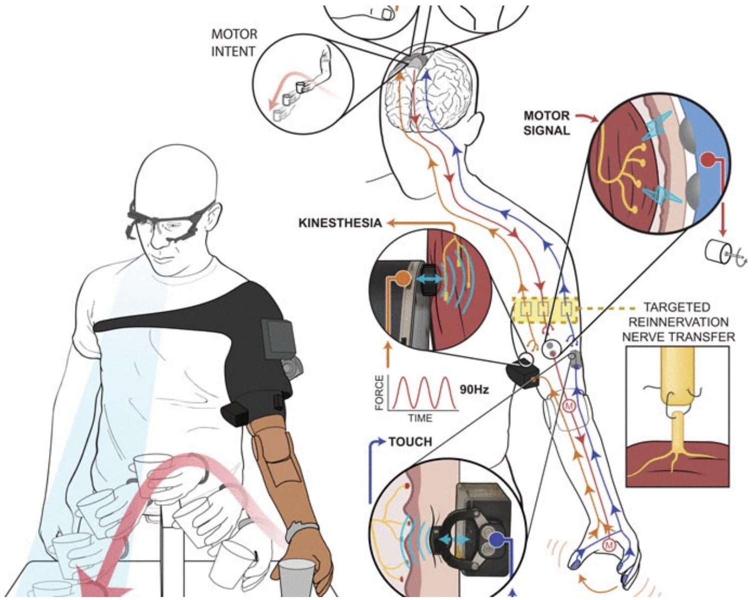
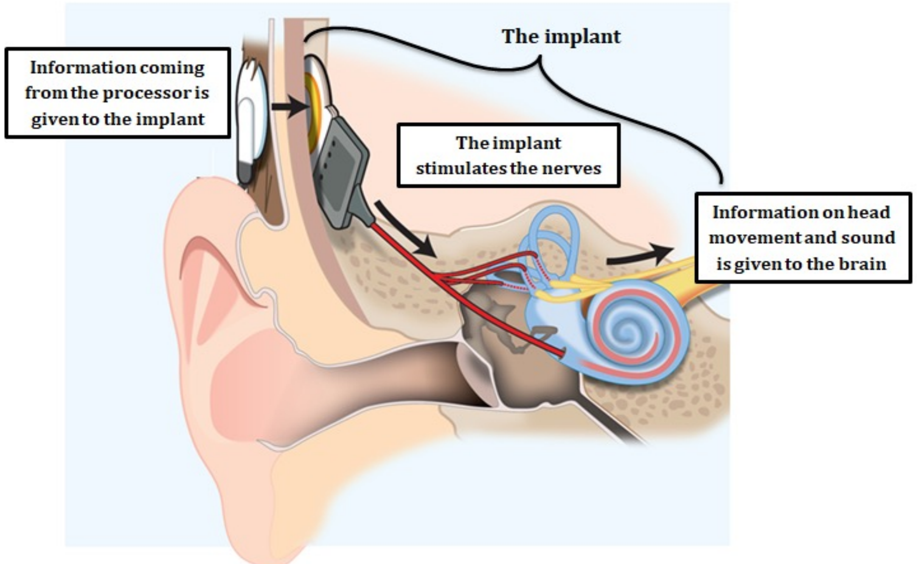
EPFL

Neuro X Institute

Vision Neuroprostheses


MOTOR INTENT
MOTOR SIGNAL
KINESTHESIA
TARGETED REINNERVATION NERVE TRANSFER
FORCE
TIME
90Hz
TOUCH


The implant
Information coming from the processor is given to the implant
The implant stimulates the nerves
Information on head movement and sound is given to the brain

Learning Goals

EPFL

Last week we started addressing the development of neurotechnologies to restore sensory information

The main steps are:

1. Understand the main building blocks necessary to provide sensation in healthy individuals
2. Identify the specific limitations of a class of people
3. Identify the ”optimal” location and stimulation modality for the interface with the natural/nervous system
4. Replicate the building blocks identified in step #1

EPFL

Learning Goals

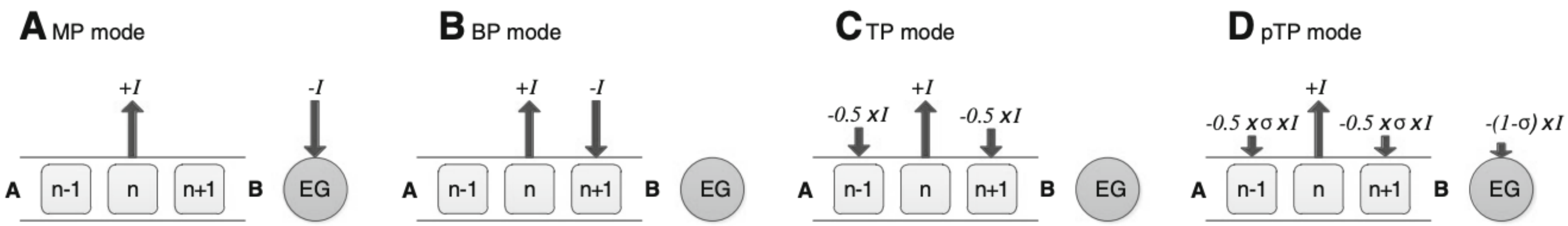


FIG. 1. Schematic illustration of stimulation modes with a fixed current level I on the main electrode n. The *arrowhead direction* indicates the phases of biphasic current pulses (*upward*: cathodic-leading; *downward*: anodic-leading), while the *arrow length* indicates the current level. *A* apex, *B* base, and *EG* extra-cochlear ground. **A** Monopolar (MP) mode: the current $-I$ is fully returned to the EG. **B** Bipolar (BP) mode: the current $-I$ is fully returned to the basal or apical (not shown) flanking electrode. **C** Tripolar (TP) mode: the current $-I$ is split and returned evenly to both flanking electrodes. **D** Partial tripolar (pTP) mode: only a fraction of the current ($-\sigma \times I$) is split and returned evenly to both flanking electrodes, while the rest [$-(1-\sigma) \times I$] to the EG. Note that these plots differ in the current return pathways.

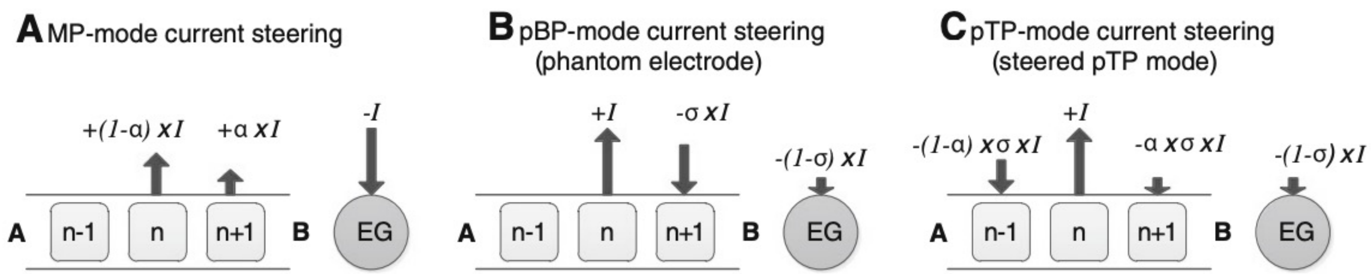


FIG. 2. Schematic illustration of current steering in MP, partial BP (pBP), and pTP modes. Refer to Figure 1 for annotations. **A** MP-mode current steering: two adjacent main electrodes are simultaneously stimulated in phase with varying ratios of current level (α and $1-\alpha$ on the basal and apical electrodes, respectively). **B** pBP-mode current steering or phantom electrode: a fraction of the current ($-\sigma \times I$) is returned to the basal or apical (not shown) flanking electrode and the rest [$-(1-\sigma) \times I$] to the EG. **C** pTP-mode current steering or steered pTP mode: a fraction of the current ($-\sigma \times I$) is split and returned to the basal and apical flanking electrodes with ratios of α and $1-\alpha$, respectively, and the rest [$-(1-\sigma) \times I$] to the EG.

Learning Goals

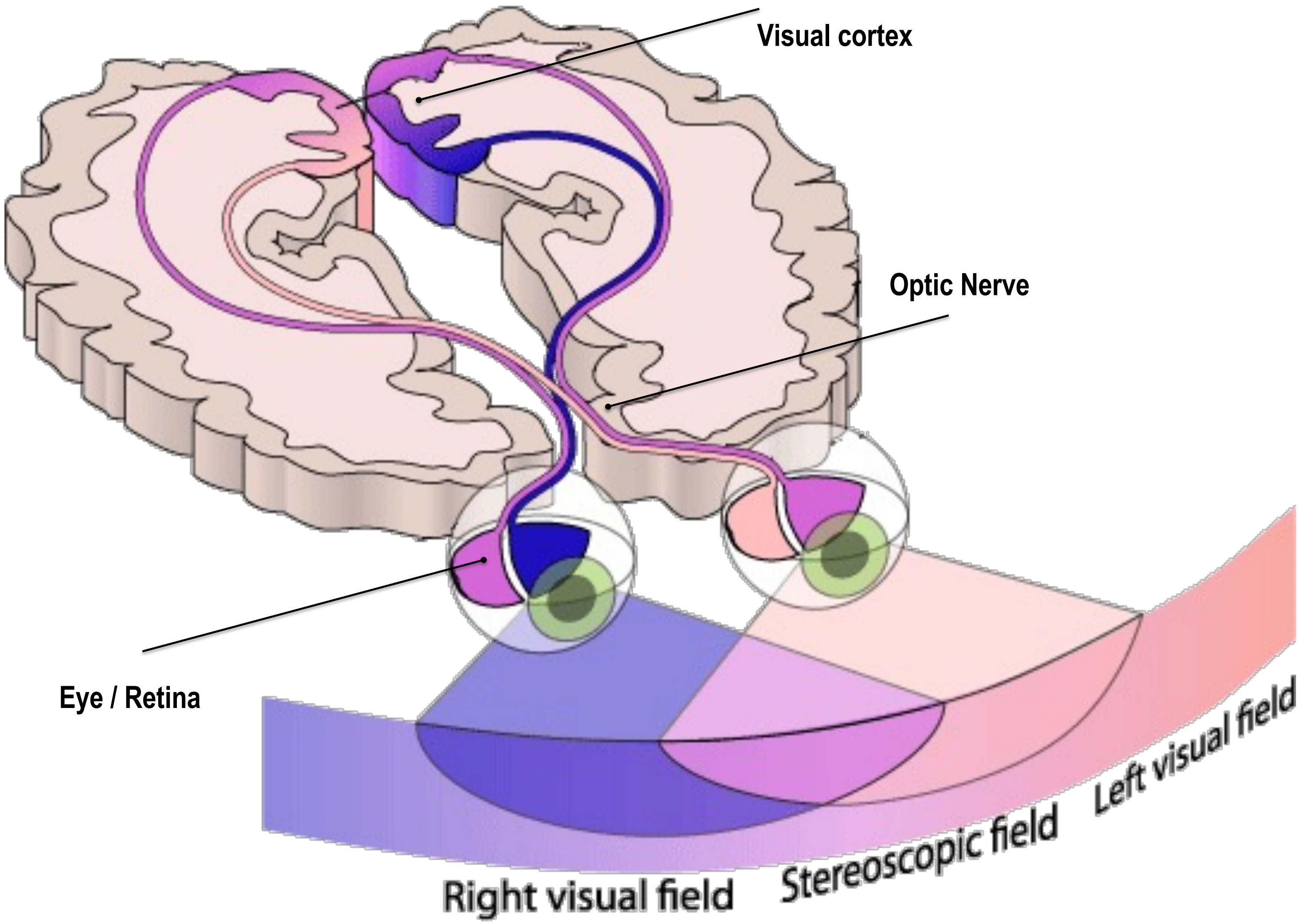
EPFL

Exercise

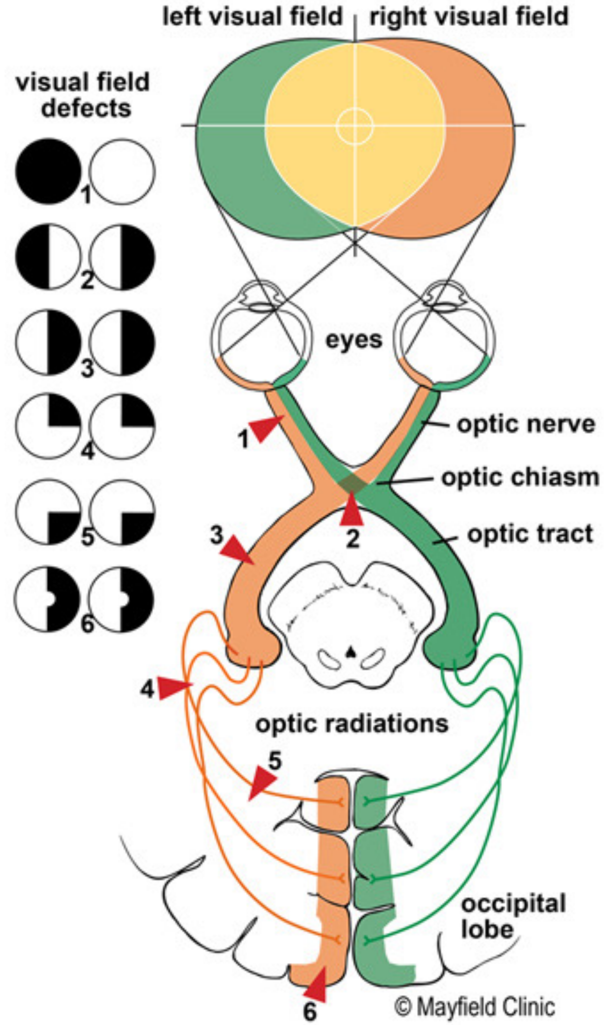
Auditory functions?

Vestibilar functions?

VISION

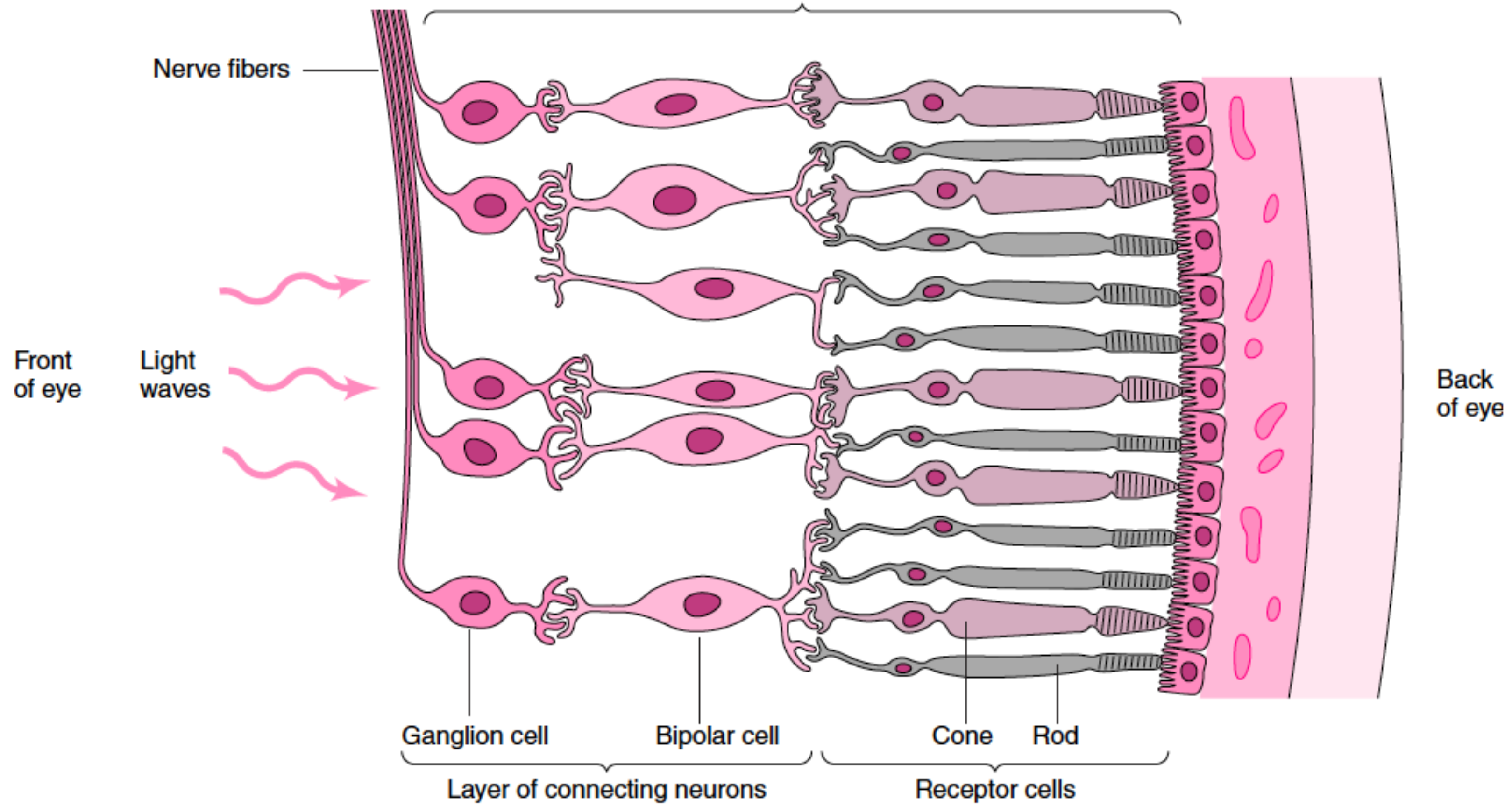


Visual cortex
Optic Nerve
Eye / Retina
Right visual field
Stereoscopic field
Left visual field



left visual field
right visual field
visual field defects
1
2
3
4
5
6
eyes
optic nerve
optic chiasm
optic tract
optic radiations
occipital lobe
© Mayfield Clinic

Retina



Not optimum design--lots of nerve cells in optical pathway

(give us a few more million years without a major extinction event…)

Retina

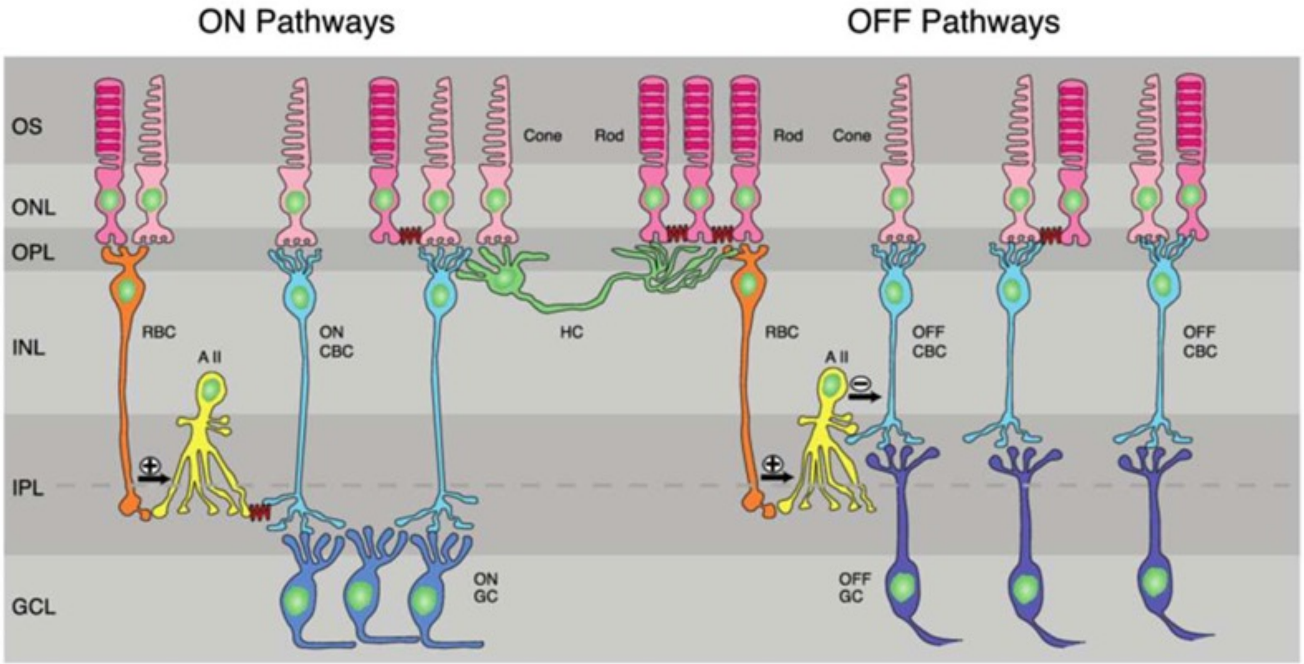
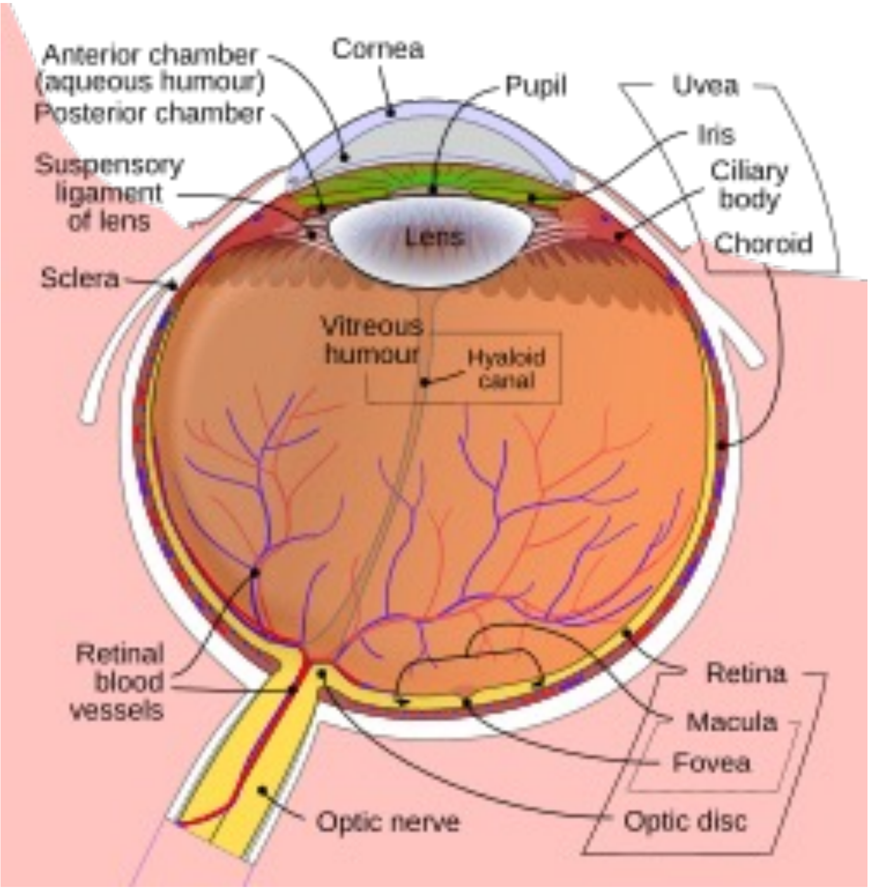


Illustration of the retinal cell layers, with a highlight on the ON and OFF pathways

The cell layering is divided into the outer segments (OS), the outer nuclear (ONL) and plexiform (OPL) layer, the inner nuclear (INL) and plexiform (IPL) layer, and the ganglion cell layer (GCL). From top to bottom, depicted are the photoreceptors (PR), both cones and rods, synapsing on either rod or cone bipolar cells (BC). These, in turn, have both ON and OFF types. Next come the horizontal cells (HC) with their dendrites making synapses exclusively with the cones and their axon terminals connecting with the rods alone. Finally, the AII amacrine cells (AC) relay the signal from the bipolar cells to the ganglion cells (GC), whose axon bundles form the optic nerve.

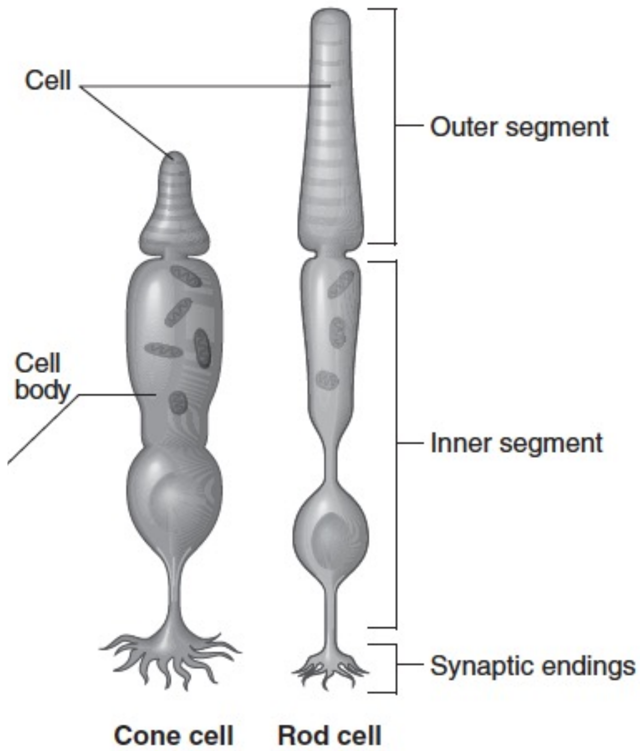
Retina



The fovea centralis is a small, central pit composed of closely packed cones in the eye. It is located in the center of the macula lutea of the retina.

The fovea is responsible for sharp central vision (also called foveal vision), which is necessary in humans for activities for which visual detail is of primary importance, such as reading and driving

The photoreceptors



Rods

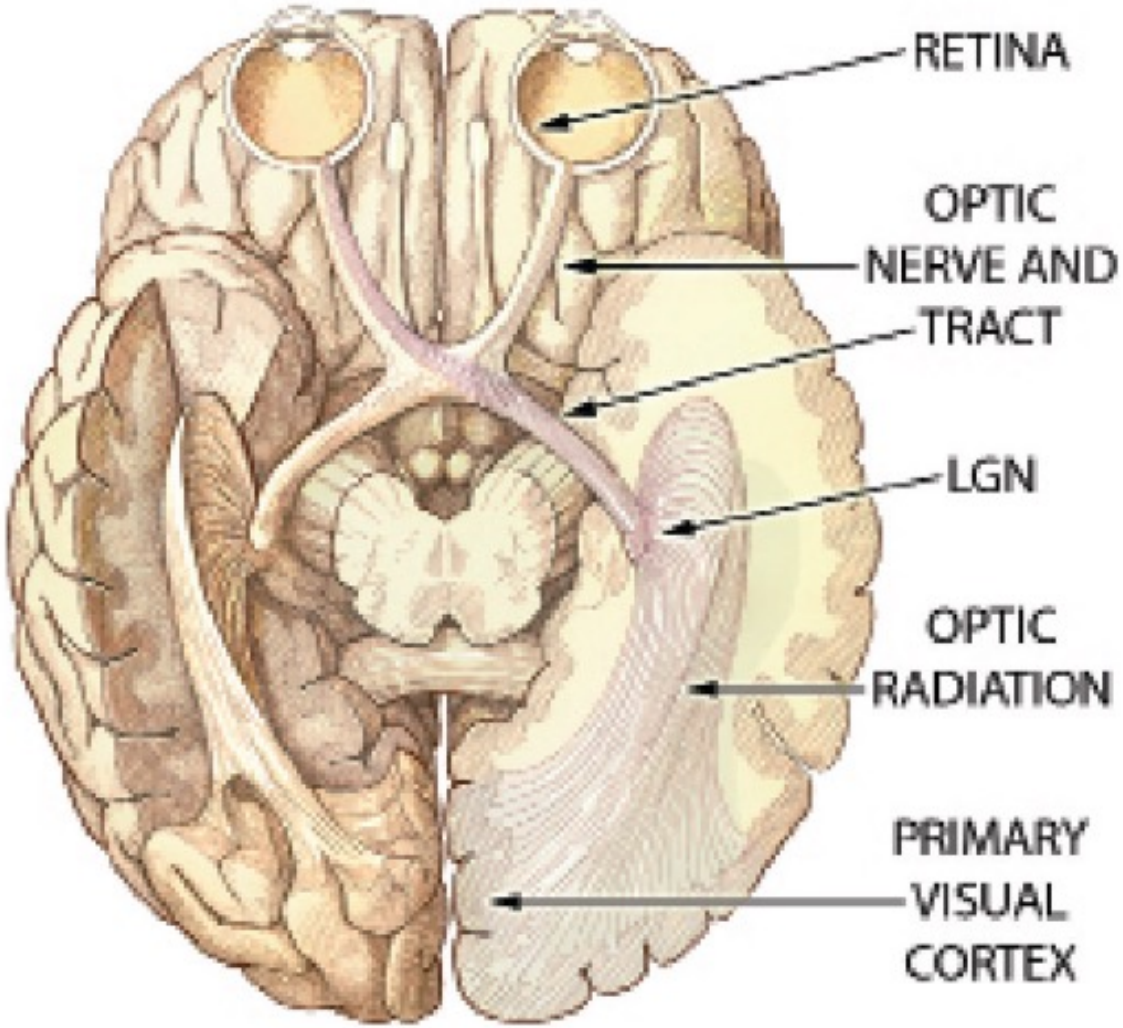
These photoreceptors are tall and have a cylindrical (tubelike) shape. They're extremely sensitive to even tiny amounts of light. About 95% of the photoreceptors in your eyes (about 100 - 125 million) are rods. They're great at helping you see in dim places, but they aren't as good at fine details, and they can't see colors at all.

Rod photoreceptors are mainly responsible for low-light vision and night vision.

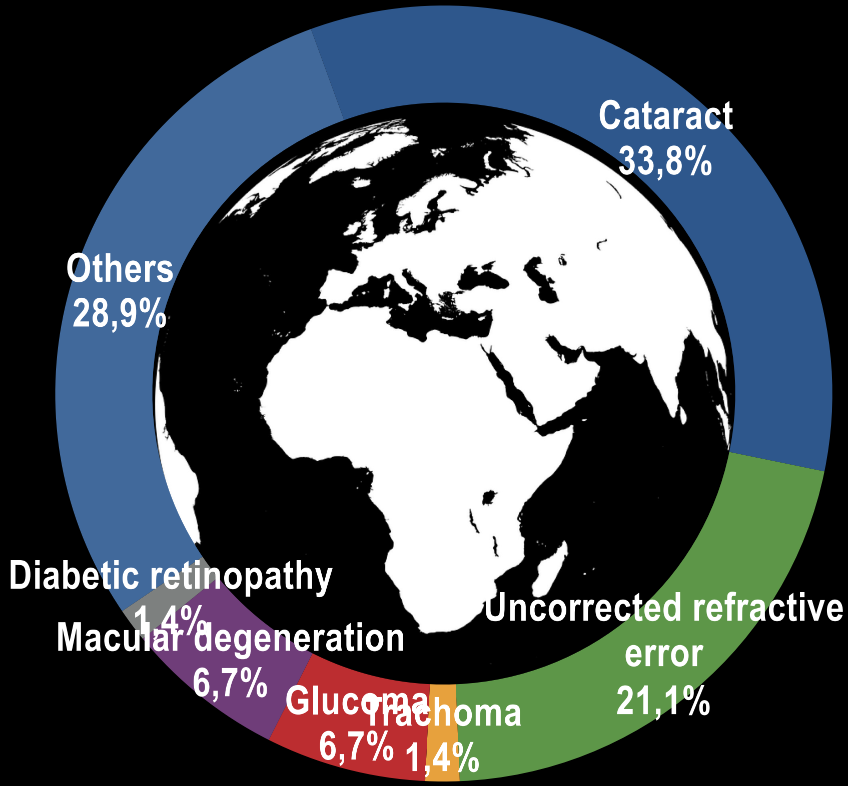
Cones

Cones are photoreceptors with a cone-like shape, meaning they're circular at the bottom and have a pointed tip at the top. They need more light to activate than rods, but they can detect colors when they're active. Most cones are in one place on your retina, the macula.

Visual Pathway



BLINDNESS

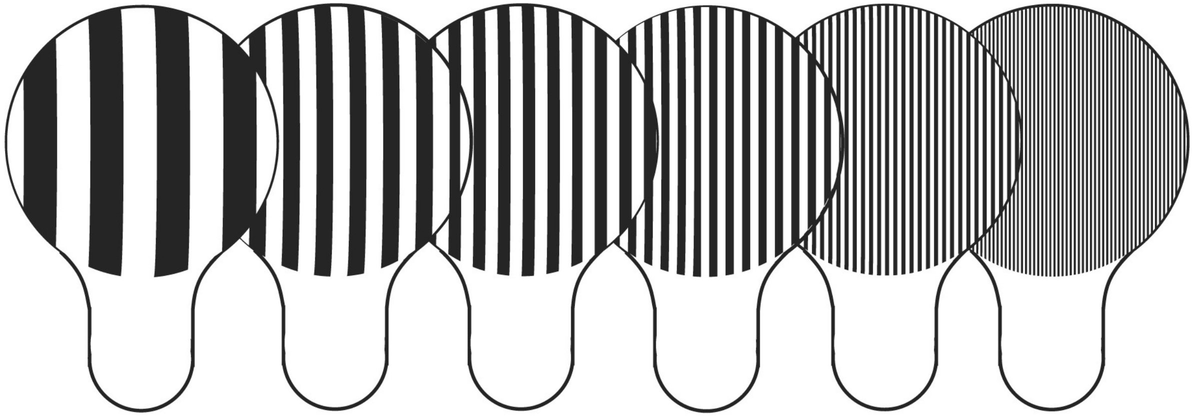


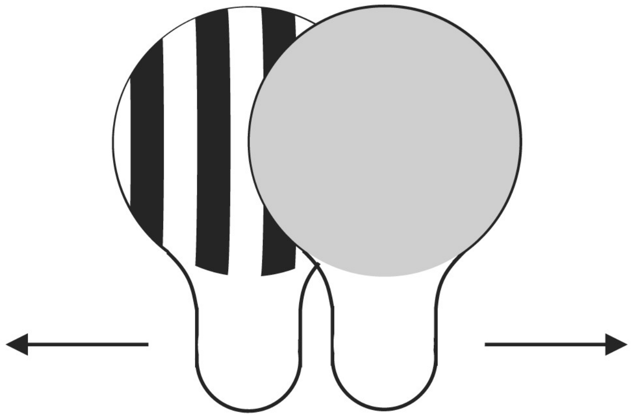
10.1016/S2214-109X(13)70113-X

WORLDWIDE 191 MILLION PEOPLE WITH MSVI AND 32.4 MILLION BLIND

VISUAL ACUITY

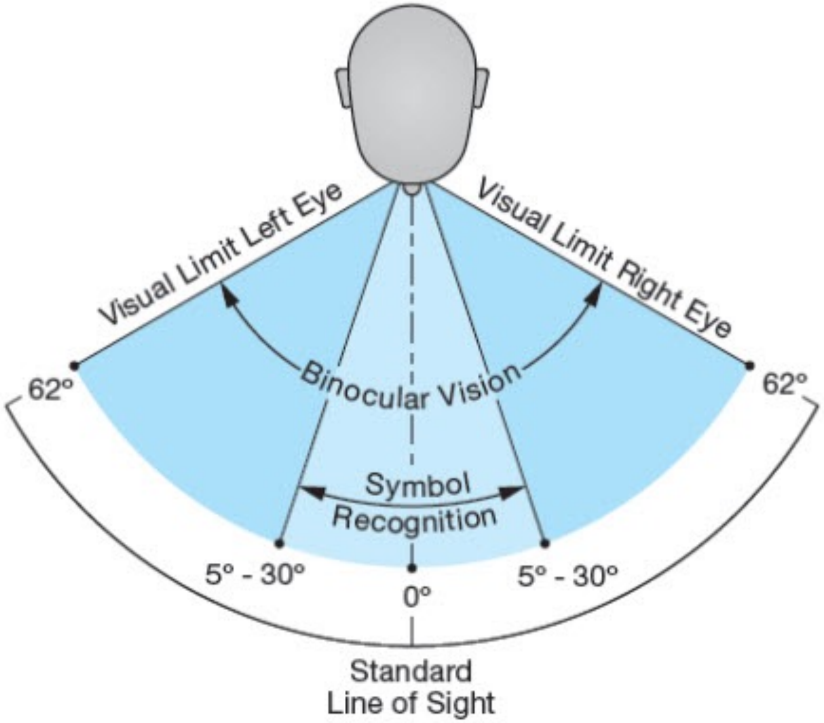
A measure of the capability in discriminating separated lines: <u>spatial resolution</u>

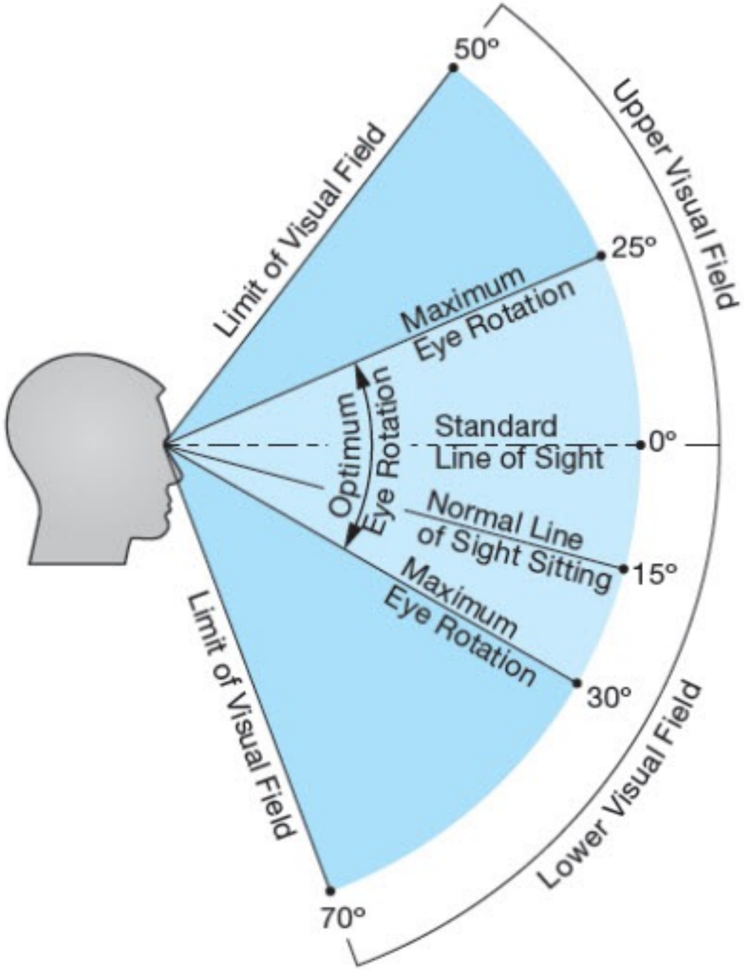




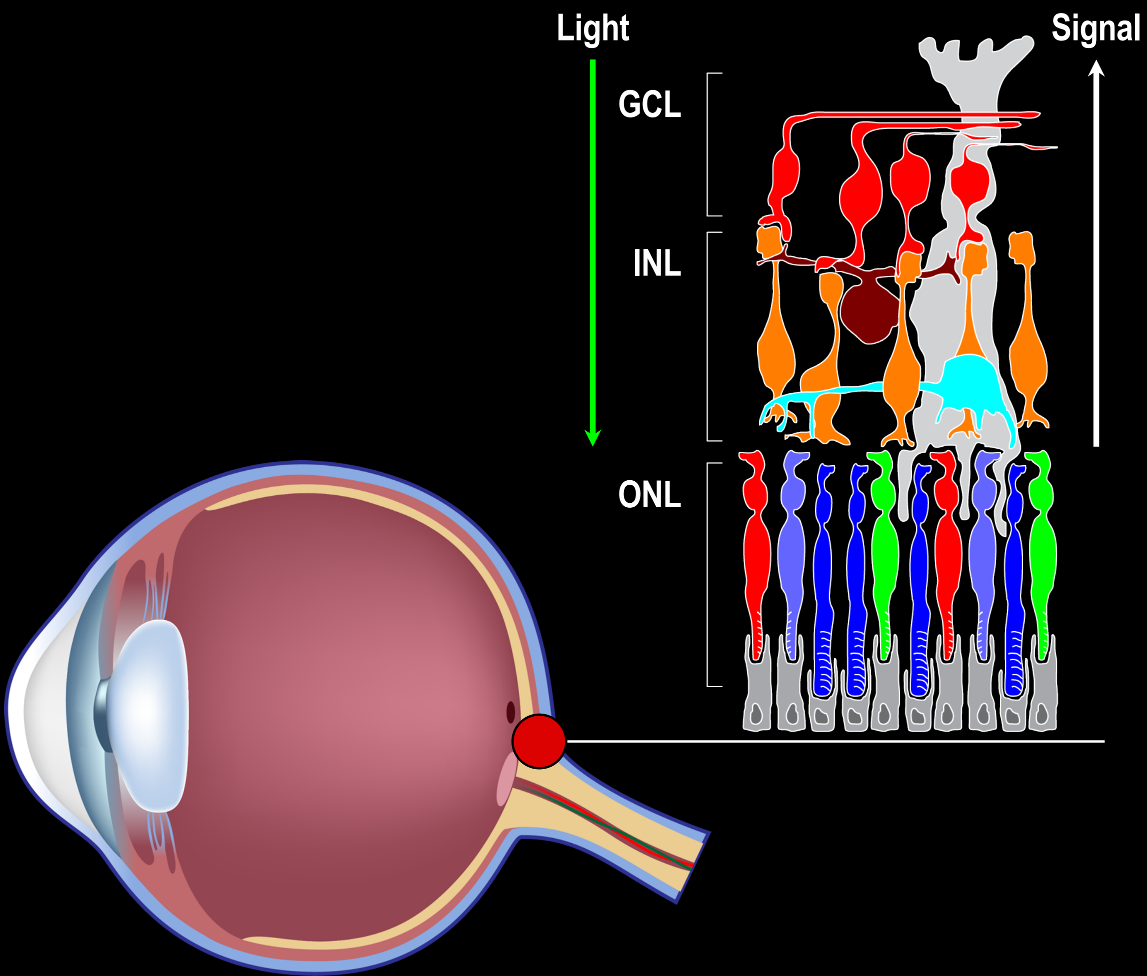
VISUAL FIELD

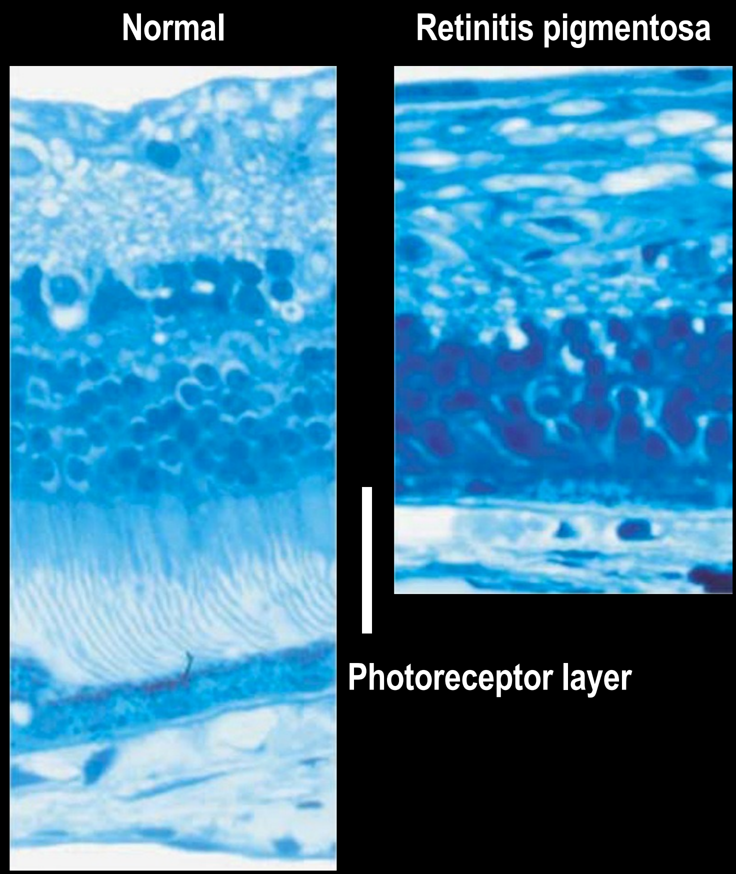
The total area in which objects can be seen in the side (peripheral) vision while you focus your eyes on a central point





OUTER RETINAL DYSTROPHIES





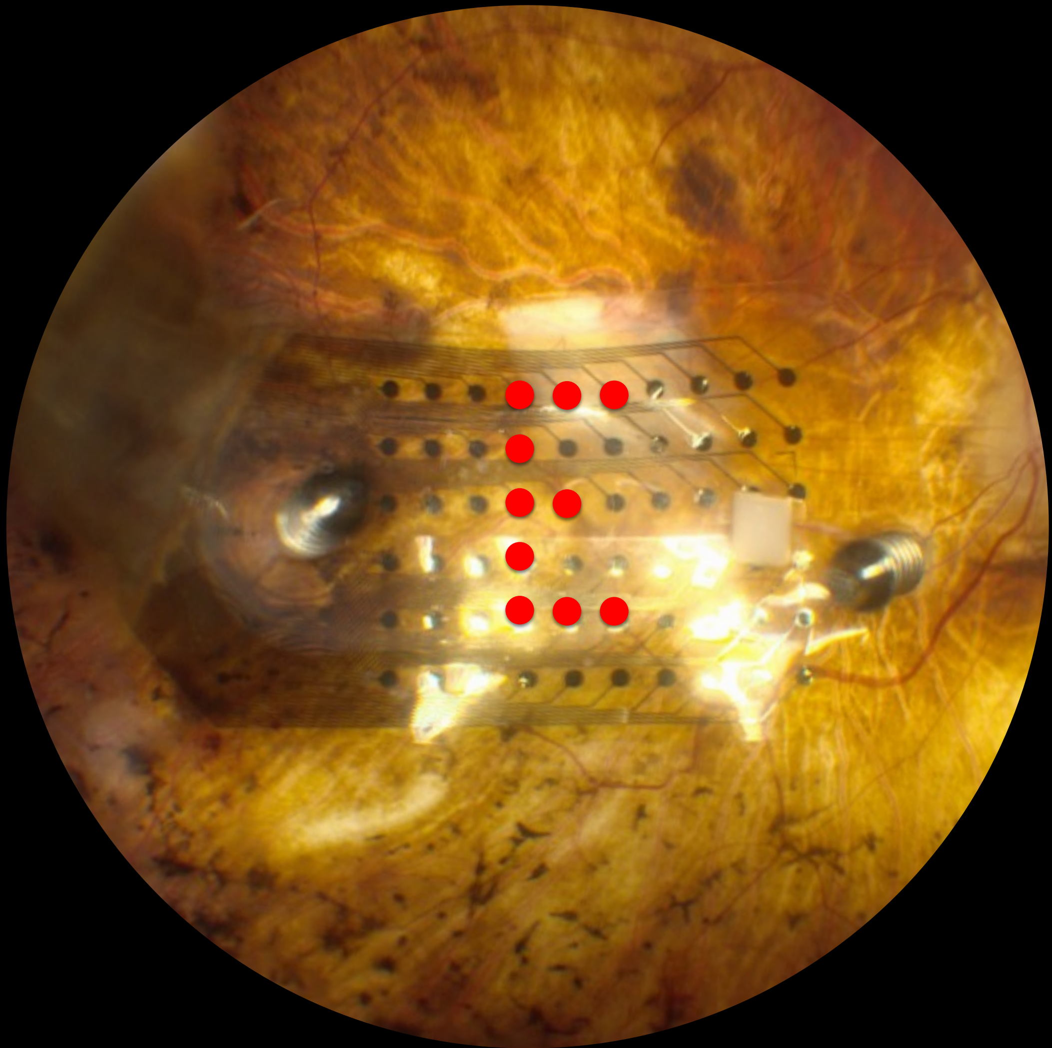
10.1159/000064650

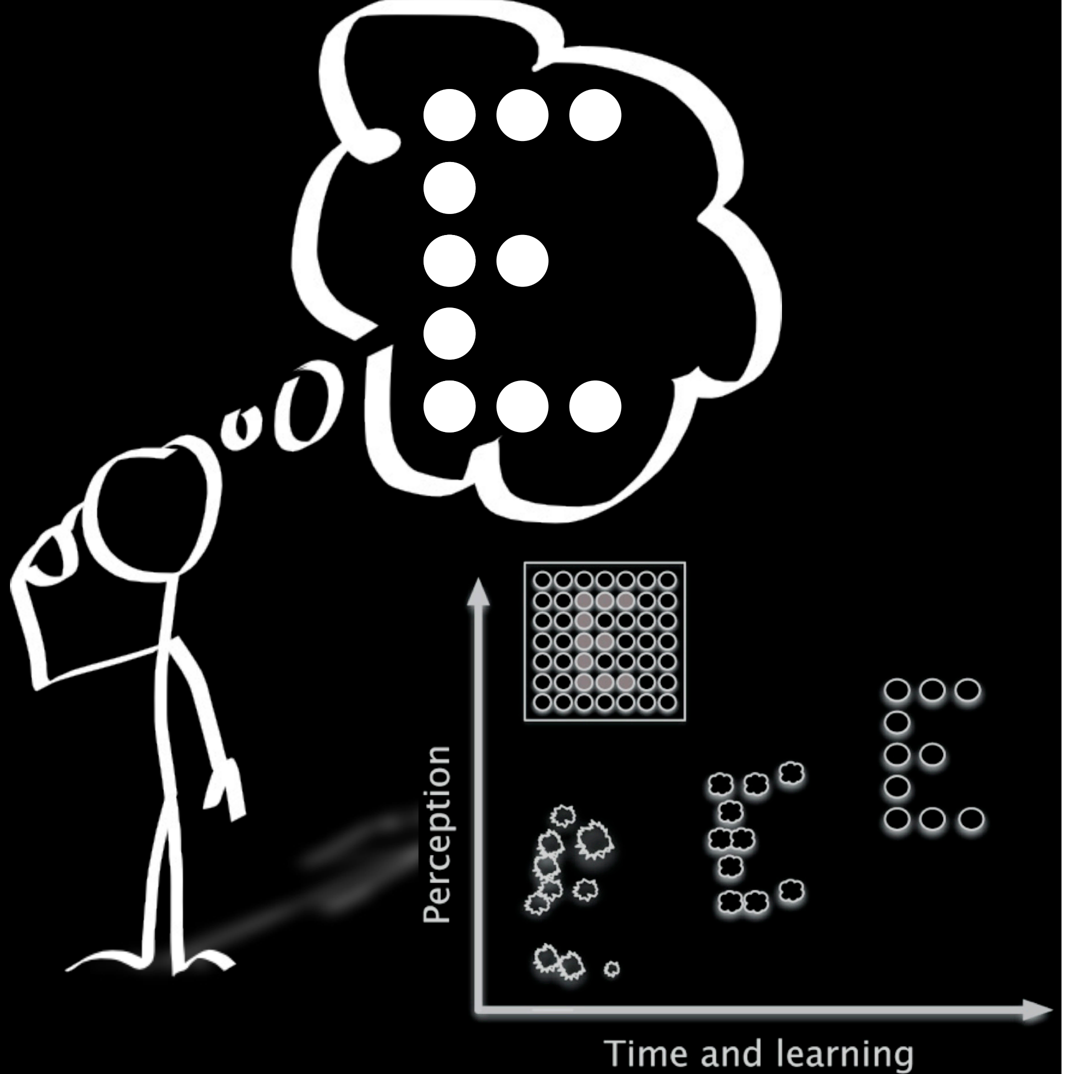
BLINDNESS

Visual acuity of less than 20/400

Visual field loss to less than 20°

WHAT IS ARTIFICIAL VISION?





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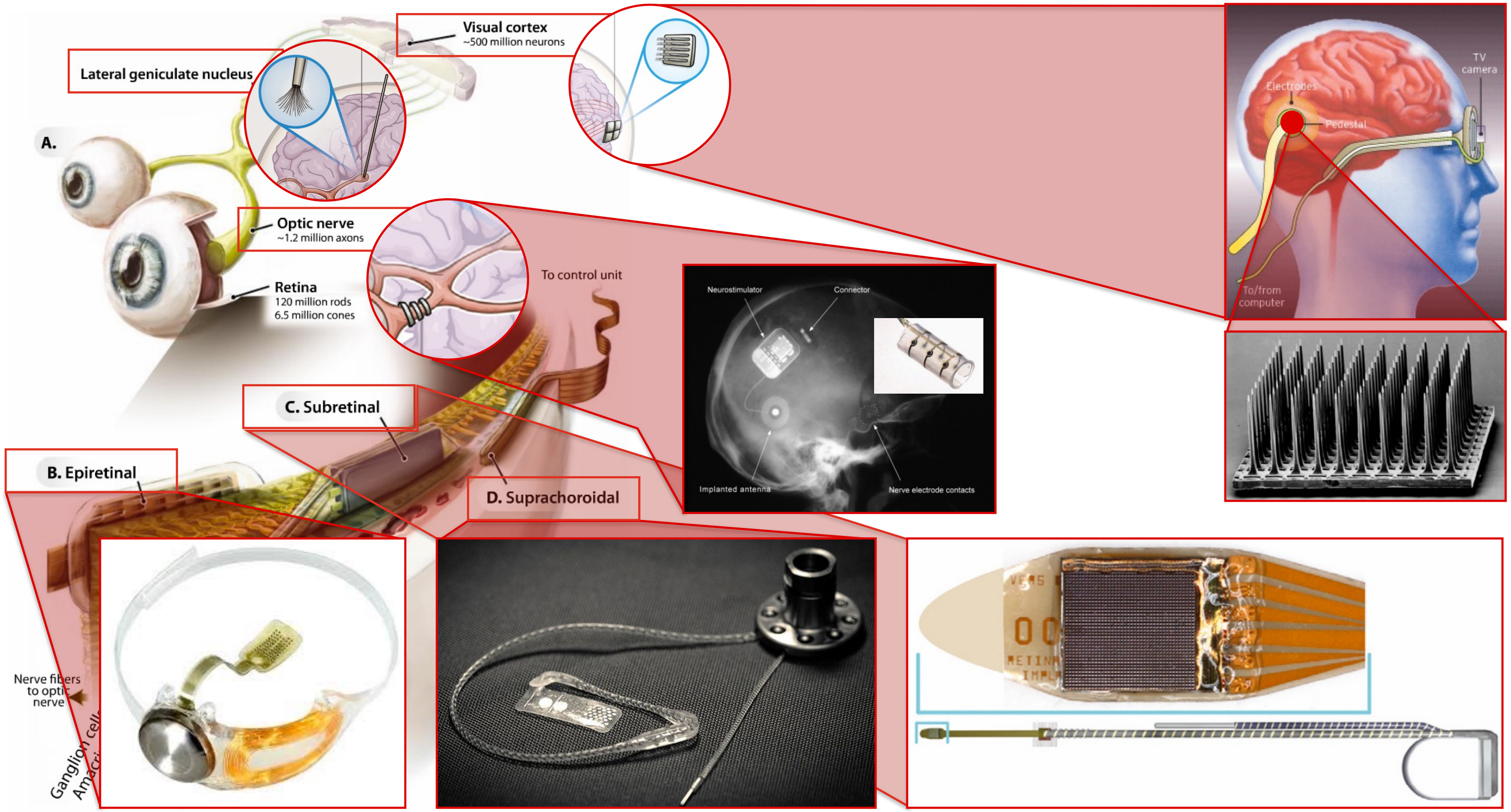
VISUAL PROSTHESIS: GENERAL DESIGN



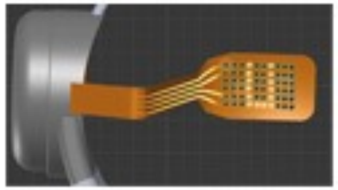
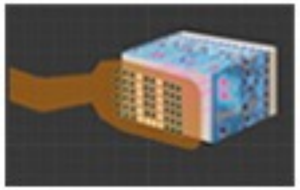
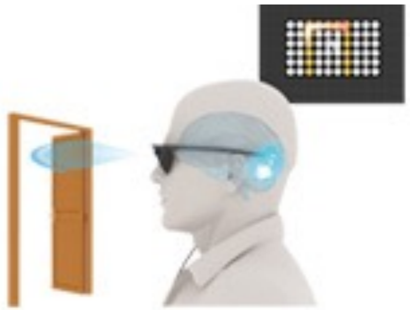
Lewis et al., Brain Research 2015
Zrenner, Science Translat Med 2013

Veraart et al., Artif Organs 2003
ARGUS II™

Shivdasani et al., IOVS 2014
Stingl et al., Proceedings biological sciences 2013

ELECTRIC-BASED PROSTHESES

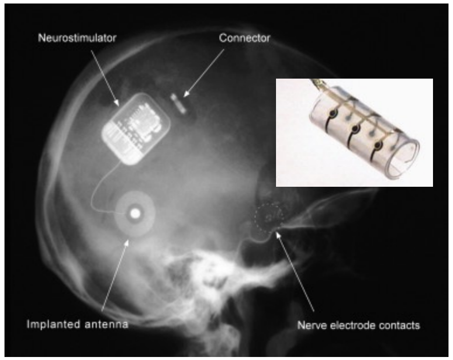


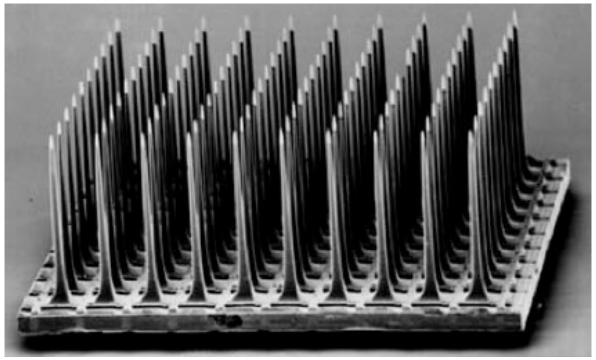
Epiretinal

Suprachoroidal

Optic nerve



Cortical



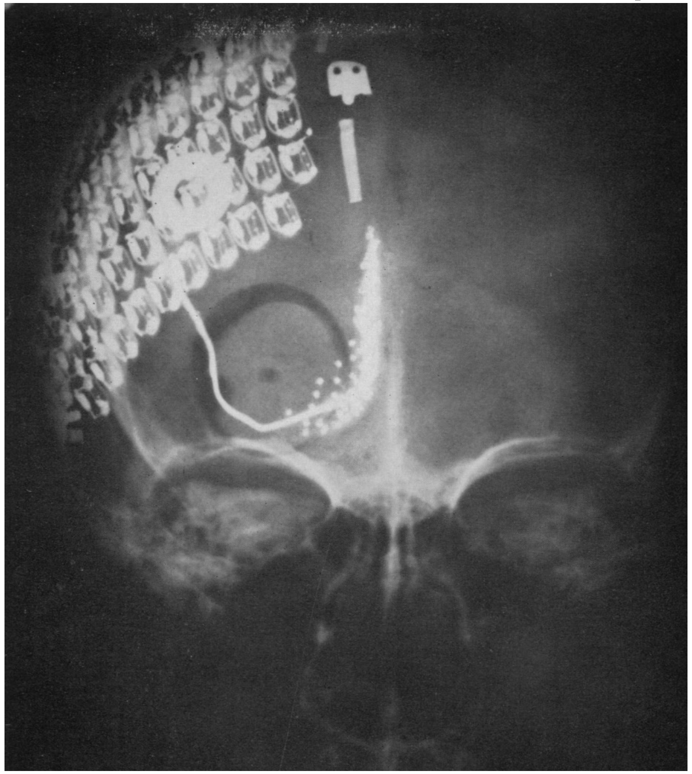
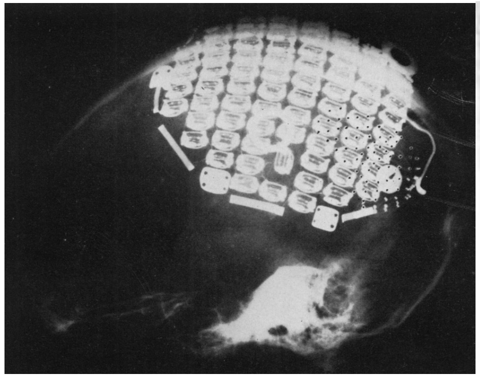
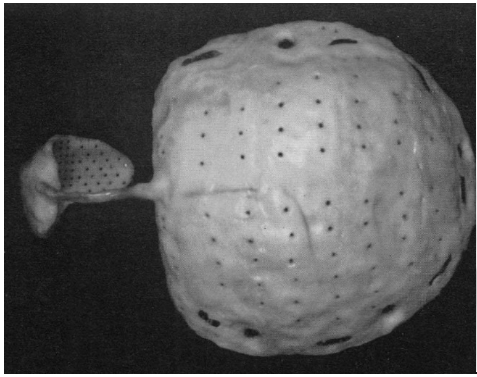
ARGUS II™

Shivdasani et al., IOVS 2014

Veraart et al., Artif Organs 2003

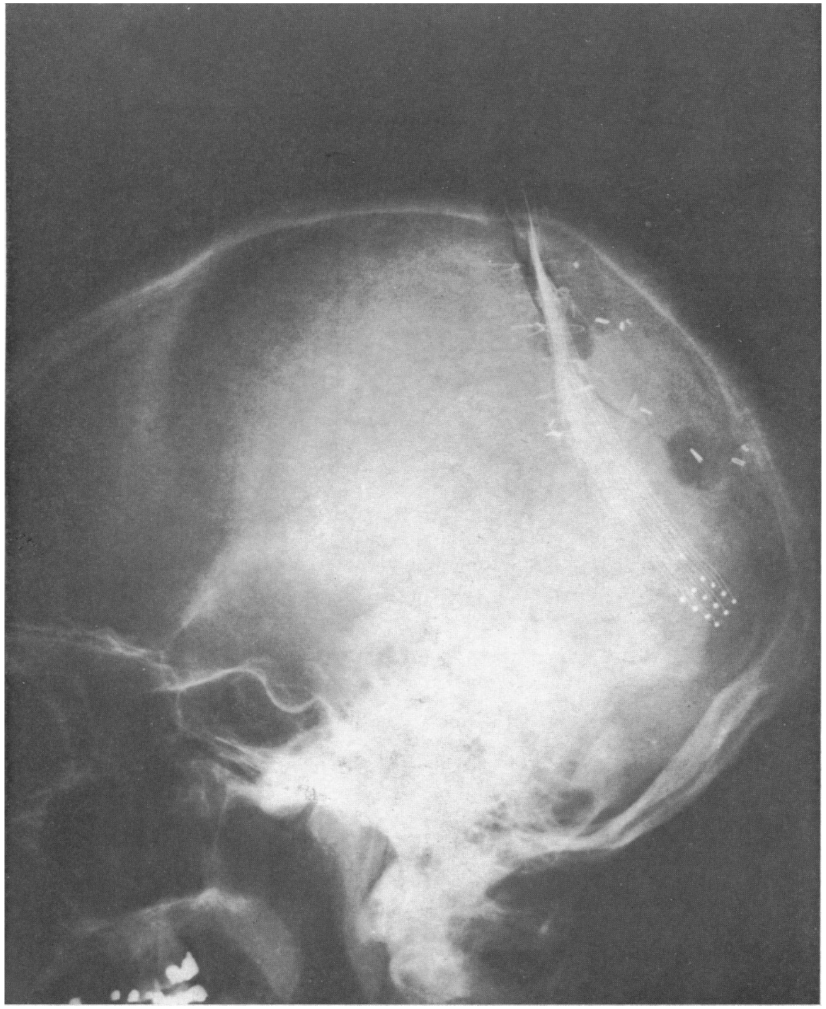
CORTICAL VISUAL PROSTHESES

In 1968, a permanent device (80 electrodes) was implanted in a 52-year-old woman who had gone totally blind six months before the operation.


Brindley & Lewin, J Physiol 1968

CORTICAL VISUAL PROSTHESES



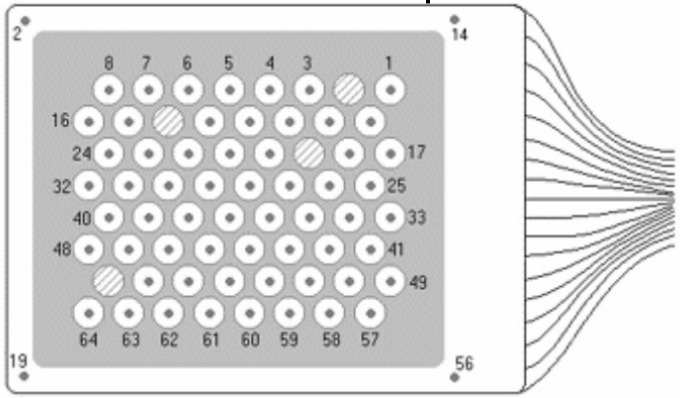
In 1974 Dobelle and Mladejovsky tested various parameters of electrical simulation of human visual cortex on 37 volunteers who were admitted as conscious volunteers undergoing other occipital lobe surgery under local anaesthesia to remove tutors and other lesions.

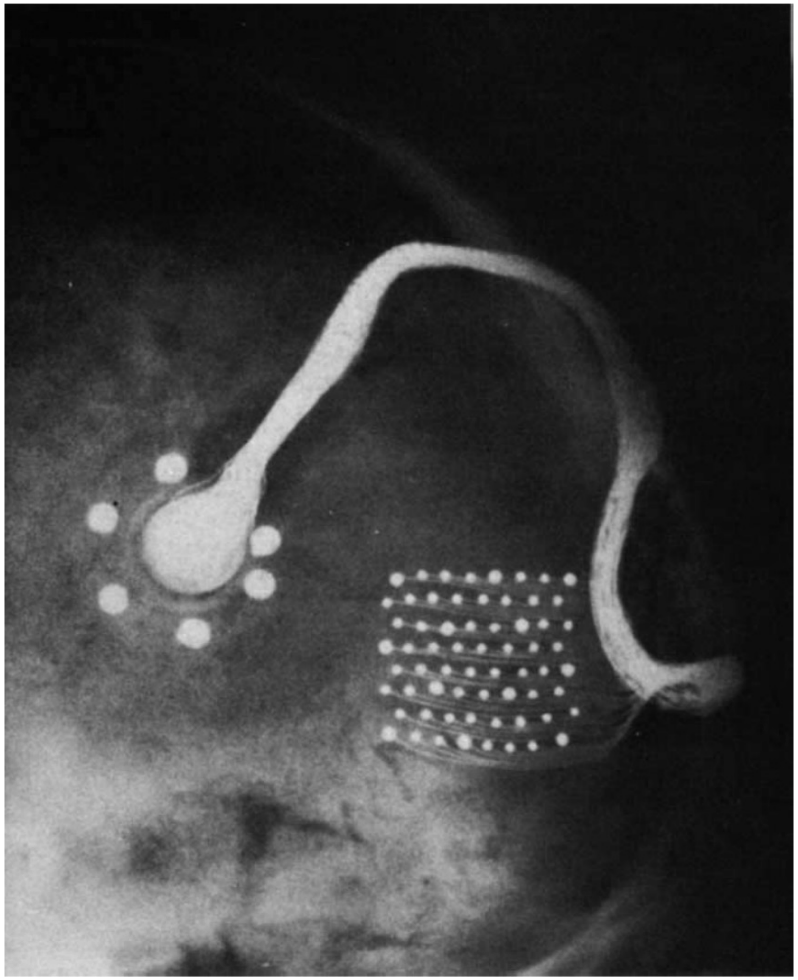
They concluded that a constant stimulus did not produce a sustained phosphene, but rather one that grew dimmer over time and eventually faded after 10-15 sec.

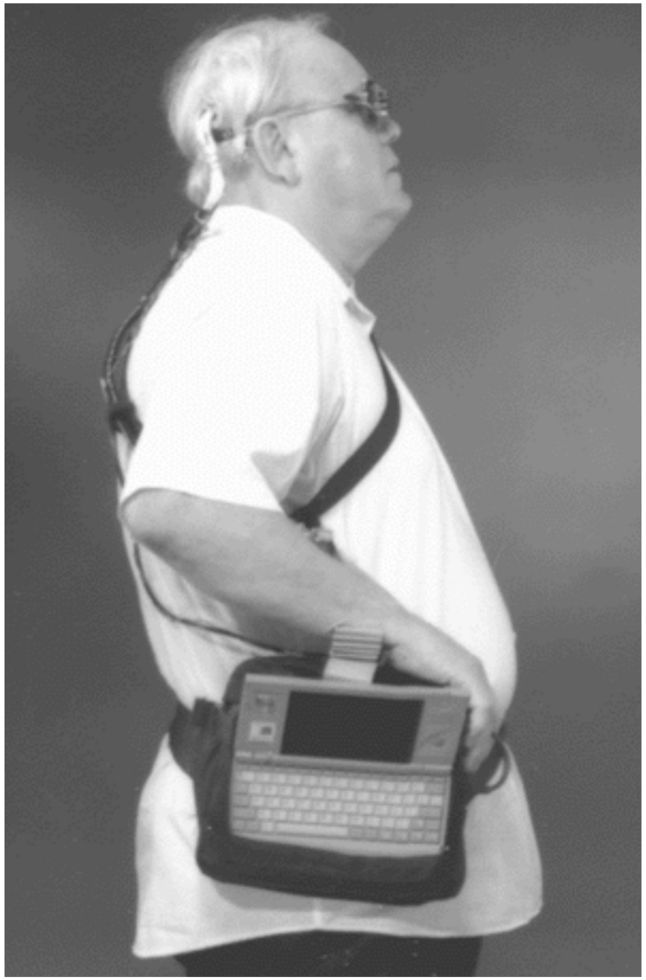
Dobelle & Mladejovsky, J Physiol 1974

CORTICAL VISUAL PROSTHESES

1mm Pt Electrodes & GND plane



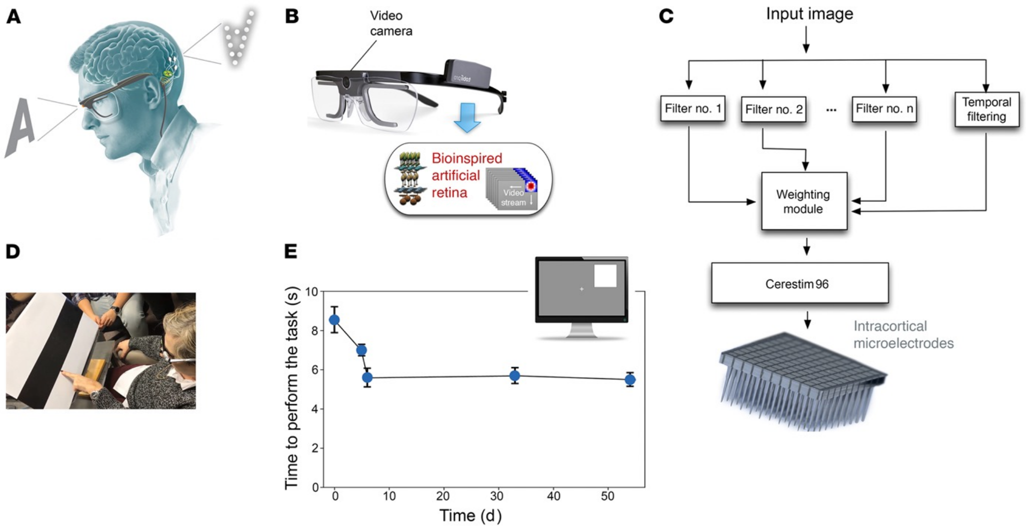


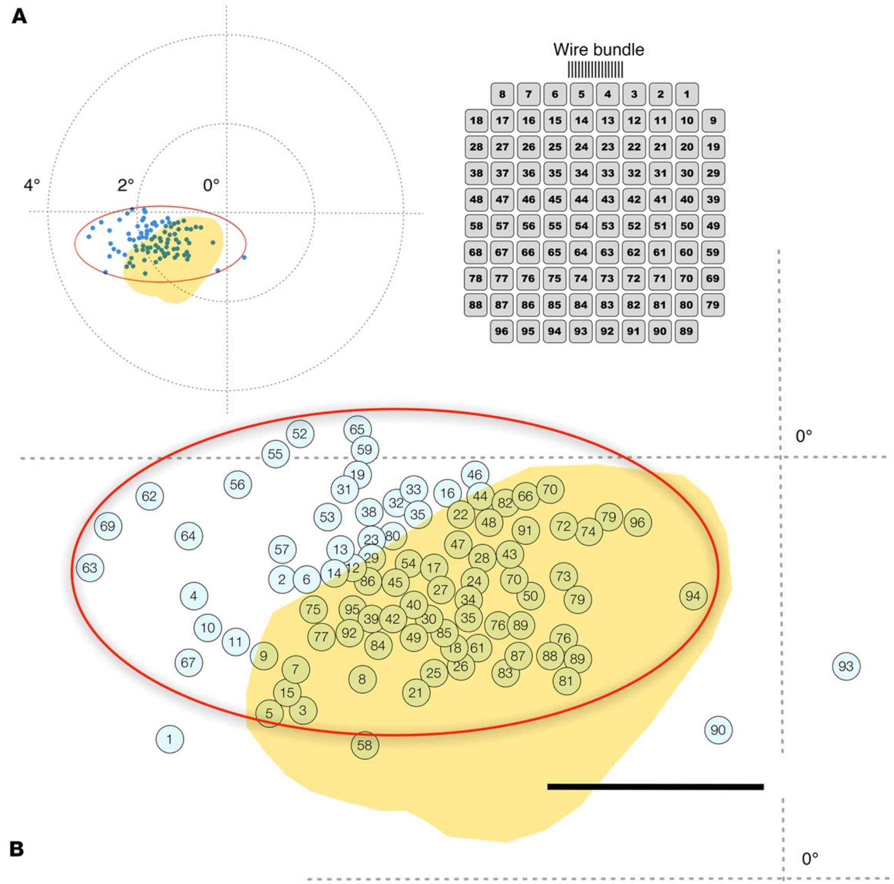


Dobelle et al., Nature 1976

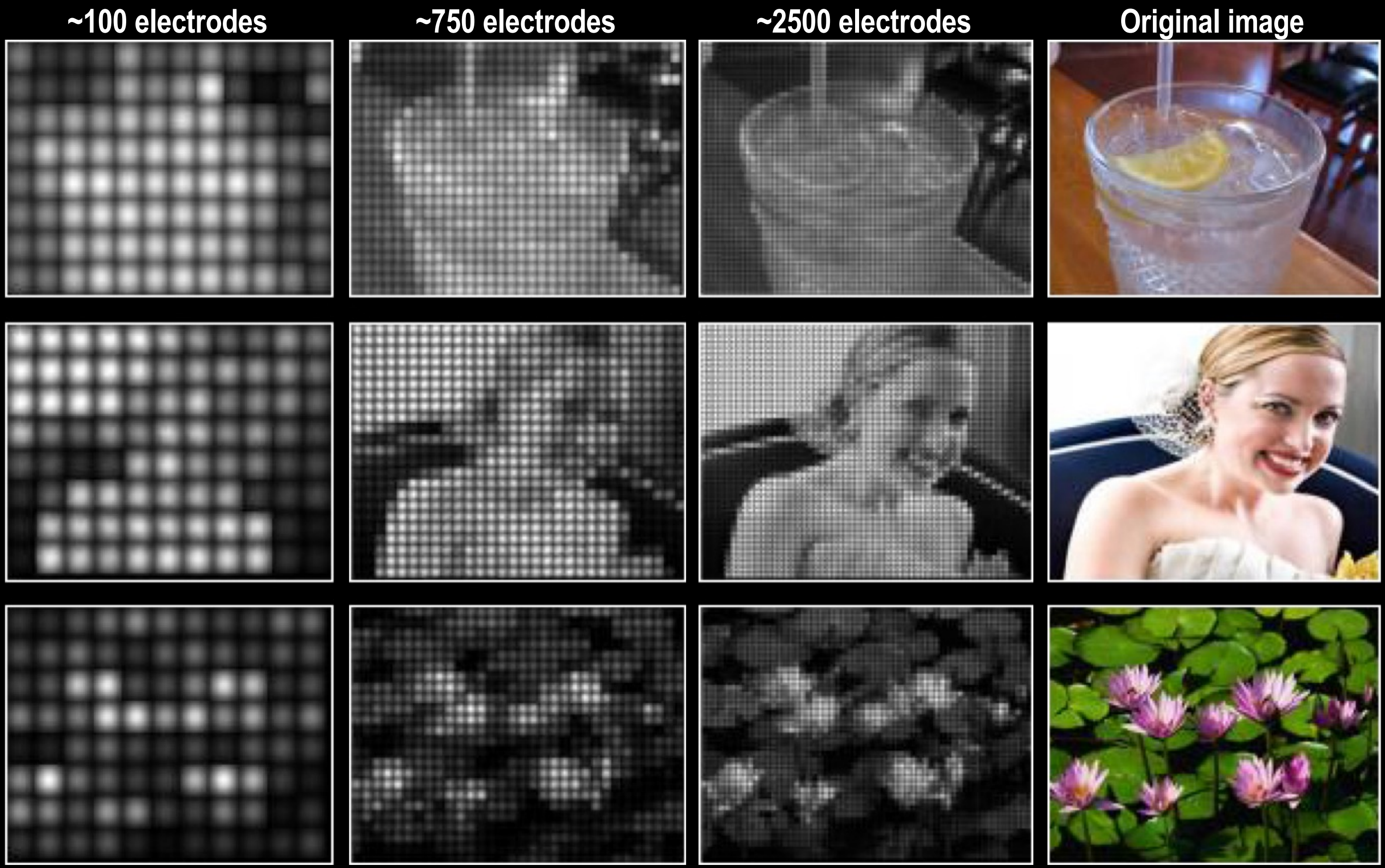
http://web.archive.org/web/20040902040027/http://artificialvision.com/ Dobelle, ASAIO Journal 2000

CORTICAL VISUAL PROSTHESES





VISUAL ACUITY



10.1088/1741-2560/8/3/035005

VISUAL FIELD

15 degrees

~1200 electrodes

25 degrees

~3250 electrodes

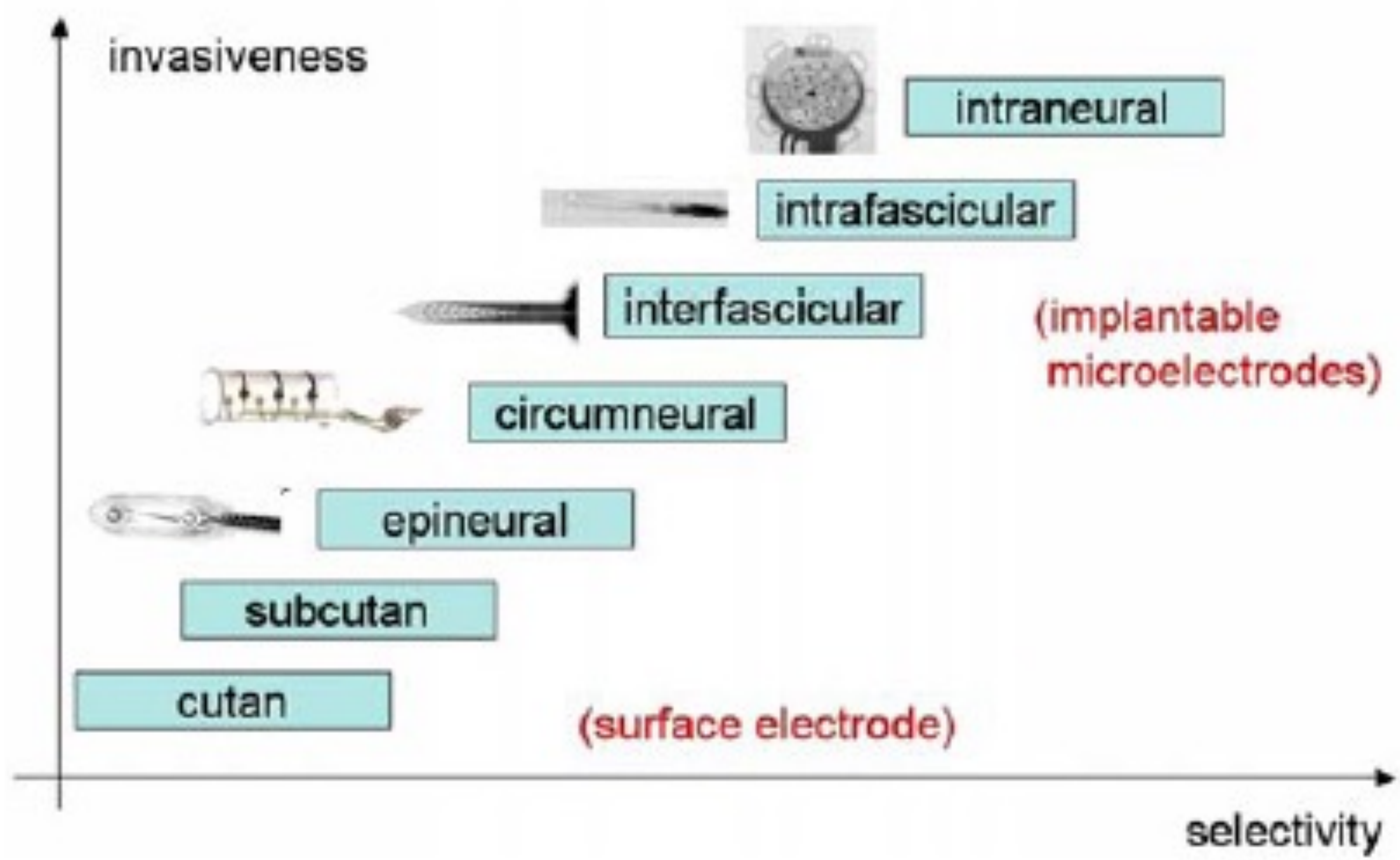
35 degrees

~6200 electrodes

45 degrees

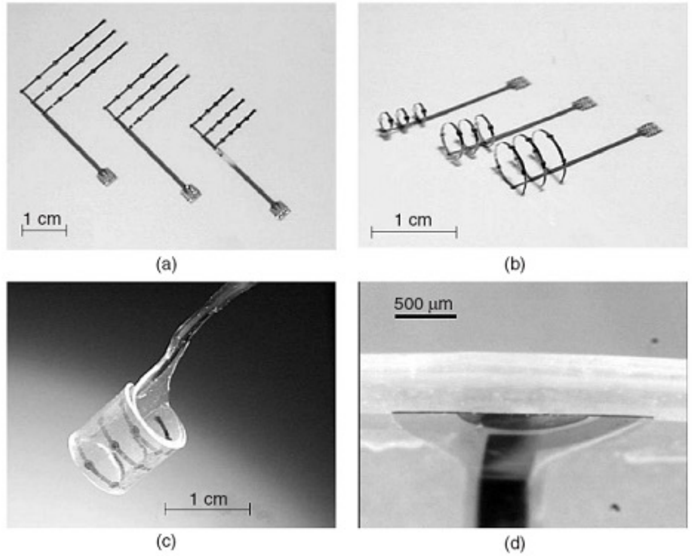
~10000 electrodes

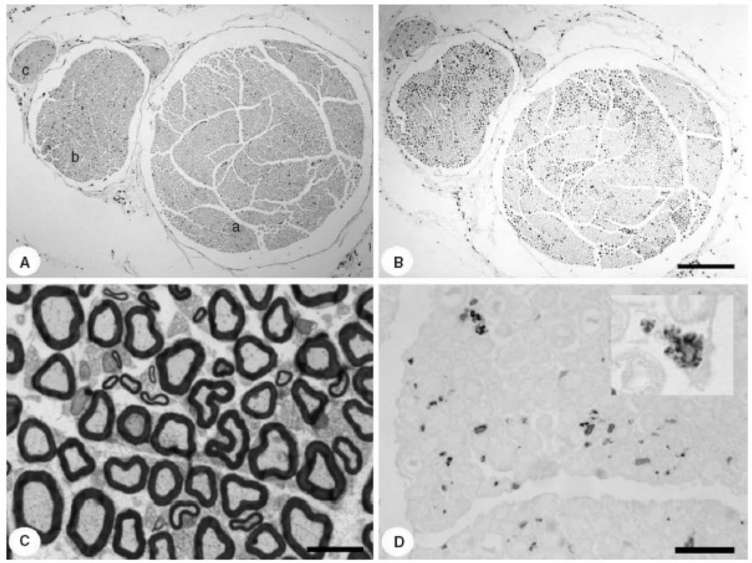
Interfaces with the PNS



Cuff electrodes

- Cuff electrodes are composed of an insulating tubular sheath that completely encircles the nerve and contains electrode contacts exposed at their inner surface that are connected to insulated lead wires





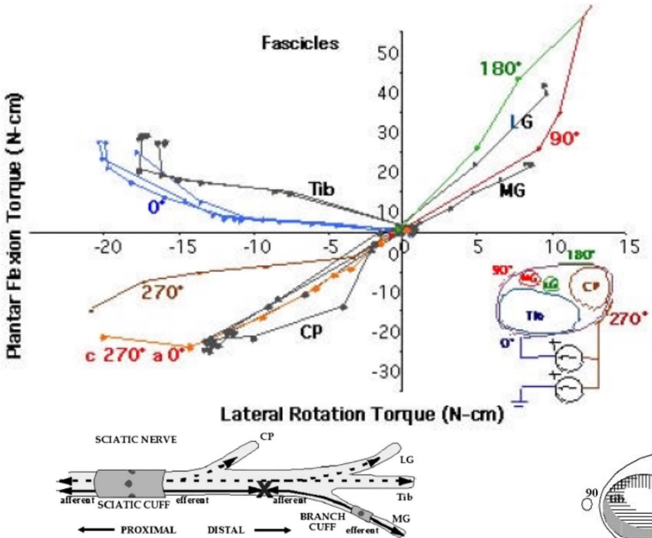


Fig. 1. Full and selective activation of an individual nerve branch was tested by using a branch cuff on the corresponding nerve branch (the MG in this example). The branch cuff was used to activate the branch nerve completely. Activation of nerve fibers serving that nerve branch, by stimulation applied to the sciatic cuff, will not change the resulting output since the branch cuff has already activated those fibers (solid lines). Activation of nerve fibers serving other nerve branches, by stimulation applied to the sciatic cuff, will propagate to different muscles and, therefore, cause a change in the resulting output (dashed lines).

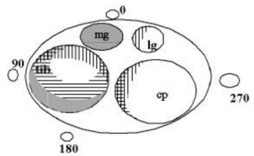
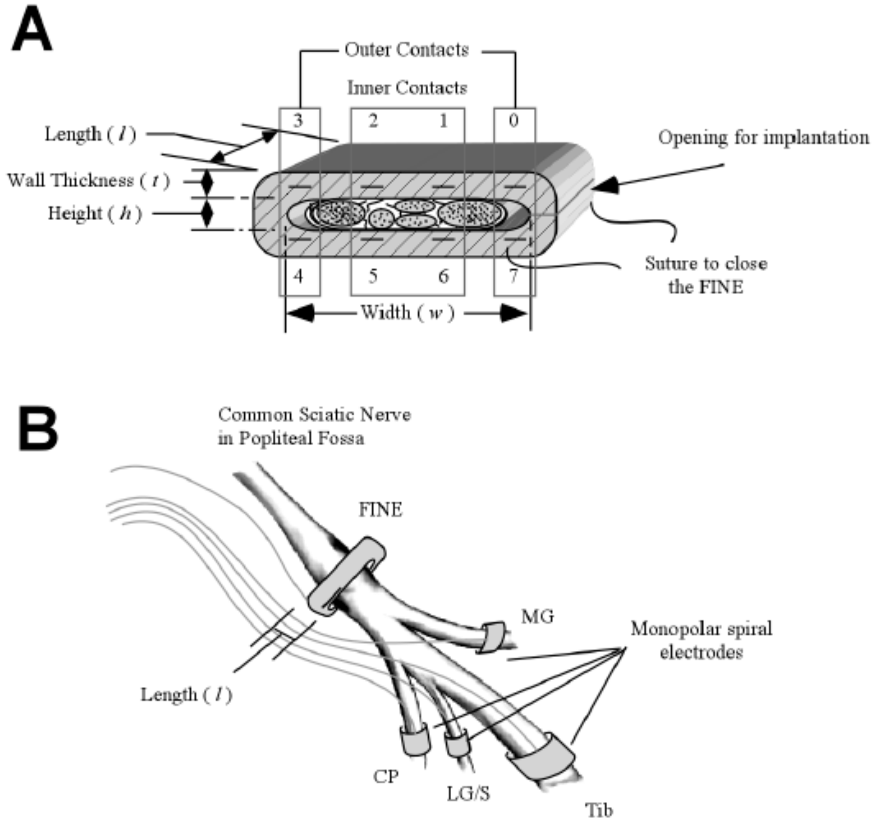
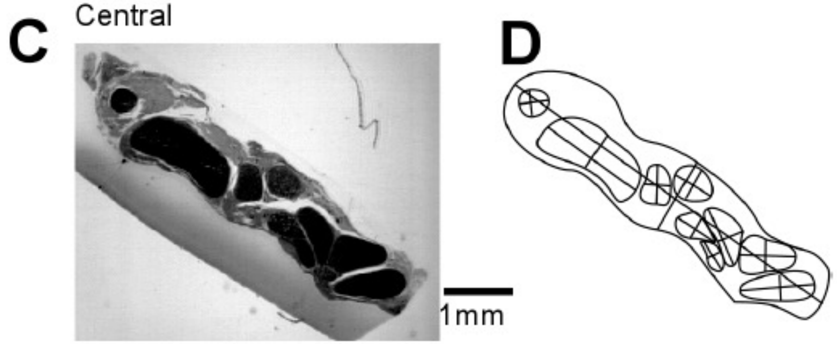


Fig. 21. Schematic representation of cat sciatic nerve containing four motor fascicles, tibial (tib), medial gastrocnemius (mg), laterial gastrocnemius (lg) and common peroneal (cp). Electrode contacts in the self-sizing spiral cuff electrode are labeled 0°, 90°, 180°, and 270°. Grayed areas represent axon populations activated when stimuli (c180°a90°) and (c0°) are separately applied. The vertically hatched areas depict axons stimulated to subthreshold levels by (c0°), and horizontal hatched areas depict axons stimulated to subthreshold levels by stimuli (c180°a90°). Regions where the two subthreshold regions overlap to create suprathreshold excitation have overlapping horizontal and vertical hatched areas.

FINE electrodes

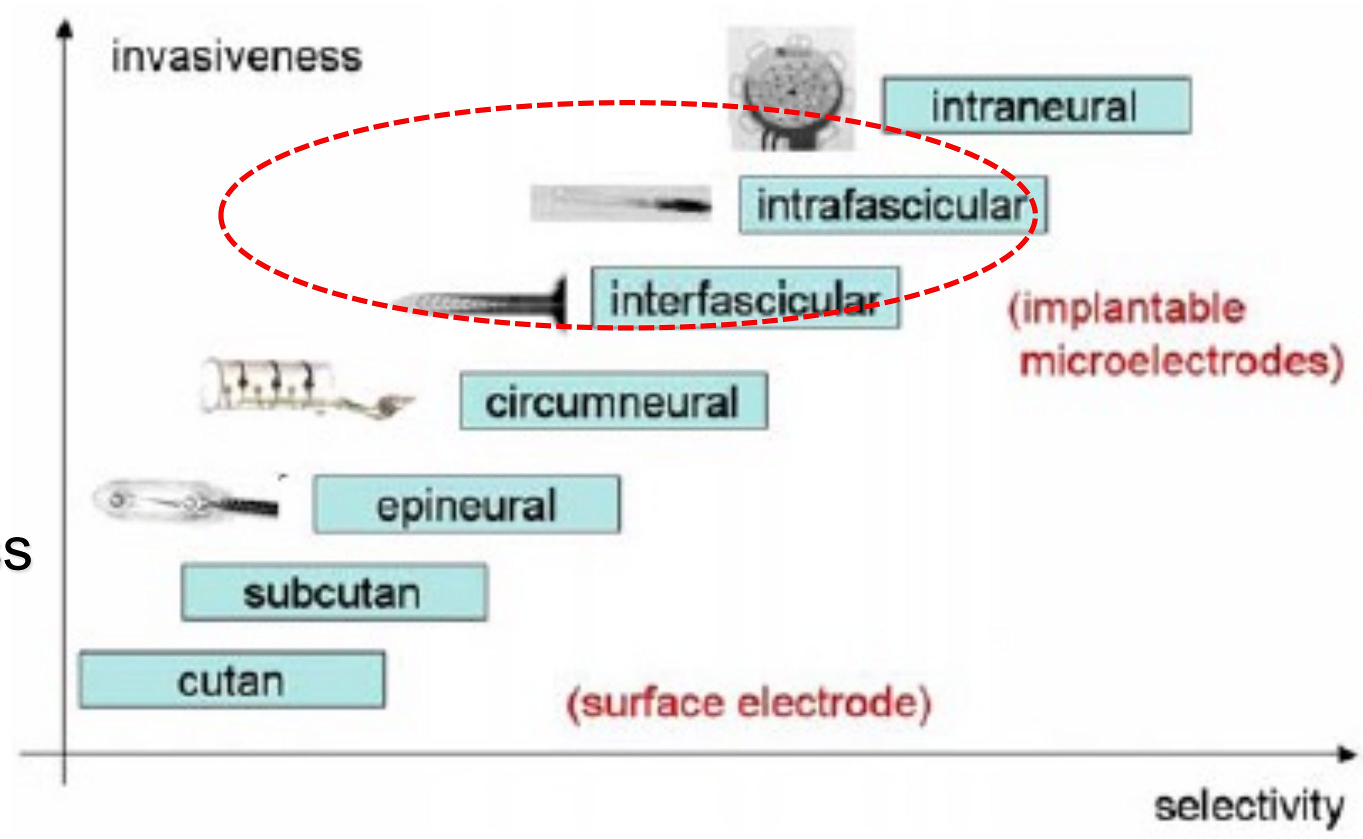
- They can provide an increased selectivity:
  - More channels
  - More “favorable” anatomy
  - Advanced signal processing
- However, the selectivity could sti be limited especially for the delivery of sensory feedback

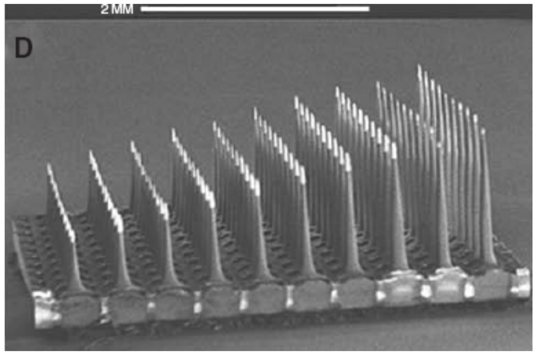




Intraneural (intrafascicular) electrodes

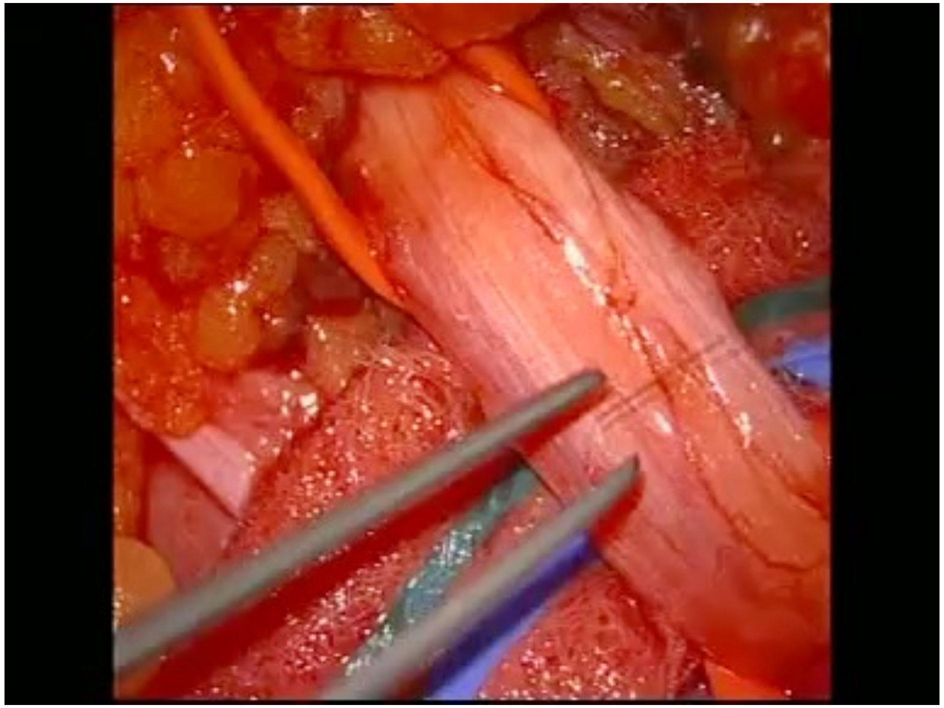
Intraneural electrodes seem to represent a good trade-off between high selectivity and reduced invasiveness

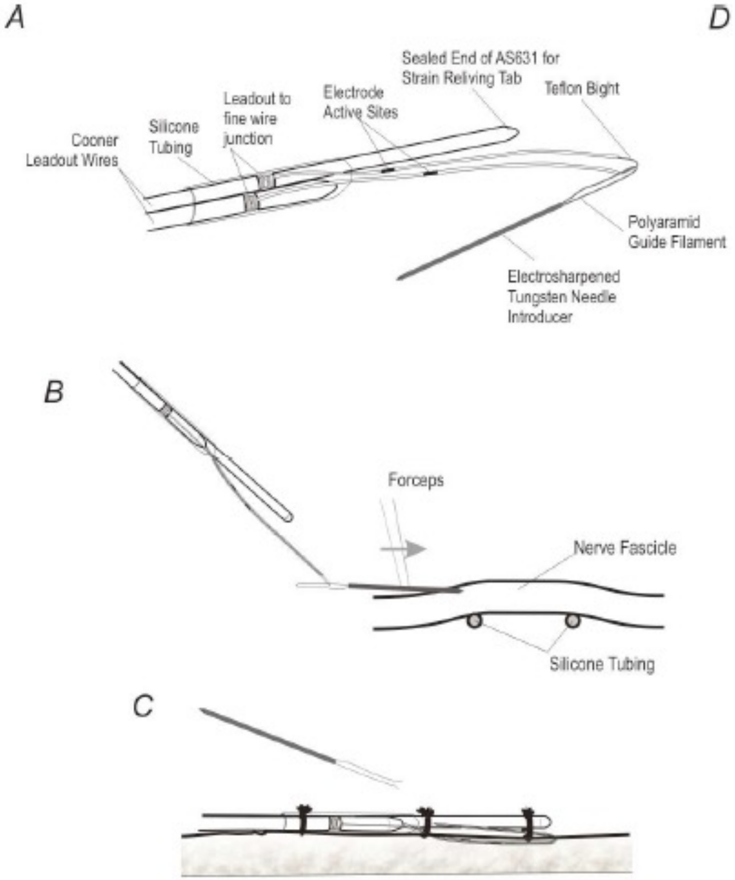




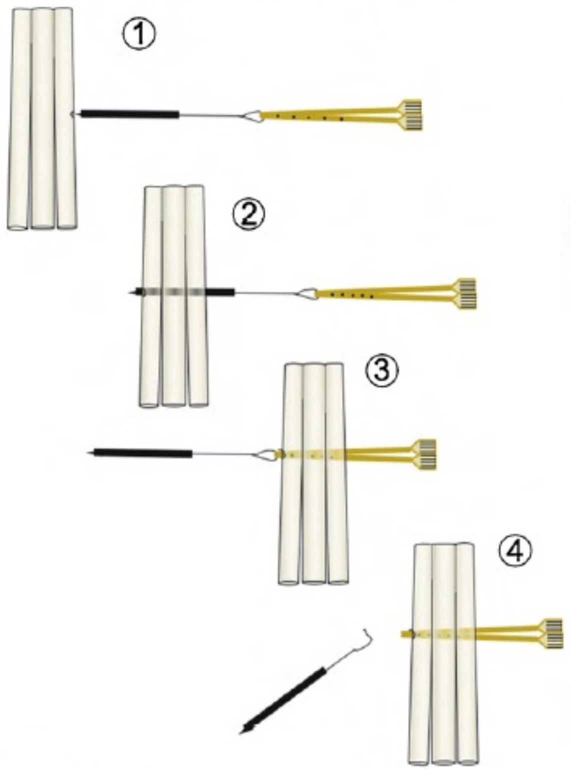
Longitudinal intrafascicular electrodes (LIFEs)

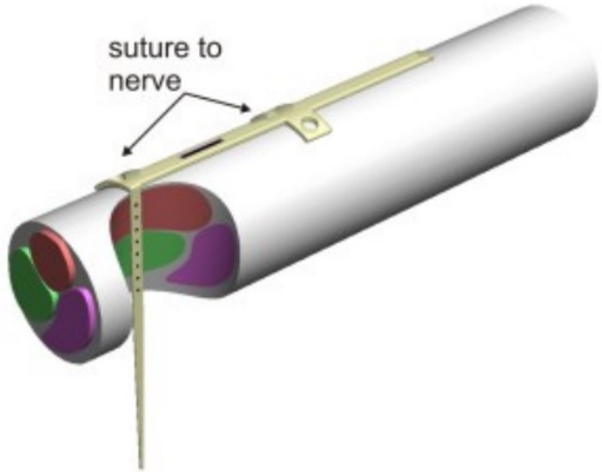
- LIFEs are relatively easy to implant
- Provide a good trade-off between reduced invasiveness and good selectivity

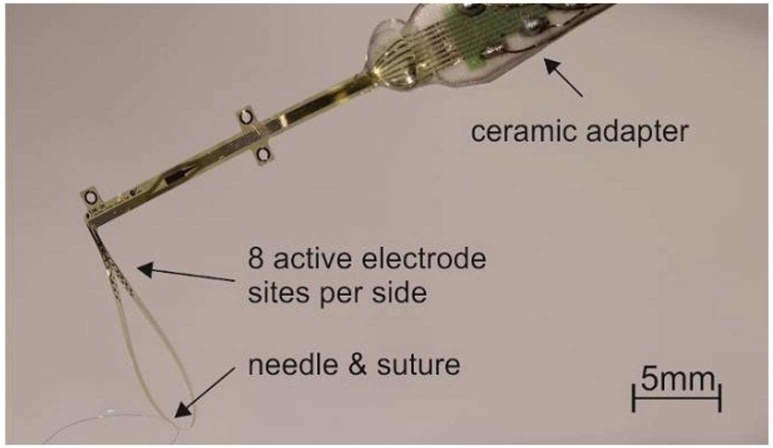


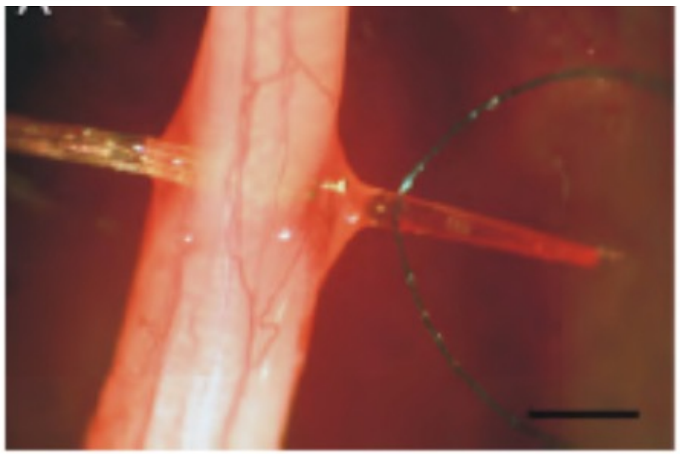


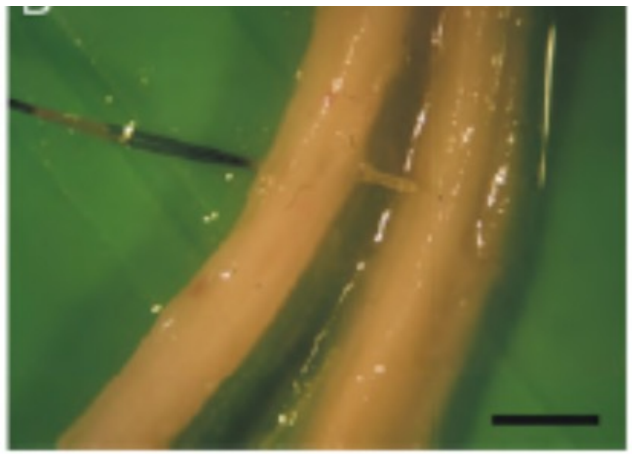
Transveral Intrafascicular Multichannel Electrode (TIME)







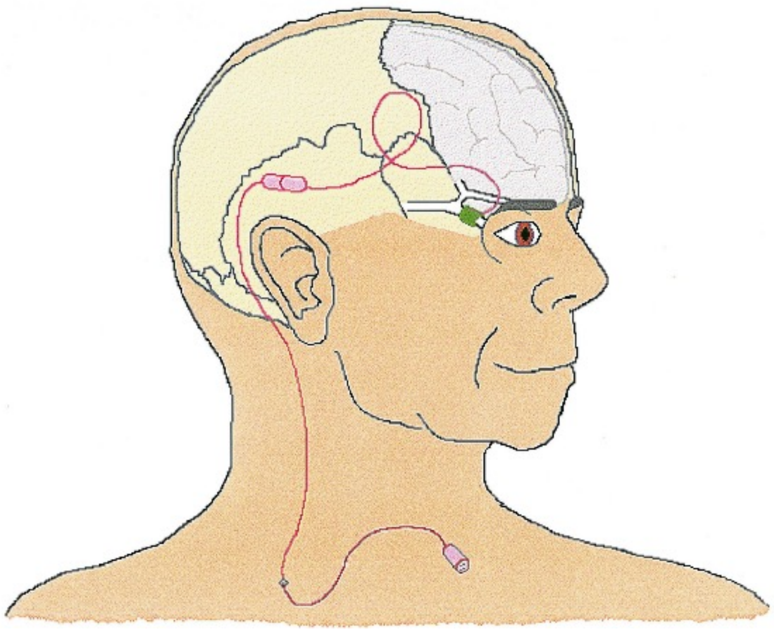




EPFL

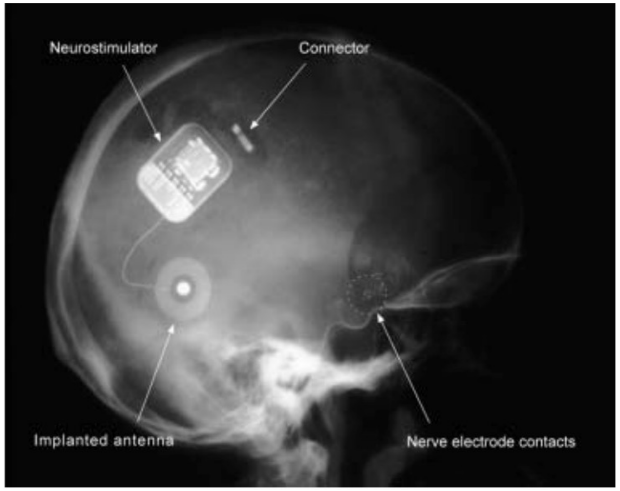
Visual prostheses by stimulating the optic nerve

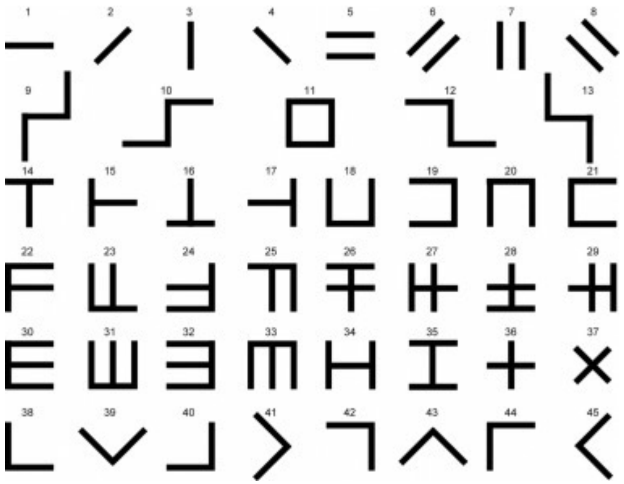
- In blind patients with functional retinal ganglion cells, the optic nerve is an alternative for electrical stimulation
- However, achieving focal stimulation and unravelling the exact retinotopic distribution within it is challenging
- Veraart et al. chronically implanted a self-sizing spiral cuff electrode around the optic nerve in two subjects



OPTIC NERVE-INDUCED PHOSPHENES (VIRTUAL ELECTRODES)

On August 2000, the percutaneous lead was replaced by an implanted stimulator and antenna for telemetry.





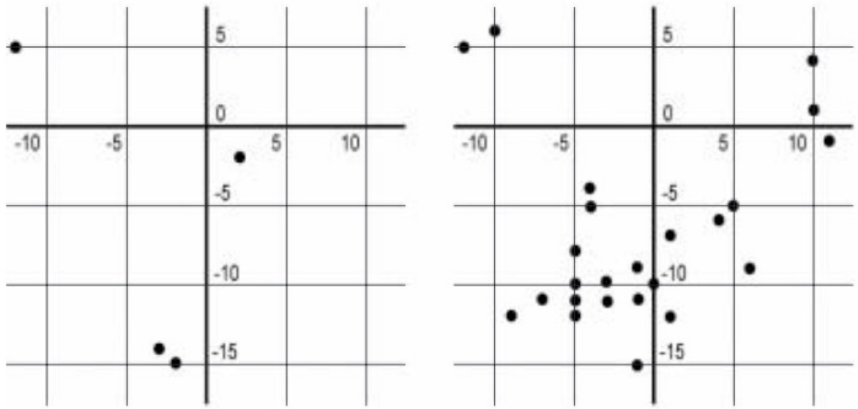
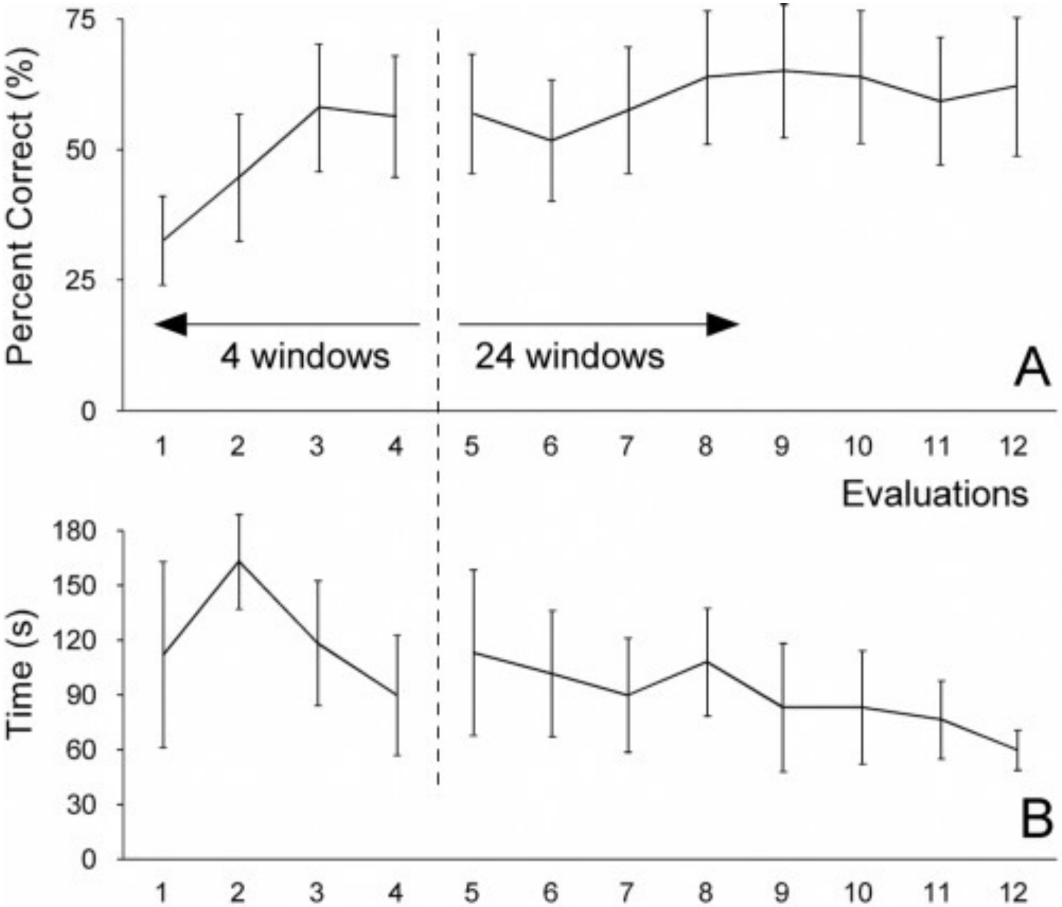


FIG. 3. Visual field mapping with the 4- and 24-window protocols. The figure illustrates mean location of the phosphene center obtained with the four different stimulating conditions selected for the 4-window protocol (left image, from top to bottom: cathodic contacts 270°, 0°, 180°, and 90°; in each case, monopolar stimulation with trains of seven pulses of 21 µs at 160 Hz; pulse amplitude ranges from 279 to 644 µA) and with the 24 different stimulating conditions selected for the 24-window protocol (right image; most stimulating conditions were bipolar, either between opposite contacts or between adjacent contacts; trains of 21-µs pulses at 250 Hz were used; pulse number ranged from 2 to 10, and pulse amplitude from 253 to 427 µA for monopolar stimulation, or from 279 to 1519 µA for bipolar stimulation). Visual field coordinates are provided in degrees of arc.

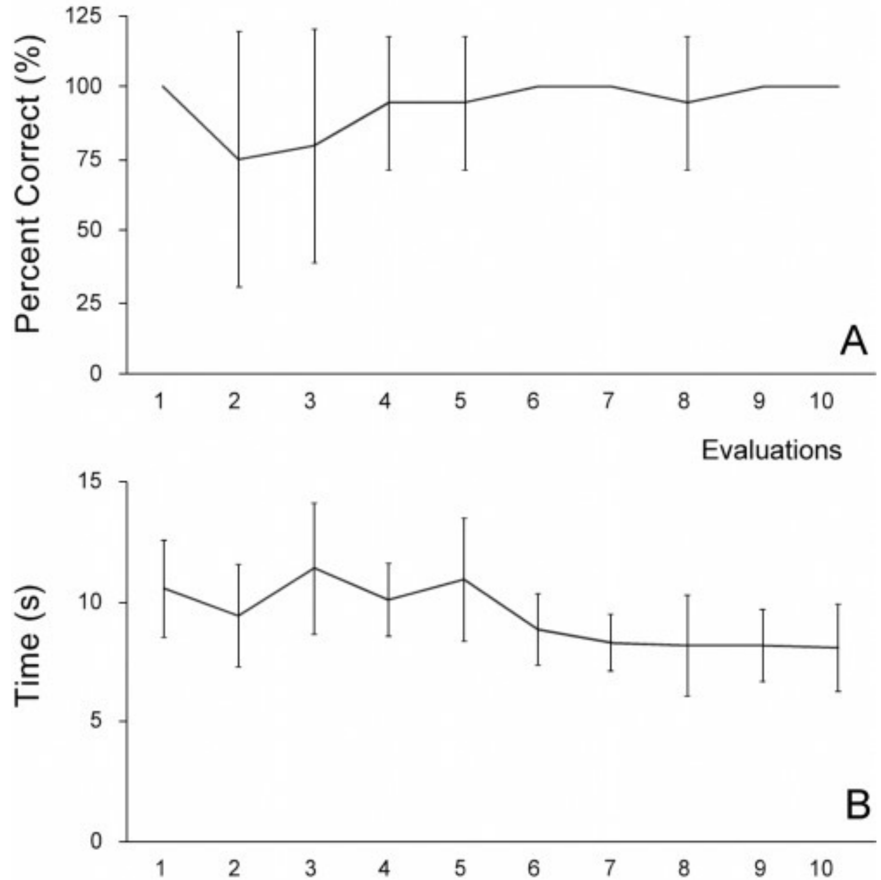
Veraart et al., Artificial Organs 2003

PERFORMANCE WITH OPTIC NERVE-INDUCED PHOSPHENES

Pattern recognition



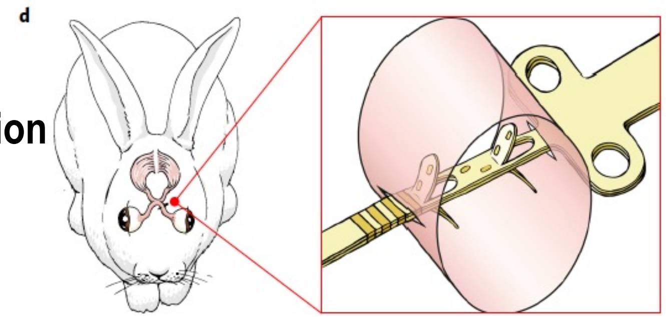
Orientation discrimination

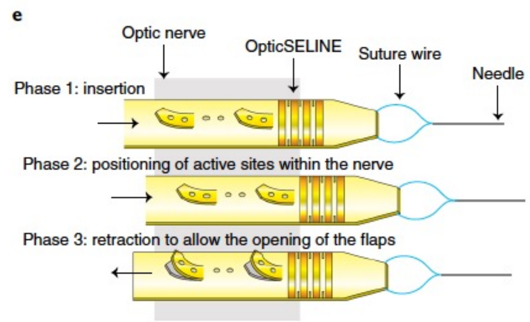


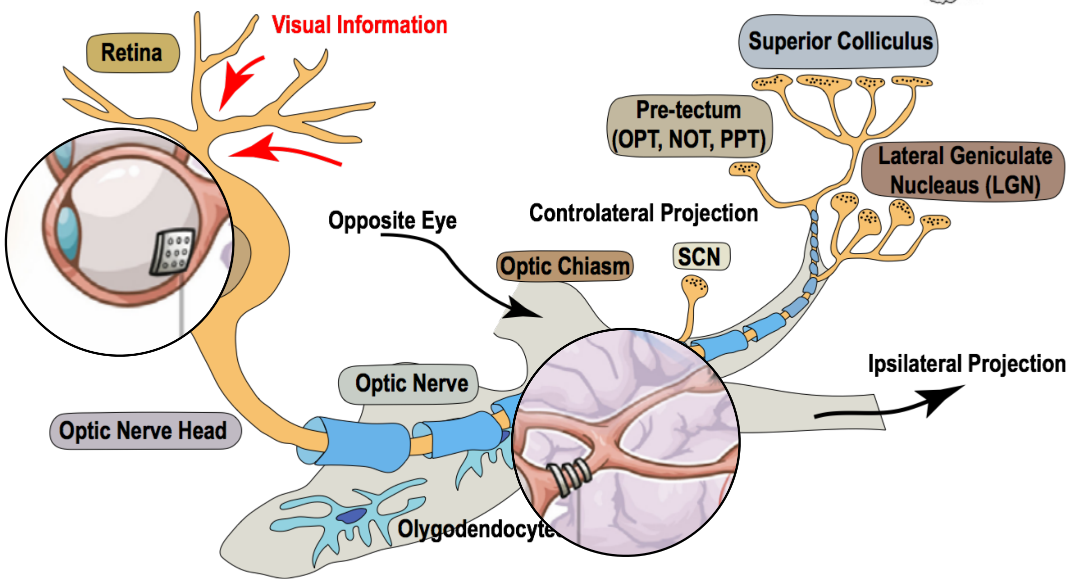
Veraart et al., Artificial Organs 2003

Optic nerve stimulation using intraneural electrodes

- Mechanical stability
- Mechanical mis/match
- Threshold of activation
- Space compression
- Synaptic circuits

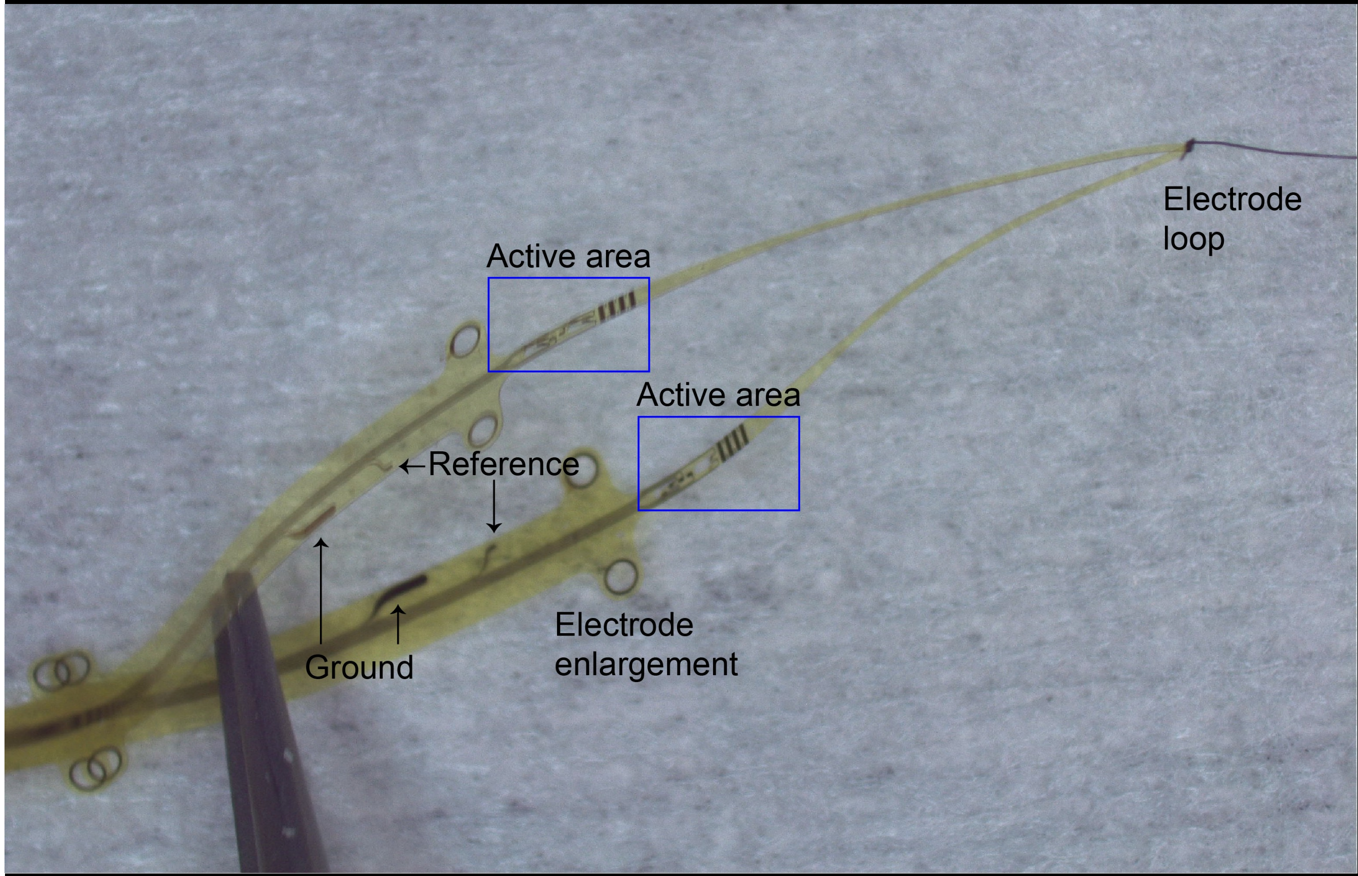


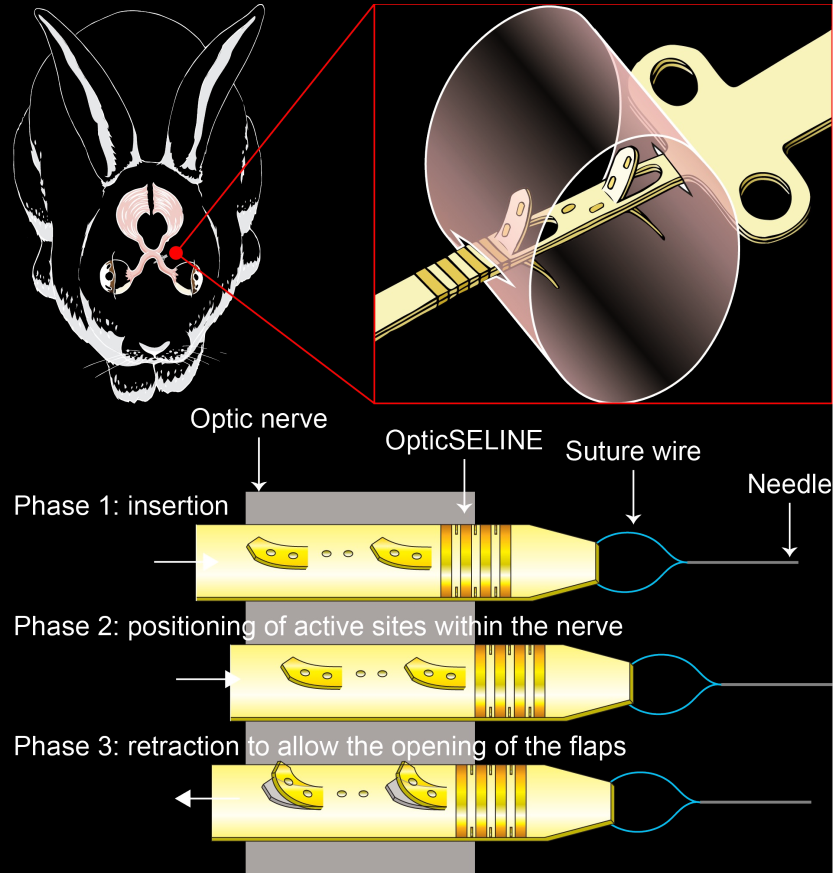




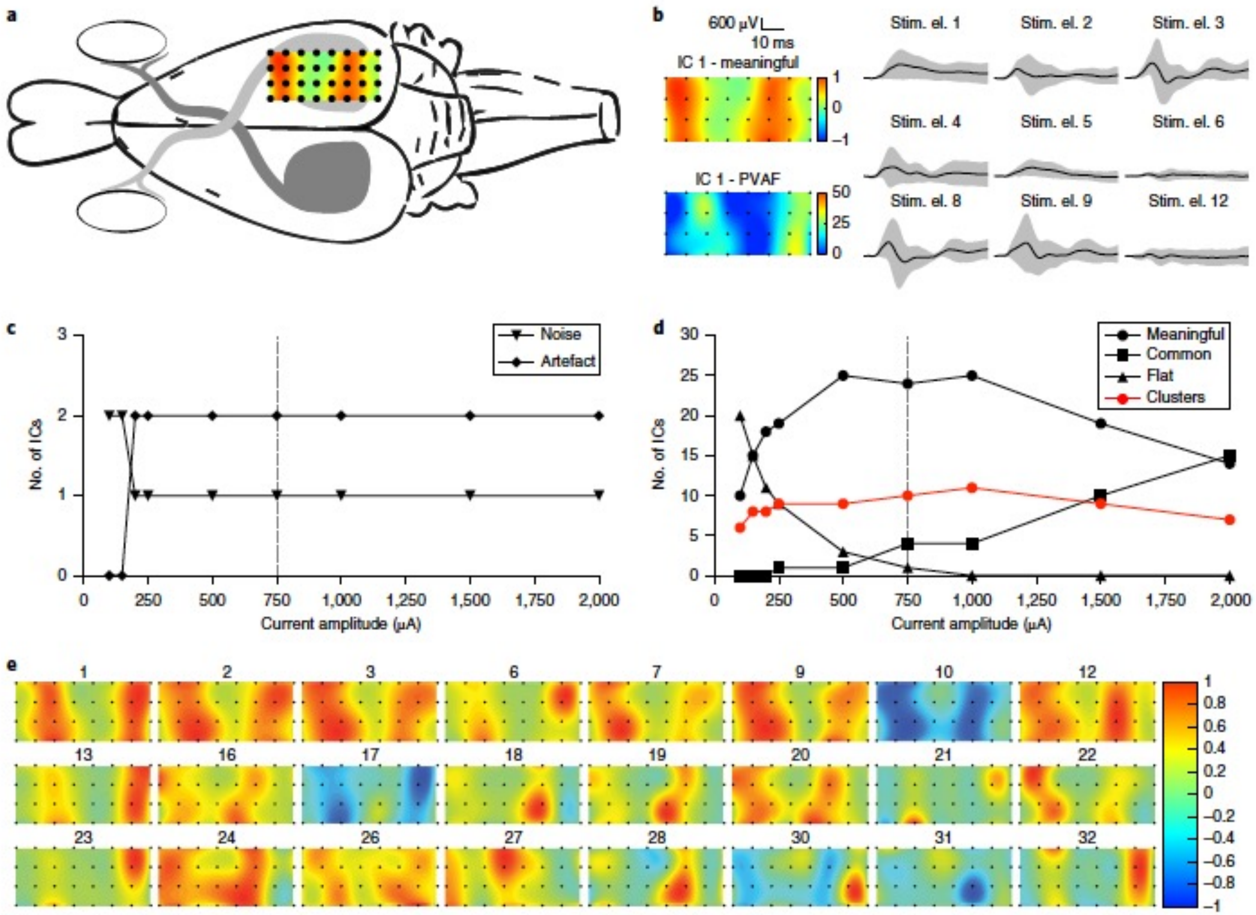
The 3D arrangement of electrodes allows the targeting with a single shank both the central part and the four surrounding quadrants; thus covering the entire visual field

OPTICSELINE





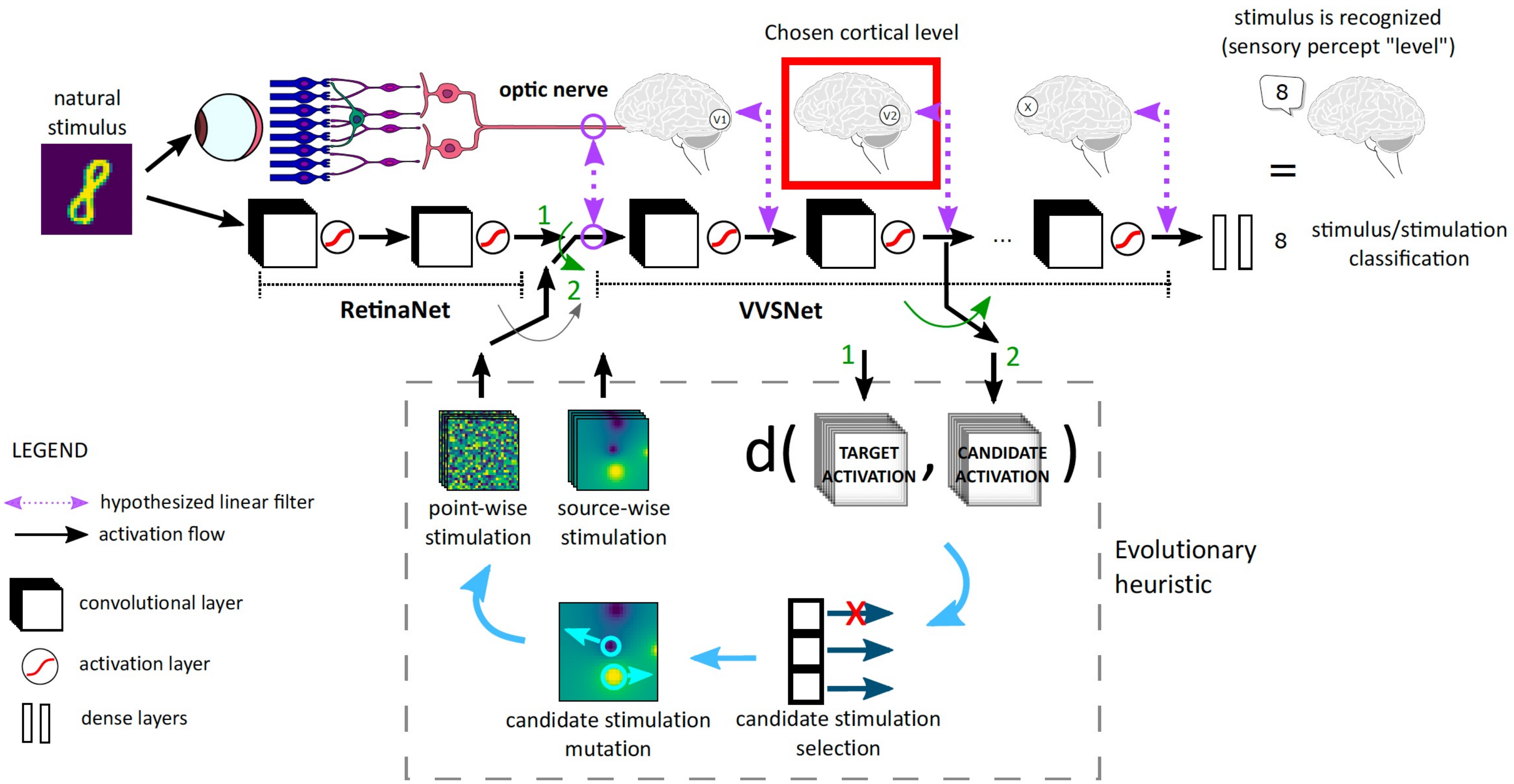
Optic nerve stimulation using intraneural electrodes



- Gaillet et al., Nature BME, 2020

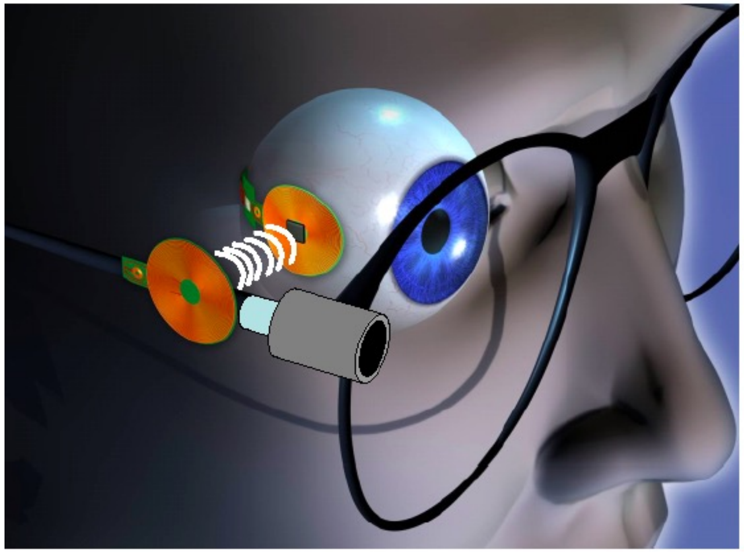
EPFL fondation bertarelli Sant'Anna Scuola Universitaria Superiore Pisa

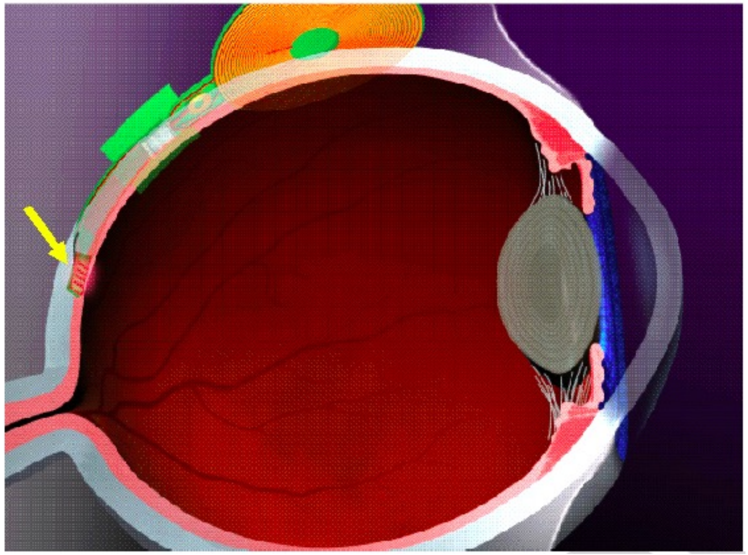
Optic nerve stimulation using intraneural electrodes



Romeni et al., Patterns, 2021

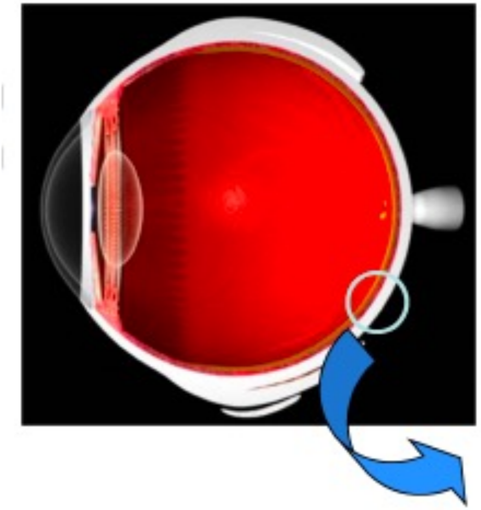
Visual prostheses based on electrical stimulation at the retina

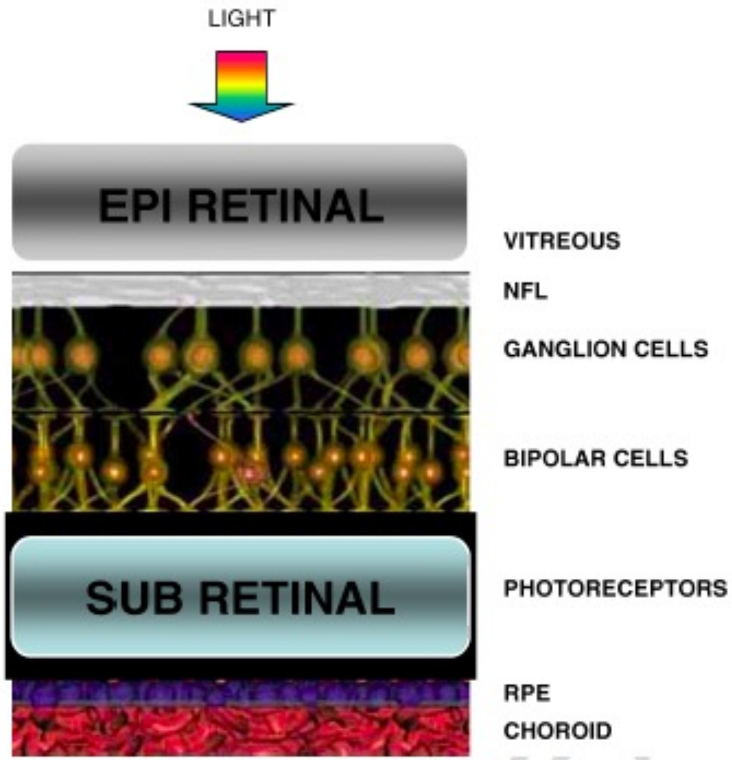


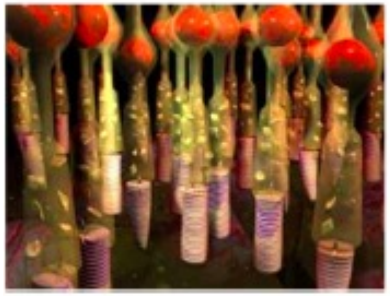


- The image obtained by an external camera is translated into an electromagnetic signal that is transmitted wirelessly to the implanted secondary data coil attached to eye. Power is transmitted similarly
- Essentially the entire volume of the implant lies outside the eye. (Right) This perspective reveals that only the electrode array (arrow) penetrates the wall of the eye.

Retinal visual prostheses



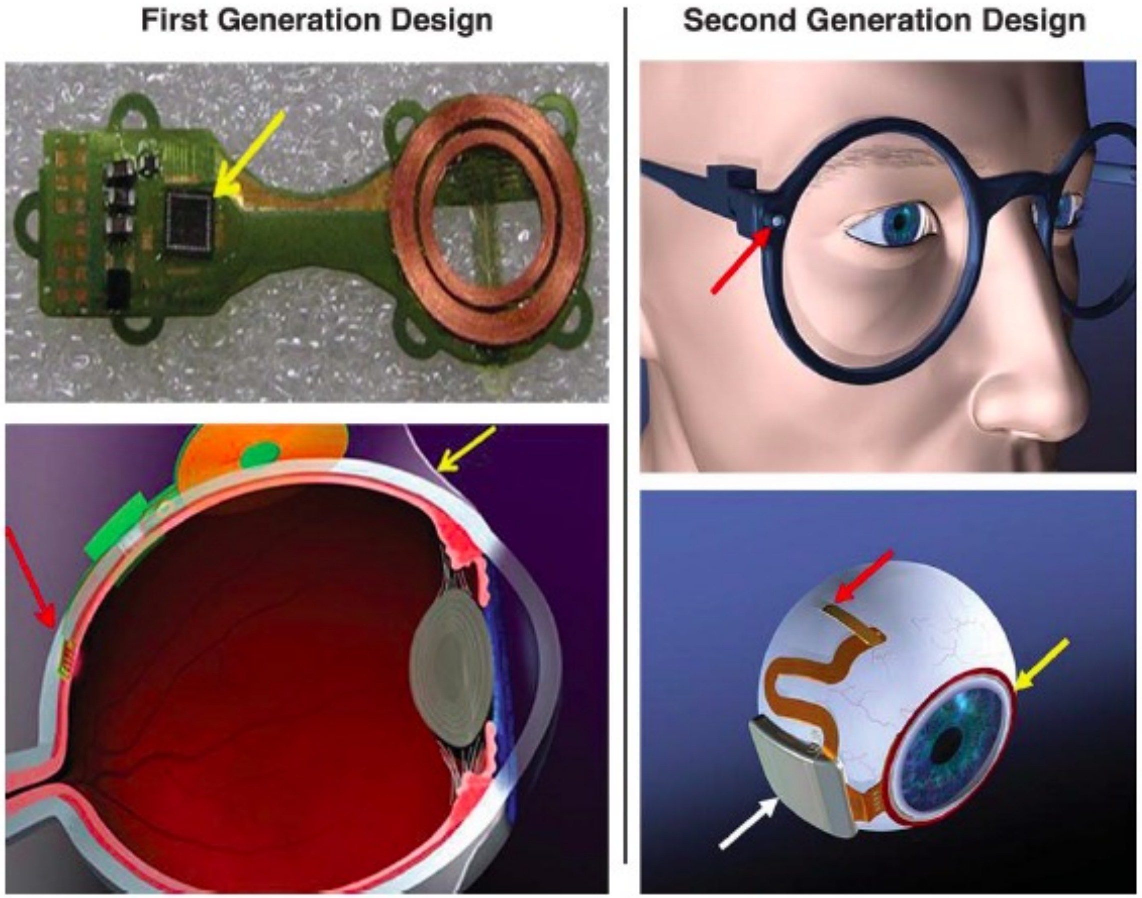




Retinal visual prostheses

- Retinal devices based on this platform have been developed by three groups
  - USC/Second Sight (Sylmar, CA, USA)
  - Intelligent Medical Implants (Bonn, Germany)
  - the Harvard Medical School/Massachusetts Institute of Technology/Veterans Administration consortium (Boston, MA, USA)
- The Second Sight and Intelligent Medical Implant devices target epi-retinal implant locations, whereas the Harvard/MIT/VA device targets a sub-retinal implant location

Sub-retinal MEA prostheses



Sub-retinal MEA prosthesis - GOALS

- Minimize disruption of the anatomy of the eye
- Use a minimally invasive surgical method to implant the device (?)
- Minimize the amount and sophistication of the electronic components implanted into the eye and orbit
- Use an ultrathin flexible substrate that can bend to match the contour of the ocular tissues
- Use wireless technology to provide a functional connection between the external and the implanted components
- Increase the number of stimulation sites
- Use means to individually control and to individually adjust the stimulation parameters to each electrode based on patient feedback

Sub-retinal MEA prosthesis

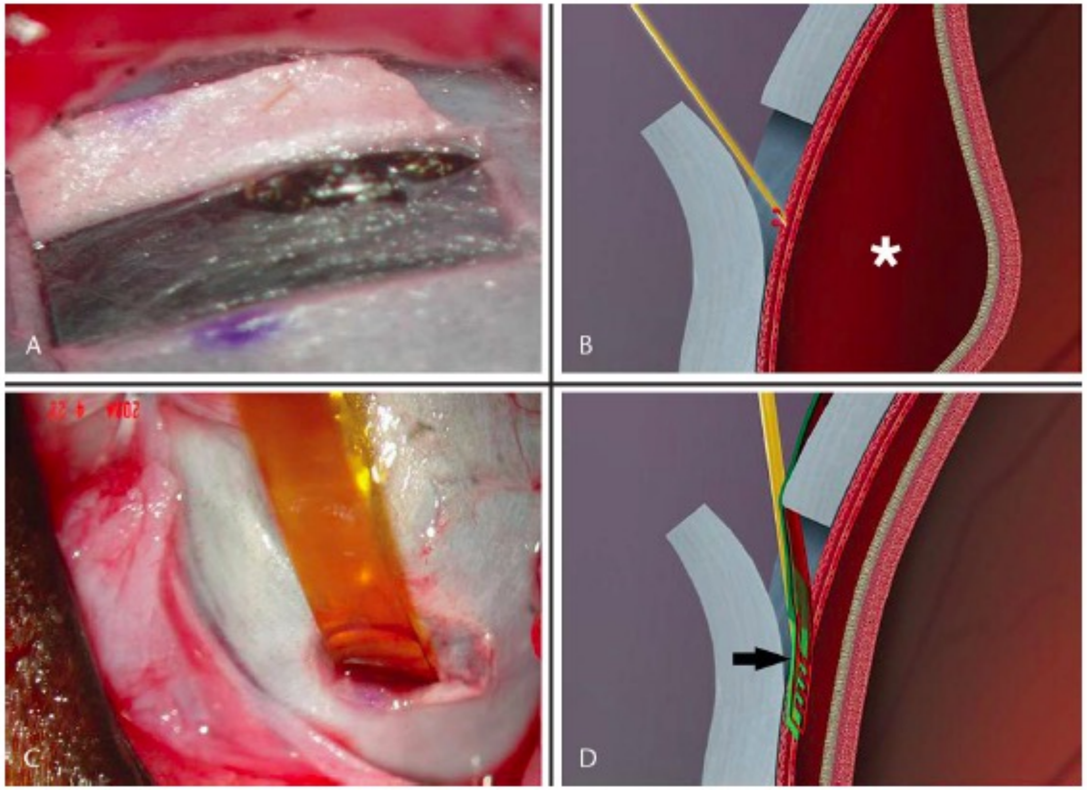
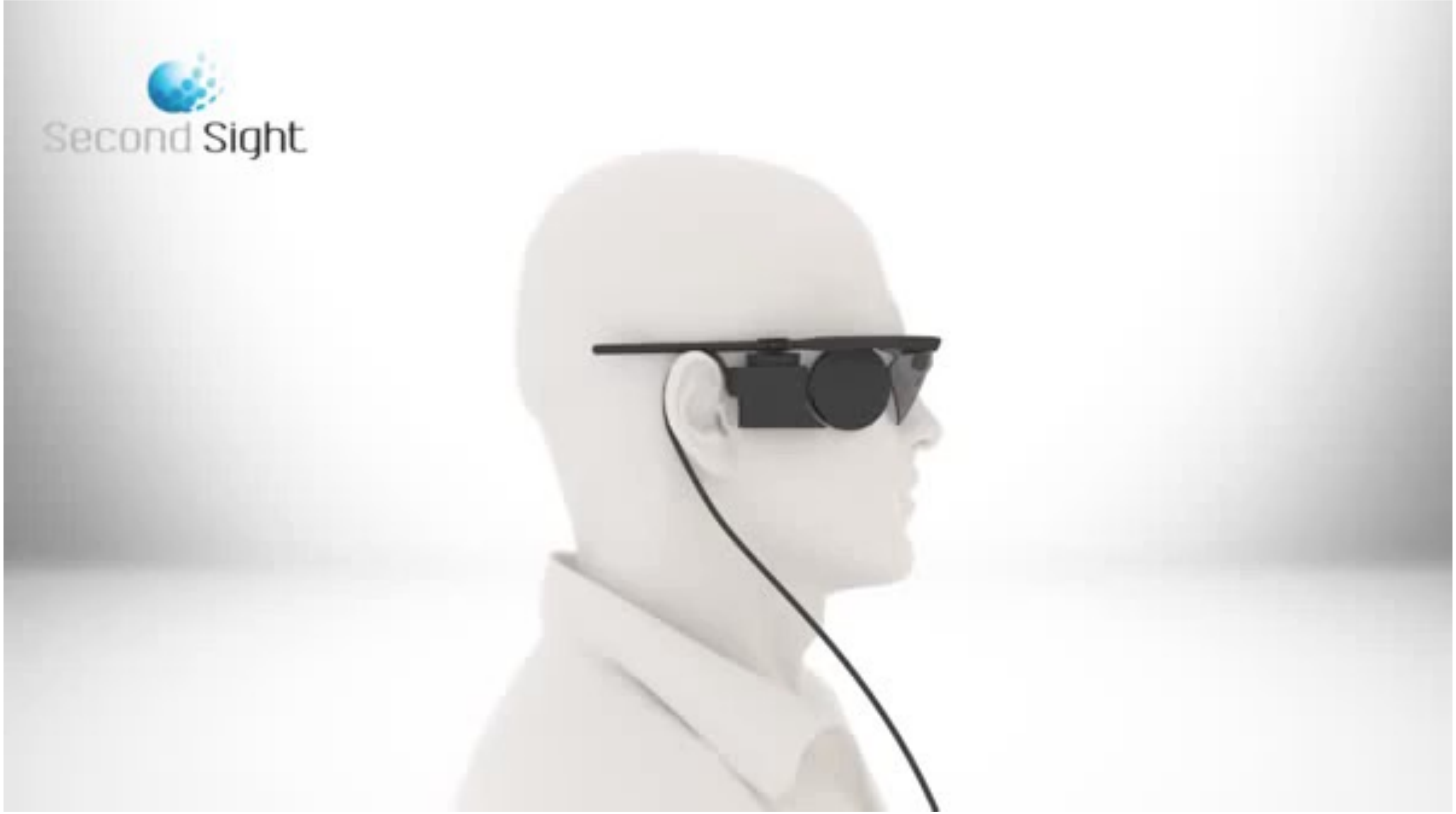
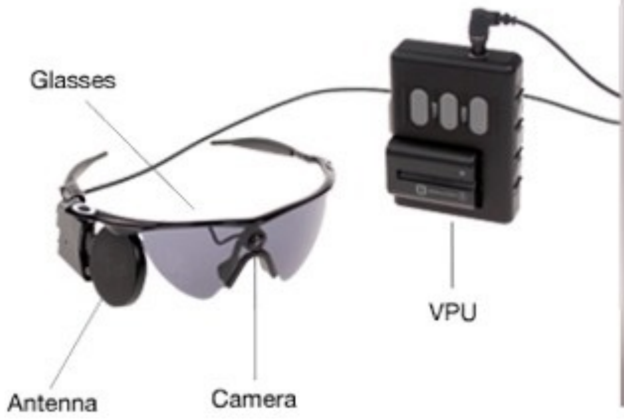


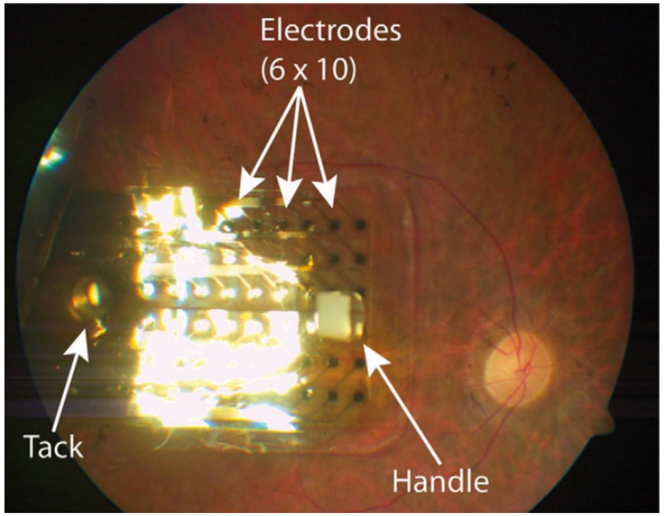
FIG. 2. Pictorial overview of our ab externo surgical approach. **A.** Creation of a scleral flap through the back wall of the eye. **B.** Raising of a retinal bleb (*asterisk*) by injecting fluid under the retina. The elevated bleb serves to reduce the potential of retinal damage when the electrode array is inserted. **C.** Insertion of a custom surgical tool (yellow membrane) that serves as a guide for the subsequent insertion of the electrode array. **D.** Digital image of the insertion of the electrode array (*arrow*) through the scleral flap and under the retina, which has returned to its original position.

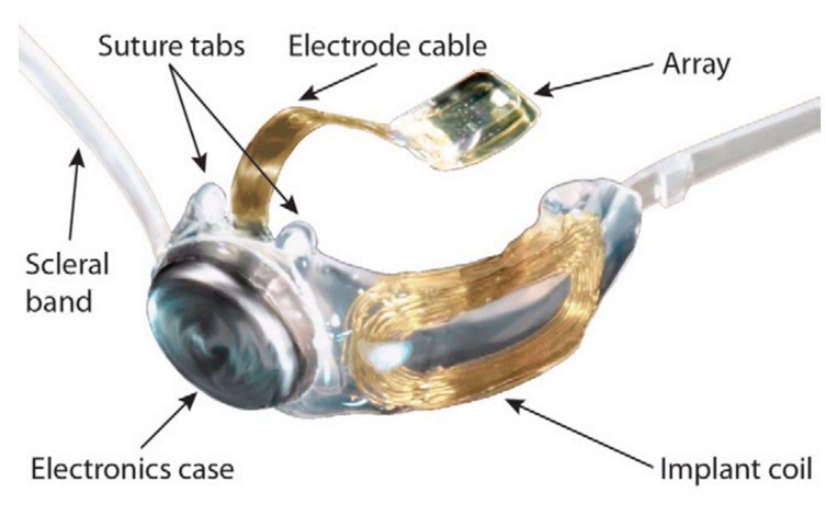
ARGUS II™

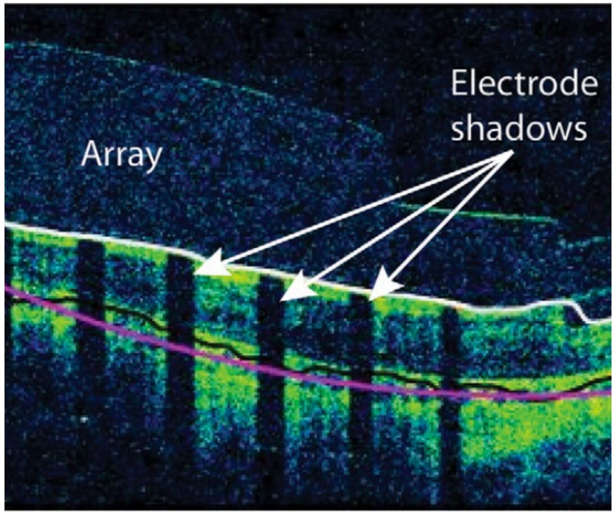


ARGUS II™





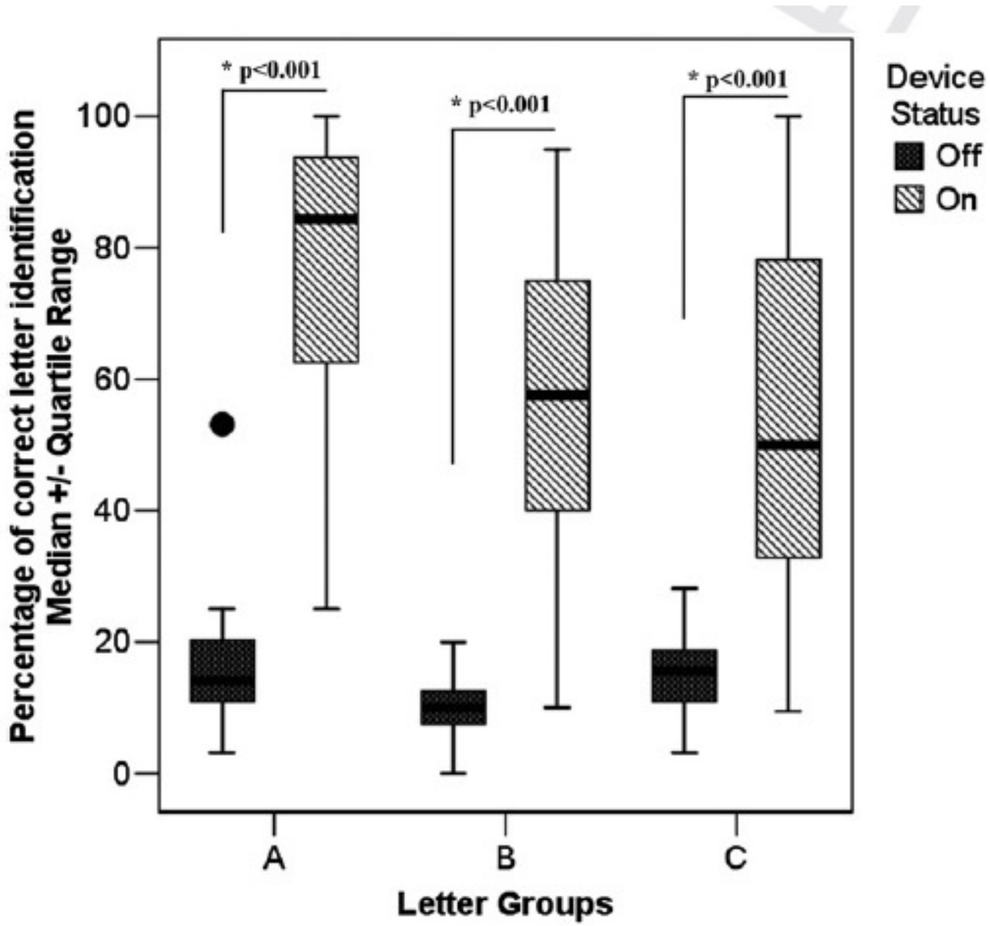




Humayun MS et al., Ophtalmology 2012

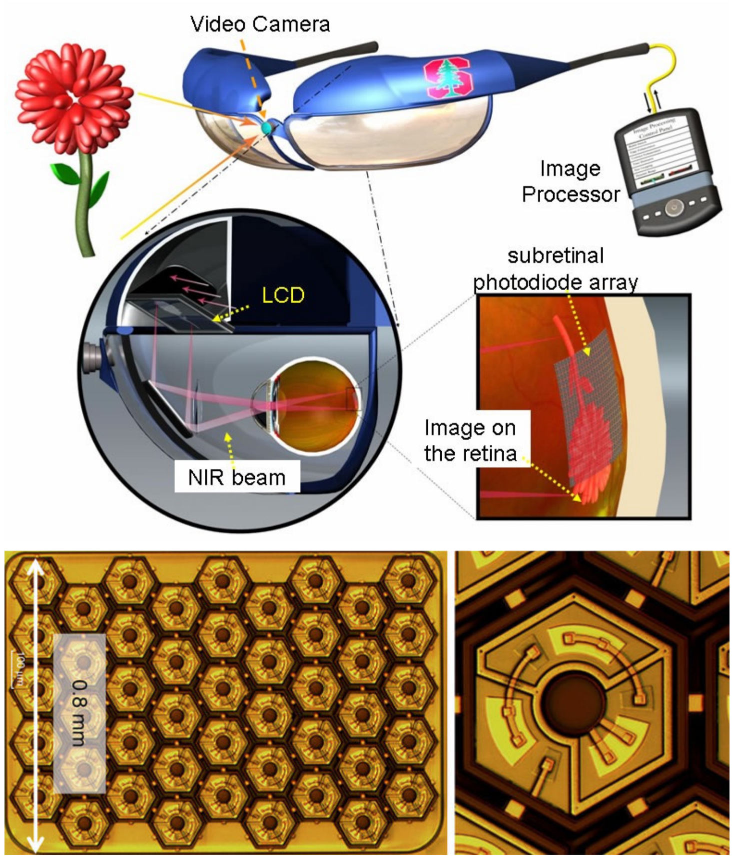
An example of a blind subjected implanted with the Argus II System correctly identifying letters in a high-contrast closed-set test. The camera's field of view and individual electrode inputs are observed on the laptop screen on the bottom right of the movie.

Epi-retinal MEA prosthesis (ARGUS II)



LIGHT-BASED PROSTHESES

Photovoltaic

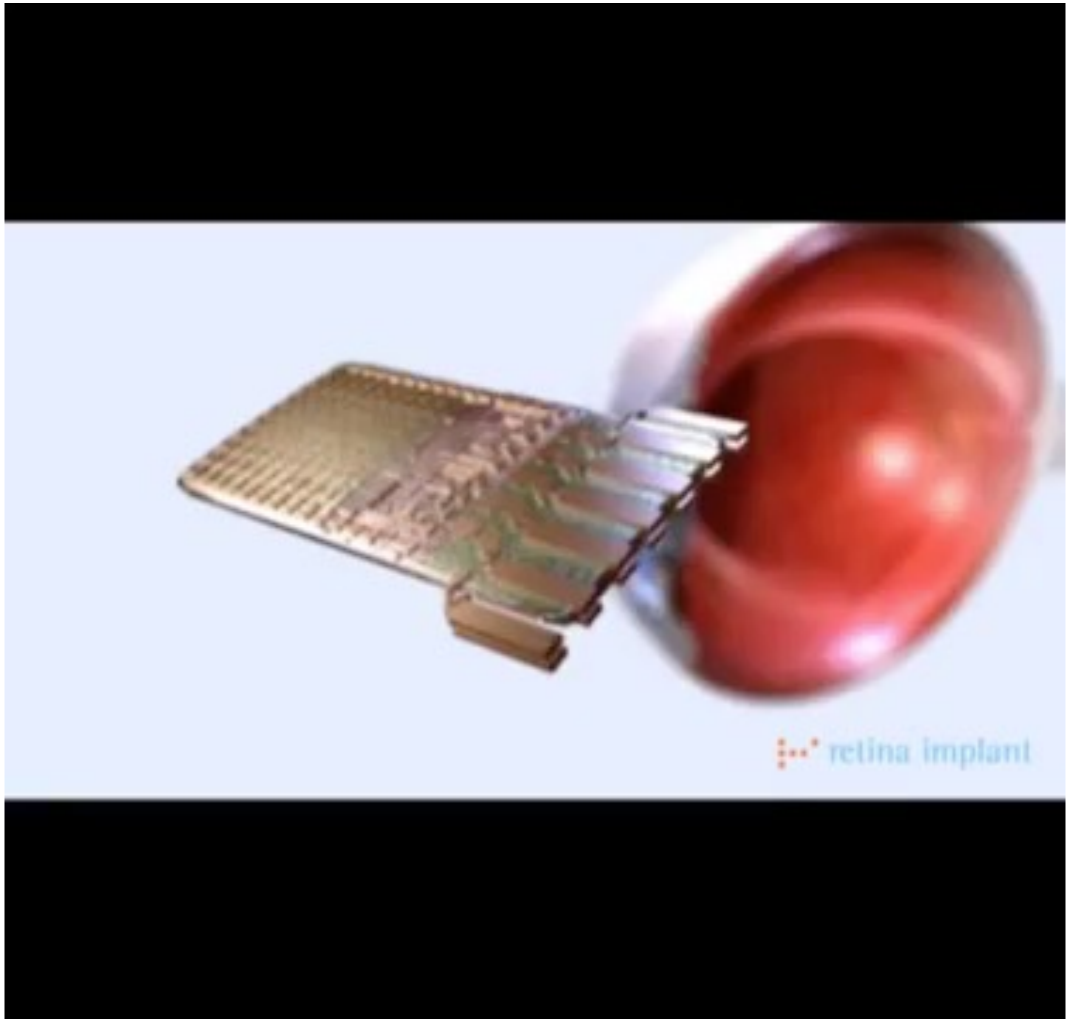


Active MPDA

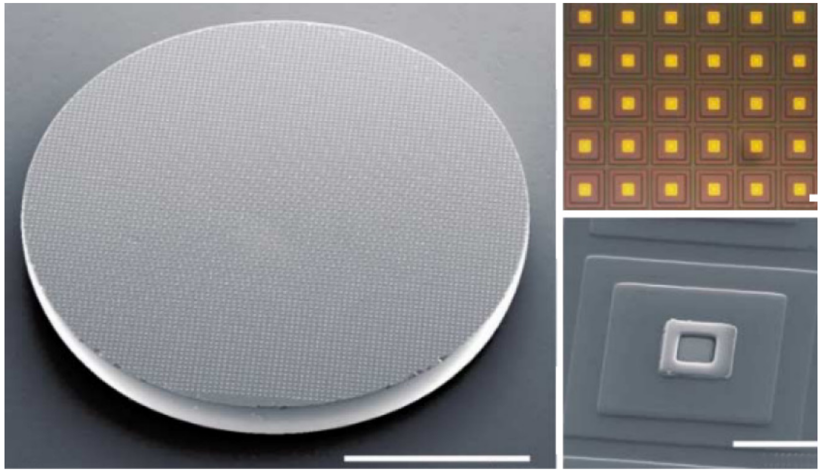
Mathieson et al., Nat Phot 2012 / Pixium Vision

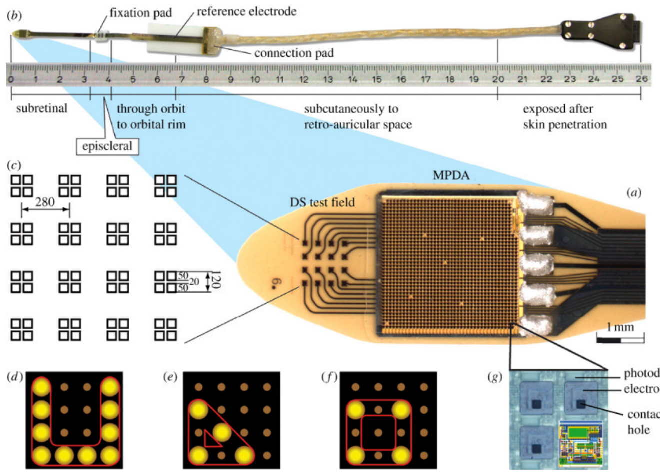
Retinal Implant AG

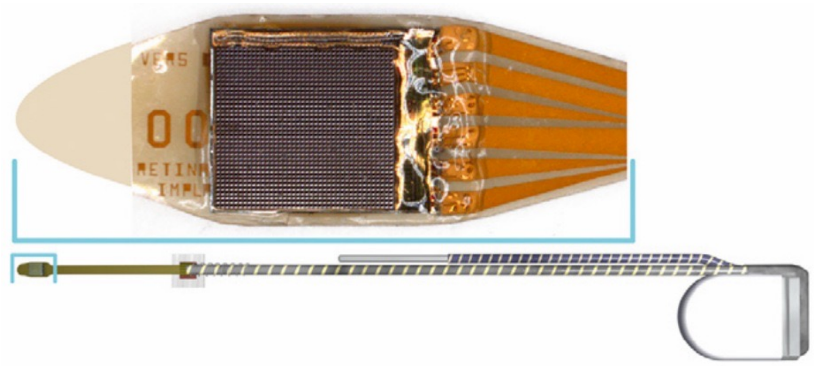
RETINAL IMPLANT AG

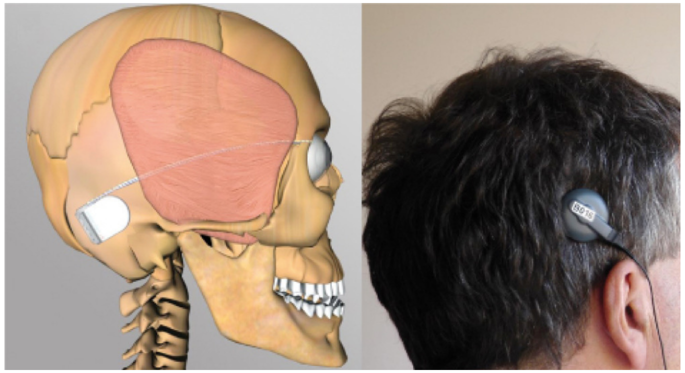


RETINAL IMPLANT AG







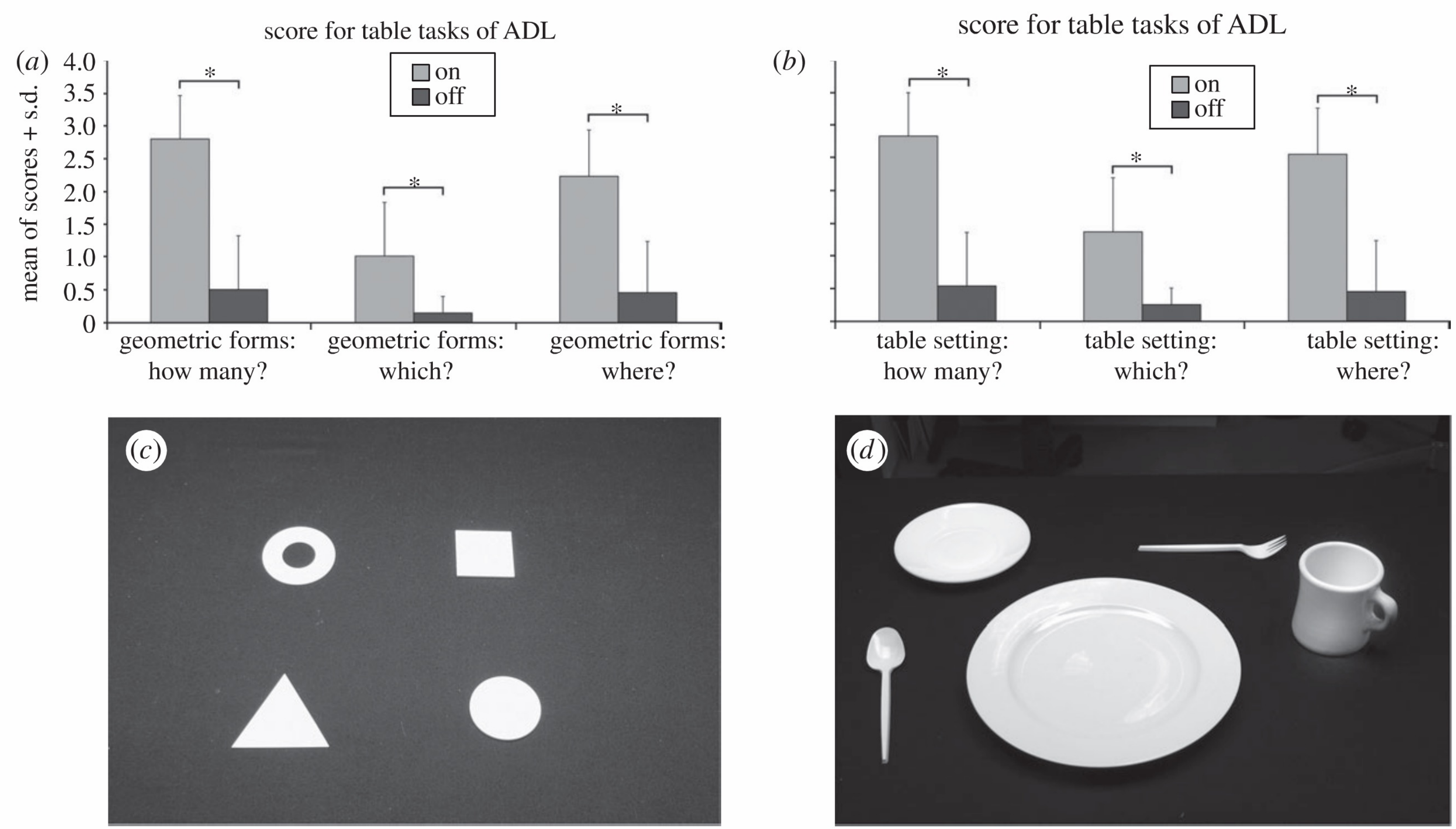


Zrenner E, Ophtalmologica 2002

Zrenner E et al., Proc R Soc B 2011

Stingl K et al., Clin Exp Optom 2013

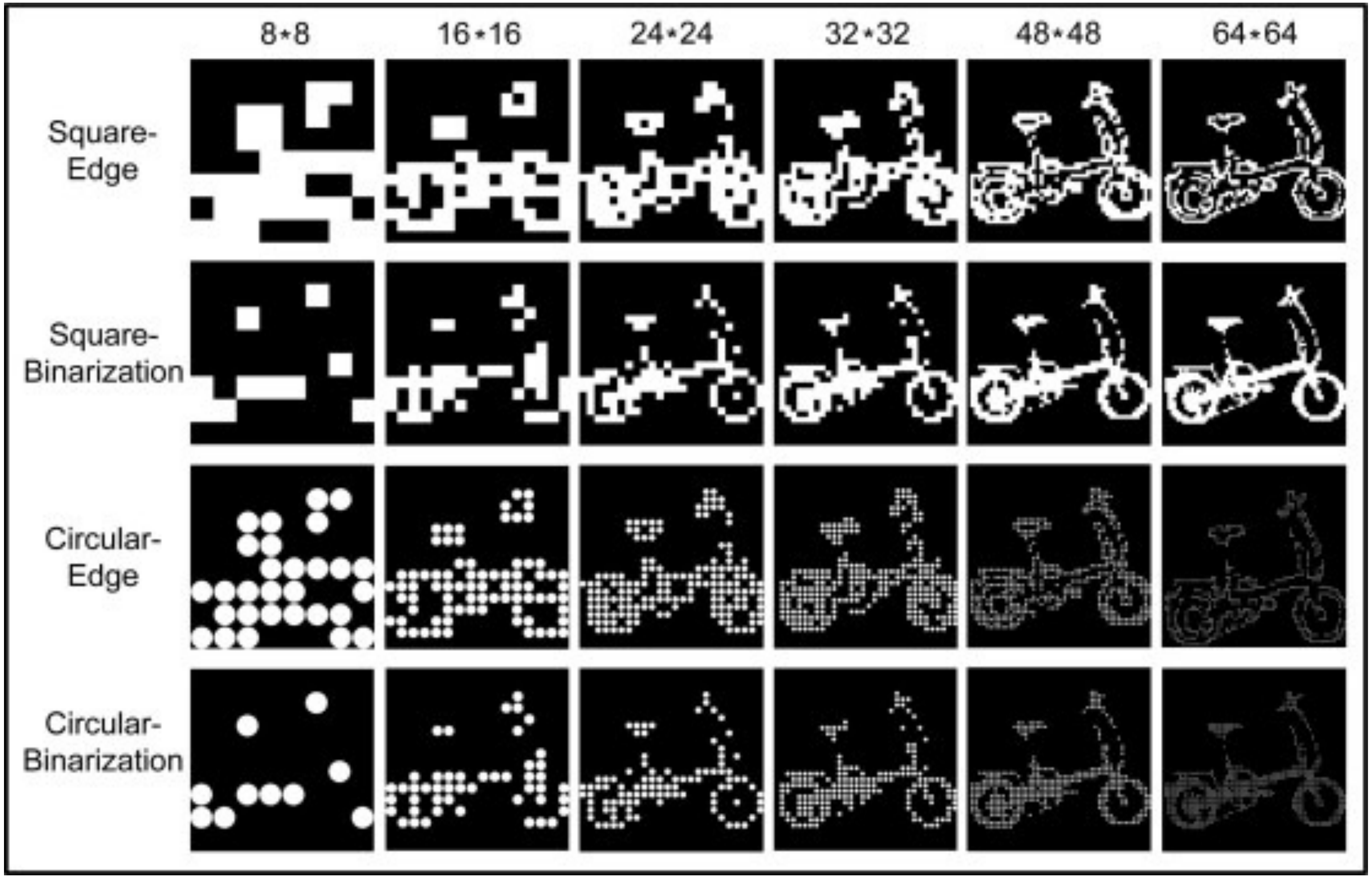
RETINAL IMPLANT AG



Stingl K et al., Proceedings of the Royal Society B 2013

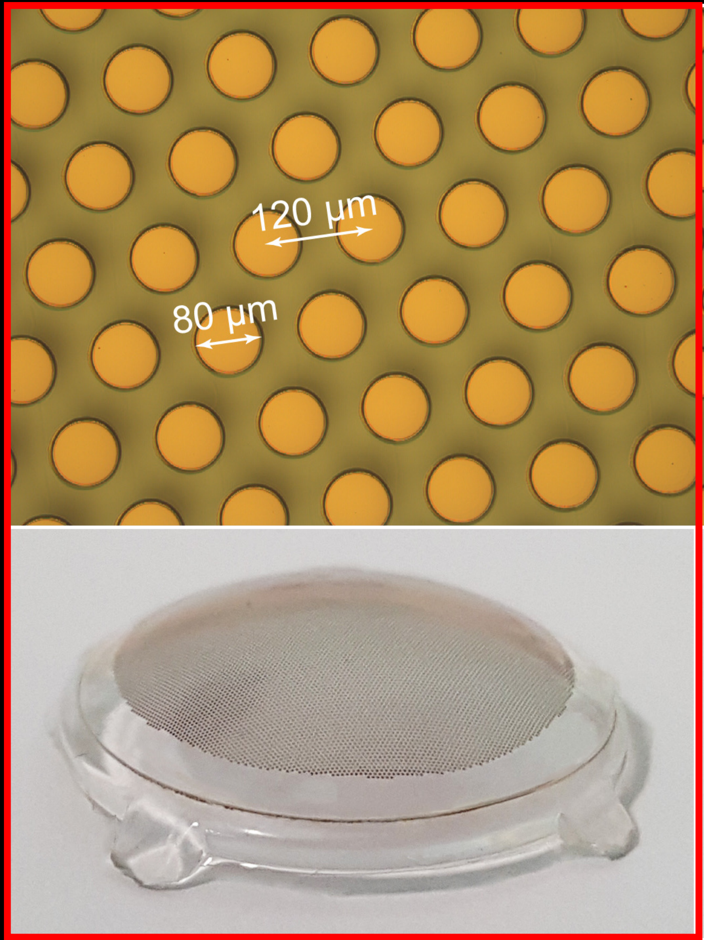
DESIGN OF PHOTOVOLTAIC IMPLANTS

IMPACT OF PIXEL DENSITY



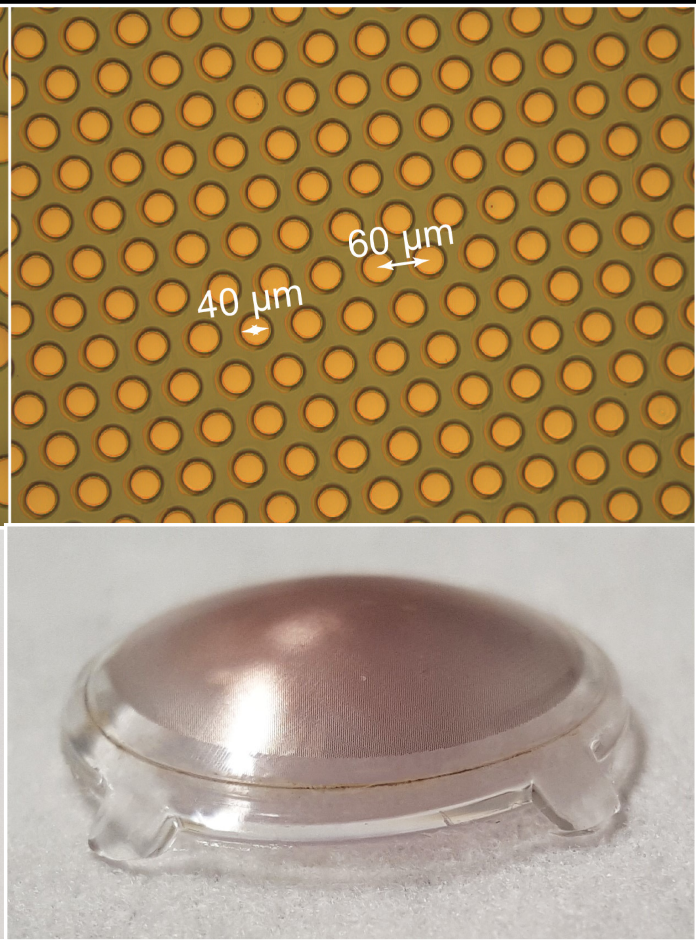
POLYRETINA LAYOUTS

Polyretina β: 10,498 pixels

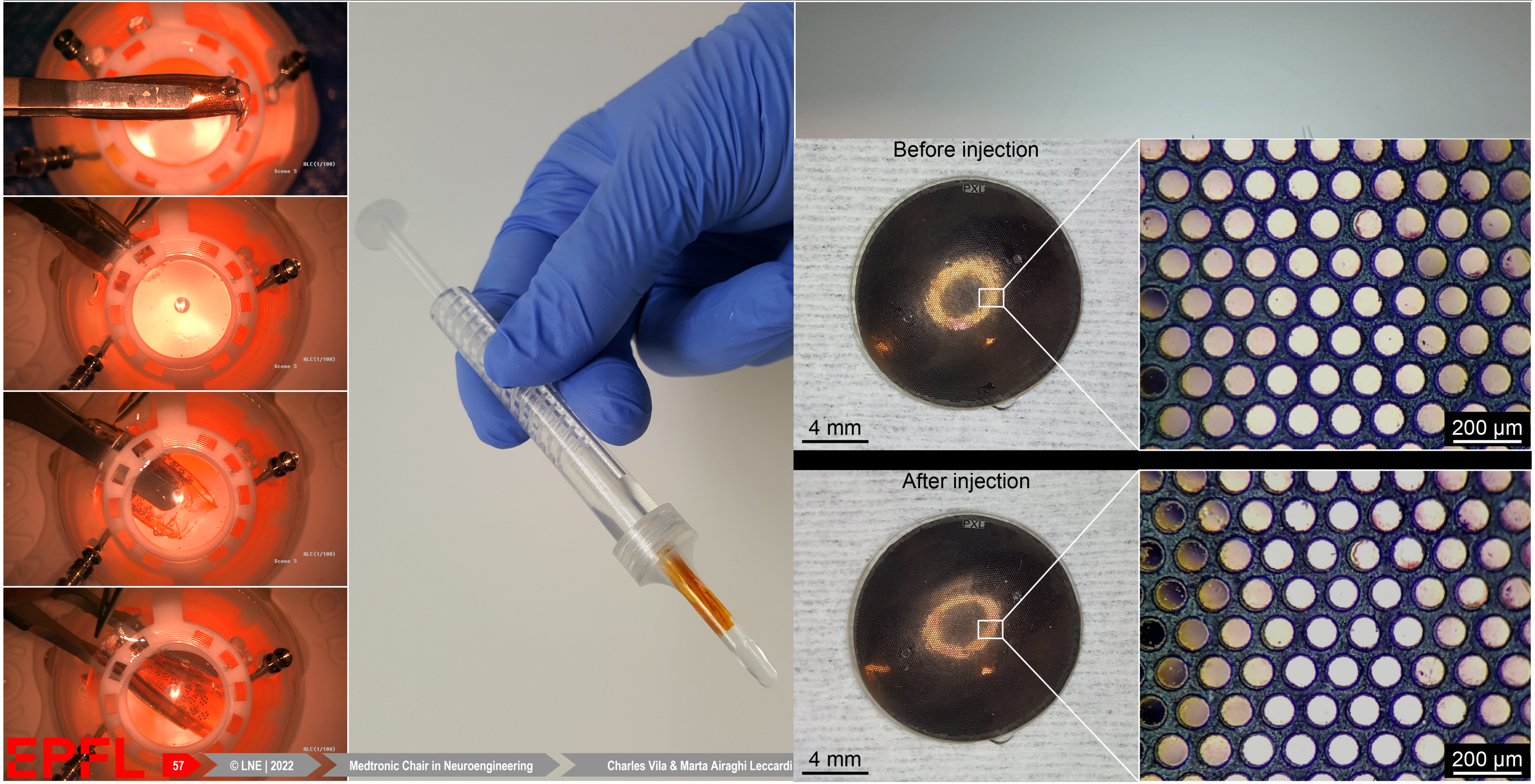


Polyretina γ: 18,693 pixels

Polyretina δ: 42,235 pixels



INJECTABLE PROSTHESIS

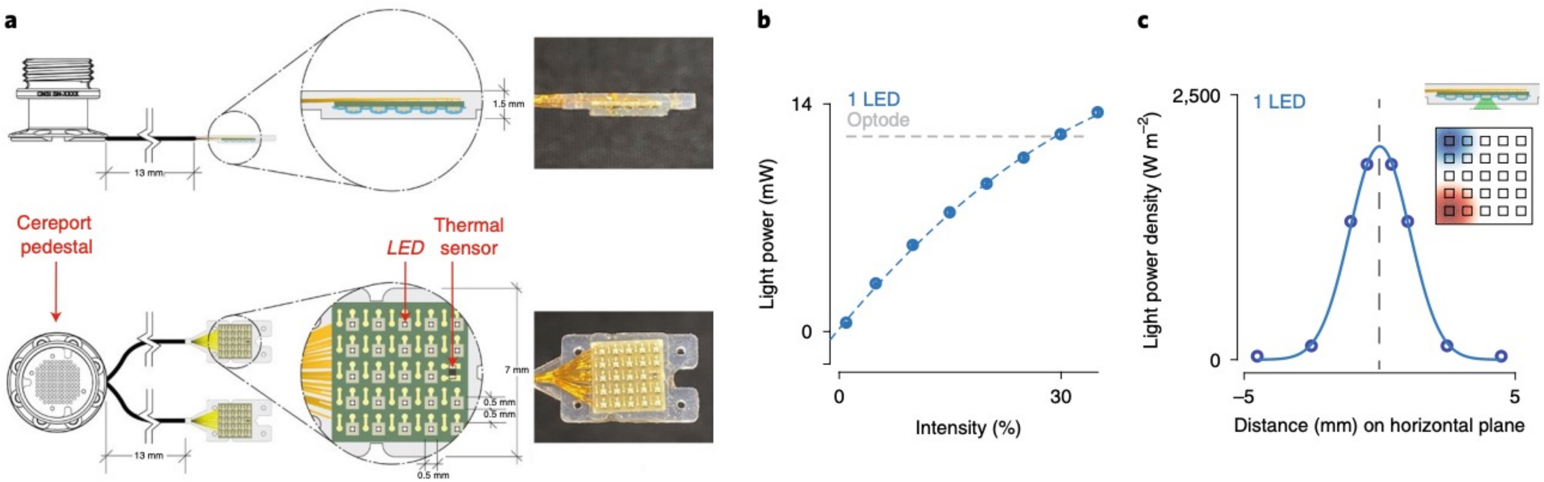


Optogenetics

ARTICLES
https://doi.org/10.1038/s41592-021-01238-9
nature methods
Check for updates

Chronically implantable LED arrays for behavioral optogenetics in primates

Rishi Rajalingham[1,2], Michael Sorenson[3], Reza Azadi[4], Simon Bohn[4], James J. DiCarlo[1,2,3,5] and Arash Afraz[4]



- The Opto-Array (Blackrock Microsystems) is a chronically implantable array of LEDs
- This tool harnesses the advantages of optogenetics but offers three additional advantages
  1. the chronic nature of this tool enables stable experimental perturbation of the same neural population over time
  2. the two-dimensional (2D) matrix array configuration of LEDs enables the flexible perturbation of a large cortical region at fine resolution
  3. It provides a safe alternative to acute methods as well as direct illumination methods, minimizing the tissue damage that results from inserting large optical fibers into the cortical tissue, as well as the risk of infection associated with open cranial windows and chambers.

EPFL

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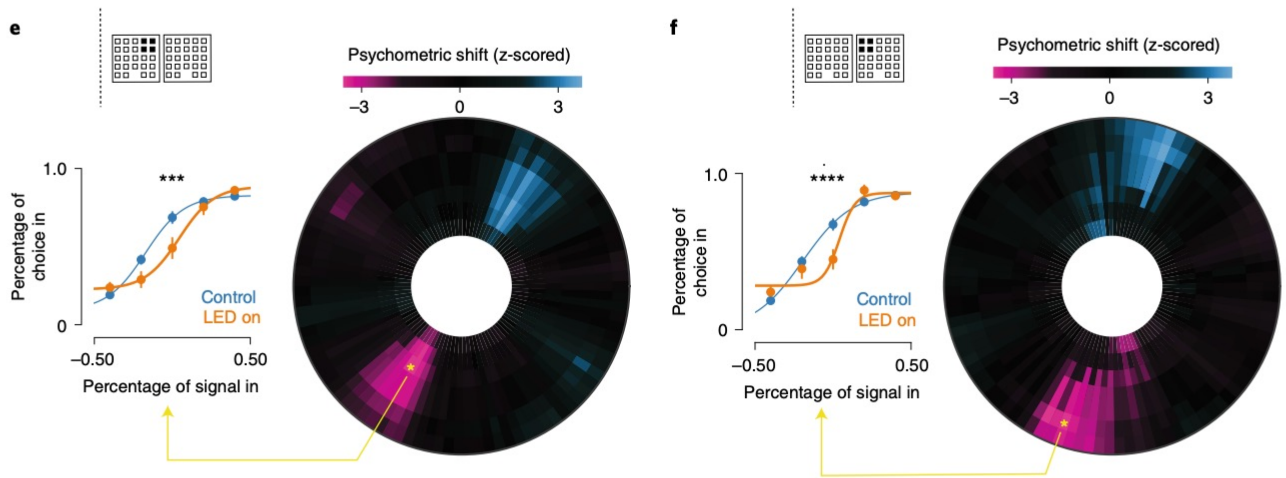


- They tested the efficacy of the Opto-Array in vivo in a primate behavioral experiment investigating the causal role of mesoscale subregions in the V1 cortex of a macaque monkey in the context of a two-alternative forced-choice luminance discrimination task
- A monkey was trained to report the location of a visual target stimulus based on its luminance, in the presence of a distractor stimulus.
- They analyzed the effects over different LED conditions and different subregions within the target ROI by acquiring psychometric shift maps for two different example activation conditions

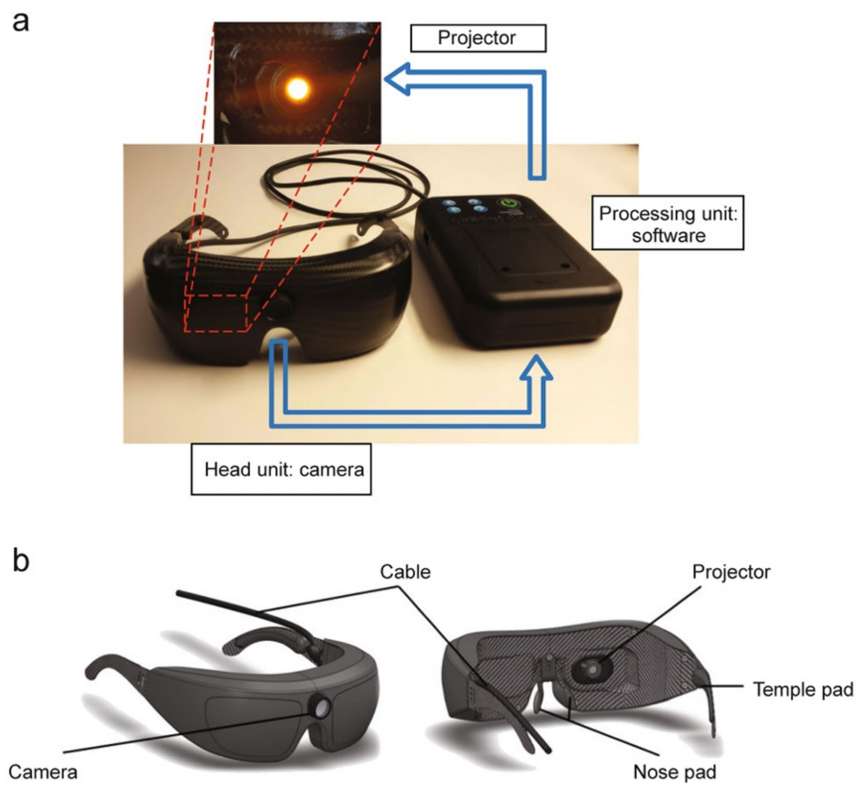
EPFL

Optogenetics

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01351-4
Check for updates

Partial recovery of visual function in a blind patient after optogenetic therapy

José-Alain Sahel[1,2,3,4], Elise Boulanger-Scemama[3,4], Chloé Pagot[5], Angelo Arleo[1], Francesco Galluppi[6], Joseph N. Martel[2], Simona Degli Esposti[7], Alexandre Delaux[1], Jean-Baptiste de Saint Aubert[1], Caroline de Montleau[5], Emmanuel Gutman[5], Isabelle Audo[1,3], Jens Duebel[1], Serge Picaud[1], Deniz Dalkara[1], Laure Blouin[6], Magali Taiel[6] and Botond Roska[8,9]



- In a blind patient, they combined intraocular injection of an adeno-associated viral vector encoding ChrimsonR with light stimulation via engineered goggles
- The goggles detect local changes in light intensity and project corresponding light pulses onto the retina in real time to activate optogenetically transduced retinal ganglion cells
- The patient perceived, located, counted and touched different objects using the vector-treated eye alone while wearing the goggles.

Optogenetics

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Table 1 | First test: finding the notebook or staple box

Stimulus	Natural binocular: both eyes open without the light-stimulating goggles			Natural monocular: untreated eye covered, treated eye open without the light-stimulating goggles			Stimulated monocular: untreated eye covered, treated eye open and stimulated with the light-stimulating goggles		
	Perceive	Locate	Touch	Perceive	Locate	Touch	Perceive	Locate	Touch
Notebook, contrast = 40%	0/1	0/1	0/1	0/1	0/1	0/1	4/4	4/4	4/4
Notebook, contrast = 55%	0/1	0/1	0/1	0/1	0/1	0/1	4/5	4/5	4/5
Notebook, Contrast = 100%	0/1	0/1	0/1	0/1	0/1	0/1	4/4	4/4	4/4
Staple box, contrast = 40%	0/1	0/1	0/1	0/1	0/1	0/1	3/6	3/6	2/6
Staple box, contrast = 55%	0/1	0/1	0/1	0/1	0/1	0/1	2/5	2/5	1/5
Staple box, contrast = 100%	0/1	0/1	0/1	0/1	0/1	0/1	1/4	1/4	1/4

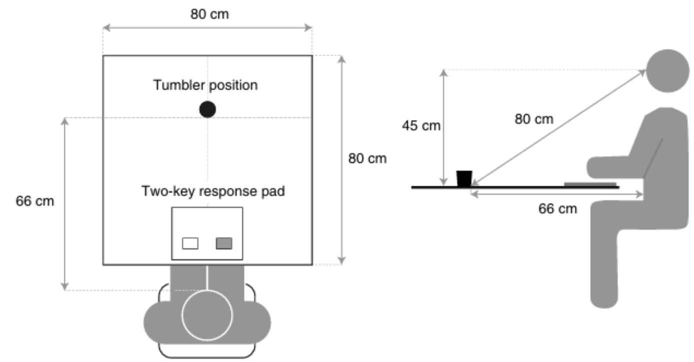
No test repetition was performed because the patient was unable to complete the task. He could not see anything and did not want to try again.

Table 2 | Second test: counting and locating tumblers

Stimulus	Natural binocular: both eyes open without the light-stimulating goggles			Natural monocular: untreated eye covered, treated eye open without the light-stimulating goggles			Stimulated monocular: untreated eye covered, treated eye open and stimulated with the light-stimulating goggles		
	Perceive	Count	Locate	Perceive	Count	Locate	Perceive	Count	Locate
Tumblers, contrast = 40%	0/1	0/1	0/1	0/1	0/1	0/1	4/6	4/6	4/6
Tumblers, contrast = 55%	0/1	0/1	0/1	0/1	0/1	0/1	5/7	5/7	5/7
Tumblers, contrast = 100%	0/1	0/1	0/1	0/1	0/1	0/1	3/6	3/6	2/6

No test repetition was performed because the patient was unable to complete the task. He could not see anything and did not want to try again.

a



Optogenetics

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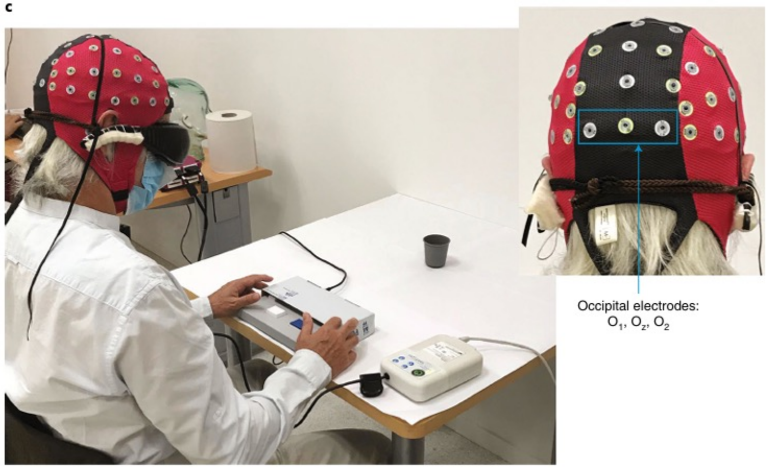

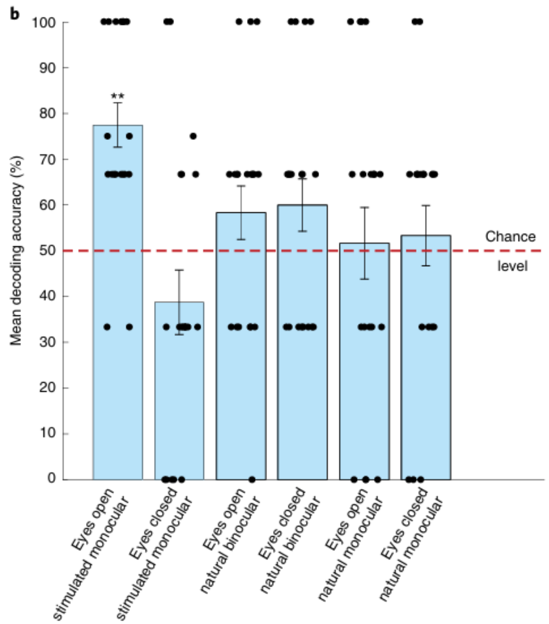

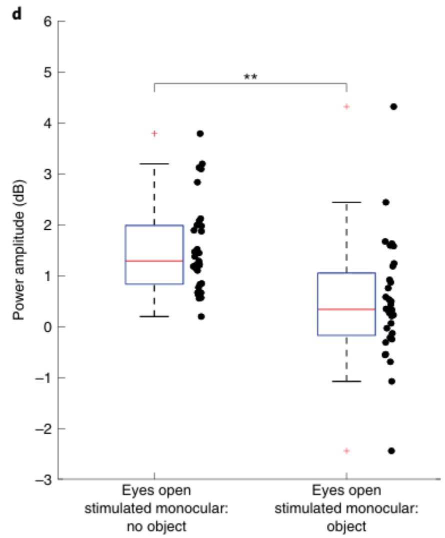

- A linear binary decoder with the mean alpha-power amplitudes of the occipital channels was trained to discriminate object versus no-object trials
-

Take-home message

- Visual functions are naturally achieved in a complex way which could be difficult to restore
- Different approaches based on
  - light or electrical stimulation
  - Central, peripheral, (sub/epi) retinal
- Interesting results but still limited

Conclusions (final take-home message)

Summary of the advantages and disadvantages of the 6 potential target sites for a visual prosthesis along the early visual pathway from retina to primary visual cortex*

Location	Advantages	Disadvantages
retina	extracranial, gaze compensation, simple encoding, full visual field	contraindicated in glaucoma/trauma, high resolution not possible?, very delicate, acceleration forces (not stable), luminance only?
optic nerve	stable, extracranial, simple encoding, full visual field	poorly organized, atrophies in many diseases, requires gaze information
optic tract	stable, simple encoding	deep, poorly organized, visual hemifield, atrophies in many diseases, requires gaze information
LGN	stable, compact, highly organized, M/P/K separation, colors possible?, simple encoding?	deep, compact, visual hemifield, corticothalamic projections, requires gaze information
optic radiation	stable, simple encoding?	deep, not compact, visual hemifield, requires gaze information
striate cortex (V1)	stable?, large, at surface	often completely within CF, large craniotomy?, some portions in sulci, visual hemifield, complex neural encoding, requires gaze information

*M/P/K refers to the magnocellular, parvocellular, and koniocellular subdivisions of the early visual pathway.