 7 electrode guide tubes) attached to another specially developed manipulator with 11 degrees of freedom (NeuroPhysics, University of Marburg). This system allowed fast, precise, and flexible electrode positioning through the small scleral opening (1.1 mm). In several experiments (see Section 3), thin-film arrays (platinum islands of 100 μm diameter on polyimide) were used for stimulation (Stieglitz, Beutel, Schuettler, & Meyer, 2000). For low energy activation, the electrodes were brought in direct contact with the inner limiting membrane under visual guidance. To control correct positioning, multiple unit activity (MUA) of retinal ganglion cell fibers was recorded via the stimulation electrodes.

2.3. Insertion of electrodes for sub-retinal stimulation

For a safe introduction of sub-retinal implants, the approach with access through the vitreous body of the eye (ab interno) as published by Peyman et al. (1998) as well as Sachs et al. (1999) was used. In short, a modified pars-plana-vitrectomy approach was used in the eyes after pupil dilation with atropine 1%. The high reflectivity of the tapetum lucidum required no endoillumination, thereby enabling two port vitrectomy. Two sclerotomies were made 6.0 mm posterior to the limbus. After partial vitrectomy between sclerotomy and area centralis, a 31 gauge cannula (Visitec, Sarasota, FL) was used to create a localized retinal bleb by injecting a small amount of balanced salt solution; the bleb was enlarged by injecting Healon® (Pharmacia, Stockholm, Sweden). A 2.5-mm retinotomy was then made circumferentially at the temporal portion on the bleb. The foil was introduced into the vitreous cavity with an intravitreal end-gripping forceps. After the foil was inserted through the retinotomy into the sub-retinal space, it was forwarded about 1 mm outside the created bleb under the retina near the area centralis (Volker et al., 2006).

The stimulation array consisted of thin-film platinum electrodes mounted on a flexible polyimide foil (Fraunhofer Instit. Biomed. Engin., St. Ingbert, Germany; model RS8-50; Stieglitz et al., 2000). The flexible foil strip was made of 50 μm thin polyimide with 8 substrate-integrated, insulated golden connection lanes terminating in a 2 by 4 array at the end of the strip with an even spacing of 330 μm (see Fig. 4). Rectangular openings (100 μm \times 100 μm) in the insulation layer at the terminals of the lanes define the size of the stimulation electrodes. The gold electrodes were covered with a thin layer of platinum to enhance the safe charge injection

capacity. At the other end of the foil strip a plug was soldered to the contact pads to allow connection with the computer controlled stimulator device (STG 1008, Multi Channel Systems, Reutlingen, Germany). At the end of each experimental session, sclera and conjunctiva were sutured, all wounds topically medicated, and infections were prevented by injections of penicillin (i.m.). The animals recovered rapidly so that after a few weeks repetitive investigations of the same eye could be performed (Gekeler et al., 2004).

2.4. Stimulation and recording

2.4.1. Epi- and sub-retinal stimulation

For epi-retinal stimulation generally rectangular constant current impulses were applied (~200–250 μs duration per polarity; ± 1 –150 μA). They consisted of charge balanced pairs of a negative and positive phase (cathodic first; controlled constant current sources developed by T. Schanze, manufactured by M. Eger, Uni-Marburg, Physics Department). In some cases, bursts of 2–10 such impulse-pairs were applied (0.4–2.0 ms burst duration). In optical imaging experiments, trains of biphasic stimuli were also applied (see below). For sub-retinal stimulation (see, e.g., Fig. 1B) biphasic impulses (anodic first) with amplitudes up to ± 50 μA were applied against a ground electrode. Stimulus duration was 0.5–1.0 ms per phase applied at intervals of ISI = 305 ms.

Before optical imaging the visual cortex, the function of the retinal implant was tested by electrode recordings from the optic tract, made with a concentric bipolar tungsten electrode (SNEX-100, Rhodes Medical, Woodland Hills, CA, USA). Penetrations were performed at Horsley-Clarke coordinates A14/L2 just behind the optic chiasm. For positioning of the recording electrode at the correct depth, recordings were made during 1 Hz stroboscopic light flash stimulation. The optimal position of the electrode was reached, when the maximal flash evoked field potentials were obtained and the electrode was fixed at this position using dental cement. To compare the visual response amplitude to the electrically evoked responses and to judge the relative efficacy of stimulation at the different electrodes in the epi-retinal array, short, single biphasic electrical stimuli (4–78 μA ; balanced current; waveform: 250 μs negative; 250 μs off; 250 μs positive) were delivered at 1 Hz via all single electrodes of the implant against ground (electrode No. 19, see Fig. 4A).

With sub-retinal stimulation, optic tract responses were evoked by electrical stimulation (± 50 μA , biphasic current pulses as described above). Electrodes 1, 2, 3, and 4, respectively, served as different electrodes, the combined electrodes 5–8 of the implant were used as ground. The small field potentials were averaged from 128 repetitive stimuli (see Fig. 4B).

Cortical electrode recordings were made in area 17 and 18 (Horsley-Clarke coordinates: A2-P7, L0.5-L3) with up to 16 microelectrodes. For technical details, see Wilms et al. (2003). Briefly, linear arrays of fiber electrodes (2–3 M at 1 kHz) were used and signals were extracted in real time from each electrode's broad band recording: single unit spike activity (SUA), multiple unit spike activity (MUA), and local field potentials (LFP, 1 or 10–140 Hz). SUA was captured as events whereas the continuous amplitude signals MUA and LFP were sampled at 500 Hz. Alternatively, the broad band raw signals (1–4000 Hz) were sampled at 20 kHz for off-line filtering to SUA, MUA, and LFP, enabling a better rejection of the stimulation artifacts (Schanze et al., 2002). All signals were stored on a hard disk for off-line data evaluations.

2.5. Receptive fields

The receptive fields (RF) of the recorded cortical neurons were determined qualitatively using a hand held projector and quantitatively with computer generated stimuli presented on a monitor (100 Hz frame rate, high contrast), composed of random m-sequences (multifocal RF-measurements, Sutter, 2001). After simultaneous on-line mapping of all cortical RFs, the positions of the retinal RFs were determined by the same MUA recording method. The tip positions of the stimulation electrodes and retinal landmarks (blind spot and area centralis) were marked by rear projection onto a tangent screen using a custom designed laser projection

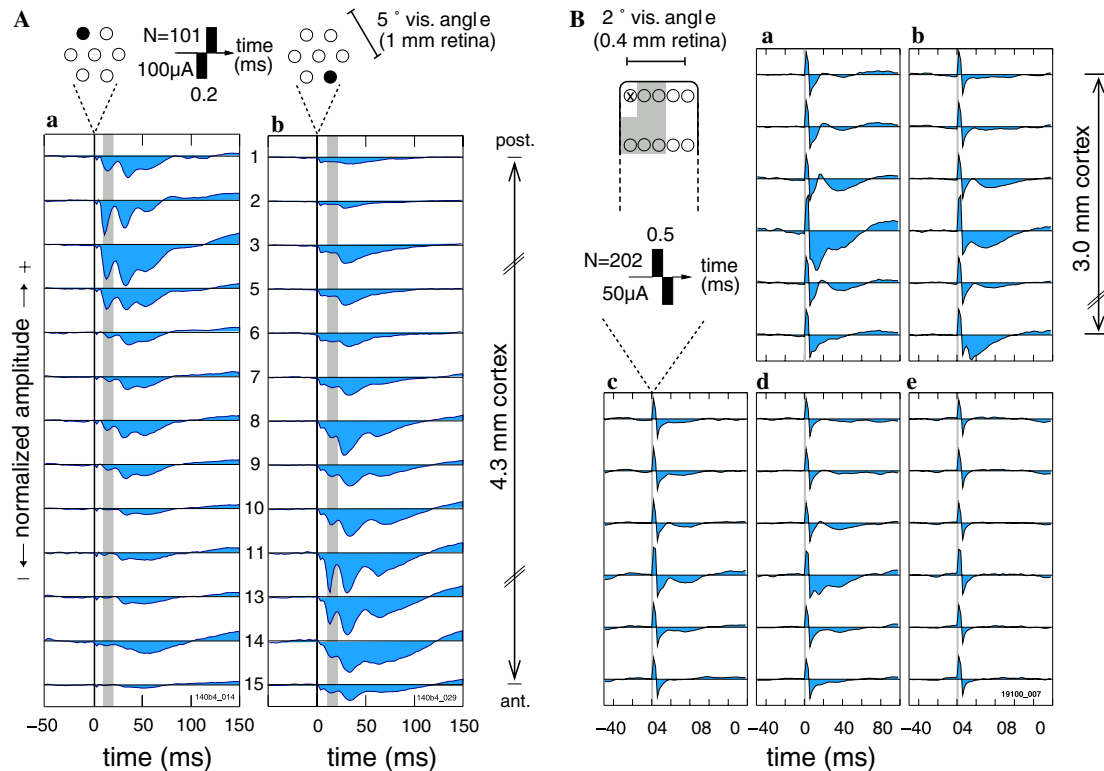


Fig. 1. Time courses of cortical population activities (LFP) in response to single-site retinal stimulation. (A) Responses to epi-retinal impulse stimulation ($N = 101$ identical stimulus repetitions) recorded simultaneously at 13 different locations by a linear electrode array (0.3 mm equi-distant pitch). The 10 ms gray band marks the primary cortical signals in direct response to the afferent stimulus evoked population spike. (B) Responses to sub-retinal impulse stimulation ($N = 202$) at five retinal electrode positions (a–e) recorded simultaneously at six different cortical locations by a linear electrode array (0.5 mm equi-distant pitch). The insets on top of column (A) and (B) depict the geometry of retinal stimulation sites and the time courses of stimulation current impulses with durations of 0.2 ms (A) and 0.5 ms (B). The retinotopic correspondence between retinal stimulation and cortical recording sites can be derived from the responses. The higher the response amplitudes the better the correspondence. This means for (Aa): best correspondence with electrode 3. For (B) the stimulation electrodes, used for the data in (Ba–e), are marked by gray background. Correspondence: electrodes used for (Ba) and (Bb): upper row left and right, respectively; for (Bc): lower row left and for (Be): lower row gray field right. Best retinotopic correspondence for data in (Ba and c–e) with electrode 4 (counted from top of each panel), for data in (Bb): el. 4 and 6.

system. Retinal electrode positions were corrected until cortical and retinal RFs sufficiently overlapped.

2.6. Optical imaging of intrinsic signals

Optical imaging of intrinsic signals was carried out using the Imager 2001 and the data acquisition software VDAQ-NT (both Optical Imaging, Germantown, NY, USA) as reported previously (Kisvarday et al., 2001). Briefly, a bilateral craniotomy was made between Horsley–Clarke coordinates AP -6 and $+12$ and LM $+0.5$ and $+7$ to expose the central visual representation of visual areas 17 and 18. A round stainless steel chamber (31 mm diameter) was mounted over the exposed cortical region, the duramater was removed and the chamber filled with silicone oil (50 cSt viscosity, Aldrich, Milwaukee, WI, USA) and sealed with a round cover-glass. During data acquisition, the camera (two SMC Pentax lenses, 1:1.2, $f = 50$ mm, arranged in a “tandem” manner, Ratzlaff & Grinvald, 1991) was focused 650–750 μm below the cortical surface and the cortex was illuminated with 609 ± 5 nm light (filter: Omega Optical, Brattleboro, VT). Imaging was carried out separately for visual stimuli through the non-operated control eye and for electrical activation via the implanted retinal electrodes.

2.6.1. Optical imaging using visual stimulation

Visuotopic mapping was performed using test stimuli presented on a video screen (SONY, Pencoed, UK) in 120 Hz non-interlaced mode 28.5 cm in front of the cats' eyes using the VSG Series 3 stimulus generator

system (Cambridge Research Systems, Rochester, UK). The test stimulus consisted of a narrow horizontal slit (0.5–3 deg width and 40 deg length) encompassing a high-contrast vertical grating (50% duty cycle) 0.6–1 cyc/deg spatial frequency moving forth and back at 1–2 Hz. Stimuli were presented at visual field elevations encompassing the central 10 degrees and displayed in a random sequence. Each data acquisition period (4.5 s during which the stimulus grating moved) was preceded by an inter-stimulus interval of 10 s when the animals viewed a blank screen (average luminance of the stimulus grating).

2.6.2. Optical imaging using electrical stimuli

For obtaining intrinsic signal images of cortical activation due to electrical stimuli of the implanted electrodes a data acquisition paradigm similar to that of the visual stimulation was used (4.5 s duration, 10 s inter-stimulus interval). During a single data acquisition period, 9 trains of current pulses were applied (250 ms train duration with 250 ms intervals). Each train consisted of a barrage of 0.75 ms bipolar current pulses (± 4 – $78 \mu\text{A}$, 250 μs negative, 250 μs positive repeated at 100 Hz).

2.6.3. Analysis of the optical images

For data analysis, single condition maps (SCMs, c.f. Bonhoeffer & Grinvald, 1996) were calculated by summing the images associated to a particular stimulus condition using the Winmix software (Optical Imaging, Germantown, NY, USA). The SCMs were filtered with a Laplace filter (high-pass: 50 pixels, 1064 μm) followed by a boxcar filter (low-pass: 5 pixels, 106 μm).

2.7. Data analysis

2.7.1. Cortical electrode recordings

The population signals, MUA and LFP, were simultaneously available at all functioning cortex electrodes (~80%) and good SUA (at ~25% electrodes) were detected after the initial electrode positioning in the upper layers without any search for large spikes. Responses to identical stimulus repetitions were averaged with respect to stimulus onset to obtain peri-stimulus time histograms (PSTHs) from which we determined the cortical response thresholds, delays, and strengths to retinal stimulation. These measures were based on average response power after scaling to the corresponding pre-stimulus values. In addition, LFP and MUA response power were plotted in relation to stimulation strength to estimate thresholds.

2.7.2. Optical recordings of intrinsic cortical signals

The optical recordings of intrinsic signals evoked by electrical retinal stimulation revealed two-dimensional activity patterns in a cortical area of 6×8 mm. The grey values of the respective maps coded the activity on a 0–255 gray scale with 0 (black) representing maximal, and 255 (white) minimal activation. The peaks in the spatial pattern of activation were used for estimation of spatial resolution.

Spatial resolution was estimated from the spread of cortical activation in response to a focal retinal stimulus, defined as the retino-cortical point spread function. It was either derived by sampling from linear electrode arrays with 0.3 or 0.5 mm spacing (7 or 16 microelectrodes) or by measuring the spread of activation with optical imaging. For electrode recordings, the spatial distribution of response amplitudes was fitted by a Gaussian function and its full width at half height was taken as the magnitude of the cortical point spread. In addition to this, the same procedure was used to determine the cortical point spread to visual retinal stimulation. In this case, a small focal flash was shown at the same retinal location in the corresponding location of the non-implanted eye (results not shown).

Most response profiles were measured with cortical microelectrode recordings between 4° and 9° retinal eccentricity. The remaining optical recordings were from 0° to 15° eccentricity. To compare these different profiles, we took the magnification factor from the cat visual cortical maps (thoroughly measured by Tusa et al., 1978 & Tusa et al., Tusa, Rosenquist, & Palmer, 1979) at the recording site of every single cortical activation profile. For comparison, we took the individual magnification factors for normalization to a reference eccentricity of 2° visual angle. We chose this reference at 2° because the retina implants in progress will probably span a total visual angle of about $\pm 4^\circ$, so that 2° eccentricity is just half way out from the center. The response profiles measured with cortical electrodes were recorded at eccentricities between 4° and 9° in the lower visual field where the magnification factor in cat does not change very much with eccentricity. The fewer optical recordings were made at eccentricities between 0° and 15° . This normalization seems appropriate when we assume that the size of a retinal patch, activated by a single electrode, is independent of eccentricity because the spread of the electrical stimulation field will not change with eccentricity. Therefore the corresponding activation patch in area 17 decreases with increasing eccentricity, and this effect has been normalized by us.

Estimates of resolutions for contrast and time were obtained with two methods. In the “direct approach,” the effective duration and variance of averaged excitatory cortical MUA and LFP activations were related to temporal and amplitude resolutions, respectively. The number of discriminable amplitudes was quantified by the difference between average post- and pre-stimulus amplitudes, and divided by the post-stimulus variance. In the “indirect approach,” the rate of transinformation T' (in bit/s) was used (e.g., Eckhorn & Pöpel, 1975; Eger et al., 2005; Shannon, 1948). It determines the amount of information transmitted from a retinal stimulus electrode to a cortical recording site. 1 bit/s here means that two different stimuli can be distinguished by an ideal observer on the basis of a single observation period of 1 s duration. If, for example, 20 bit/s are transmitted from a retinal stimulation electrode to a cortical recording site (a realistic example), a series of twenty 2-level discriminations (e.g., black/white) are safely transmitted during one second (or 5 consecutively transmitted values per second at a resolution of $2^4 = 16$ different levels; e.g., local contrast

values, which also gives $5 \times 4 \text{ bit} = 20 \text{ bit/s}$). Hence, temporal and intensity resolutions are inversely correlated, the higher the temporal the lower the intensity resolution. The Shannon information measure has the advantage that the actual noise level is taken into account so that potential resolutions can be estimated quantitatively for single responses without averaging.

3. Results

3.1. Spatial activation profiles in visual cortex

3.1.1. Microelectrode recordings in visual cortex

The cortical responses evoked by single retinal impulses show different time courses (e.g., Figs. 1A, a and b), depending on the recording location relative to the retinal stimulation site. These differences in time course are, in essence, a sign of fast dynamic changes in the spatial activation profiles. We measured the spatial width of these profiles to estimate the potential spatial resolution obtainable with retina implants. The narrowest distribution is generally present at the first afferent cortical activations (Fig. 1A, gray time slices). One millimeter difference in epi-retinal stimulus location causes in this example a cortical offset in the maximal primary response of ~ 3 mm (Figs. 1A, a vs. b). The later (secondary) response components display a broader distribution.

The spatial activation profiles (retino-cortical point spread) to epi-retinal stimulation have almost equally often a single (Fig. 2A) or a double peak (Fig. 2B). It can also be noticed that the width of the activation increases slightly with stimulation current (Figs. 2A and B), probably due to an increase in the number of recruited ganglion cells and the related broader and stronger activation of the cortex. A coarse estimate of the full width at half height (FWHH) obtained was 1.0 mm (Fig. 2A; stimulation: each phase 0.2 ms, negative first, $24 \mu\text{A}$), 2.7 mm (2B; stimulation: each phase 0.2 ms, negative first, $25 \mu\text{A}$) and 1.7 mm (2C; stimulation: each phase 0.5 ms, positive first, $50 \mu\text{A}$). For a better comparison of these values, obtained at different retinal eccentricities, we normalized these FWHH values to an eccentricity of 2° visual angle by using the cortical magnification factors corresponding to each of our cortical recording locations (Tusa et al., 1978; Tusa et al., 1979). Normalization resulted in 1.4° (A), 3.8° (B), and 2.4° (C) of visual angle, respectively (see also Section 4).

3.1.2. Optical recordings in visual cortex

Optical recordings revealed results that corresponded well to the microelectrode recordings. While the fast response components could not be monitored separately because of the relatively low temporal resolution of the optical signals, the compound signals of optical recordings revealed activation profiles similar to the late components of the microelectrode recordings. This is demonstrated in Fig. 3 showing different cortical activation profiles in response to different single site retinal stimuli (visual stimulation (Fig. 3A), as well as epi- (Fig. 3B), and sub-retinal (Fig. 3C) electrical stimulation). In line with the

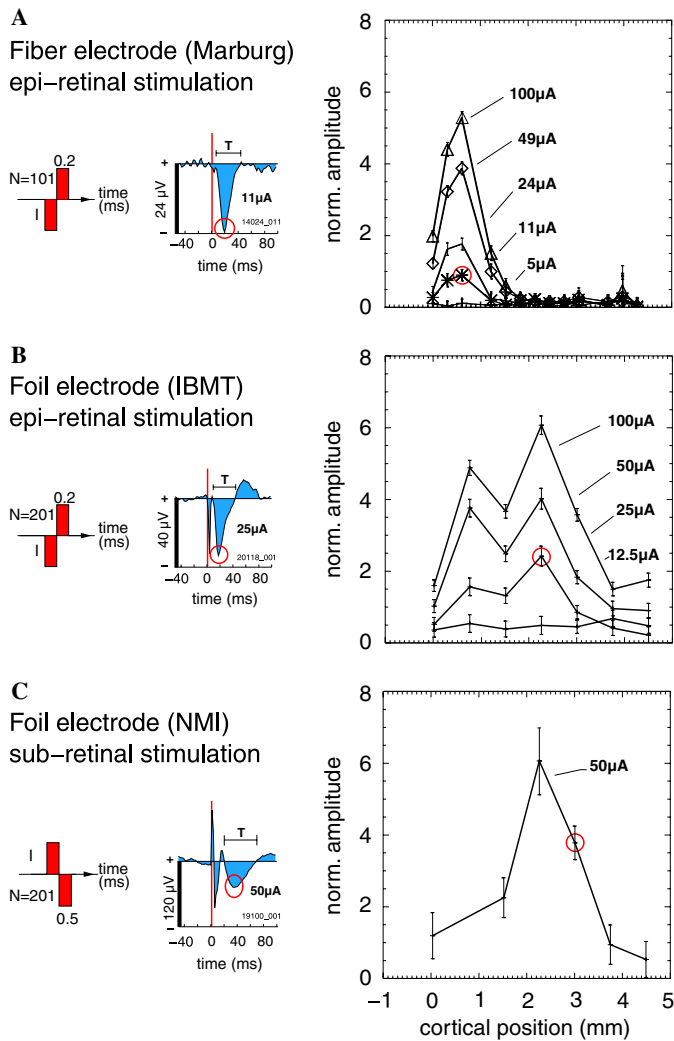


Fig. 2. Spatial cortical activation profiles (right panels) recorded with microelectrodes in response to para-centrally applied single retinal stimulation impulses of different currents I . The normalized amplitudes of the responses for deriving the spatial profiles were taken from the maxima of the first cortical response component after the stimulation artifact (indicated by circles in middle panels, showing example time courses of averaged LFPs at the indicated stimulation currents I ; delays of maxima 20–30 ms. T denotes the duration of the first cortical response component). (A) Epi-retinal stimulation with cone electrodes. (B) Epi-retinal stimulation with single electrode of foil array (manufactured by IBMT St. Ingbert, Germany). (C) Sub-retinal stimulation with foil electrode array (manufactured by NMI, Tübingen, Germany). Left panels: time courses of the stimulus current I ; number at first impulse indicates its duration in ms, N denotes the number of identical stimulus repetitions used for averaging the responses (examples shown in middle panels).

retinotopic organisation of the visual cortex (Tusa et al., 1978, 1979), the cortical activation was localized more posterior when the stimulation was located at lower positions in the retina and moved progressively towards anterior for stimulation sites at upper retinal locations. For a semi-quantitative analysis of the cortical activity, two-dimensional activation profiles were computed on the basis of the gray scale values of the images (Figs. 3B and C). From such data the width of the distributions and

their offsets with changes in retinal stimulus location were estimated. A shift of the stimulus by 1.5 mm on the retina led to a shift of the maximum of cortical activation by 3.72 mm (left and rightmost panels in Fig. 3B). The full width at half height (FWHH) of the activity modulation in space was on average 1.78 mm. This FWHH is taken as a measure to estimate the possible spatial resolution (possible discrimination of two adjacent activity profiles) at a given eccentricity along the antero-posterior axis in visual area 18. We have calculated this resolution for the chosen retinal reference eccentricity of 2° (see Section 2: spatial resolution) where 1.78 mm in the visual cortex corresponds to about 2.5° visual angle (Tusa et al., 1979). For these measurements stimulation currents were $\pm 150 \mu\text{A}$ (250 μs duration of each phase was used for epi-retinal stimuli; s. Fig. 3B) and $\pm 50 \mu\text{A}$ for the sub-retinal stimuli (1 ms each phase; s. Fig. 3C).

Sub-retinal stimulation and optical recordings revealed similar results as obtained with epi-retinal stimulation. The examples in Fig. 3C show optically recorded activations in response to impulses applied to two different retinal electrodes 0.33 mm apart. They are clearly different in their cortical extent and position of the optical signals. This is demonstrated by the one-dimensional profiles in Fig. 3C. With a 0.33 mm shift of retinal stimulation in the immediate vicinity of the area centralis, the maximum of the cortical signal moves about 1.75 mm on the visual cortical surface. From the 2-D distribution of the activity profiles the spatial extent of activation was measured as FWHH in the same way as for the epi-retinal stimulation. The average value of 1.79 mm FWHH corresponds to approximately 2.5° visual angle at the reference retinal eccentricity of 2° (see Section 2) along the antero-posterior axis in cat visual area 18. This spatial resolution of the optical imaging signal is equivalent to that obtained with epi-retinal stimulation.

Table 1 gives an overview of the estimated spatial resolutions obtained with epi- and sub-retinal stimulation assessed with cortical microelectrode and optical recordings. Resolutions obtained with microelectrode recordings were about a factor of two higher than those with optical recordings. While we measured the highest resolutions (0.68°) with cone-shaped three-dimensional electrodes and epi-retinal stimulation, best results with flat two-dimensional film electrodes (0.9°) were obtained with sub-retinal stimulation.

3.2. Temporal properties of the retino-cortical pathway with electrical activations

Temporal properties of the retino-cortical pathway were analyzed with microelectrode recordings of single and multiple unit spikes (MUA) as well as local field potentials (LFP).

3.2.1. Spike activation patterns of retinal ganglion cells

Spike patterns of microelectrode recordings from the optic tract and retinal stimulation by thin-film arrays were

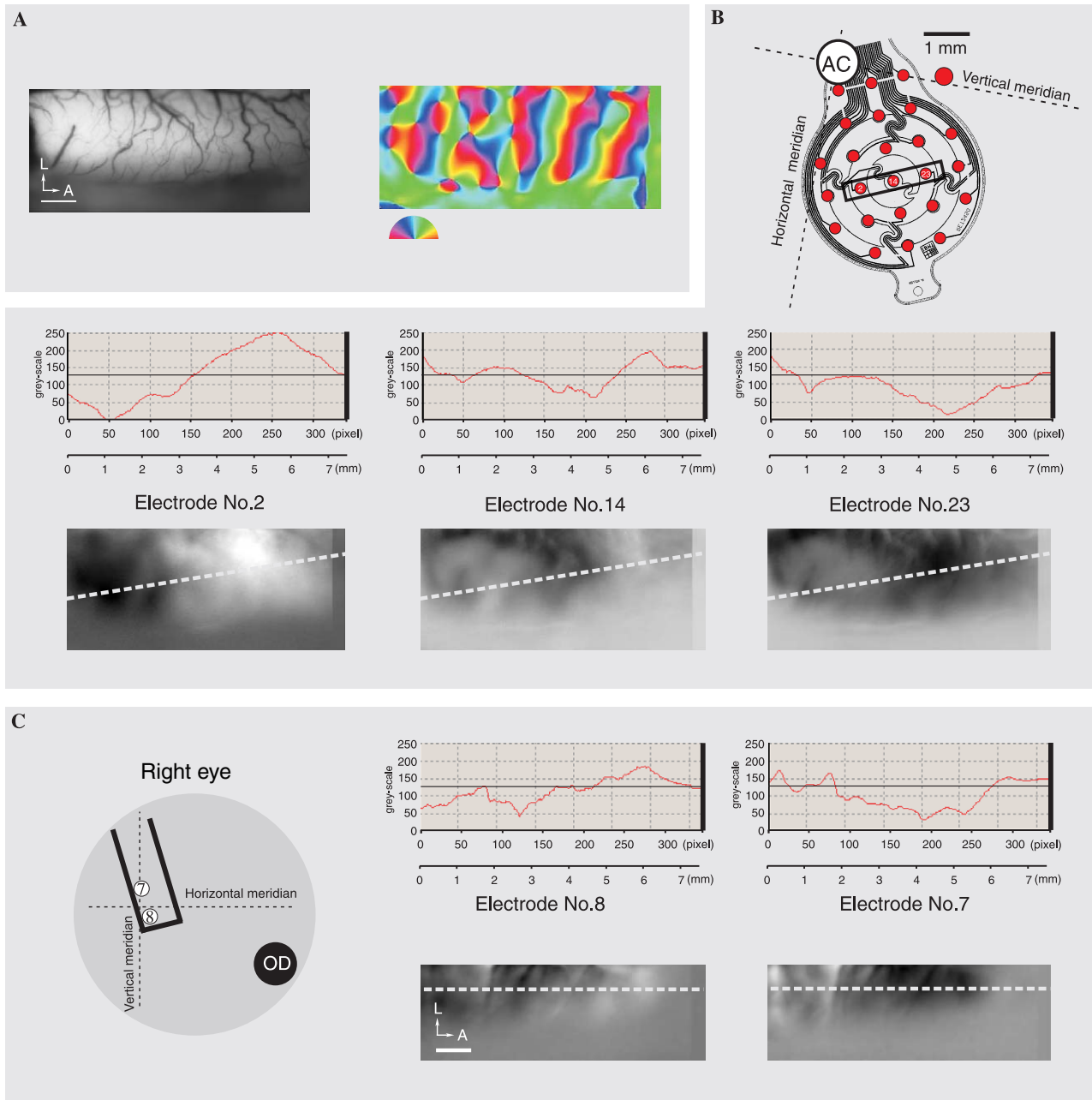


Fig. 3. Optically recorded cortical activations by visual (A), electrical epi- (B), and sub-retinal (C) stimulation with neighboring retinal electrodes. (A) Visual stimulation through a stationary horizontally oriented slit (0.5° width, 40° length) with a moving grating (see Section 2) positioned at vertical retinal eccentricities (elevation) corresponding (from left to right) to the electrode positions 2, 14, 23 in (B). The optical recordings demonstrate the spread and retinotopic displacement of visually evoked cortical activation profiles in cat area 18 (SCMs, see Section 2). (B and C) Optically recorded activation profiles (SCMs) during stimulation with spatially displaced retinal electrodes. Graphs above each optical image show one dimensional activation profiles transformed from the intensity (gray scale) levels along the broken lines (minima represent maximal activation). Considerable cortical activation is represented by the darkest black spots. They move successively from left to right with visual and electrical stimuli and are of similar size with visual and electrical stimuli. Differences are mainly due to the long slit visual and the focal electrical stimulation. The optical images show responses to stimulation of neighboring electrodes separated by $750\ \mu\text{m}$ (epi-retinal, (B); stimulation current: $\pm 150\ \mu\text{A}$, $250\ \mu\text{s}$ for each phase) and $330\ \mu\text{m}$ (sub-retinal, (C); stimulation current: $\pm 50\ \mu\text{A}$, $1\ \text{ms}$ for each phase), and reveal activity shifts up to $3.7\ \text{mm}$ along the anterior–posterior axis of the cortex (B). Importantly, the cortical magnification factor decreases about exponentially with increasing distance from the projection of the area centralis, and the shifts of the activated cortical locations correspond well to the published retinotopic maps (Tusa et al., 1978; Tusa et al., 1979). The exact position of the stimulation electrodes resulting in the activity images in (B and C) are shown in corresponding insets. Scale bars at optical images $1\ \text{mm}$ in (A–C). L, lateral, A, anterior.

analyzed. Fig. 4A shows example montages in which the averaged population responses in the optic tract to single site stimulation are plotted together with the applied cur-

rent amplitudes. Two important facts are demonstrated here. First, the currents for evoking similar response amplitudes differ by a factor of up to ~ 20 (from ± 4 to $\pm 78\ \mu\text{A}$;

Table 1
Spatial resolutions obtained with epi- and sub-retinal stimulation

Cortical recording	Epi-retinal stimulation	Sub-retinal stimulation
Optical	2.50° (thin-film electrodes)	2.50° (thin-film electrodes)
Microelectrode array	0.68° (cone electrodes)	
Microelectrode array	1.20° (thin-film electrodes)	0.90° (thin-film electrodes)
		1.30° (thin-film electrodes)

The spatial resolution for microelectrode array recordings represents the resolution of the primary response. The lower resolution obtained with optical recordings corresponds well to the spatial resolution of the late responses of microelectrode recordings (see text). The high resolution of 0.68° with epi-retinal stimulation were not obtained with currently available and implantable electrode arrays but with singly in the eye inserted microelectrodes having cone-shaped tips.

epi-retinal stimulation). Second, the response delays (2–3 ms) and their durations (1–2 ms) are very short, indicating that the electrical impulses activate ganglion cells directly and evoke only a single spike per neuron (with epi- and sub-retinal stimulation, Fig. 4A). Fig. 4B shows responses to short light flashes recorded for comparison with the same optic tract electrodes. The composite visually and electrically evoked field responses were observed in a range of 30–200 μ V. Compared with the responses to electrical stimuli (delay: 2–3 ms, duration: 1 ms) the visual responses have much longer latencies (\sim 20 ms) and duration (20–35 ms) as is typical for visual population responses in the optic tract to which single ganglion cells generally contribute sequences of several spikes at a broad range of delays and with a higher degree of jitter compared to electrical impulse activation.

3.3. Activation of cortical neurons

3.3.1. Temporal precision of primary cortical action potentials

Retinal electrical stimuli evoked single impulses in ganglion cells with a repetition jitter of <1 ms (Figs. 4 and 5). Because signal transmission across geniculate synapses is highly stable in the applied frequency range of electrical stimulation (Eysel, Grüsser, & Pecci Saavedra, 1974) effective activation volleys will arrive at the primary cortical synapses also with low temporal jitter. Hence, primary cortical spikes can also be generated with high temporal precision. This is demonstrated in Fig. 5. The retino-cortical delay for the first evoked spike in this example is about 6 ms with a jitter <1 ms. For a given cortical recording location, delay and jitter depend on stimulation current and electrode type. The stronger the retinal activation the shorter the latency and the less variable the response. Fig. 5 also shows a pause after the primary spikes of about 2 ms followed by a less precise second spike. We cannot decide on our present data whether the second spikes are due to a primary activation by parvo- or konio-cellular afferents or whether they are secondary spikes in response to magnocel-

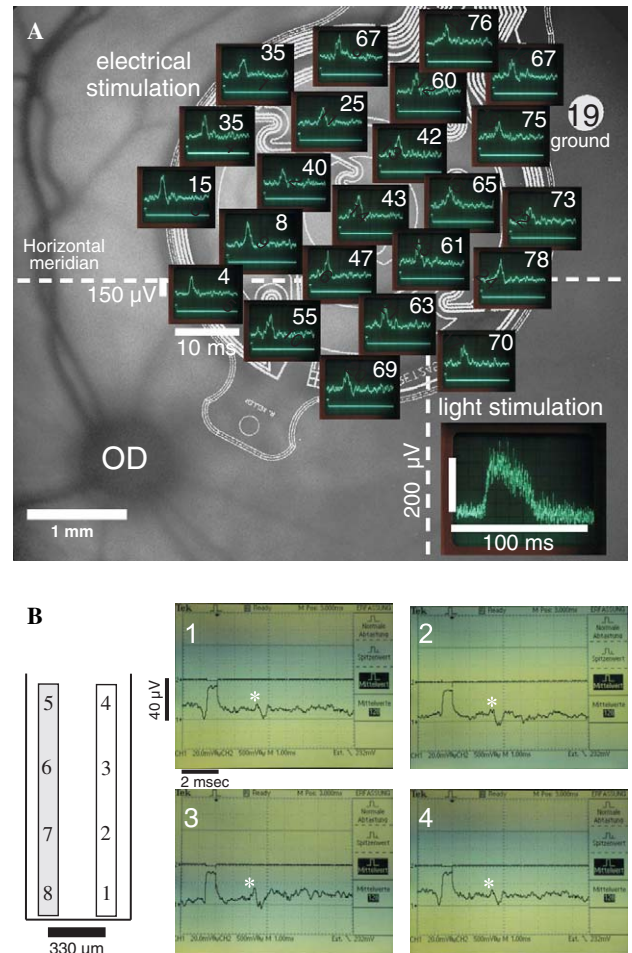


Fig. 4. Epi- and sub-retinal stimulation with thin-film electrodes and population spike recordings from the optic tract. (A) Image of the retinal implant (inter-electrode distance 750 μ m) in the upper nasal quadrant of the retina overlapping area centralis. Schematic montage of thin-film array in front of retinal background superimposed by average response waveforms (small insets) evoked by short, single biphasic stimuli (± 4 to ± 78 μ A; balanced current; waveform: 250 μ s negative; 250 μ s off; 250 μ s positive) delivered at 1 Hz via single electrodes of the implant against ground (19). Optic tract recordings were made with a concentric bipolar tungsten electrode (SNEX-100, Rhodes Medical, Woodland Hills, CA, USA). For positioning of the recording electrode and comparison to electrical stimulation, recordings were made during 1 Hz stroboscopic light stimulation (lower right inset). Note the difference in the latency from stimulus onset to the peak responses for optical (about 20 ms) and electrical stimulation (about 2.5 ms). OD: optic disk. (B) Position of the dual in line thin-film array relative to area centralis (case S-R02) is shown to the left. The tip of the array (electrodes 1, 8) covered the foveal zone whereas the other electrodes extended along the vertical meridian in the upper hemi-retina (inter-electrode distance 330 μ m). Evoked potentials to electrical stimulation (50 μ A, biphasic current pulses, averaged response to 128 identical repetitions) delivered by electrodes 1, 2, 3, and 4, respectively, against the combined electrodes 5–8 of the implant as ground. Please note the slightly longer latency (about 3 ms) after sub-retinal in comparison to epi-retinal electrical stimulation.

lular input (for comparison of these cell types, see: Xu, Ichida, Allison, Bonds, & Casagrande, 2001). In summary, our results show that the visual pathway, from electrical stimulation of retinal ganglion cells to the primary responses in visual cortex, shows a high temporal precision,

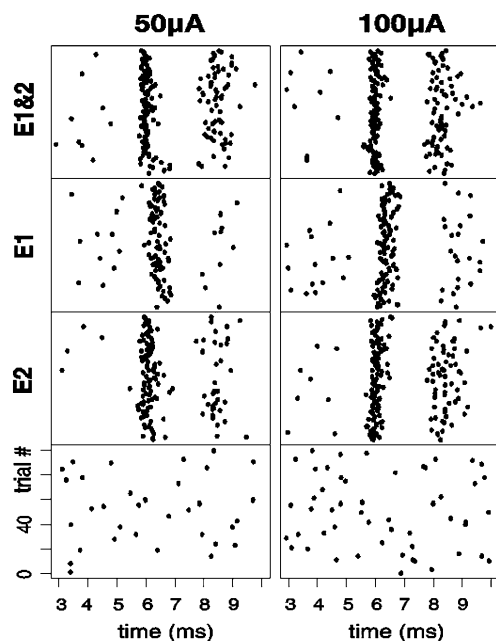


Fig. 5. Variability of cortical single unit spike responses to single site epi-retinally applied impulse-pairs (2×0.2 ms at $50\mu\text{A}$ (A) and $100\mu\text{A}$ (B)). The raster plots of 32 identical stimulus repetitions show from top to bottom: retinal stimulation via cone electrodes E1 and E2 synchronously, E1 and E2 separately, and maintained activity (no stimulation). Note the short retino-cortical activation delays of ~ 6 ms for the first spikes. Note also that the higher stimulus current (B) and the synchronous stimulation of E1 and E2 (A, B top row) lead to higher numbers of spikes and reduced temporal jitter.

because the relatively slow retinal input stages (phototransduction, synaptic transmission in the retinal network) are not in use. However, temporal resolution in visual perception should also be limited by the temporal properties of cortical circuits. These upper limits can be estimated from the time courses of cortical population responses (MUA, LFP) to electrical retinal impulse stimuli.

3.3.2. Resolution from signal approach

One coarse method for estimating the temporal resolution from the cortical responses is the measurement of the response duration at a certain amplitude (e.g., 10% of maximum). Figs. 1 and 2 (inset) show a variety of cortical peristimulus time histograms (PSTHs) in response to repetitions of single electrical impulses. In these examples, response durations are about 40–100 ms corresponding to an upper frequency limit of about 25–10 Hz. It is known that the retino-cortical pathway changes its temporal transfer properties with the rate of stimulation. This was found with stimulus patterns (Gamma interval distributions) which were systematically varied in their average impulse rates between 1 and 80 imp/s (Eger et al., 2005; Wilms et al., 2003).

Table 2 shows the average values of temporal resolutions obtained with epi- and sub-retinal stimulation. The types of electrodes, two-dimensional thin-film and three-dimensional cone-shaped stimulation electrodes revealed about the same values. Temporal resolutions with sub-retinal stimulation are only slightly lower compared to those

Table 2

Temporal resolutions for focal epi- and sub-retinal stimuli obtained from cortical microelectrode recordings, estimated directly from response time courses of microelectrode recordings (LFP)

Cortical recording	Epi-retinal stimulation	Sub-retinal stimulation
Microelectrode array	33 ms or 30/s (cone electrodes)	40 ms or 25/s (thin-film electrode)
Microelectrode array	33 ms or 30/s (thin-film electrode)	45 ms or 22/s (thin-film electrode)

The temporal resolution is derived from the duration of the activation period t/ms and is also expressed in possible frames/s ($1000/\text{activation period}$).

with epi-retinal stimulation. This might be due to the longer and slower retinal pathway including bipolar and ganglion cells with the sub-retinal activations while epi-retinal stimulation directly activate ganglion cells.

As the results for temporal resolutions in Table 2 were derived from averaged responses and therefore do not reveal the variability of responses to single stimuli we chose another approach. Here, we have applied information theory that can capture the amount of stimulus–response information by taking the variability of cortical responses to single impulses quantitatively into account.

3.3.3. Resolutions from information approach

The rate of information, transmitted by a stimulus train with Gamma interval distribution (Eger et al., 2005) to a single cortical recording site was calculated for identical sequences of focal light flashes and electrical impulses applied to the same retinal site. Patterns of light flashes at rates between 2 and 10 Hz show a maximum of transmitted information of about 20–40 bit/s. At high flash rates (20–50 Hz) transmission of information steeply declined, probably due to the retinal high frequency cut-off above 10 Hz (e.g., Shapley & Victor, 1981). While most of the LFP recordings showed a clear maximum, this was only the case in few MUA recordings, most likely due to the different spatial ranges contributing to an LFP and MUA recording. With stochastic stimulus sequences striking differences between electrical and visual stimulation were observed. First, in contrast to visual stimulation (with a spread of information across several recording locations) electrical stimulation delivered high rates of information only to single focal cortical patches (input range of a single cortical recording location) with very little information spread towards neighboring cortical locations. Second, using electrical stimulation and cortical LFP recordings, information rates increased continuously in parallel with stimulation rates up to the highest applied rate of 80 Hz (details in Eger et al., 2005) whereas they showed a peak at 4–8 Hz flash rates when visual stimuli were applied.

4. Discussion

The most important results are the relatively high spatial and temporal resolutions obtained with electrical retina activations in the visual cortex: about 1° visual angle (Table 1)

and 25 Hz (Table 2). Epi- and sub-retinal stimulation revealed similar results. As our resolution estimates were derived from recordings in primary visual cortex, there are good reasons to believe that they can directly be related to visual perception in the blind with retinal implants, as is argued below.

4.1. Spatial resolution

Spatial resolution was estimated on the basis of the retino-cortical spread of activation in response to a focal electrical stimulation of the retina (Table 1). We transformed this retino-cortical point spread function to degrees of visual angle in visual space at a reference eccentricity of 2° (see Section 2; assumed average electrode eccentricity of retinal implants). From the point of view of human application the cortical activation spread is an important measure because it is directly related to the spatial extent of perceived phosphenes, and cortical neurons outside the activation range, not coupled to the focal stimulus, will thus not contribute to perception. The cortical activation spread, on the other hand, may underestimate the actually obtainable spatial resolution, because stimulation with focal visual stimuli results in comparable cortical distributions of activity (Fig. 3A; see also Grinvald, Lieke, Frostig, & Hildesheim, 1994) and are associated with visual perceptions of much higher resolutions.

With the current technology of retinal stimulation, we could not activate individual ganglion cells in isolation by a single electrical impulse, instead we evoked near-synchronized responses from a spatially circumscribed population of cells in the retina. Each activated ganglion cell contributed only with a single spike to epi- and sub-retinal impulse stimuli (Figs. 4 and 5). In contrast to this, in the isolated chick retina, sub-retinal single impulse stimuli evoked groups of action potentials in retinal ganglion cells (Stett et al., 2000). The spatial resolution derived from these in vitro experiments was between 50 and 100 μm on the retina and corresponded to a retinal spatial resolution of 0.3–0.5°, as has been shown in rats suffering from complete retinal degeneration as well (RCS-rats) by the same technology.

Quite importantly, we could not differentiate which types and combination of types of retinal ganglion cells were activated, i.e., on- or off-center, magno-, parvo- or konio-cellular neurons (for cell types, see: Nirenberg, Carceri, Jacobs, & Latham, 2001; Waessle & Boycott, 1991). We assume, however, that all types contributed to the population responses. This may render vision transmitted by such arrays as color-less since the S-, M-, and L-cone systems would be activated simultaneously. This has experimentally been confirmed with epi-retinal stimulation in human subjects evoking phosphenes that were reported as *bright*, not *dark* (Humayun et al., 1999). It also implies that we were not able to activate the retino-cortical network with electrical stimulation in the same way as with visual stimuli. Accordingly, with electrical stimulation, local contrasts will probably be processed at lower spatial and intensity resolu-

tions than are obtained with visual stimuli in the intact system. In addition, perceptual resolutions may not adequately be estimated by the activity distributions obtained by extracellular microelectrode recordings of LFP and optical imaging signals. Both types of signals are correlated with the local superpositions of post-synaptic potentials without significant contributions from action potentials (Grinvald et al., 1994; Grinvald et al., 1999; Mitzdorf, 1987). Excitatory and inhibitory neurons contribute to these signals and it remains unclear how they are precisely related to perceptual resolution. The spatial resolutions calculated from the width of cortical activation profiles after electrical stimulation in the anesthetized cat retina should therefore be taken as a conservative approach most probably underestimating the obtainable perceptual spatial resolution in humans.

The smallest cortical activation profiles were represented by the early cortical components (10–20 ms) in response to the afferent input volley (layers 4 and 6 in area 17; Fig. 1). Previous work showed that early cortical components evoked by visual stimuli (30–50 ms post-stimulus) code local visual properties, including contour orientation, contrast and movement direction (Eckhorn, Frien, Bauer, Woelbern, & Kehr, 1993; Shevelev, Eysel, Lazareva, & Sharaev, 1998), while later components are mainly influenced by cortico-cortical interactions representing visual context (Gail, Brinksmeyer, & Eckhorn, 2000; Lamme, Rodriguez-Rodriguez, & Spekreijse, 1999). Correspondingly, later cortical responses to electrical stimulation are probably dominated by cortico-cortical lateral and feedback interactions from outside the classical RF (Angelucci et al., 2002; Bullier et al., 2001), which explains the observed dynamic expansion of the activation spread by factors of 2 to 3 during the later 50–100 ms of the response profiles (Fig. 1; see also Wilms et al., 2003). This might also partially explain the larger spread seen with the optical imaging method that is characterized by a low temporal resolution making it inevitable to include later—though also weaker—parts of the responses (Kisvarday et al., 2001).

Interestingly, two types of cortical response profiles were obtained, single- and double peak activity distributions (Fig. 2). We assume that double peaks seen with epi-retinal stimulation might be due to the simultaneous activation of local ganglion cell bodies and passing axons of slightly remote ganglion cells having offset receptive fields (Wilms & Eckhorn, 2005). In this regard, future studies using voltage sensitive dye imaging will be helpful for tracking the spatio-temporal evolution of cortical activity to single vs. multisite activation of the retinal implant.

4.1.1. Influence of electrode size on spatial resolution

The size of the thin-film stimulation electrodes considerably influence the width of the estimate of the cortical activation profile, if their diameter is larger than about 50 μm . At the cat's retinal surface, one millimeter corresponds to about 5° visual angle, i.e., 50 μm is about 0.25° (15') (in the human eye 1 mm corresponds to approximately 3.4°;

Drasdo & Fowler, 1974). The thin-film electrodes normally used by us had contact points of 100 μm diameter. Thus, a single electrode already covered 0.5° of visual angle and accordingly the spread of retinal and cortical activation covered even larger angles of visual representation. In fact, electrodes giving rise to more localized high current densities like the fiber-cone electrodes with $\sim 20 \mu\text{m}$ base diameter (Reitböck, 1983) revealed highest resolutions of about 0.7° with epi-retinal stimulation while epi-retinal film electrodes of 100 μm diameter reached only 1.2° (estimated from cortical response distribution; normalized to reference eccentricity of 2° , see Section 2). With sub-retinal stimulation (film electrodes, rectangular electrode areas $100 \times 100 \mu\text{m}$) similar resolutions were obtained (0.9° to 1.3° ; see Table 1).

4.1.2. Influence of recorded signal type

In electrical recordings by microelectrodes, the width of the cortical activation depends on the spatial recording characteristics (“seeing” ranges) of the electrodes and the particular properties of the recorded neural signals, which are different for different signal types. The spatial spread of multiple unit activity (MUA) is in the range of 40 μm in the upper layers of area 17 of the cat (Gray, Maldonado, Wilson, & McNaughton, 1995) and of local field potentials (LFP) about 400 μm (measured with current injection and recording by a linear array of microelectrodes by the authors of the Neurophysics group, University of Marburg). Both values are cortical distances for half height decline. For the smallest measured width of cortical activations (around 1 mm here) this means that we potentially overestimated values based on MUA by about 8% and those with LFP by 80%. However, these influences must be considered in conjunction with the effective lateral coupling width of the neural network involved in the stimulus evoked responses and with the size and form of the stimulation electrodes.

The recording technique of optical imaging captures averaged signals from the cortical surface down to a depth of approximately 700 μm . The recorded intrinsic signals are mainly based on the oxygen consumption and the related deoxygenation of hemoglobin in active cortical regions (for review, see Grinvald et al., 1999); their spatial resolution is influenced by the intercapillary distances in the brain (approximately 50 μm in the cat visual cortex). Inhibitory and excitatory post-synaptic potentials as well as spike responses contribute to the intrinsic signals. Thus, they represent above threshold spike responses and all subthreshold synaptic activity, which all contribute to the width of the distribution of intrinsic signal changes evoked by retinal stimulation.

4.1.3. Influence of lateral connectivities

Our estimate of the spatial resolution on the basis of the cortical activation width may also depend on the effective lateral couplings among evoked signals in the retina, geniculate nucleus, and cortex, which are due to the lateral connectivities in these structures. They include divergent

excitatory feed forward connections, of which magno cellular geniculate neurons are particularly broadly projecting to the cortex (Freund, Martin, Soltesz, Somogyi, & White-ridge, 1989; Humphrey, Saul, & Feidler, 1998) and lateral intracortical facilitatory and disinhibitory connections (Kisvarday & Eysel, 1992). The superimposed influences of all these connectivity-based lateral spreads of activation are about 2–3 mm in the cat primary visual cortex (half height decline measured by signal correlations; Brosch, Bauer, & Eckhorn, 1991). Hence, these widths are equal or even larger than the highest resolutions given in our present report. This is due to the fact that we could take the early cortical response components (from the electrical recordings) which are locally confined, whereas the lateral spread of the activation increases considerably about 20 ms after stimulation (Fig. 1A).

The estimated minimal requirements of spatial resolution for useful artificial vision, investigated by psychophysical methods can be compared and combined with our physiological estimates of achievable spatial resolution under optimal conditions. Reading at central retinal projection sites requires about 300 pixels (20×15) within about 5° retinal eccentricity (Sommerhalder et al., 2003). If we take a physiologically achievable resolution of 0.75° and substitute each image pixel by a stimulation electrode with constant spacing, the stimulation array will cover 3.9 by 2.8 mm^2 retina ($\sim 7.1^\circ$ by $\sim 5.3^\circ$ visual eccentricity). If safe navigation in dynamic out-door environments is required, stimulation should include eccentricities of at least 15° (Cha, Horch, Normann, & Boman, 1992b; Geruschat et al., 1998). Since the spatial resolution required for safe navigational purposes outside the reading area can be chosen much coarser (at about 2° electrode pitch) this would add about another 200 electrodes for the outer “navigational belt.” Hence, as a minimal condition a total of about 500 well functioning electrodes with comparable stimulation capabilities would be required for an implant usefully spanning a retinal stimulation area of about 8 mm in diameter.

4.2. Temporal resolution

The rate of possible temporal modulation can coarsely be estimated from the duration of cortical responses to single electrical impulses applied in the retina. With stimulus currents twice the threshold we measured response durations of about 40 ms at one second stimulus repetitions. However, with higher stimulation rates of 10–50 impulses per second mimicking more natural interval distributions (Gamma), response durations decreased considerably (to 20–30 ms, estimated from the stimulus–response cross-correlations). This corresponds to an increase in temporal resolution which can be caused by several factors such as an increase in the average level of cortical inhibition that keeps the late response phases subthreshold. In addition, higher stimulation rates lead to increased average activations of both excitatory and inhibitory synapses which, in turn, reduce the time constants and increase the frequency

bandwidths of dendrites and somata of ortical neurons (Agmon-Snir & Segev, 1993; Nelson, 1994). Hence, near physiological patterns and high rates of retinal stimulation can result in cortical response durations which are able to code 30–50 temporal changes of two-level intensities per second. However, the pilot experiments of Humayun et al. (1999) with electrical stimulation in human patients suggest somewhat lower frequencies. They created non-flickering perception with rhythmic stimulation already at frequencies between 40 and 50 Hz. Nonetheless, fast temporal changes may be also perceivable with non-rhythmic (stochastic) stimulation patterns generating non-rhythmic spike patterns in ganglion cells similar to visual responses.

4.2.1. Discrimination among somal and axonal stimulations

We found that epi-retinal stimulation has to deal with the problem of activation of ganglion cell somata in the vicinity of the electrode tip and of passing axons originating from remote ganglion cell bodies (results not shown here). This problem cannot be neglected, since a simultaneous activation of ganglion cell bodies in the vicinity of the electrode and passing axons may lead to multisite or ambiguous phosphenes (Wilms & Eckhorn, 2005). For a solution of this problem fur-

ther investigations are required. Cone electrodes protruding to ganglion cell somata through the internal limiting membrane could selectively activate the cell bodies. For selective fiber stimulation, electrode pairs with tips aligned parallel to the fibers and specific stimulation current/time patterns might provide a solution. Finally, offsets of single focal phosphenes due to activation of passing fibers by epi-retinal electrodes can be compensated by an adaptable retina-processor outside of the eye (Eckmiller, 1997). On the other hand, sub-retinal stimulation at retinal eccentricities smaller than 8° would have to face systematic and increasing mislocation of phosphenes with decreasing eccentricity due to the displacement of bipolar and retinal ganglion cells in the central retinal region (Sjöstrand, Olsson, Popovic, & Conradi, 1999). However, the physiological resolution providing a visual acuity of 0.1–0.2 at the desired location of 8° eccentricity corresponds well with the spatial characteristics of sub-retinal chips.

5. Conclusions

We obtained relatively high spatial and temporal resolutions of 0.7–1.3° visual angle and 30–40 ms, respectively, with both epi- and sub-retinal stimulation. Spatial resolution can

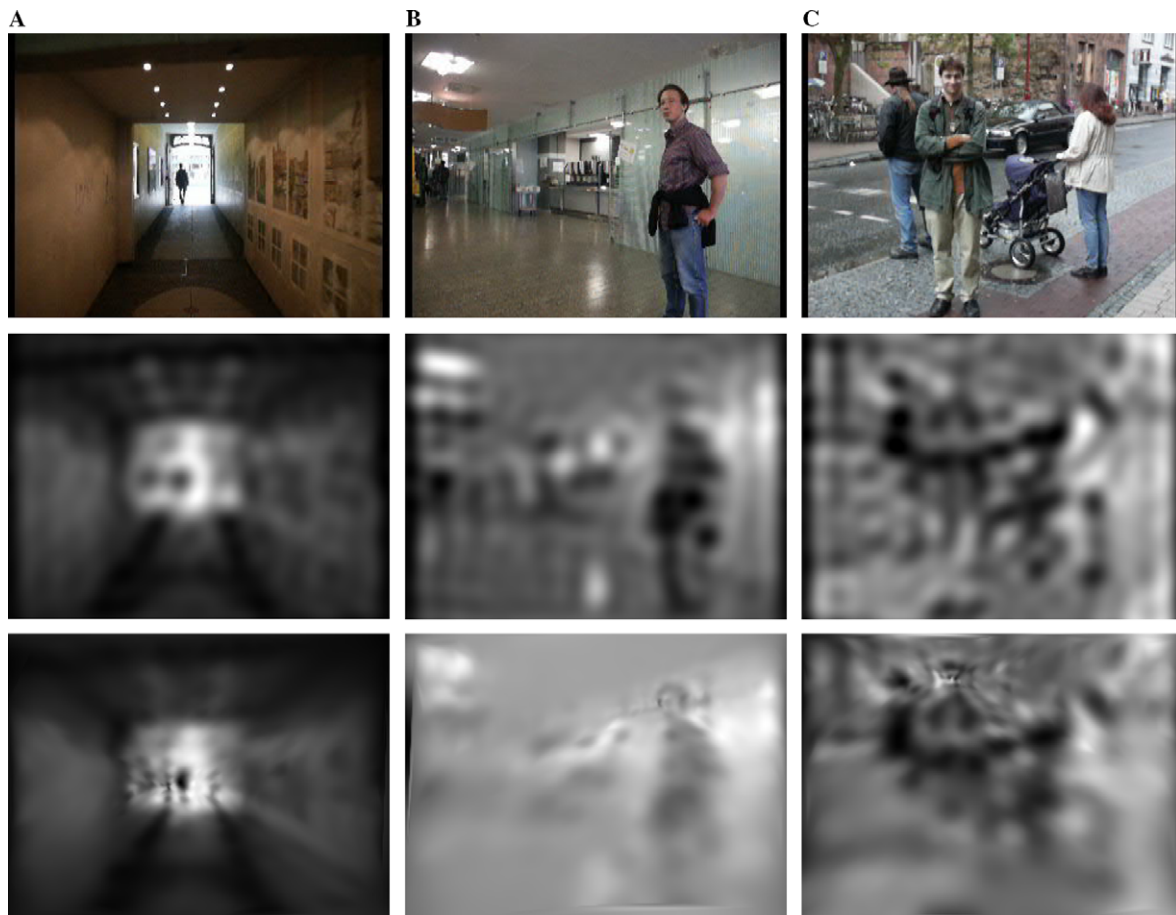


Fig. 6. Real scenes filtered with resolutions obtained in this investigation. (A) Person at the end of a tunnel; (B) person standing in a hall; (C) group of persons on a street. (a) Unfiltered; (b) resampled on a regular cartesian raster; (c) resampled on a irregular hexagonal grid with spatial frequency increasing from periphery to center. Highest resolution is centered on the person at the end of the tunnel (A), head of person (B and C). Gaussian filter kernels at 500 grid positions, simulating Gaussian shaped phosphenes evoked by 500 stimulation electrodes. The output images are restricted to 8 gray tones.

probably be increased up to 0.5° visual angle by choosing smaller-area flat or cone tip electrodes made from materials with higher charge transfer capacity. The highest resolution estimates were reported for electrical stimulation in isolated retinae (Stett et al., 2000) which may be 0.3° visual angle. The upper limit obtained for temporal resolution can further be increased by using higher stimulation rates, mimicking physiological spike patterns of retinal ganglion cells. Since the resolutions reported here were estimated from cortical recordings, direct relations to visual perception are possible, including the expected perception by the blind patients, but may underestimate the finally achievable resolution. We assume that the resolutions obtainable with electronic retinal implants are sufficient for visuo-motor coordination in many in- and out-door situations of daily life. We demonstrate this by movie presentations of simulated perceptions (example clips in Fig. 6) obtained by filtering typical visual scenes with the resolution values obtained in this investigation (accessible under <http://neuro.physik.uni-marburg.de/~retina-implant/>). Our results indicate that spatial resolution achieved by sub- or epi-retinal stimulation should be sufficient to gain useful object recognition in dynamic environments.

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