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Towards the cortical representation of form and motion stimuli generated by a retina implant

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Abstract *Background:* A retina implant for restoring basic visual perception in patients who are blind due to photoreceptor loss should not only evoke focal phosphenes at high resolution, but should also generate cortical representations of form and motion. We are currently exploring these potential capabilities in anaesthetised cats. *Methods:* Fibre electrodes were inserted through a small scleral incision onto the retinal surface for stimulation. For the recording of cortical population activities we placed up to 16 fibre electrodes in areas 17 and/or 18. Retinal and cortical electrodes were adjusted to corresponding sites, i.e., overlapping receptive fields. Electrical stimuli were charge-balanced impulses (200 μ s, 10–100 μ A). Basic form stimuli were generated by the selective and synchronous activation of some of the seven retinal stimulation electrodes. Movement stimuli were generated by spatio-temporal shifting of form stimuli. From multiple microelectrode recordings we computed stimulus-related spatio-temporal cortical activation profiles. We used these profiles to estimate the relations between stimulation distance and spatial resolution (form) and between stimulus velocity and spatio-temporal resolution (movement). Influences by the retino-cortical pathway were assessed by comparing cortical activations evoked by true form or motion stimuli with synthet-

ic responses composed by superpositioning of responses to appropriate subsets of form and motion stimuli. In addition, we compared cortical responses to form and motion stimuli by a receptive-field-based back-projection of cortical activities. *Results:* We confirmed our previous finding that electrical retina stimulation may yield a spatial resolution of 1–5° visual angle and a temporal resolution of about 20 ms. We found that the spatio-temporal cortical activation profiles are commonly related to retinal form and motion stimuli. Cortical activity analyses showed that for two-point form stimuli the neuronal interaction depends on the stimulation electrodes' distance and that local cortical group activities can exhibit some tuning to the directions or the velocities of moving electrical bars'. Projections of cortical activations to visual space were consistent with electrical form and motion stimulation of the retina. *Conclusions:* Our data indicate that retinal stimulation with electrical form and motion stimuli can lead to spatio-temporally related cortical activations. However, the selective activation of single cortical neurones with specific visual tuning properties by electrical retina stimulation and the potential adaptation of the visual system to long-term stimulation with retina implants should be addressed in future work.

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Introduction

Vision is an enormously complex process. Seeing starts when light, passing the optical parts of an eye, reaches the retinal photoreceptors. Within the retina complex neuronal circuits compress visual information from 130 million photoreceptors into action potentials transmitted by 1.2 million axons of the optic nerve to higher visual centres of the brain [11, 33, 36, 38, 49]. Blindness can result when any step of the visual pathway—the optics, the retina, the optic nerve, the lateral geniculate body or the visual cortex—is damaged. In Germany, 17,000 people become blind every year, and about 50% of all these cases of blindness are caused by retinal damage [31, 32]. Abundant blinding diseases are retinitis pigmentosa or macular degeneration, which cause progressive degeneration of the outer retina. Up to now, no medical treatment exists to cure blindness. However, the restoration of vision could be achieved by electronic devices called visual neuroprostheses [1, 3, 4, 6, 7, 8, 9, 10, 14, 15, 16, 20, 24, 25, 26, 27, 34, 35, 37, 43, 46, 48, 51, 52, 53].

A retina implant for restoring basic visual perception by electrical stimulation in patients that are blind due to photoreceptor loss should not only evoke focal phosphenes at high resolution, but should also evoke the sensation of visual objects. Thus, we started to analyse the cortical representation of electrical retina stimulation. Here we present analyses of intracortical population responses evoked by electrical retina stimulation with basic form and motion stimuli.

Materials and methods

Surgical and electrophysiological procedures were performed with anaesthetised cats. The procedures were in accordance with the guidelines of the European Communities Council Directive (86/609/EEC) and were approved by an official German Animal Care and Use Committee. In addition, we followed the NIH Principles of Laboratory Animal Care (publication no. 85–23, revised 1985), the OPRR Public Health Service Policy on the Human Care and Use of Laboratory Animals (revised 1986), the U.S. Animal Welfare Act and the ARVO guidelines.

Anaesthesia and surgical procedures

Three adequately fasted adult cats (3 to 5 kg) were premedicated with atropine sulphate (0.03 mg/kg). Anaesthesia was induced by intramuscular injection of a mixture of ketamine hydrochloride (ketanest, 10–20 mg/kg) and xylazine hydrochloride (ropun, 1 mg/kg). After orotracheal intubation, anaesthesia was maintained by ventilation with N₂O/O₂ (70/30%) and isoflurane (0.5–1.5%) or with air and isoflurane (0.6–2.0%). During surgical procedures we additionally applied local anaesthesia (bupivacaine, lidocain) and/or supplementary doses of ketamine hydrochloride (ketanest, 3–10 mg/kg). Continuous monitoring of rectal temperature (38°C), end-expiratory CO₂ (3.8–4.2%), ECG, EEG and reflexes were used to control anaesthesia. Nutrition was provided by a continuous infusion of Ringer's solution enriched with glucose (3–20 ml/h, 1.5%). For head fixation we positioned the cats in a standard Horsely-Clarke support. A craniotomy was performed above visual areas V1

and/or V2 for subsequent recording of intracortical activities, leaving the dura mater intact. After a lateral canthotomy of one eye the lateral conjunctiva was incised. Next we performed a sclerostomy 4–5 mm posterior to the limbus. An incision of about 1.1 mm was sufficient for transscleral positioning of the stimulation electrodes onto the retinal surface. If necessary, we applied alcuronium chloride to attenuate potential residual eye movements (alloferin, 0.03–0.1 mg/kg). In general, at the end of a recording and stimulation session sclera and conjunctiva were closed with polygalactine sutures. Atropine, gentamycin, and dexamethason were topically applied. The opening of the skull was closed by implanting the previously removed and adequately supplied bone cylinder or a plexiglass window. After the sewing of the scalp incision the cats prophylactically received a streptomycin-penicillin combination (tardomyocel, 0.1 ml/kg) and were allowed to recover. However, in one case a cat was killed for histological analyses. A schematic drawing of our experimental set-up was recently published [42].

Stimulation and recording

We used quartz-isolated platinum-tungsten fibre electrodes (80 µm shaft diameter) in different designs for retinal stimulation and cortical recording. Stimulation electrodes were arranged in a hexagonal array and had ground metal cone tips with a geometrical surface of about 2,500 µm² [42]. However, these electrodes remained stable for biphasic charge-balanced current impulses consisting of cathodic-anodic pairs of rectangular impulses of up to 100 µA amplitude and 200 µs duration. The ground tips of the tapered recording electrodes were 25 µm in diameter and had impedances of 2–3 MΩ. The positioning of the seven retinal stimulation electrodes was achieved with a specially adapted Eckhorn manipulator drive [42]. We verified both the movement of the fibre electrodes and their close retinal contact optically (Fig. 1) and by the recording of spontaneous or visually evoked retinal activity. Retinal and cortical receptive fields were estimated by projecting light stimuli on a tangent screen 1.3 m in front of the cat according to Barlow's approach [2]. The tip positions of the retinal stimulation electrodes were projected on the screen in order to achieve a match between retinal stimulation sites and cortical receptive fields/recording sites. Repetitive control of electrode and receptive field positions was used to check their positions and to detect potential eye movements. Small eye movements of up to 100 µm (0.3° visual angle) could be compensated by allowing our electrodes to be guided over a relatively large distance of about 6 mm by the vitreous gel/cortex instead of the stainless steel guiding tubes of the electrode manipulator (Fig. 1).

Electrical form and motion stimulation were performed in four experiments by using computer-generated sequences of voltage wave forms and fast voltage-current converters with zero offset current [42]. The multifocally applied stimulation currents consisted of short charge balanced rectangular impulses (200 µs) with amplitudes ranging from 10 to 100 µA. Electrical stimulation was performed centrally or para-centrally (up to 15° visual angle). The currents were applied by the fibre electrodes in mechanical contact with the inner limiting membrane against a distant large reference electrode located at the rectal body temperature sensor. The form stimuli were composed by simultaneous stimulation with neighbouring electrodes. Simple examples of form stimuli are (contrast) edges or bars. For motion stimulation we used moving 'electrical bars'.

Recordings in V1 or V2 were made with up to 16 µ-electrodes placed in corresponding cortical locations to retinal stimulation sites. Amplified broadband cortical signals were hardware-filtered into single unit activities, multiple unit activities (MUA) and local field potentials (LFP) for on-line display on oscilloscopes and were made audible. The amplified and bandpassed (1–4,000 Hz, 12 dB/oct.) cortical signals were recorded at about a 40 kHz sampling rate with a PC-based 128 channel data acquisition system (Multichannel Systems, Reutlingen, Germany).

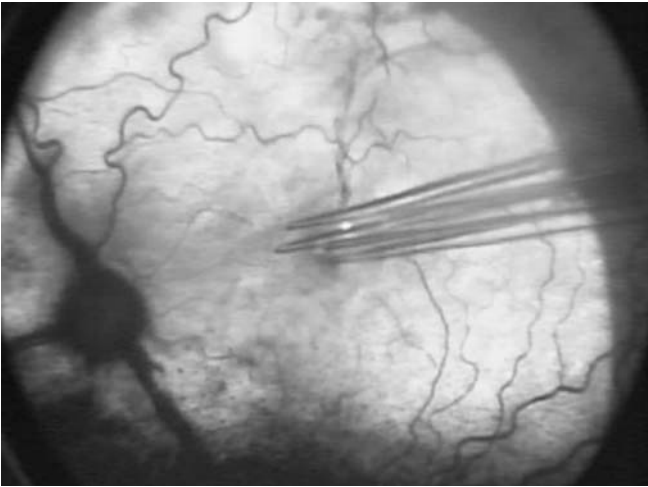


Fig. 1 Instance of fibre electrode positioning onto the retinal surface. Note that the fibre electrodes are guided over a relatively large distance by the vitreous gel

Data analysis

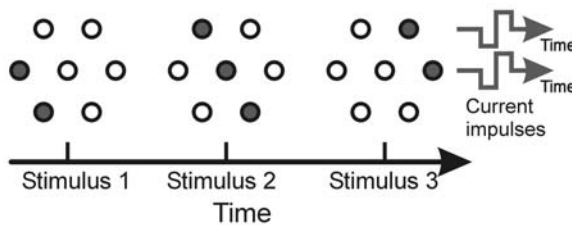
We used the digitally stored broadband intracortical recordings to remove electrical stimulation artefacts and to compute MUA and

LFP signals with the aid of digital filters for subsequent analyses [42]. However, MUA and LFP extracted from one electrode represent the average spike density and the average post-synaptic activity of a local group of neurones within a sphere with diameters of about 200 and 500 μm , respectively [41]. Since the cortical activation distribution in cat primary visual cortex is about 1 mm in diameter for single-site retinal stimulation [42, 50], these signals can be used to analyse the cortical responses to electrical form and motion stimulation of the retina.

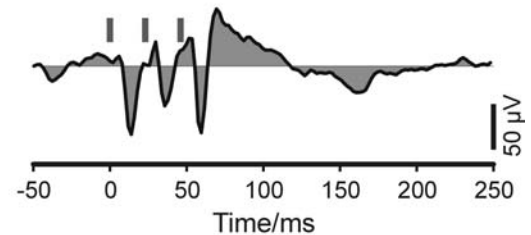
By virtue of the lucid retinotopic organisation of the first visual areas of the cortex, a multifocal retinal stimulation should evoke a broader cortical activity distribution compared to a single-site retinal stimulation. Thus, a form stimulus, consisting of at least two retinal stimulation sites, should be identifiable by its evoked cortical activity. Since a moving visual object evokes a related spatio-temporal cortical activity distribution, moving electrical stimuli applied to the retina should also be identifiable in cortical recordings.

Due to convergent and divergent as well as to lateral connections in the visual system [18, 19, 28, 36, 39, 40, 44, 45], the cortical representation of two neighbouring simultaneously presented stimuli should be different compared to the superimposed responses of the singly presented stimuli. Using this hypothesis, we can construct a measure for cortical representations of electrical form or motion stimuli. For this we have to give some definitions. A compound stimulus is made up of elementary stimuli. For example, an electrical form stimulus consists at least of two point stimuli, and an electrical moving stimulus may be constructed from a form stimulus by shifting its spatial retinal stimulation position in time. If the neuronal response to a compound stimulus is identical to the superimposed responses of the corresponding elementary

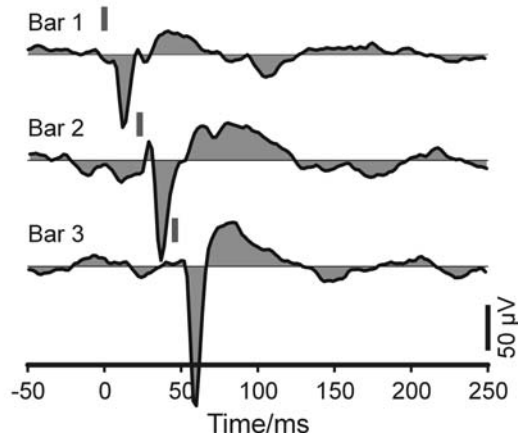
A Electrical moving bar



B Moving bar cortex response



C Static bar cortex responses



D Predicted bar cortex response

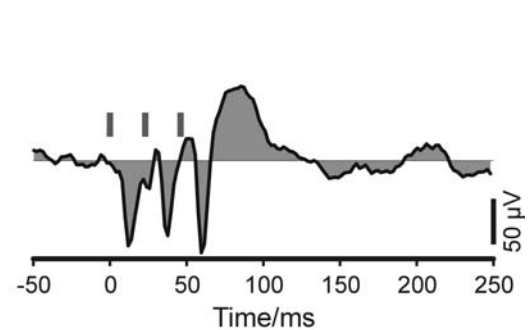


Fig. 2 Prediction of cortical responses. **A** An illustration of the generation of a moving electrical bar stimulus. **B** Cortical LFP response to a moving electrical stimulus (average response). **C** Cor-

tical LFP responses to static bar stimulations. **D** Prediction of the moving bar response by superimposing the corresponding static bar responses

stimuli, we cannot state whether there is interaction between the neurones or not. But if the signals differ, we can conclude that there is a neuronal interaction between the neurones activated by the elementary stimuli of the compound stimulus. In other words, if there is any signal difference, then the different stimuli may be differently processed by the neurones. In mathematical terms we have to show that:

$$r_c(t) \neq r_s(t) = \sum_{k=1}^K r_{s,k}(t), \quad (1)$$

where $r_c(t)$ is the response of the compound stimulus and $r_s(t)$ is the response constructed by superimposing the responses $r_{s,k}(t)$ of the K elementary stimuli. An example of this approach is shown in Fig. 2.

Instead of comparing the time courses of the responses directly, we compared the square roots of the average signal power of the responses:

$$P(r) = \sqrt{\frac{1}{NT} \sum_{i=1}^N \sum_{t=0}^{T-1} r_i^2(t)}, \quad (2)$$

where $r_i(t)$ denotes a single response and T is the number of its sampled values. However, the average power of a response is close to the spike count in single-cell response analysis. This gave us the possibility to compute tuning curves of the local neuronal groups for the orientation of simple electrical bars and for the direction of moving electrical bars. Standard deviations of mean values were computed according to the Gaussian law of error propagation [30]. The response powers of measured and corresponding synthetic responses were assumed to be different, if their absolute difference was larger than twice the sum of the corresponding standard deviations of the means (two-sigma rule).

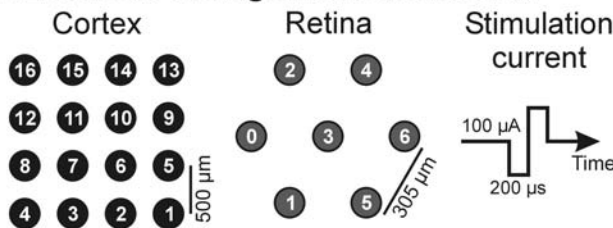
The spatio-temporal sampling of cortical activities evoked by visual or electrical retinal stimulation will enable a backprojection of the cortical activations to retinal or visual space, if the receptive fields of the cortical neurones recorded from are known. If we know the positions of the retinal stimuli, we will be able to compare them with the backprojections of the cortical activities. We estimated these backprojections by computing the instantaneous power of the average responses by a sliding window technique and used the centres of the receptive fields as samples for the computation of visual/retinal space maps of the cortical activities. Temporal sequences of these maps were used for comparing moving electrical stimuli and their evoked responses.

Results

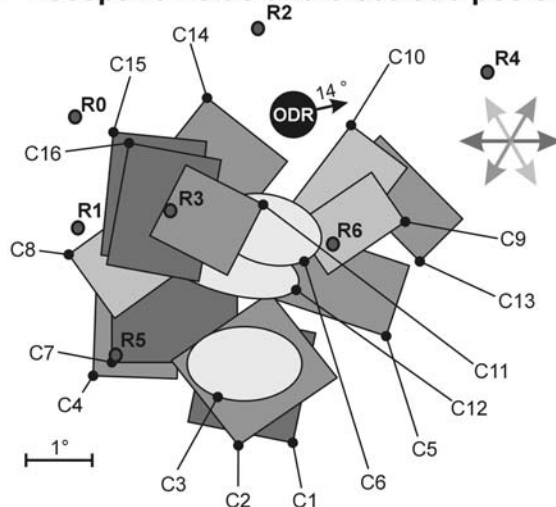
Figure 3 shows some retinal and cortical electrode arrangements, the time course of the stimulation current, the cortical receptive fields, stimulation electrode locations and cortical responses to single-site electrical stim-

Fig. 3 Example of experimental parameters. **A** Arrangement of stimulation and recording electrodes and time course of the applied stimulation currents. **B** Retinal positions of stimulation electrodes and cortical receptive fields. Orientation preferences of the cortical neurones are coded by different grey scales; an oval plotted receptive field indicates no orientation preference to visual stimulation. **C** Cortical LFP responses to single site electrode stimulation with biphasic charge balanced currents consisting of consecutive cathodic-anodic rectangular 100 μA impulses, each with a duration of 200 μs . Note that the response amplitudes may vary considerably according to different retinal stimulation sites

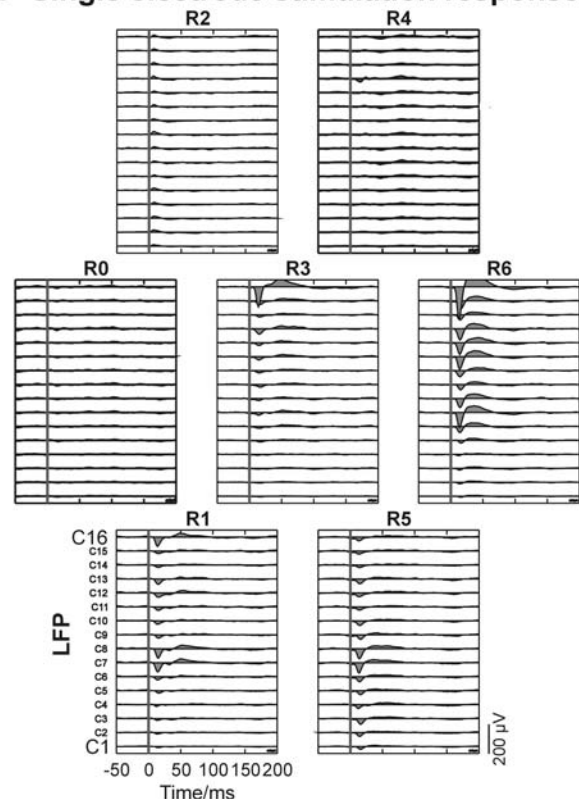
A Electrode arrangements and stimuli



B Receptive fields and electrode positions



C Single electrode stimulation responses



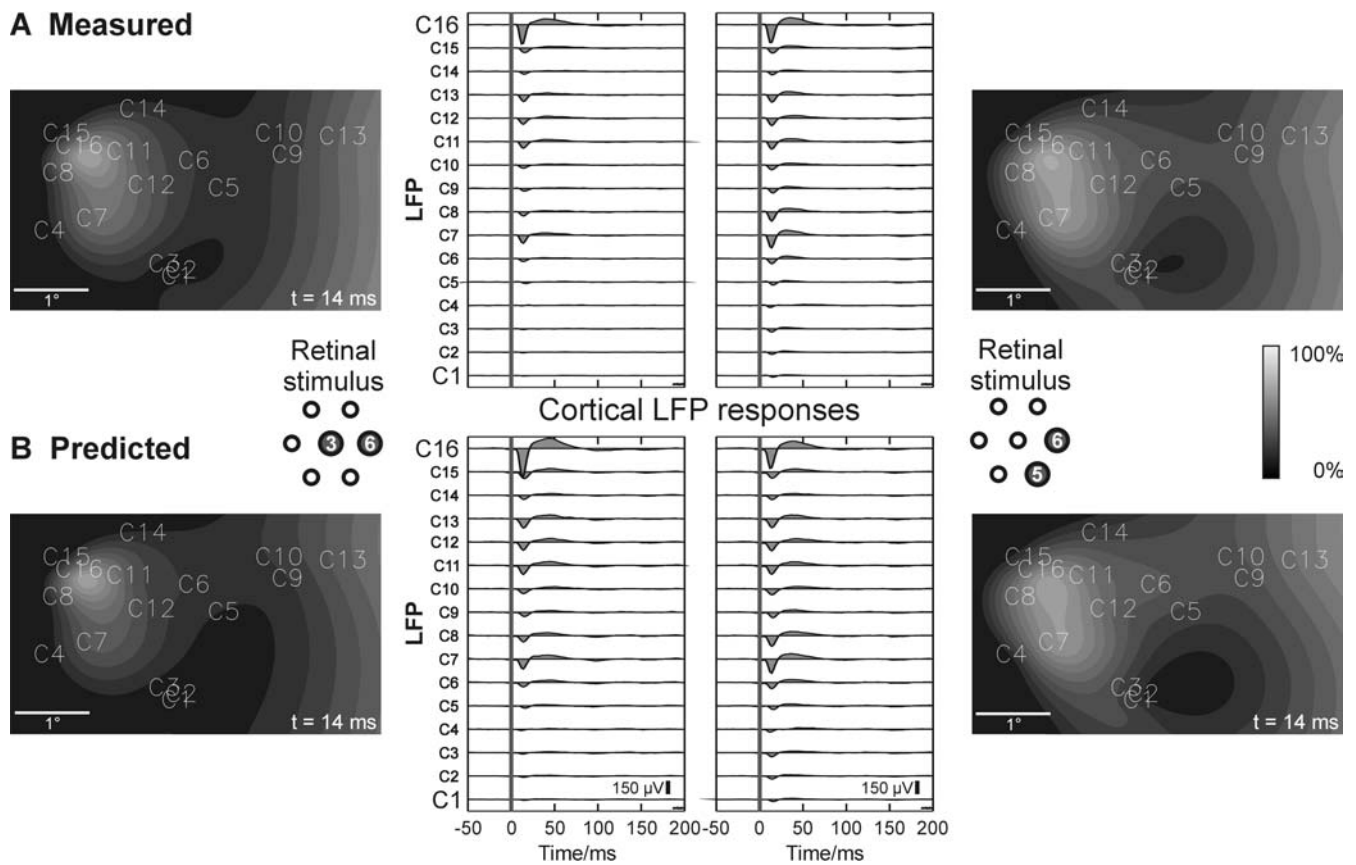


Fig. 4 Cortical LFP responses to different form stimuli and their projections into visual space. The upper half of the charts (A) were obtained from stimulation with true electrical form stimuli, whereas the lower half of the charts (B) are the computed response predictions for the two different stimuli, as shown between the upper and lower *contour plots* on the left and right side, respectively. Note the small projected activation zones, calculated at $t=14$ ms post stimulation, with diameters of about 1° . However, the time course and the projected activations were different for both stimuli. The comparison of the responses evoked by form stimulation with the corresponding predicted responses revealed that predicted response amplitudes were often larger, indicating an inhibitory-like interaction between neighbouring stimulation sites. In addition, the spatial activation distributions are slightly broader for the predicted than for the measured data

ulation. Note that all retinal electrodes evoked cortical activations detectable in MUA and LFP, respectively. Furthermore, we verified our previous findings [42] that, for a successful retina stimulation with $200 \mu\text{s}$ rectangular current impulses, current amplitudes in the lower μA range will be sufficient if the electrodes are in close retinal contact. Note that these values correspond to charges in the nano Coulomb (nC) range.

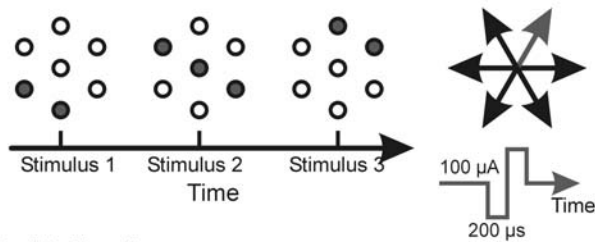
Depending on both the retinal stimulation and the cortical recording site, the evoked activities can vary vigorously. Calculations of the cortical activation distribution revealed sizes of about 1 mm in diameter, depending on the stimulation currents' amplitudes and the contact be-

tween the stimulation electrode and retina, which was, as the temporal resolution of about 20 ms, in conformance with previous results [42].

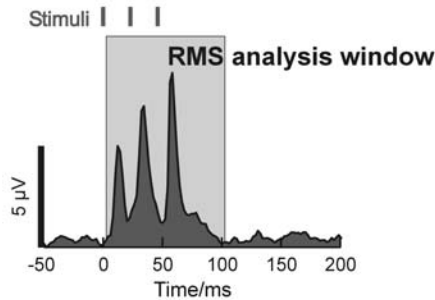
The evidence that slightly different electrical form stimulations of the retina can result in related different cortical activation distributions is shown in Fig. 4. The simplest electrical form stimulus is a simultaneous stimulation with two neighbouring electrodes. Comparison of the responses to form stimuli and to corresponding predicted responses showed that the amplitudes of the predicted responses can be larger or smaller than those of true form stimuli, indicating an inhibitory- or excitatory-like interaction, respectively. Analyses for 15 different two-point electrical stimuli, achievable with our electrode array, revealed that the interactions in the visual pathway (retina, geniculate body, visual cortex) depend on the distance of the retinal stimulation electrodes. A more detailed analysis revealed that the superimposed LFP responses were larger than the measured responses for retinal electrodes with distances ranging from 3 to 4° visual angle (Table 1) and vice versa for smaller and larger distances between the stimulation sites.

The backprojection of the cortical activation to visual or retinal space revealed activation spots with diameters of about 1° visual angle. The comparison of the response profiles to form stimuli and their slightly rotated counterparts showed that the stimuli generated different corti-

A Stimulus parameters



B Method



C MUA tuning: measured vs. predicted

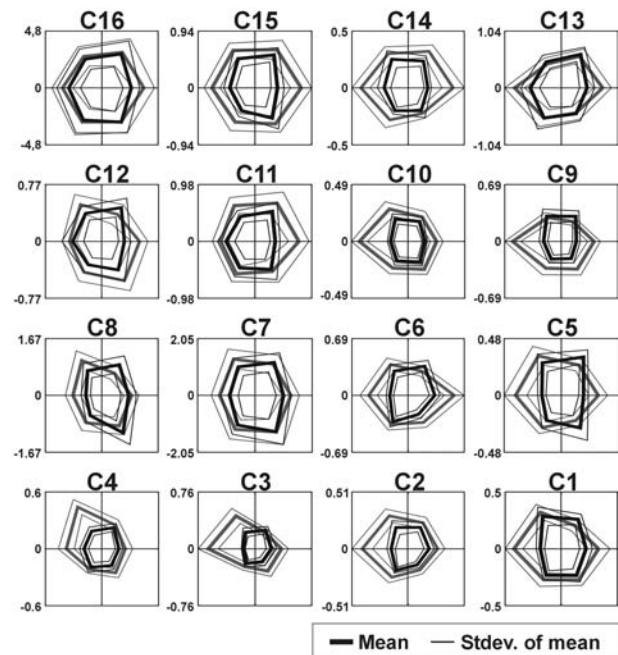


Fig. 5 Tuning of multiple unit activities to moving electrical bars. **A** Parameters of the moving electrical bars. Bars moved in six different directions. The interval between two subsequent form stimuli was 23 ms. **B** Schematic illustration of the time window used for the subsequent root mean square analysis. **C** Tuning of 16 simultaneously recorded spike activities of local intracortical groups of primary cortex neurones (*MUA*) to six different directions of the moving electrical bar. Note the different scaling of the normalised amplitudes. The *thick black lines* signify the mean response amplitudes for true stimuli/responses, the *thin black lines* indicate the distance of the respective standard deviations of the means. The means and standard deviations of the means for predicted responses are drawn in *grey lines*

Table 1 Differences of normalised LFP response powers for two point form electrical stimuli and the predicted response powers obtained by superpositioning the responses to corresponding single-site electrical retina stimulations ($P_{\text{form}} - P_{\text{pred}}$). Class denotes the distance of the retinal stimulation electrodes; n is the number of the analysed data sets, and σ denotes the standard deviation of the mean. Note that all power differences are highly significant ($P < 0.05$)

Class	n	$P_{\text{form}} - P_{\text{pred}}$	$2\sigma_{\text{form}} + 2\sigma_{\text{pred}}$
1–2	48	3.99	0.84
2–3	32	2.94	1.25
3–4	80	–1.01	0.32
4–5	48	1.20	0.32
5–6	48	3.70	1.63
6–7	16	2.08	0.46

cal activations and differentiable and stimulation pattern-related visual space projections. This also indicates that electrical form stimuli can be transmitted to the visual cortex by electrical stimulation and that the retinotopic projection was somewhat preserved.

The tuning of local groups of cortical neurones to moving electrical form stimuli is shown in Fig. 5. The prominent differences in direction-related response amplitudes between measured and predicted data show that slightly different moving stimuli can lead to distinguishable cortical response distributions. This indicates that different moving electrical stimuli are processed differently in the early stages of the visual system. Here we analysed 288 MUA data sets (including the reference data used for prediction) and found that the number of significant neuronal interactions depended on stimulus velocity: 46 of 96 for 35 °/s and 20 of 96 for 91 °/s. However, we expected to find by chance about five significant interactions. In addition, we found that the tuning to moving electrical stimuli is two to three times less pronounced for LFP recordings acquired in parallel with the MUA recordings.

Discussion

It is well known that single neurones of the primary visual cortex exhibit orientation and direction tuning or selectivity, i.e., they respond best to a specific orientation and/or movement of a visual contrast edge or a light bar [22, 23, 33]. Thus, we used elongated electrical stimuli generated by synchronous stimulation with retinal electrodes. Since neighbouring cortical neurones have similar coding preferences we restricted our analysis in this first investigation to the relation between electrical retinal form and motion stimuli and intracortical group signals.

In accordance with our previously published data [42], we found that single-site retinal stimulation evoked single

localised cortical activation zones of about 1 mm in diameter. However, as a result of retinal anatomy epiretinal stimulation may evoke multiple cortical activation spots if a retinal stimulation electrode stimulates neighbouring ganglion cells and passing axons of distant ganglion cells. The stimulation of passing axons can be detected by comparing retinal stimulation sites with the positions of cortical receptive fields; i.e., if the stimulation electrode's retinal location and the cortical recording site are in non-corresponding positions, we can assume that axon stimulation will evoke the appendant cortical activation. This can be tested in future work by a sophisticated re-positioning of stimulation and recording electrodes or by increasing the number of recording electrodes to extend the cortical area simultaneously recorded from.

In 1999 Humayun and colleagues [26] reported on pattern electrical retinal stimulation in humans. They were able to evoke the perception of phosphenes by a hand-held intraocular electrode array. They stated that charge thresholds were in the μC range, which is about three orders of magnitude larger than in our findings. Despite this, the subjects were able to differentiate between different stimulation patterns. Unfortunately, they were not able to record cortical responses to electrical retina stimulation. However, our results indicate that electrical form and motion stimulation of the retina can be assessed by the distribution of cortical responses. We found initial hints for temporal and spatial processing of electrical form and motion stimuli. The highest inhibitory-like neuronal interaction was obtained for form stimuli consisting of two stimulation sites being 3.5° apart, for other distances we found an excitatory-like interaction, and for motion stimuli with an interstimulus interval for two sub- or elementary stimuli of about 60 ms (35 %/s). However, for higher velocities (91 %/s, 23 ms), the interaction decreases. Note that this is in correspondence with Humayun's [26] result that flicker fusion occurs for stimulation rates of about 50 Hz = 1/(20 ms) as well as with our data for temporal resolution for single-site electrical retina stimulation [42].

A closely related issue concerns the minimal time difference for which two stimuli can be resolved in cortical responses as single events. This topic, which addresses both repeated identical stimuli and subsequent elementary stimuli of a compound stimulus, is of importance for the estimation of an upper limit of transferable information to the visual system by retinal implants. We have addressed this in part by wave and information theoretic analyses for single-site stimulation [42] and found a temporal response resolution as far as 50 ms or 30 bit/s. If we contemplate on the multiple unit response shown in Fig. 5B, we see that the single responses to the elementary stimuli can be clearly differentiated. In order to find the minimal time difference for which two stimuli can be separated by their corresponding responses, the interstimulus time interval must be decreased until the single responses merge.

Preliminary, analyses of our data indicate that interstimulus time intervals of much less than 23 ms have to be used and that the stimulation current's amplitude and the temporal neuronal resolution are correlated, i.e., the higher the stimulation current the higher the resolution. However, this important issue should be addressed in future experiments in combination with more realistic electrical stimulation sequences mimicking the activities of retinal neurones to more natural visual stimuli.

Our estimates for spatio-temporal interactions on the basis of cortical activation may also depend on the effective coupling among neurones in the retina, the geniculate body and the cortex. This effect can be due to divergent excitatory feed-forward connections (cat V1:0.5–1 mm; [18, 19, 40]) and lateral intracortical facilitatory, inhibitory, and disinhibitory connections [28, 29] or by feedback projections from higher cortical areas [21, 39]. However, all these connections can lead to interaction zones in cat V1 of about 2 to 3 mm as measured by signal correlations of intracortical activities evoked by visual stimulation [5, 12, 13, 17, 47] that are compatible with our results for electrical retina stimulation.

The comparison of measured (true) and predicted (synthetic, superpositioned) responses to electrical form and motion stimuli revealed stimulus-dependent interactions in the visual pathway. Since our analyses have merely allowed to test whether there is an interaction or not, a more detailed analysis of the cortical recordings should clarify the nature of the interactions, i.e., whether they are inhibitory or excitatory, as presumed by us, or not. In addition, the strongest interaction for electrical stimulation occurred for velocities that were about two to three times higher than those expected for visual stimulation [36]. This could be due to the fact that we performed a coarse spatial electrical stimulation and recording. Thus, this issue should be addressed again with many more and more narrowly spaced electrodes and more sophisticated stimulation waveforms.

Our data have shown that electrical form stimuli and moving electrical form stimuli can generate different cortical activation zones, indicating that different stimuli can be differently represented. Furthermore, our results indicate that the stimulation of the retina with electrical form and motion stimuli can lead to spatio-temporally related cortical activations. However, the selective activation of single cortical neurones with specific tuning or classical receptive properties by electrical retinal stimulation and the potential adaptation of the visual system to long-term stimulation with retina implants should be addressed in future work.

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References

1. Bak M, Girvin JP, Hambrecht FT, Kufta CV, Loeb GE, Schmidt EM (1990) Visual sensation produced by intracortical microstimulation of the human occipital cortex. *Med Biol Eng Comput* 28:257–259
2. Barlow HB (1953) Summation and inhibition in the frog's retina. *J Physiol* 119:69–88
3. Brindley GS (1973) Sensory effects of electrical stimulation of the visual and paravisual cortex in man. In: Jung R (ed) *Handbook of sensory physiology*, vol 7, sect 3B. Springer-Verlag, Berlin, pp 583–594
4. Brindley GS, Lewin WS (1968) The sensations produced by electrical stimulation of the visual cortex. *J Physiol (Lond)* 196:479–493
5. Brosch M, Bauer R, Eckhorn R (1995) Synchronous high-frequency oscillations in cat area 18. *Eur J Neurosci* 7:86–95
6. Chow AY, Chow VY (1997) Subretinal electrical stimulation of the rabbit retina. *Neurosci Lett* 225:13–16
7. Chow AY, Pardue MT, Chow VY, Peyman GA, Liang C, Perlman JI, Peachy NS (2001) Implantation of silicon chip microphotodiode arrays into the cat subretinal space. *IEEE Trans Neural Sys Rehab Eng* 9:86–95
8. Dobelle WH (2000) Artificial vision for the blind by connecting a television camera to the visual cortex. *ASAIO J* 46:3–9
9. Dobelle WH, Mladejowsky MG (1974) Artificial vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis. *Science* 183:40–444
10. Dobelle WH, Mladejowsky MG, Evans JK, Roberts TS, Girvin JP (1976) 'Braille' reading by a blind volunteer by visual cortex stimulation. *Nature* 259:111–112
11. Dowling JE (1970) Organization of vertebrate retinas. *Invest Ophthalmol* 9:655–680
12. Eckhorn R, Bauer R, Jordan W, Brosch M, Kruse W, Munk M, Reitboeck HJ (1988) Coherent oscillations: A mechanism of feature linking in the visual cortex? *Biol Cybern* 60:121–130
13. Eckhorn R, Schanze T, Brosch M, Salem W, Bauer R (1992) Stimulus-specific synchronizations in cat visual cortex: multiple microelectrode and correlation studies from several cortical areas. In: Basar E, et al (eds) *Induced rhythms in the brain*. Birkhäuser, Boston, pp 47–80
14. Eckmiller R (1995) Towards retina implants for improvement of vision in humans with retinitis pigmentosa—challenges and first results. In: *Proc WCNN 95*. INNS Press 1, Washington DC, pp 228–233
15. Eckmiller R (1997) Learning retina implants with epiretinal contacts. *Ophthalm Res* 29:281–289
16. Eckmiller R, Eckhorn R, et al (1994) Final report of the feasibility study for a neurotechnology program. In: Eckmiller R (ed) *Neurotechnology report*. BMBF, Bonn, Germany
17. Engel AK, Koenig P, Gray CM, Singer W (1990) Stimulus-dependent neuronal oscillations in cat visual cortex: inter-columnar interactions as determined by cross-correlation analysis. *Eur J Neurosci* 2:588–606
18. Gilbert C (1993) Circuitry, architecture, and functional dynamics of visual cortex. *Cereb Cortex* 3:373–386
19. Gilbert C, Wiesel T (1989) Columnar specificity of intrinsic horizontal and corticocortical connections. *J Neurosci* 9:2432–2442
20. Girvin J (1988) Current status of artificial vision by electrocortical stimulation. *Can J Neurol Sci* 15:58–62
21. Henry GH, Salin PA, Bullier J (1990) Projections from areas 18 and 19 to cat striate cortex: divergence and laminar specificity. *Eur J Neurosci* 3:186–200
22. Hubel DH, Wiesel TN (1965) Receptive fields and functional architecture in two non-striate visual areas (18 and 19) of the cat. *J Neurophysiol* 28:229–289
23. Hubel DH, Wiesel TN (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J Physiol* 160:106–123
24. Humayun M, Propst R, de Juan E, McCormick K, Hickingbotham D (1994) Bipolar surface electrical stimulation of the vertebrate retina. *Arch Ophthalmol* 112:110–116
25. Humayun MS, de Juan E, Dagnelie G, Greenberg RJ, Prost RH, Phillips DH (1996) Visual perception elicited by electrical stimulation of retina in blind humans. *Arch Ophthalmol* 114:40–46
26. Humayun MS, de Juan E Jr, Weiland JD, Dagnelie G, Katona S, Greenberg R, Suzuki S (1999) Pattern electrical stimulation of the human retina. *Vision Res* 39:2569–2576
27. Ito N, Shirahata A, Yagi T, Matsushima T, Kawase K, Watanabe M, Uchikawa Y (1997) Development of artificial retina using cultured neural cells and photoelectric device: a study on electric current with membrane model. *Proc 4th International Conf Neural Information Processing (ICONIP)*, pp 124–127
28. Kisvarday ZF, Eysel UT (1992) Cellular organization of reciprocal patchy networks in layer III of cat visual cortex (area 17). *Neuroscience* 46:275–286
29. Kisvarday ZF, Toth E, Rausch M, Eysel UT (1997) Orientation-specific relationship between populations of excitatory and inhibitory lateral connections in the visual cortex of the cat. *Cereb Cortex* 7:605–618
30. Kreyszig E (1982) *Statistische Methoden und ihre Anwendungen*. Vandenhoeck Ruprecht, Göttingen
31. Krumpaszky HG, Klauss V (1996) Epidemiology of blindness and eye disease. *Ophthalmologica* 210:1–84
32. Krumpaszky HG, Lüdtke R, Mickler A, Klauss V, Selbmann HK (1999) Blindness incidence in Germany. A population-based study from Württemberg-Hohenzollern. *Ophthalmologica* 213:176–182
33. McIlwain JT (1996) *An introduction to the biology of vision*. Cambridge University Press, Cambridge, UK
34. Normann RA, Maynard EM, Guillory KS, Warren DJ (1996) Cortical implants for the blind. *IEEE Spectrum* 112:54–59
35. Normann RA, Maynard EM, Rousche PJ, Warren DJ (1999) A neural interface for a cortical vision prosthesis. *Vision Res* 39:2577–2587
36. Orban GA (1984) *Neural operations in the visual cortex*. Springer Verlag, Berlin
37. Rizzo JF, Wyatt J (1997) Prospects for a visual prosthesis. *Neuroscientist* 3:251–262
38. Rodiek RW (1979) Visual pathways. *Ann Rev Neurosci* 2:193–235
39. Salin PA, Girard P, Kennedy H, Bullier J (1992) Visuotopic organization of corticocortical connections in the visual system of the cat. *J Comp Neurol* 320:415–434
40. Salin PA, Bullier J, Kennedy H (1989) Convergence and divergence in the afferent projections to cat area 17. *J Comp Neurol* 283:486–512
41. Schanze T (1996) *Struktur und Kopplung reizabhängiger rhythmischer Aktivität der Sehrinde* (Dissertation, Philipps-Universität Marburg, 1995). Görlich und Weiershäuser, Marburg
42. Schanze T, Wilms M, Eger M, Hesse L, Eckhorn R (2002) Activation zones in cat visual cortex evoked by electrical retina stimulation. *Graefes Arch Clin Exp Ophthalmol* 240:947–954

-
43. Schmidt EM, Bak MJ, Hambrecht FT, Kufta CV, O'Rourke NA, Vallabhanath P (1996) Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. *Brain* 119:507–522
 44. Shatz CJ, Lindstroem S, Wiesel TN (1977) The distribution of afferents representing the right and left eyes in the cat's visual cortex. *Brain Res* 131:103–116
 45. Stone J, Dreher B, Leventhal A (1979) Hierarchical and parallel mechanisms in the organization of visual cortex. *Brain Res Rev* 1:345–394
 46. Tassiker GE (1956) US patent 2760483
 47. Ts'o DY, Gilbert CD, Wiesel TN (1986) Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. *J Neurosci* 6:1160–1170
 48. Veraart C, Raftopoulos C, Mortimer JT, Delbeke J, Pins D, Michaux G, Vanlierde A, Parrini S, Wanet MC (1998) Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. *Brain Res* 813:181–186
 49. Wässle H, Boycott BB (1991) Functional architecture of the mammalian retina. *Physiol Rev* 71:447–480
 50. Wilms M (2001) Electrical receptive fields and cortical activation spread in response to electrical retina stimulation. Assessment of spatio-temporal resolution for a retina implant. PhD Thesis, Department of Physics, University of Marburg, Germany
 51. Wyatt J, Rizzo J (1996) Ocular implants for the blind. *IEEE Spectrum* May: 47–43
 52. Zrenner E (2002) Will retina implants restore vision? *Science* 295:1022–1025
 53. Zrenner E, Miliczek K D, Gabel VP, Graf HG, Guenther E, Haemmerle H, Hoefflinger B, Kohler K, Nisch W, Schubert M, Stett A, Weiss S (1997) The development of subretinal microphotodiodes for replacement of degenerated photoreceptors. *Ophthalmic Res* 29:269–280
 54. Zrenner E, Stett A, Weiss S, Aramant RB, Guenther E, Kohler K, Miliczek KD, Seiler MJ, Haemmerle H (1999) Can subretinal microphotodiodes successfully replace degenerated photoreceptors? *Vision Res* 39:2555–2567