Retinal Bioengineering, part I

April 24th, 2008

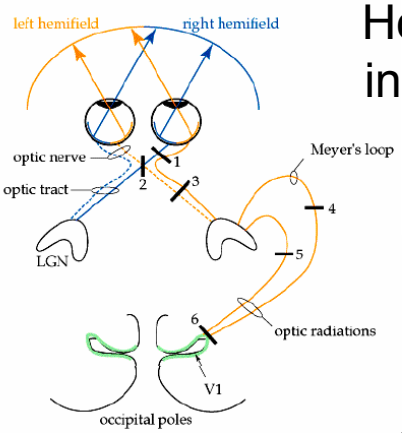
http://www.eye-chip.com/
http://www.bostonretinalimplant.org/
http://www.eyesight.org/
http://www.amdcanada.com/
http://www.seeingwithsound.com/newpubs/retinal_implant/cached.html#
http://www.seeingwithsound.com/
http://ophthalmology.stanford.edu/research/basic_retinal_prosthesis.html
http://hubel.med.harvard.edu/bcontex.htm - Eye, Brain, and Vision (Hubel)

A lot of the material in the first part of this lecture is available online:
http://webvision.med.utah.edu/index.html

outline

- Intro: retina, eye, visual system.
- Retinal structure and function.
- Retinal diseases (rp, md, glaucoma, detachment)
- Engineering contributions to retinal physiology and implants: Saugandhika's presentation.

How do light stimuli “travel in”, and get translated into electrical potentials?



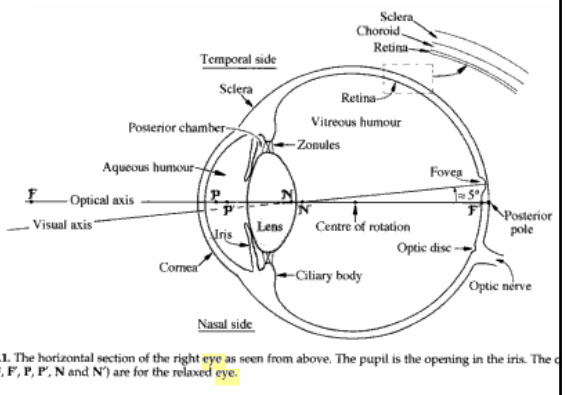


Figure 1.1. The horizontal section of the right eye as seen from above. The pupil is the opening in the iris. The c points (F, F′, P, P′, N and N′) are for the relaxed eye.

http://thalamus.wustl.edu/course/bvis2.gif

Optics of the Human Eye
By David A. Atchison, George Smith

Anatomy of the eye

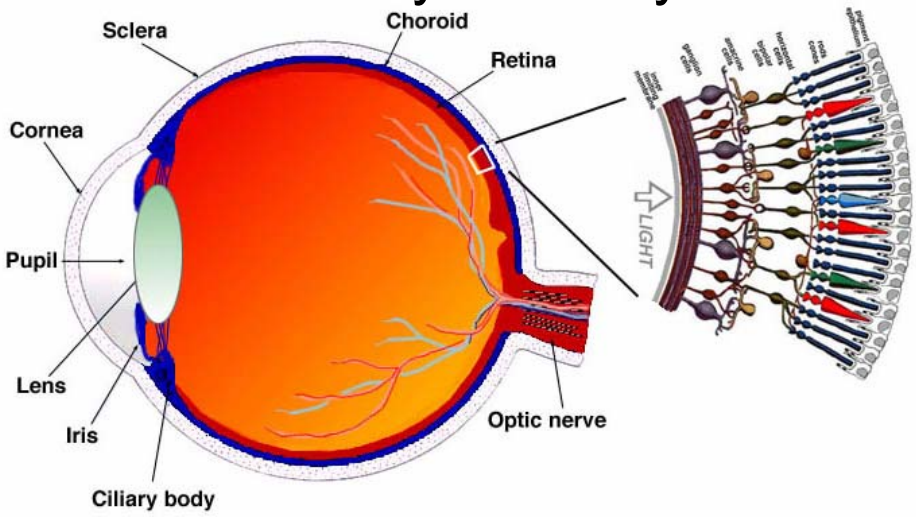
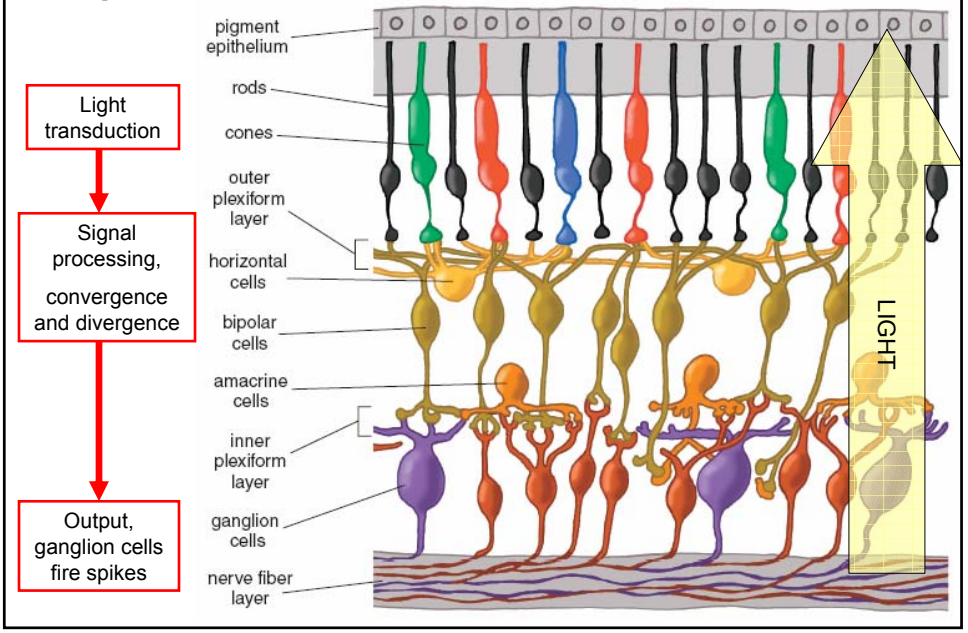


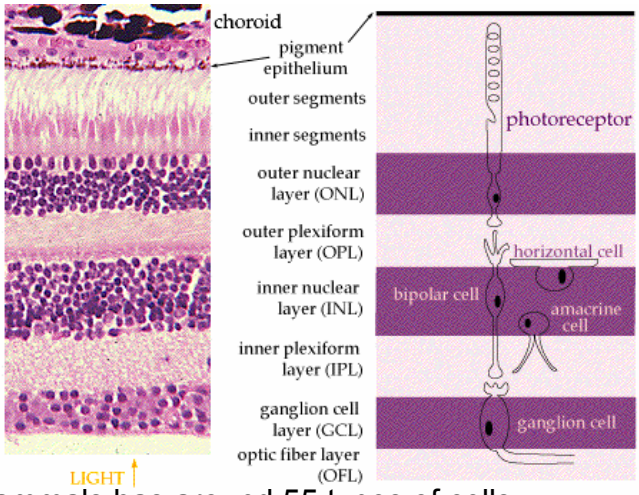
Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.

http://webvision.med.utah.edu/sretina.html

Signal transduction and processing



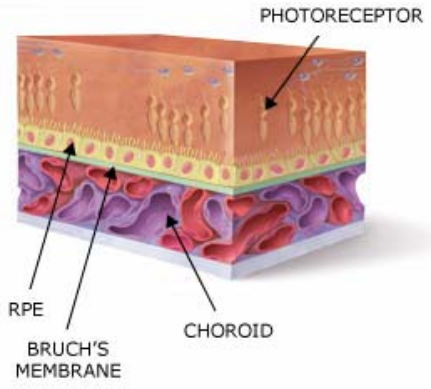
Retinal layers: nomenclature refers to cell types and synaptic connections



Retina in mammals has around 55 types of cells.

http://thalamus.wustl.edu/course/eyeret.html

Retinal pigment epithelium



- RPE: life support for photoreceptors.
- RPE: single layer of retinal cells.
- Densely packed with pigment granules
- Each RPE cell contacts approx. 25 rods and/or cones.
- Rod and cone cells each shed approximately 100 discs (waste products)/day.
- Waste is cleared by the RPE.
- Total of 70 million discs are cleared or "digested" by each RPE cell

http://www.amdcanada.com/template.php?section=4&subSec=2d&content=4_2

Muller glial cells: special glia cells, only in the retina.

- Span from inner limiting membrane (ILM) all the way to ganglion cell layer (GCL).
- Vertically positioned, like the bipolar cells.

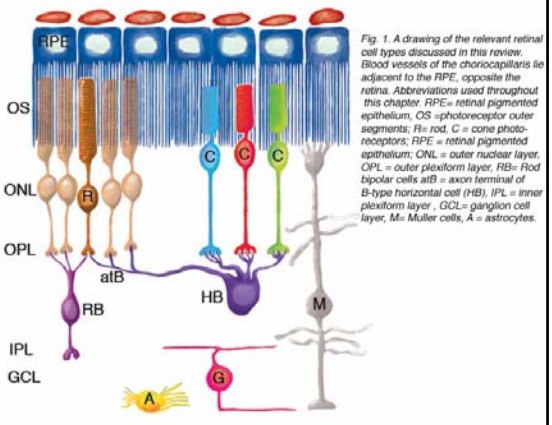


Fig. 1. A drawing of the relevant retinal cell types discussed in this review. Blood vessels of the choriocapillaris lie adjacent to the RPE, opposite the retina. Abbreviations used throughout this chapter. RPE= retinal pigmented epithelium, OS =photoreceptor outer segments; R= rod, C = cone photo-receptors; RPE = retinal pigmented epithelium; ONL = outer nuclear layer, OPL = outer plexiform layer, RB= Rod bipolar cells atB = axon terminal of B-type horizontal cell (HB), IPL = inner plexiform layer , GCL= ganglion cell layer, M= Muller cells, A = astrocytes.

http://webvision.med.utah.edu/imageswv/FisherFig1.jpg

Muller glial cells

- Form gap junctions in several species.
- Control of homeostasis in extracellular environment through uptake and redistribution of extracellular potassium.

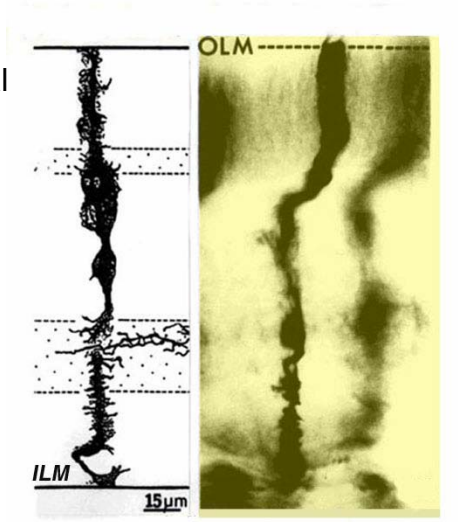


Fig. 11. Vertical view of Golgi stained Müller glial cells.

Phototransduction

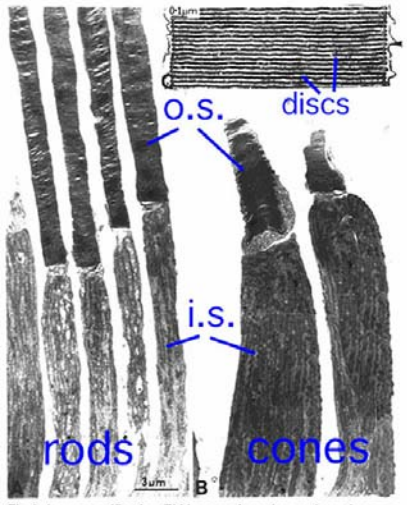


Fig 2. Low magnification EM image of monkey rods and cones with an enlargement of the outer segment discs.

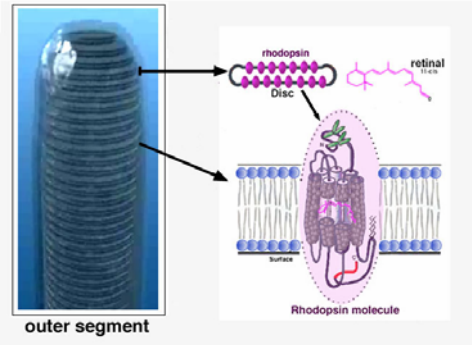
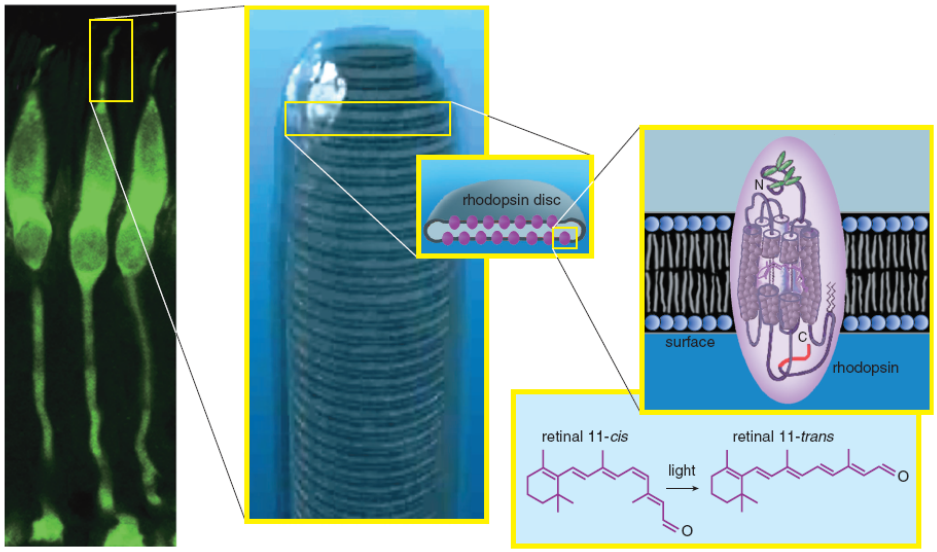


Fig 8. Schematic diagram of Rhodopsin in the outer segment discs.

Pathways from rods and cones to ganglion cells are not the same, even though each single ganglion cell receives input from both rods and cones. Amacrine cells intermediate connections from rods to ganglion cells (through bipolar cells)

http://webvision.med.utah.edu/imageswv/rodcoEM.jpeg

Light transduction



cones from monkey

Humans have two types of light transducers: rods and cones. There are three basic kinds of cones, with different spectral sensitivities. When it's dark, we "see" with rods. When it's bright, we "see" with cones.

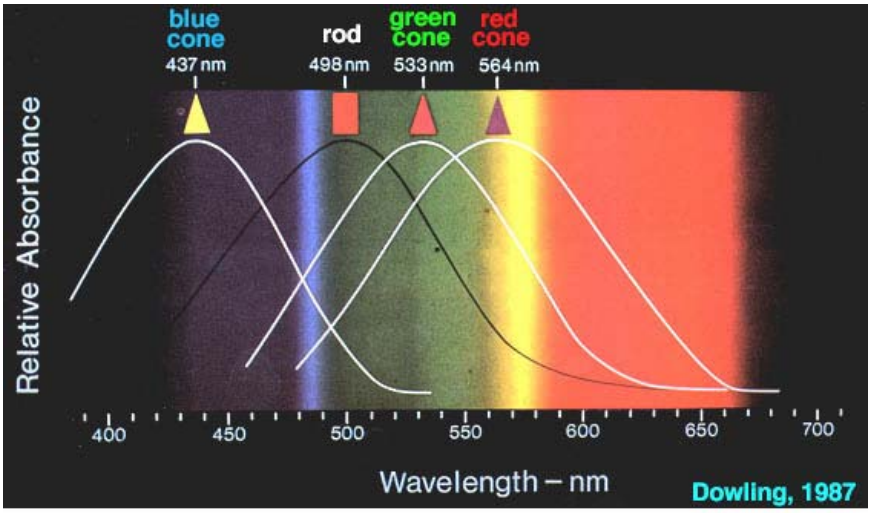
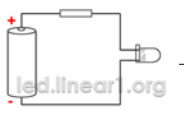


Fig. 14.The peak spectral sensitivities of the the 3 cone types and the the rods in the primate retina (Brown and Wald, 1963). From Dowling's book (1987).

http://webvision.med.utah.edu/imageswv/spectra.jpeg

Differential sensitivity of rods and cones



light

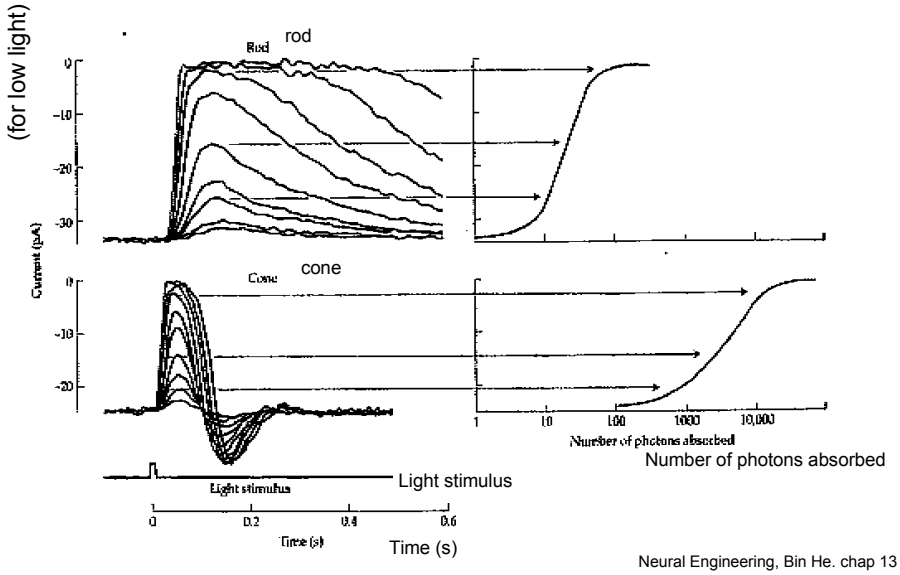
Rod = 0.7pA	**30 rods/bipolar**
Cone = 0.033pA	**4 cones/bipolar**

Current: Result of the photoisomerization in the outer segments of rods and cones.

Bottom line: Rods are 21 times more sensitive than cones!

Visual angle of common objects (degrees, deg)
The sun or moon = 0.5 deg
Thumbnail (at arm's length) = 1.5 deg
Fist (at arm's length) = 8-10 deg

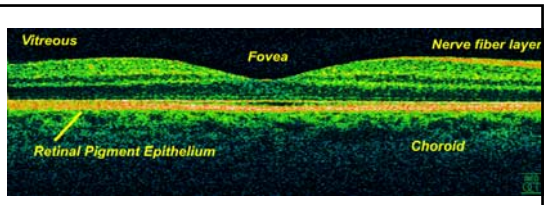
Photons absorbed and time response



Neural Engineering, Bin He. chap 13

Fovea

- Central area of retina.
- Highest visual acuity.
- Directed at what is in front of you.
- Highest density of cones.



http://upload.wikimedia.org/wikipedia/en/2/2d/Retina-OCT800.png

- **Fovea**: cones packed together, form hexagonal pattern

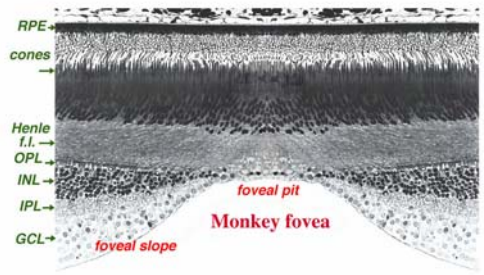


Fig. 12b. Vertical section of the monkey fovea from Hagerman and Johnson (1991).

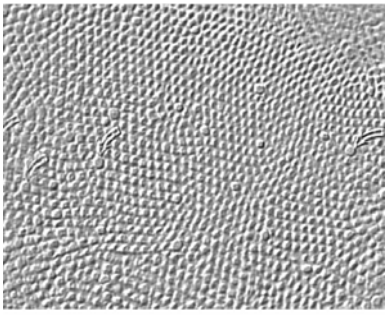
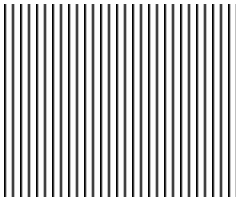


Fig. 13. Tangential section through the human fovea. Larger cones (arrows) are blue cones.

http://webvision.med.utah.edu/sretina.html#muller

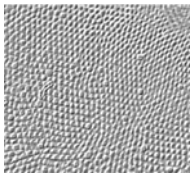
How small can you see?

Stimulus: black & white bars



Distance between two lines: one cycle

Our best sensors: cones in the fovea.



Cone: one element.
Packed densely: 2.5μm center to center
(this is the element spacing).

R = 300μm/degree x [1 cycle / (2 x element spacing)],

Where R is the resolution in cycles of the grating per degree.

What is the resolution of your eye?

Temporal resolution of your system

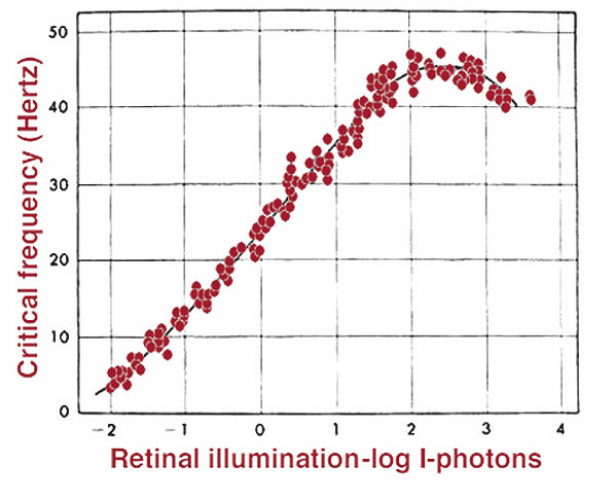


Fig. 7. CFF at the fovea over a range of retinal illuminance (photon = troland) of the test field, showing conformity of the Ferry-Porter Law over four logarithmic units. Hecht and Verrijp's data from Hart Jr, W. M., The temporal responsiveness of vision. In: Moses, R. A. and Hart, W. M. (ed) Adler's Physiology of the eye, Clinical Application. St. Louis: The C. V. Mosby Company, 1987.

http://webvision.med.utah.edu/imageswv/KallTemp7.jpg

Luminance levels, definition of Troland

- Typical ambient luminance levels (in cd/m^2):
- Starlight: 0.001
- Moonlight: 0.1
- Indoor lighting: 100
- Sunlight: 10,000
- Maximum intensity of CRT monitors: 100

- One Troland (Td) of retinal illumination: produced when an eye with a pupil size of 1 mm^2 looks at a surface whose luminance is 1 cd/m^2.
- Lens focal length: f(meters); lens power= 1/f (diopters).

- Obs: Lux are units of illumination. Light intensity of 1 candela produces an illumination of 1 lux at 1 meter.

- X/Y vision: the numerator person can see at X feet what a normal person can see at Y feet.
  Usual numbers are 20/20 (normal vision); 80/100 (means the patient has to be at 80 feet to see what a normal subject would see at 100 feet).

Modified from http://webvision.med.utah.edu/

Signal path through the retina

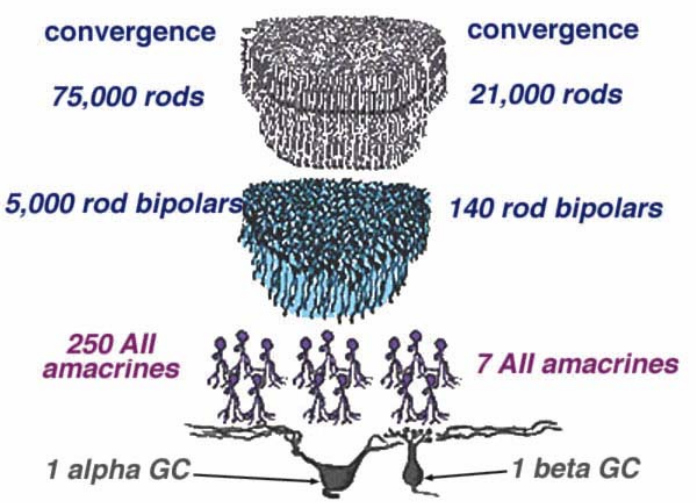


Fig. 16. Convergence of rods, rod bipolar and AII amacrine cells to alpha and beta cells of cat retina.

http://webvision.med.utah.edu/imageswv/rod-GC.jpeg

Spikes recorded from ganglion cells (output of retina)

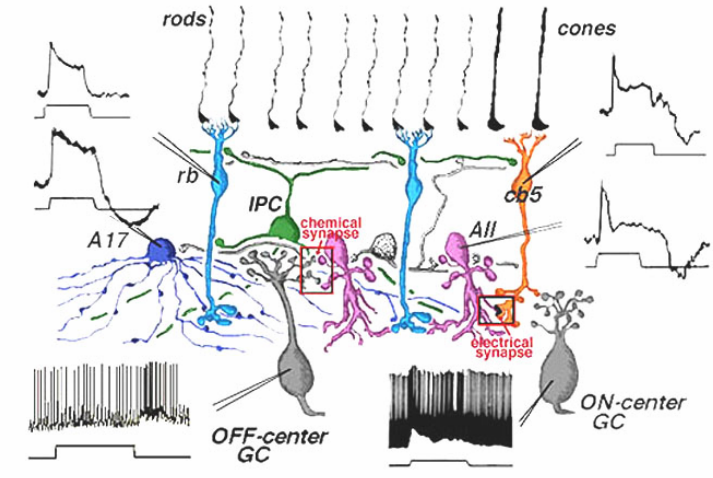


Fig. 20. Summary diagram of the rod pathway neurons and their responses. Amacrine cells intervene between rod bipolar and ON and OFF center ganglion cells.

ON/OFF bipolar cells

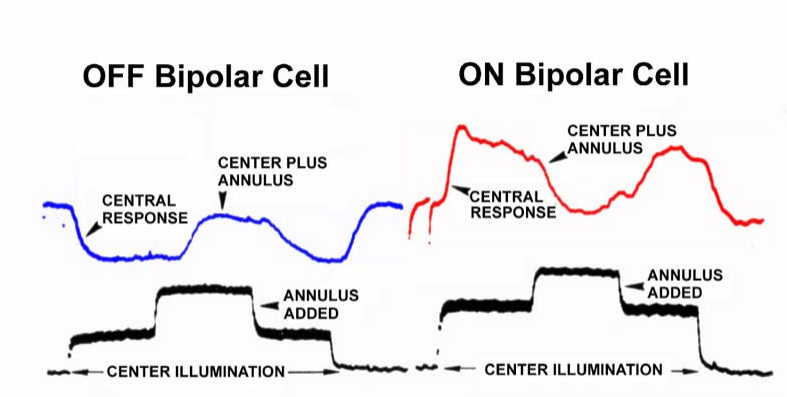


Fig. 1. Intracellular recordings from mudpuppy retina revealed two sorts of retinal bipolar cells: OFF bipolar cells and ON bipolar cells. From Werblin and Dowling (1969).

http://webvision.med.utah.edu/imageswv/bcfig1.jpg

On/off center bipolar cells

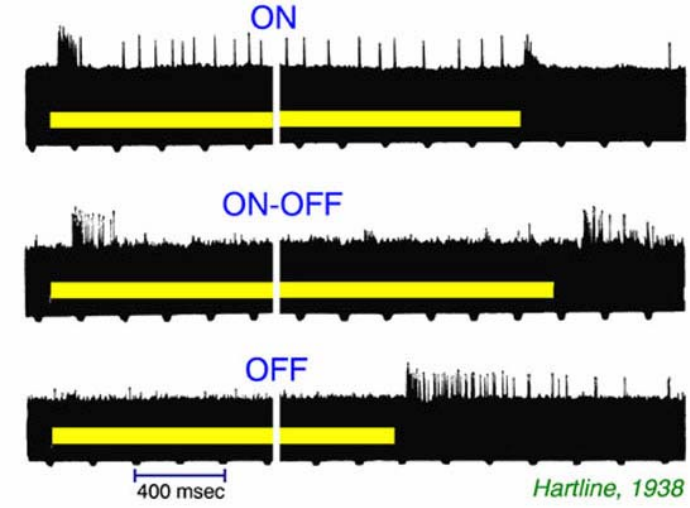


Fig. 3. ON, OFF and ON-OFF ganglion cells (after Hartline, 1938; 1967).

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Receptive fields: space mapping of light stimuli to ganglion cells

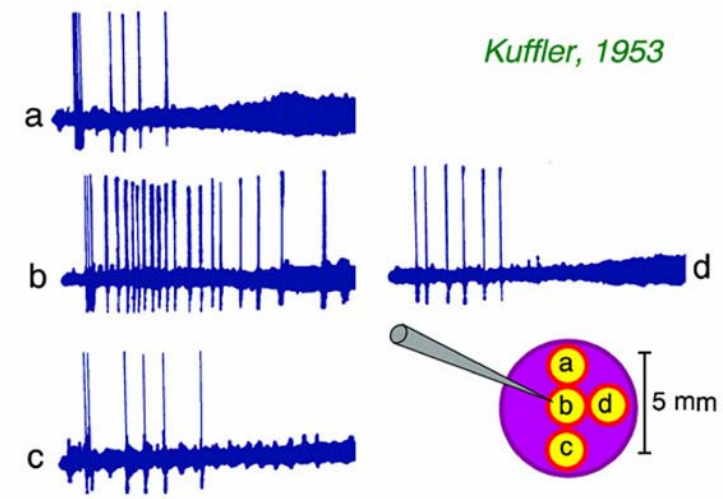

Fig. 5. Spot mapping of cat retinal ganglion cell receptive-field center (Kuffler, 1953).

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Retinal vasculature

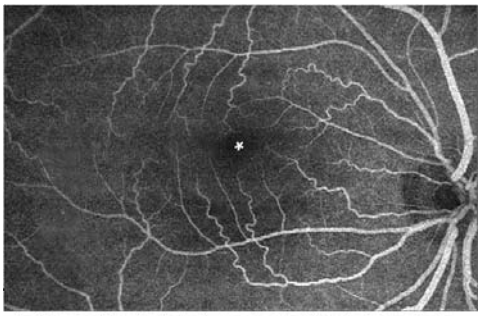


Fig. 17. Fundus photograph showing flourescein imaging of the major arteries and veins in a normal human right eye retina. The vessels emerge from the optic nerve head and run in a radial fashion curving towards and around the fovea (asterisk in photograph). (Image courtesy of Isabel Pinilla, Spain).

Two sources of blood supply to the mammalian retina:

(1) the central retinal artery (15-35% of the blood flow, supply to the inner retinal layers;

(2) the choroidal blood vessels. (65-85% of the blood flow, supply to photoreceptors through the pigment epithelium).

http://webvision.med.utah.edu/imageswv/FlorretBV.jpg

Retinal diseases: 15 million people visually impaired in the U.S.A.

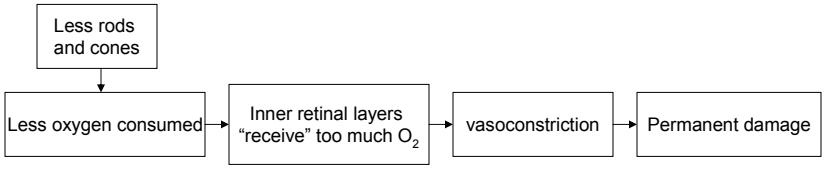
- Retinitis pigmentosa
- **Macular degeneration**
- **Glaucoma**
- **Diabetic retinopathy**
- Vascular occlusive disease
- Retinal detachment

Most prevalent diseases. (4th: age-related cataract)

http://www.mdsupport.org/library/numbers.html

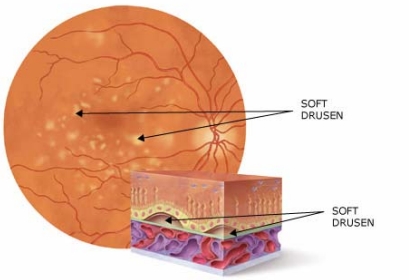
Retinitis pigmentosa

- Affects one in 4k to 3k;
- Characteristics: photoreceptor loss (rods first, cones second);
- Cause: more than 50 genetic defects in photoreceptor or pigment epithelium proteins.



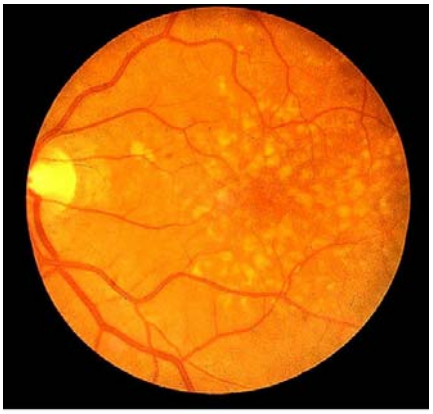
Age-related macular degeneration

- Prevalence: 1 in 100 (adults over 40y.o.)
- Incidence: higher over 65 y.o.
- Photoreceptor degeneration (similar to RP): incomplete digestion of outer segment disks (lipids and proteins)
- Drusen → traffic jam between the choroid and the retina → prevents metabolites from being delivered → neovascularization (choroidal vessels proliferate and enter the retina).



http://www.amdcanada.com/images/content/3_3_2_2_fig3.jpg

Macular degeneration diagnosis



Fundas photograph of a patient with age related macular degeneration.

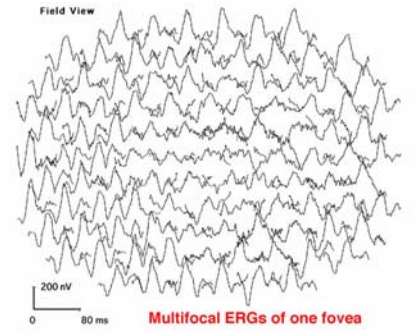


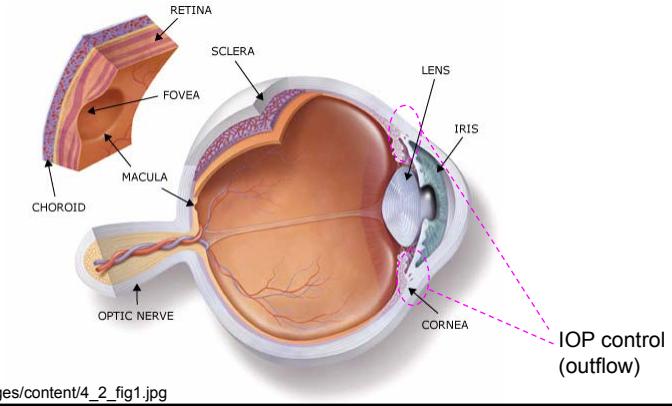
Fig. 41b. Multifocal ERG recordings in a patient with age related macular degeneration (AMD).

Vascular occlusive disease

- Atherosclerosis in arteries or veins (like a stroke in the retina)
- No redundancy in circulation (remember theory of cell assemblies), so occlusion leads to scotoma.
- if t>2h, then (damage = permanent)
- Venous occlusion → hemorrhages → less damaging than arteries.

Glaucoma

- Prevalence: 0.8 in 100 (to 3 in 100 Caucasians)
- Damaged ganglion cells due to elevated intraocular pressure (IOP).
- Normal: 15mm Hg. Glaucoma: 22mm Hg.
- High pressure compresses optic nerve, axonal transport is blocked, retrograde degeneration of ganglion cells.



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Retinal detachment

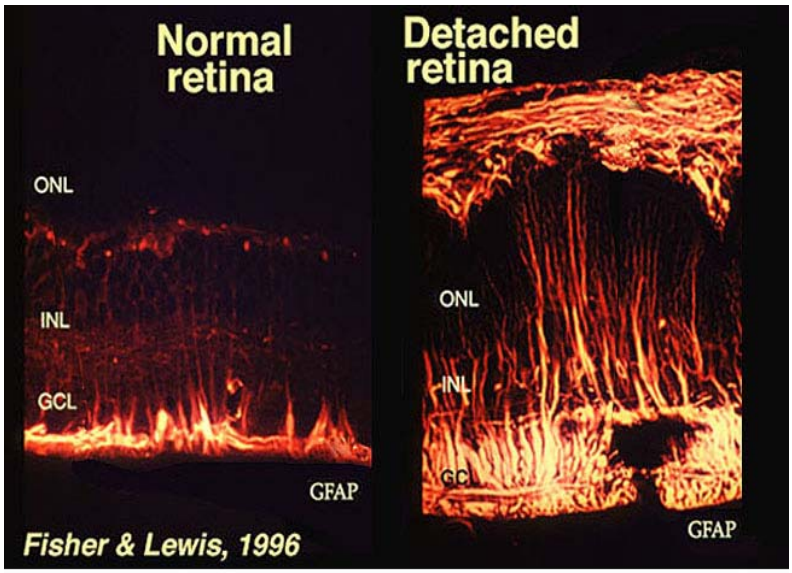


Fig. 3. GFAP immunoreactivity in Muller cells increases greatly when there is trauma to the retina such as detachment.

Fundus photo of retinal detachment

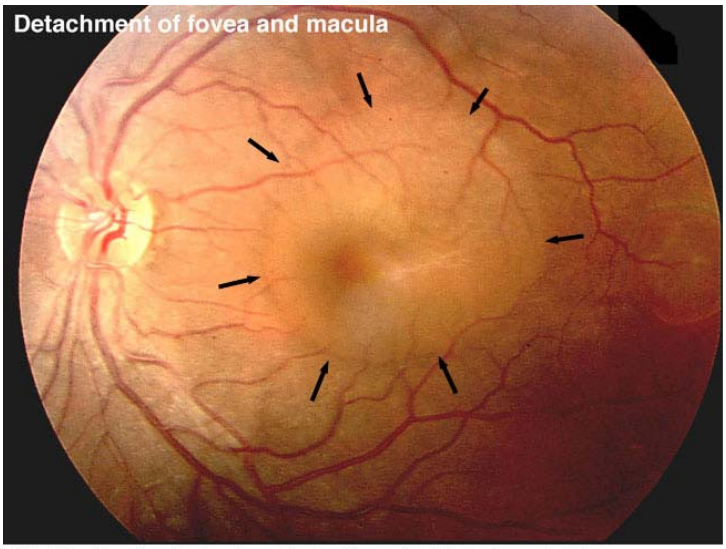


Fig. 31a. Fundus photo of a patient with a retinal detachment at the fovea and macula (arrows) in one eye.

OCT of macular detachment

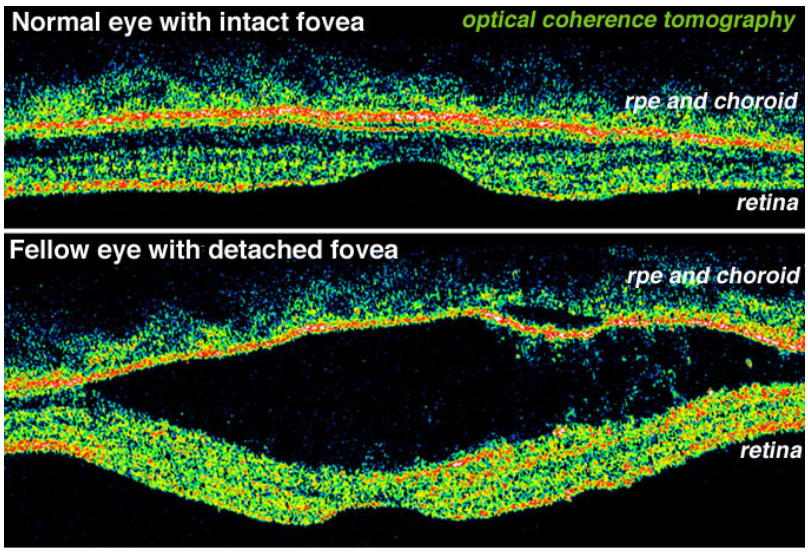


Fig. 31b. Optical coherence tomography (OCT) images of the patient's normal macula and of the retina in the other eye with the macular detachment.

Electroretinogram

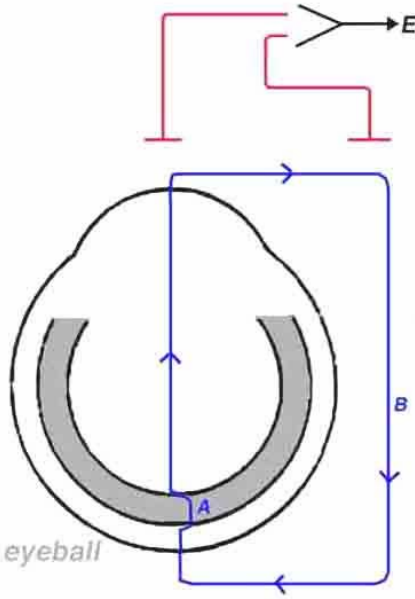


Fig. 3a. A schematic representation of the extracellular currents that are formed following light stimulation. Pathway A represents local currents within the retina, while pathway B shows the currents leaving the retina through the vitreous and the cornea and returning to the retina through the choroid and the pigment epithelium. ERG recording in human is done along the B path.

http://webvision.med.utah.edu/imageswv/ERGFig3.jpg

Electroretinograms are multiphasic

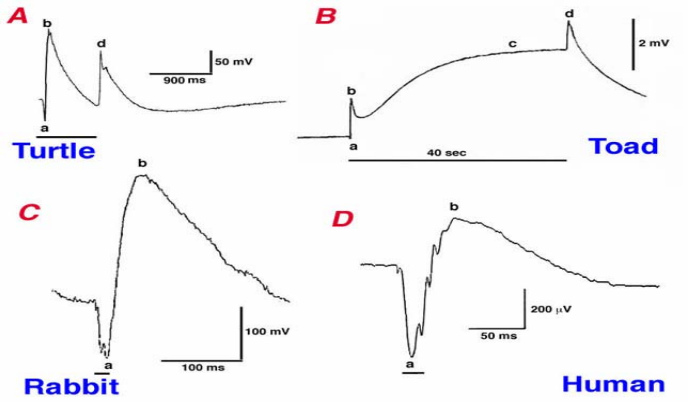


Fig. 1. (A) ERG response of turtle Pseudemys scripta elegans elicited by a 900ms light stimulus in order to separate the a-wave and b-wave from the d-wave. (B) The ERG of the bullfrog elicited by a long (40sec) light stimulus in order to show the c-wave in addition to the a-, b- and d-waves (Oakley, 1977). (C) The ERG response of a rabbit to a flash (20_s) flash of white light. (D) The ERG response from a human as typically recorded in the clinic. Note the fast oscillations on the ascending limb of the b-wave. Calibration bars are denoted separately for each ERG response.

Waves within the ERG

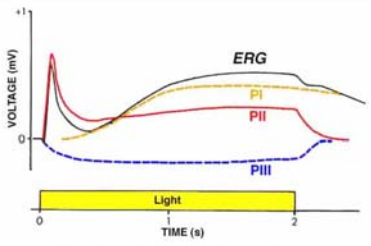


Fig. 2b. The ERG of a cat in response to a 2 sec light stimulus. The components, P-I, P-II and P-III, have been isolated by deepening the state of anesthesia (Granit, 1933).

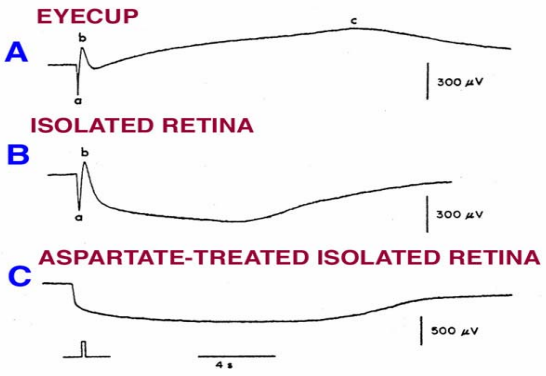


Fig. 4. ERGs recording from the skate. The recording was done from the whole eyecup (upper trace), following the separation of the retina from the pigment epithelium (middle trace) and after exposing the retina to aspartic acid (lower trace) (Pepperberg et al., 1978).

http://webvision.med.utah.edu/imageswv/

Amplitude and time in a and b waves.

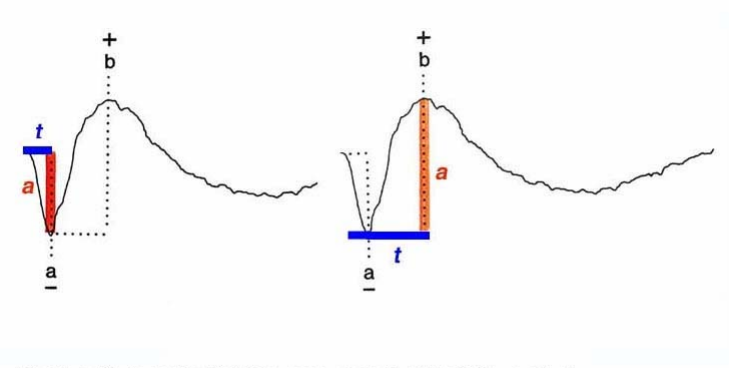


Fig.2 Amplitude and implicit time measurements of the ERG waveform.

Wave origin

• Each wave can be traced back to certain cells in the retina.

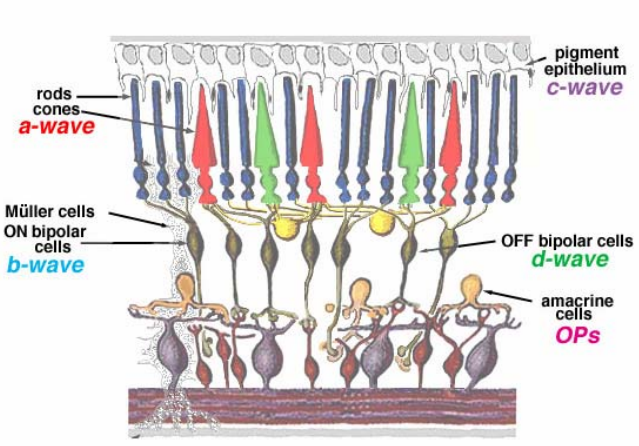


Fig.3 Cartoon of the retina to show where the major components of the ERG originate.

Photoreceptor models: based on the ERG

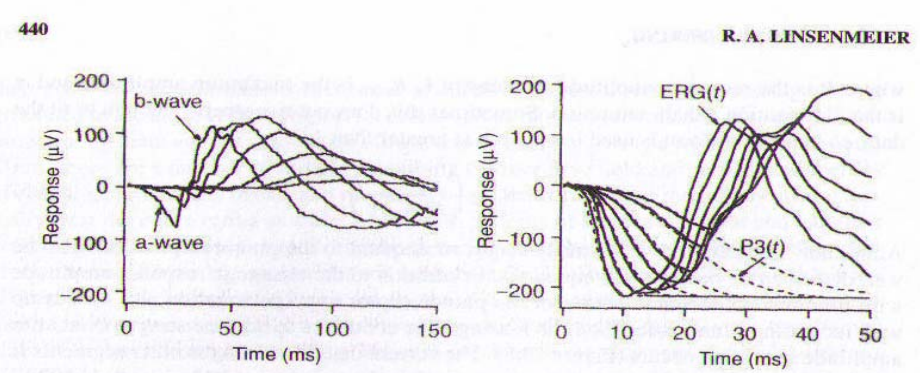
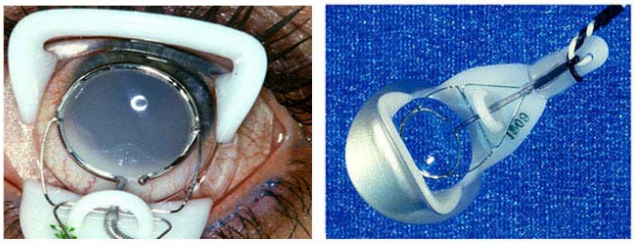


FIGURE 13.9. *Left*: Electroretinograms (ERGs) in response to flashes of several intensities in the dark-adapted human retina, showing the a-wave, originating from the photoreceptors and the b-wave, originating from the bipolars. *Right*: Fits of the photoreceptor model (P3(t)) described in the text ($n = 4$; $t_p = 189$ ms) to the early part of the ERGs. The intensities used for the right half of the figure were 2 to 4 log scotopic td-sec, which were higher than those on the left. (Reprinted from Hood and Birch, 1995, with permission from IEEE)

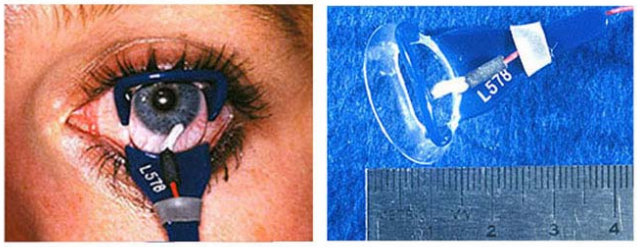
Neural Engineering, Bin He. chap 13

ERG electrodes

Burian speculum type electrodes

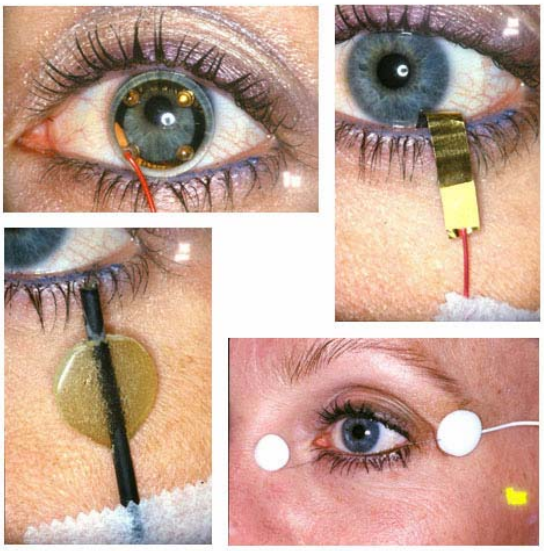


Cotton wick electrodes



http://webvision.med.utah.edu/imageswv/DONFig4.jpg

Corneal ERG electrodes



some corneal ERG electrodes

ERG amplitudes are electrode dependent

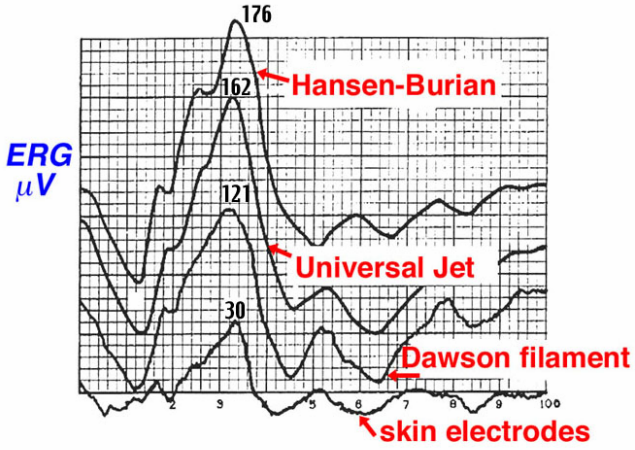


Fig. 6 Typical ERGs as recorded with different electrodes.

ERG uses

• Diagnosis of several eye diseases.

•E.g. diagnosis of RP.

• Development of retina, ageing.

• Isolation of which block in signal pathway is not functional.

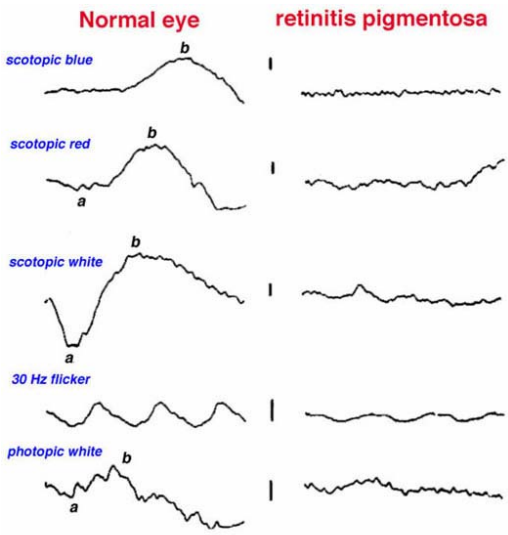


Fig. 13. ERG recordings in a normal patient and one with retinitis pigmentosa.

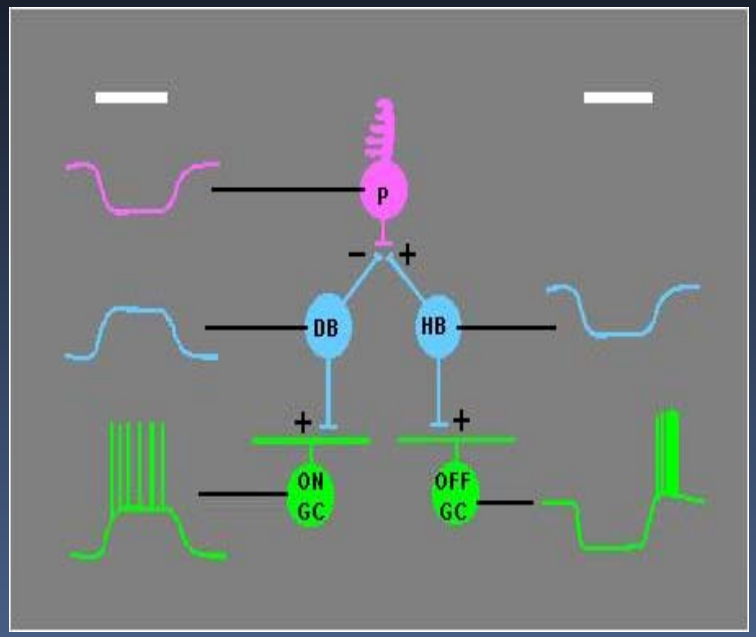
Engineering insights

What can you do to help?

Considerations on designing an implant:

- do users (patients) want to be helped?
- what do you think they'd answer as to what the most important specification of your implant/system would be?

Visual Pathway



Photons

RPE

Graded membrane potentials

Horizontal, Bipolar, Amarcine

Biological filtering
(sensitivity & high contrast)

Retinal Ganglion Cells

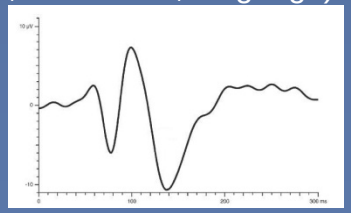
conversion to digital
Action Potentials

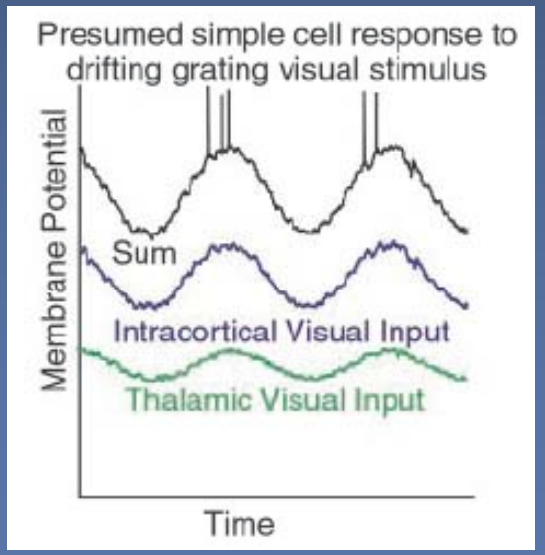
Via the Optic Nerve to LGN

Binocular representation of
visual space

VISUAL CORTEX

Extracted specific features of visual field
(faces, movement, language)





Source: (Odom et al-2004),

Visual prosthesis

- Phosphene

  A sensation on light produced by electrical or mechanical stimulation of the visual pathway

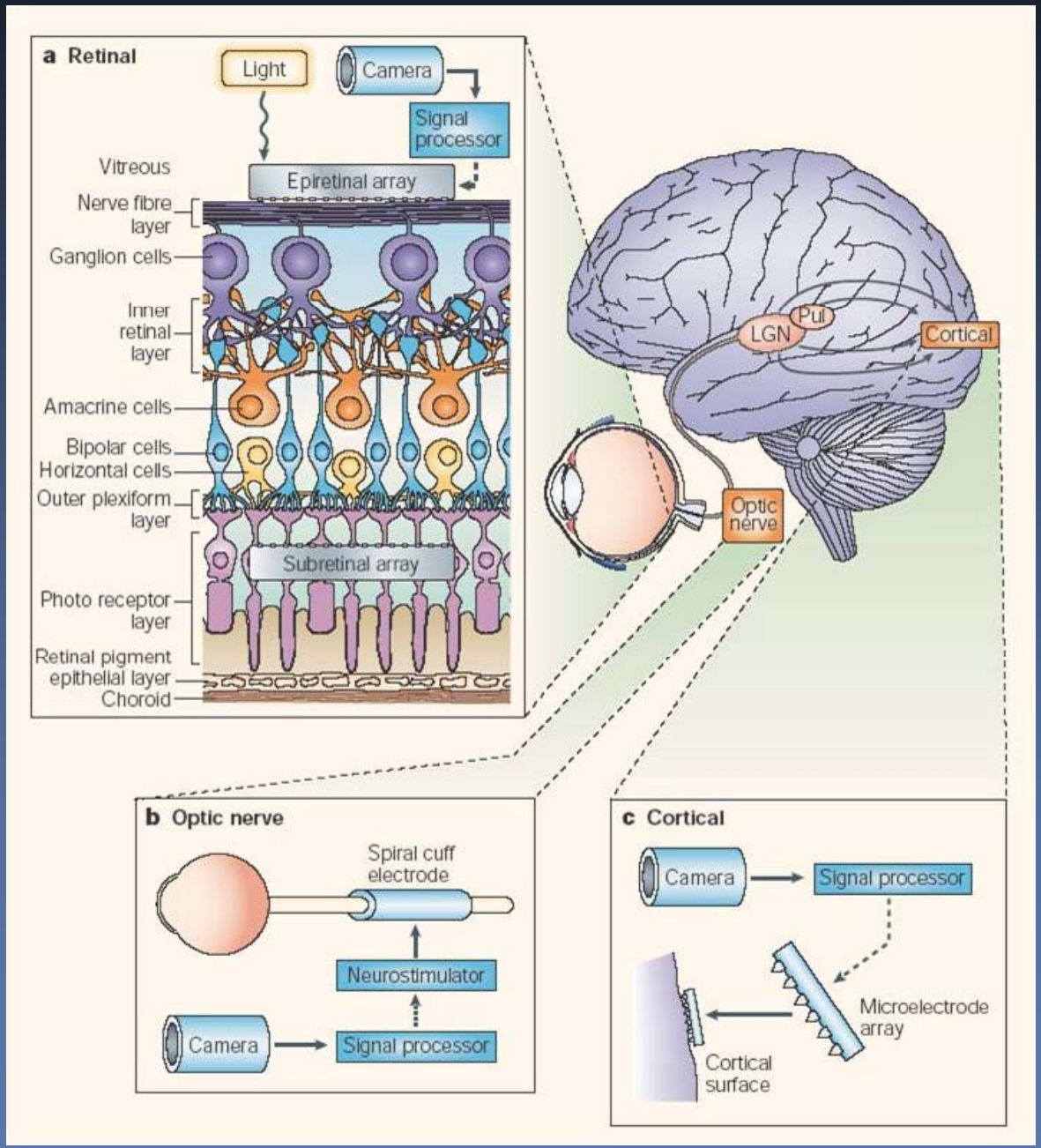
- Retinotopic

  A notion that receptor cells in the retina are mapped to points on the surface of visual cortex

Questions to be asked

- Can the Visual pathway of a blind person be activated?
- Can we stimulate few sets of neurons and have stable visual perception?

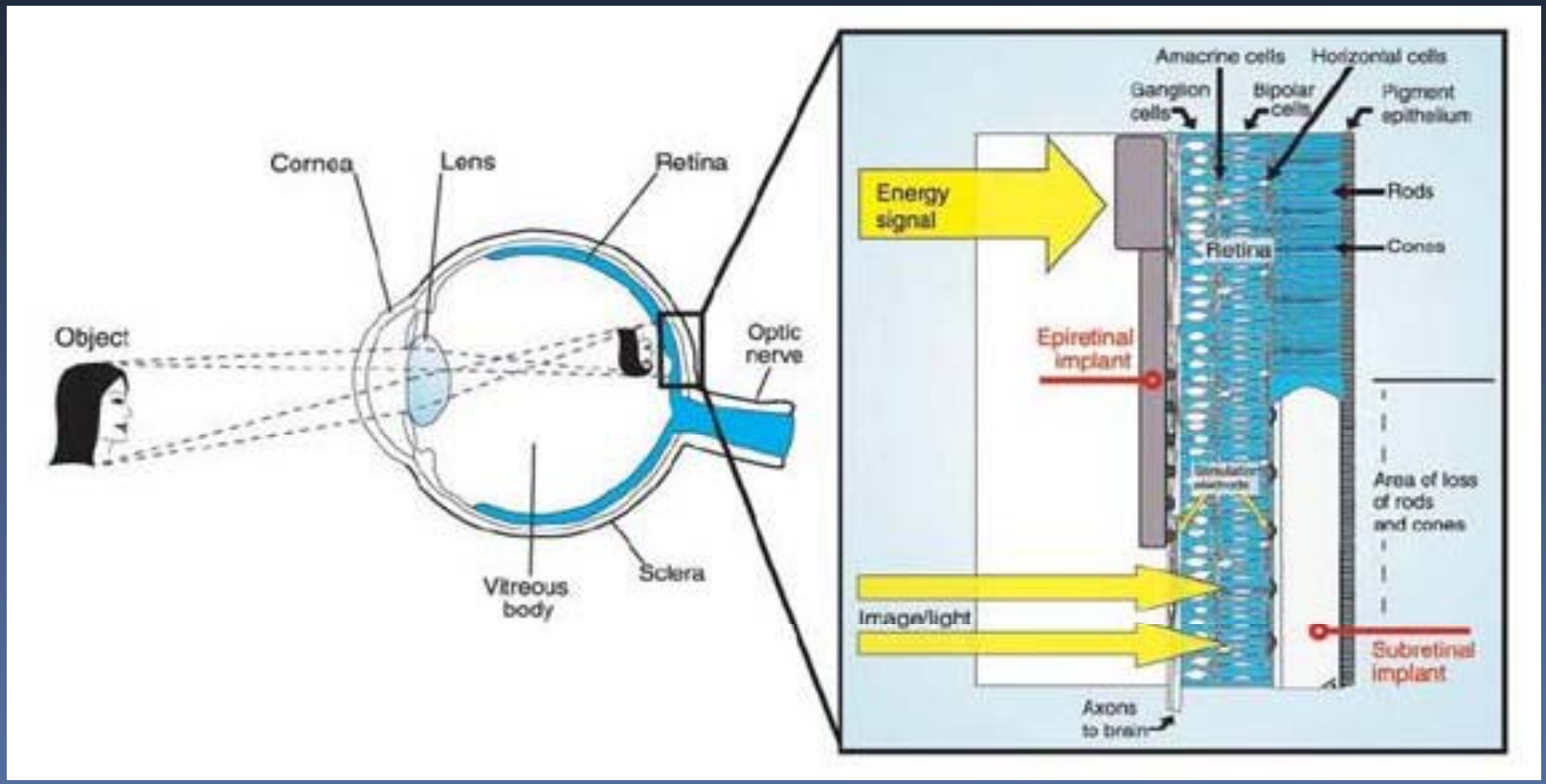
Types of Visual Prosthesis



I. Retinal
II. Optic Nerve
III. Lateral Geniculate Body
IV. Cortical

Source: (Merabet, 2005)

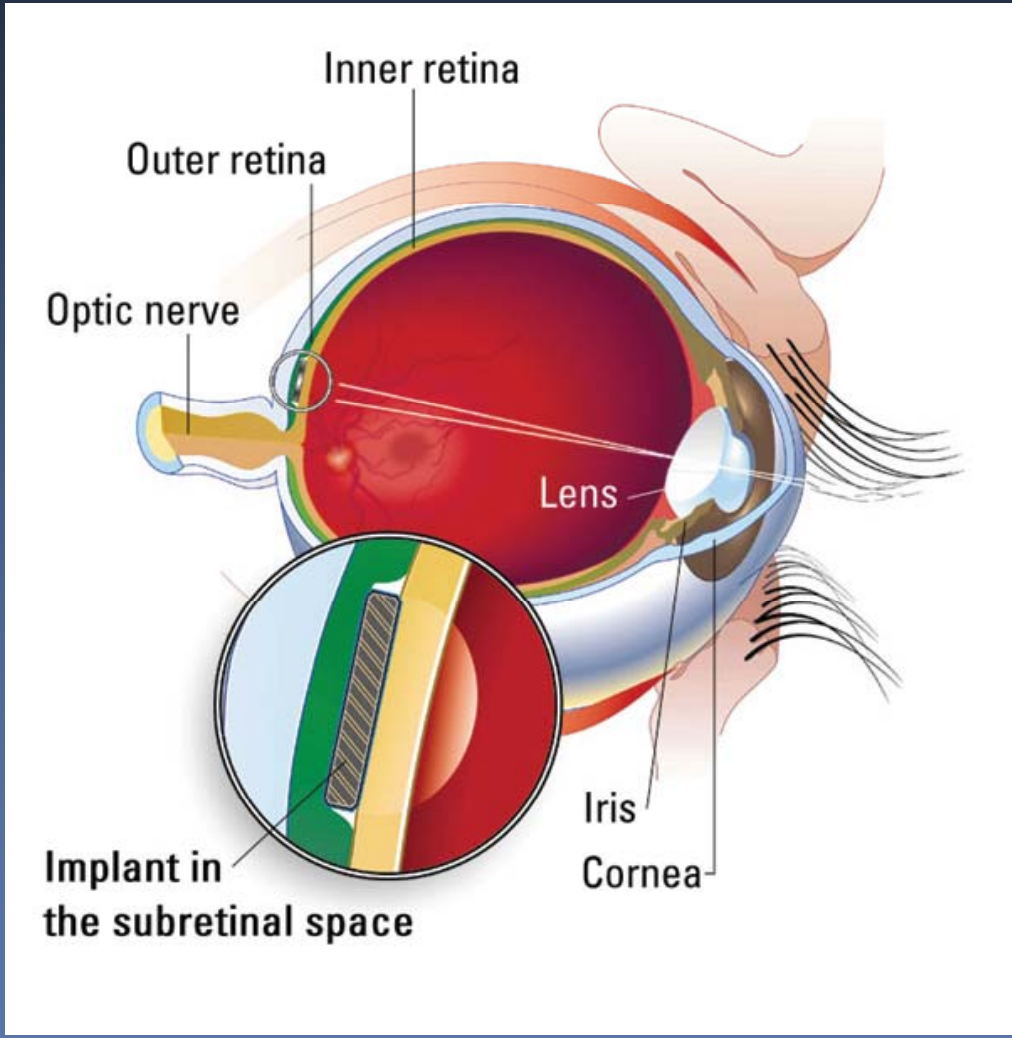
Retinal Prosthesis



- Epiretinal: “Stimulating the retina from front”
- Subretinal:“Stimulating the retina from back”

Source: (Scholtz,2007)

Subretinal Approach



- Replacing the RPE by
  - Microphotodiode (MPD) Array
  - Silicon Microphotodiode Array (SMA)
- Placed b/w the sclera and bipolar cells

Source: (Chow, 2004)

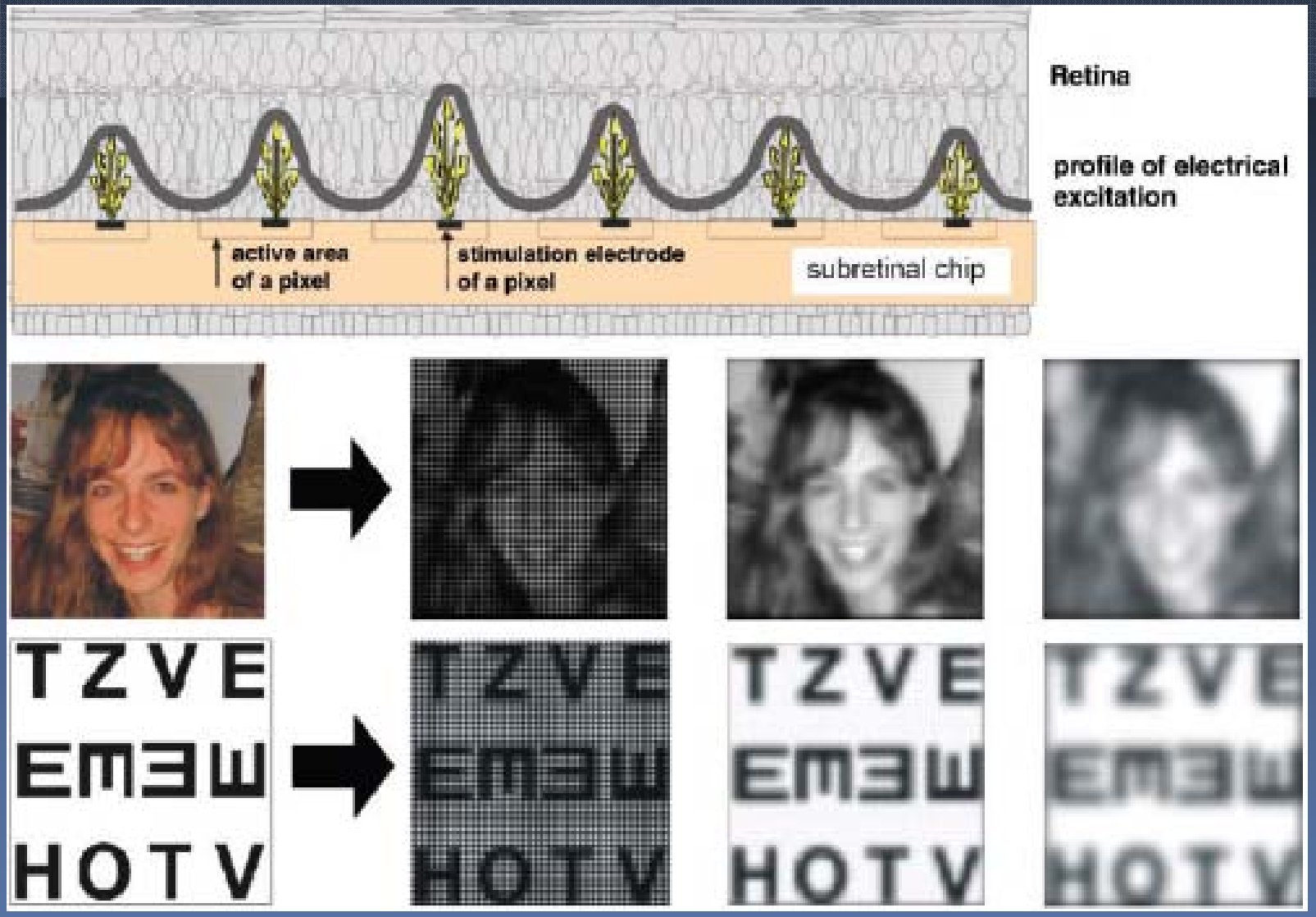
Subretinal

Advantages

- Uses natural signal processing
- No need of retinal tacks
- Lower stimulation thresholds

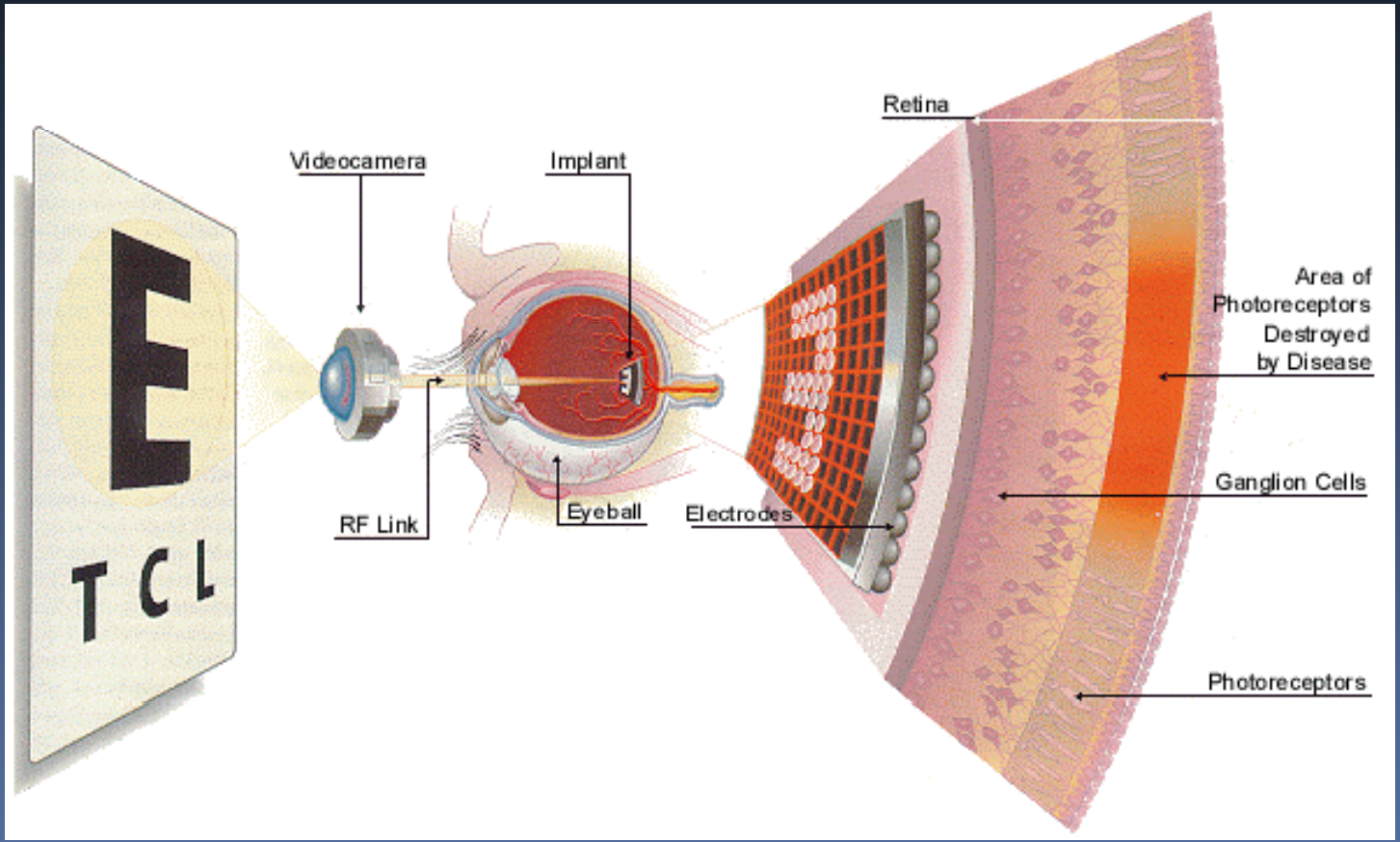
Disadvantages

- Low quantum efficiency
- Occludes the vasculature
- Rigid structures
- Possible retinal detachment



Source: (Zrenner,2002)

Epiretinal approach



- Placed b/w the vitreous and the Retinal Ganglion Cells (RGC)
- Stimulates the RGC bodies and axons

Source:

Epiretinal

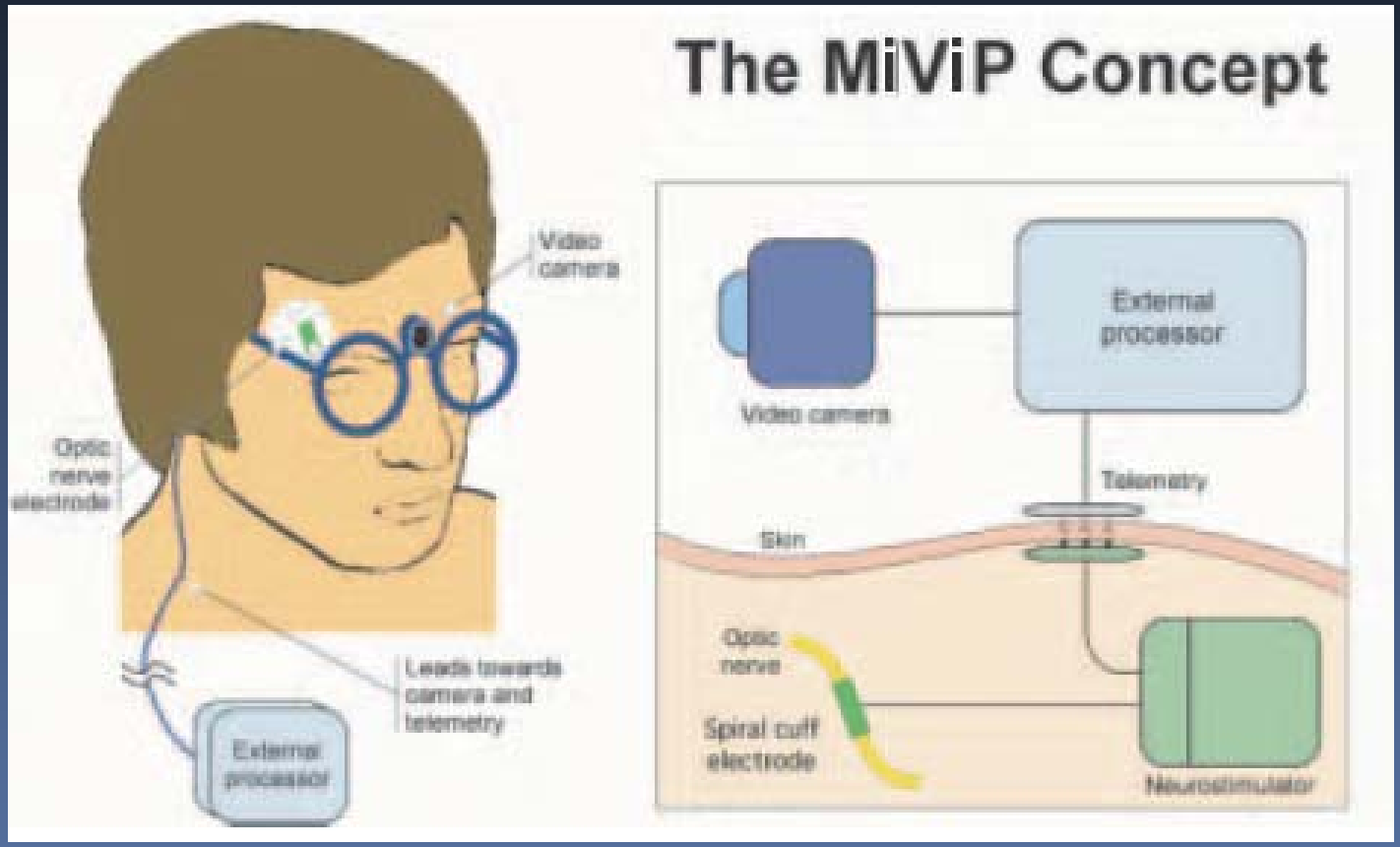
Advantages

- Doesn't occlude the choroidal vasculature
- Bypasses the damaged or missing photoreceptors and remnant circuitry
- Vitreous activity as heat sink
- Opthalmoscopically monitored

Disadvantages

- Active Elements
- Unstable positioning
- Stimulates the RGC cell bodies and passing axons of periphery
- Eye movements

Optic Nerve approach



- Optic nerve is a neural cable about 3mm thick and 50mm
- ~ one million fibres clustered into bundles surrounded by encased membranes

Source:

Optic Nerve

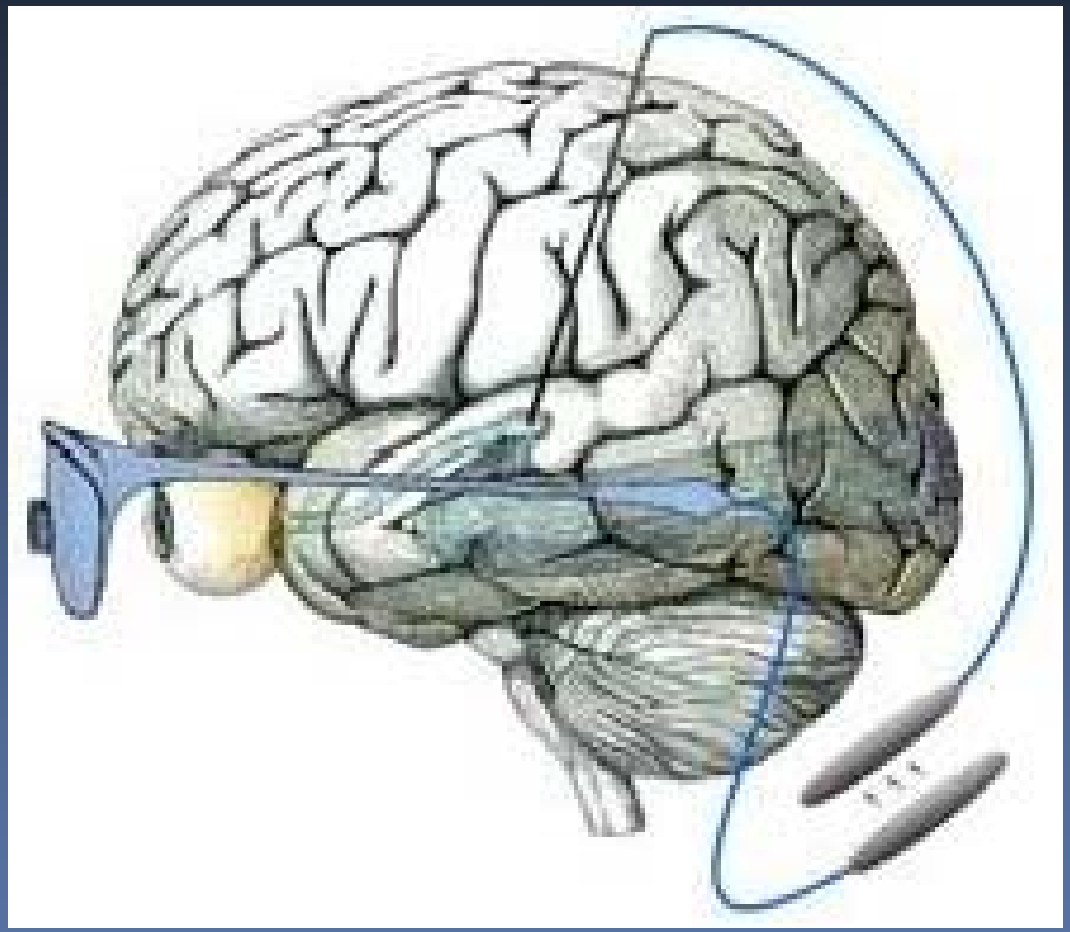
Advantages

- Easy surgical access
- Stimulating passing fibers
- Less interference of artificial signals with complex synaptic processing of the retina

Disadvantages

- Fibers not organized according to their orientation in the visual field
- Difficulty stimulating only a desired fibers.

LGN approach



- Relay station of signals from retina to Visual Cortex

Source: Technology Review,April 24, 2007 **Brain Implants to Restore Vision**

LGN Approach

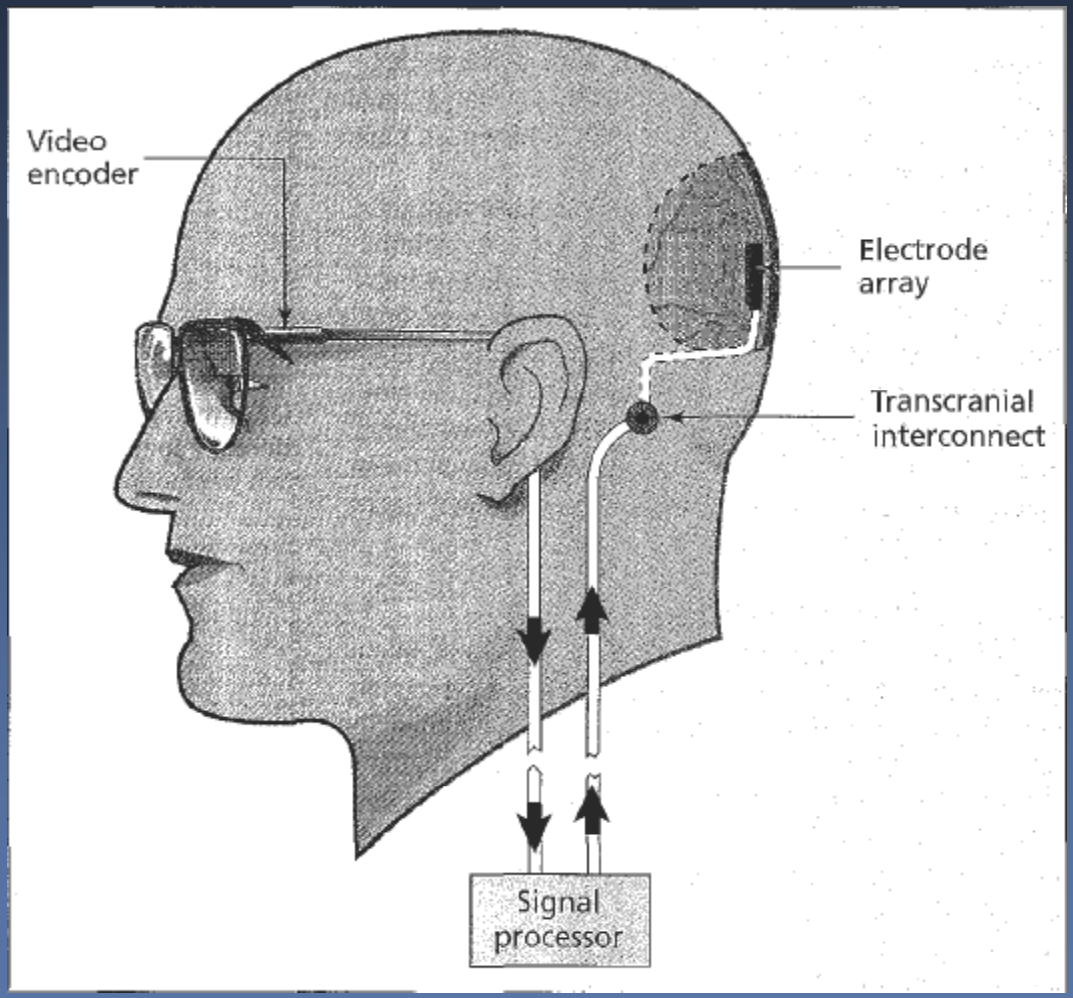
Advantages

- Encoded neural signals not yet extensively processed and spread throughout the brain.
- Straightforward mapping of the visual scene
- Patients with extensive retina/optic nerve damage can be treated

Disadvantages

- Surgical difficulty
- Spaced too closely together to be stimulated individually

Cortical approach



Source: (Normann,1999)

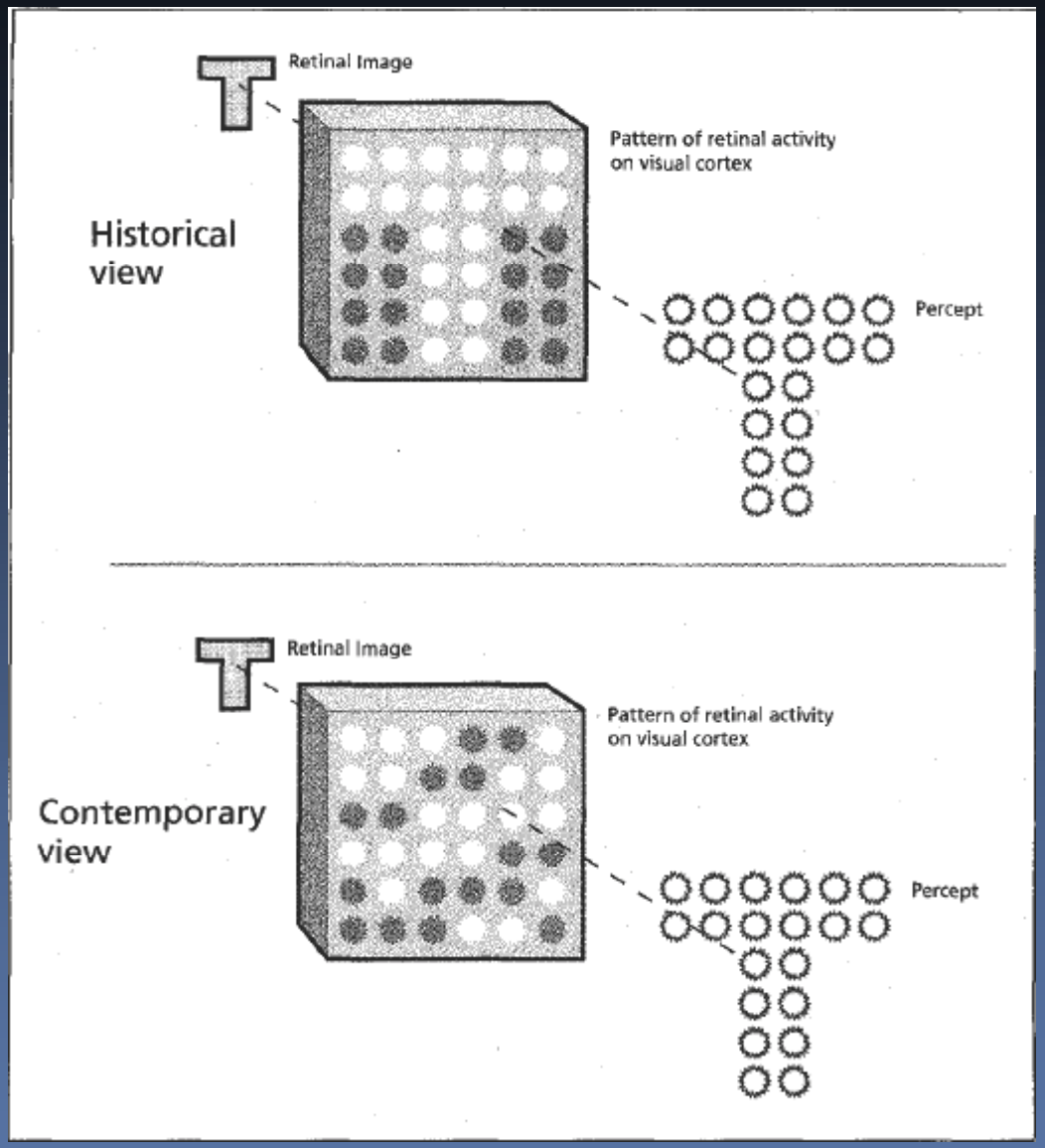
Cortical Approach

Advantages

- Skull will protect both electronics and electrode array
- Bypass the diseased neurons distal to visual cortex
- Potential to restore the vision to largest number of blind patients.

Disadvantages

- Spatial organization is too complex
- Convoluted cortical surface
- Surgical complications



- Patterned electrical stimulation may not produce patterned perception.

Source: (Normann,1999)

Types of Cortical Stimulation

Surface

- Higher threshold currents (mA)
- Larger spacing b/w electrodes.
- Multiple closely spaced phosphenes unachievable
- Phosphene interaction
- Not in demand

Intracortical

- Lower threshold current (μA)
- Closely spaced electrodes
- Predictable forms of generated phosphenes
- Reduction of phosphene interaction
- Greater two point resolution

Materials Used (Epiretinal)

- Parylene with Ti and Pt electrodes
  - superior barrier properties
- Polyimide flexi-circuits with Au/Ir/Pt electrodes
- Tacks (Co-Ni-Cr-Mo-W) alloy
- Adhesive glues (Cel-Tak, PEG based hydrogels)

Materials Used(Subretinal)

- Amorphous Aluminium oxide
  - high blood compatibility
  - excellent barrier properties
- Diamond like carbon (DLC)
- PEG
- Atomically ordered oxide films (NASA)

Epiretinal Electrode Arrays
Materials Concerns

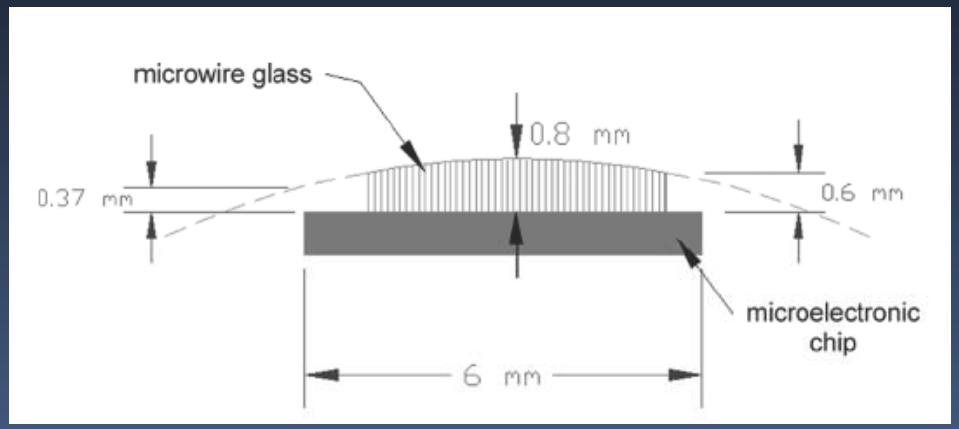
- The subcutaneous cable
- Tacks for stapling the arrays
- Glues turn solid and brittle, change the pH, cause severe inflammation and damage
- Platinum degrades under stimulation conditions in presence of proteins
- Gold also dissolves over an extended period
- TiN stable in subretinal space but adverse on retinal tissue

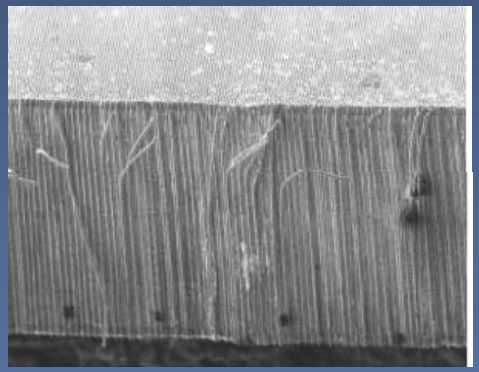
“Currently IrOx the only suitable high charge electrode”

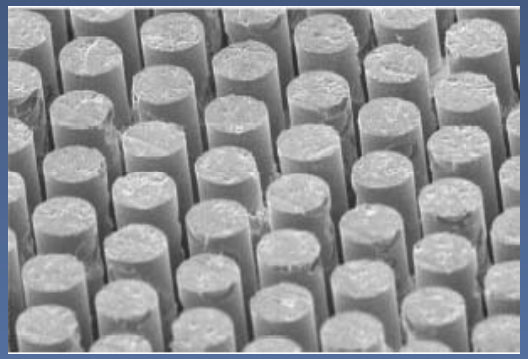
Subretinal Electrode Arrays Materials concerns

- PI (mixed reports)
  - suitable material (need additional coating for active components)
  - Not suitable (retina disorganization)
- AAO good from extraocular unit only
- MPD diverse reports on toxicity
  - Silicon chemically unstable in retina
- Passivation layers
  - Silicon oxide dissolves in the physiological medium
  - SiC mixed reports
  - Benzocyclobutene (best results) doesn't adhere well to TiN or IrOx

Ex: Epiretinal Intraocular Prosthesis





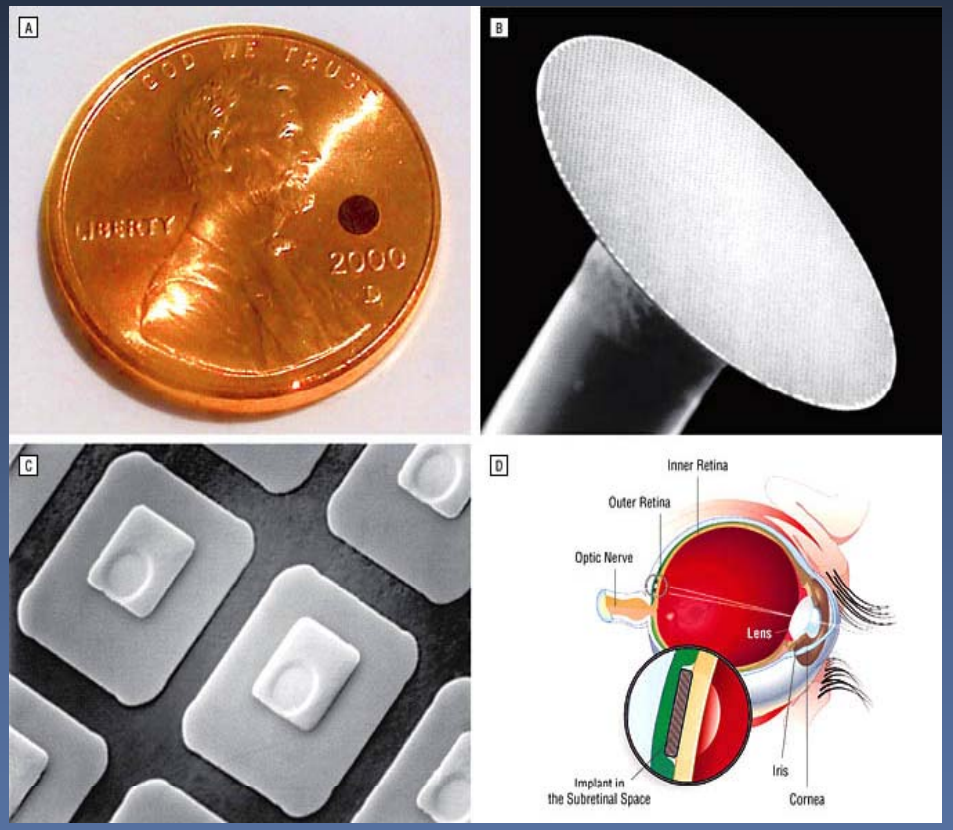


- Joint effort of U.S. NRL and John Hopkins Univ. Hospital
- Test device for short term human experiments
- No Clinical trials
- Design combines
  - electrode arrays fabricated from nanochannel glass
  - infrared focal plane array mux

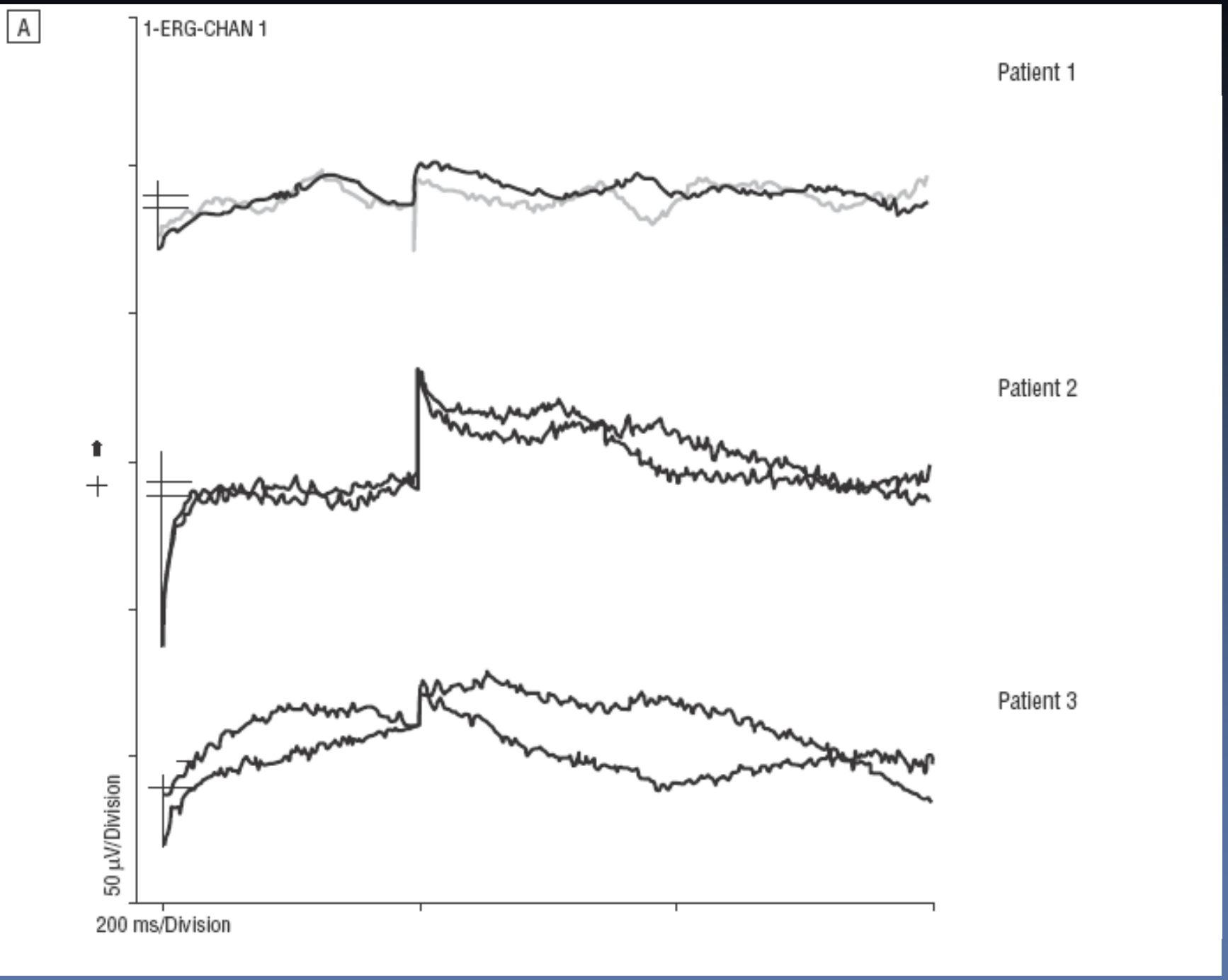
Source: (Scribner, 2007)

Ex: Subretinal Artificial Silicon Retina

- Clinical trials (6 RP patients)
- A 2-mm-diameter semiconductor MPDA chip,
- 25 μm in thickness
- ~ 5000 independently functioning electrode-tipped MPD
- powered solely by incident light.
- Into Clinical Trials

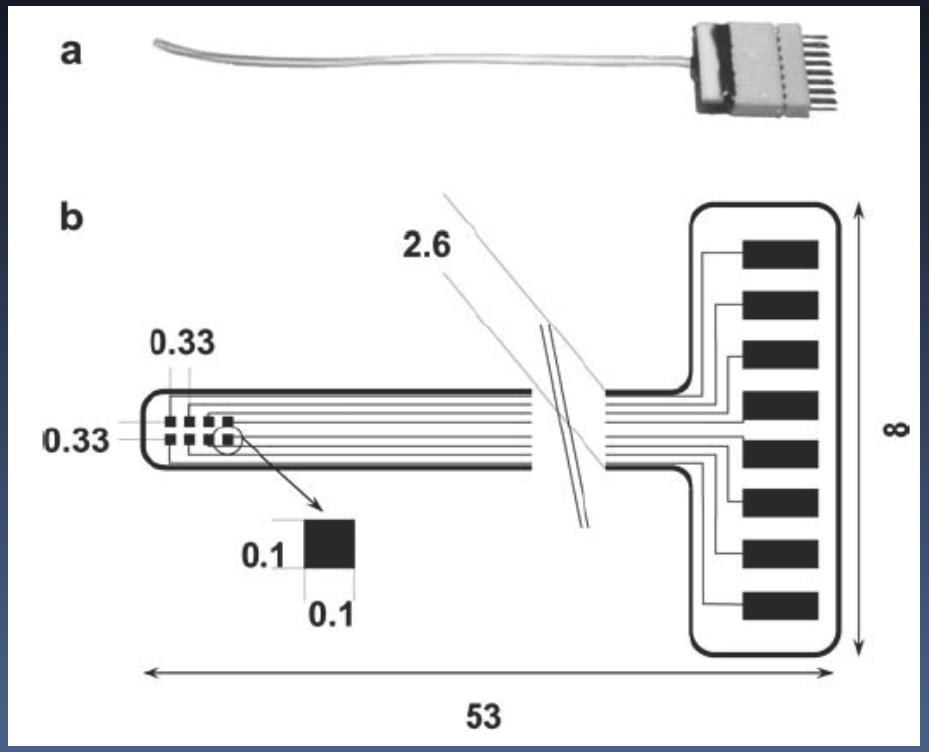


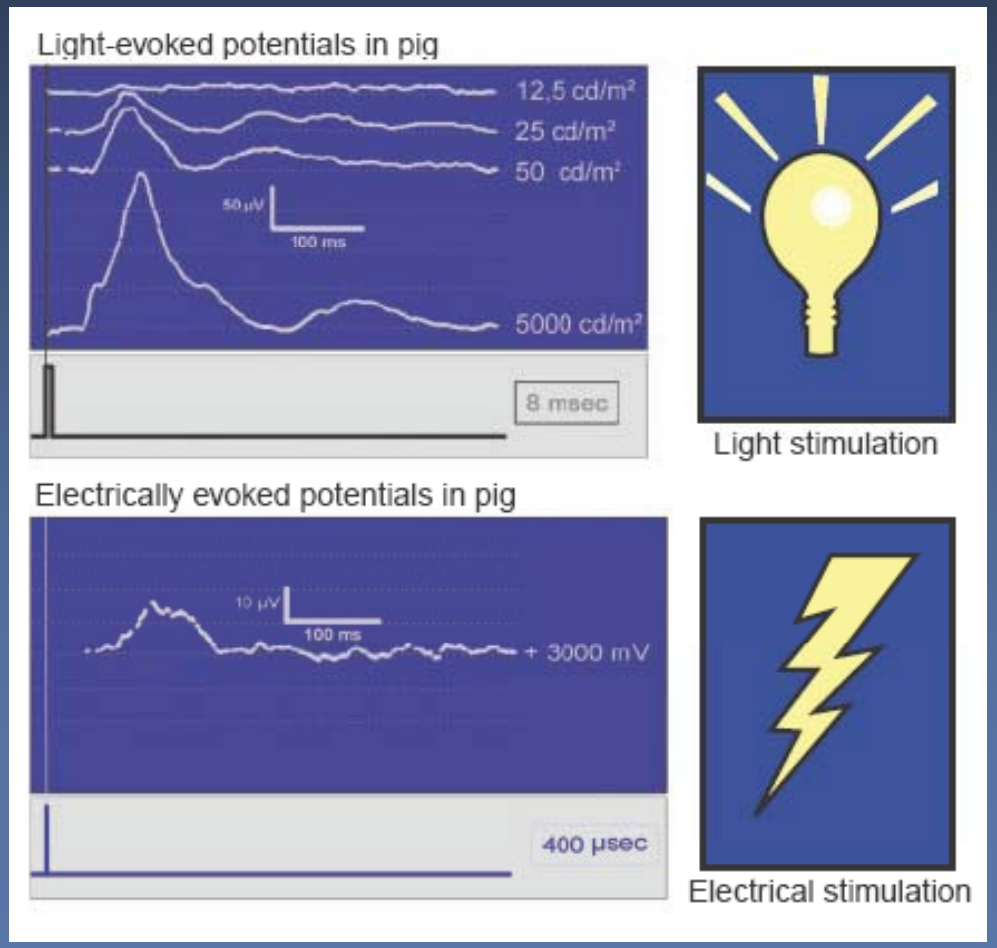
Source: (Chow 2004)



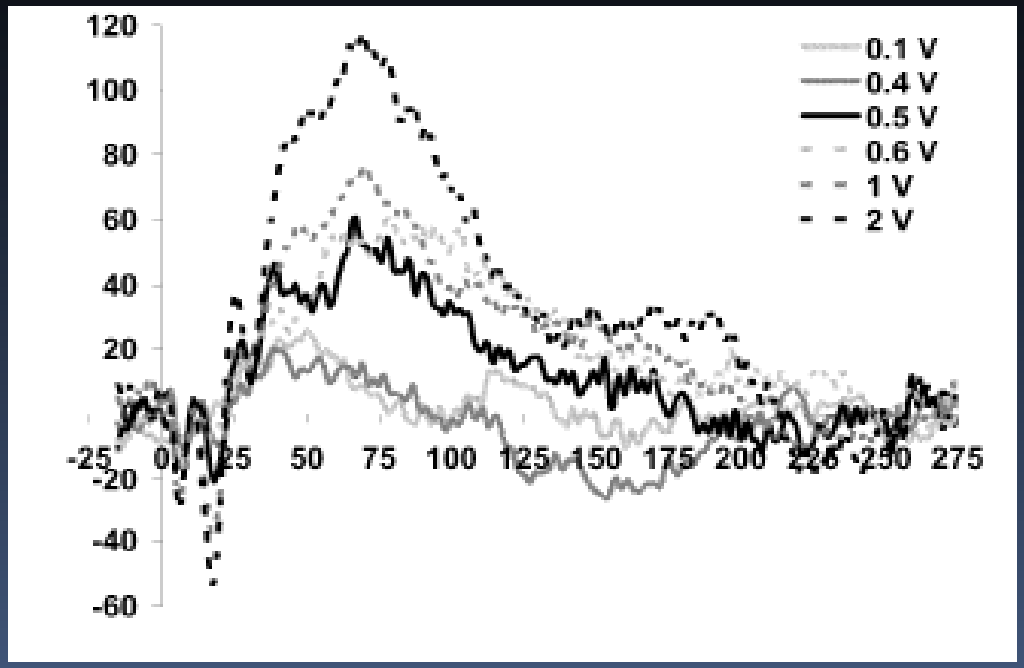
Source: (Chow 2004)

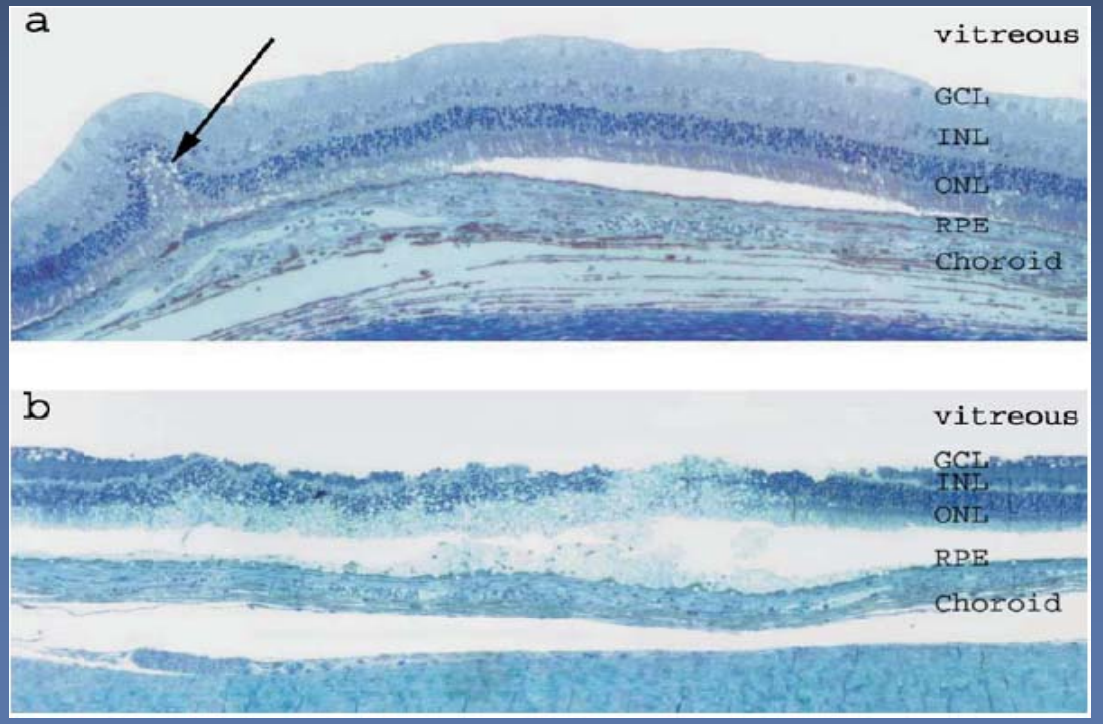
Ex: Subretinal electrode array (Zrenner group)





Source:(Zrenner,2004)





Source:(Zrenner,2004)

Ex:Biohybrid Retinal Implant

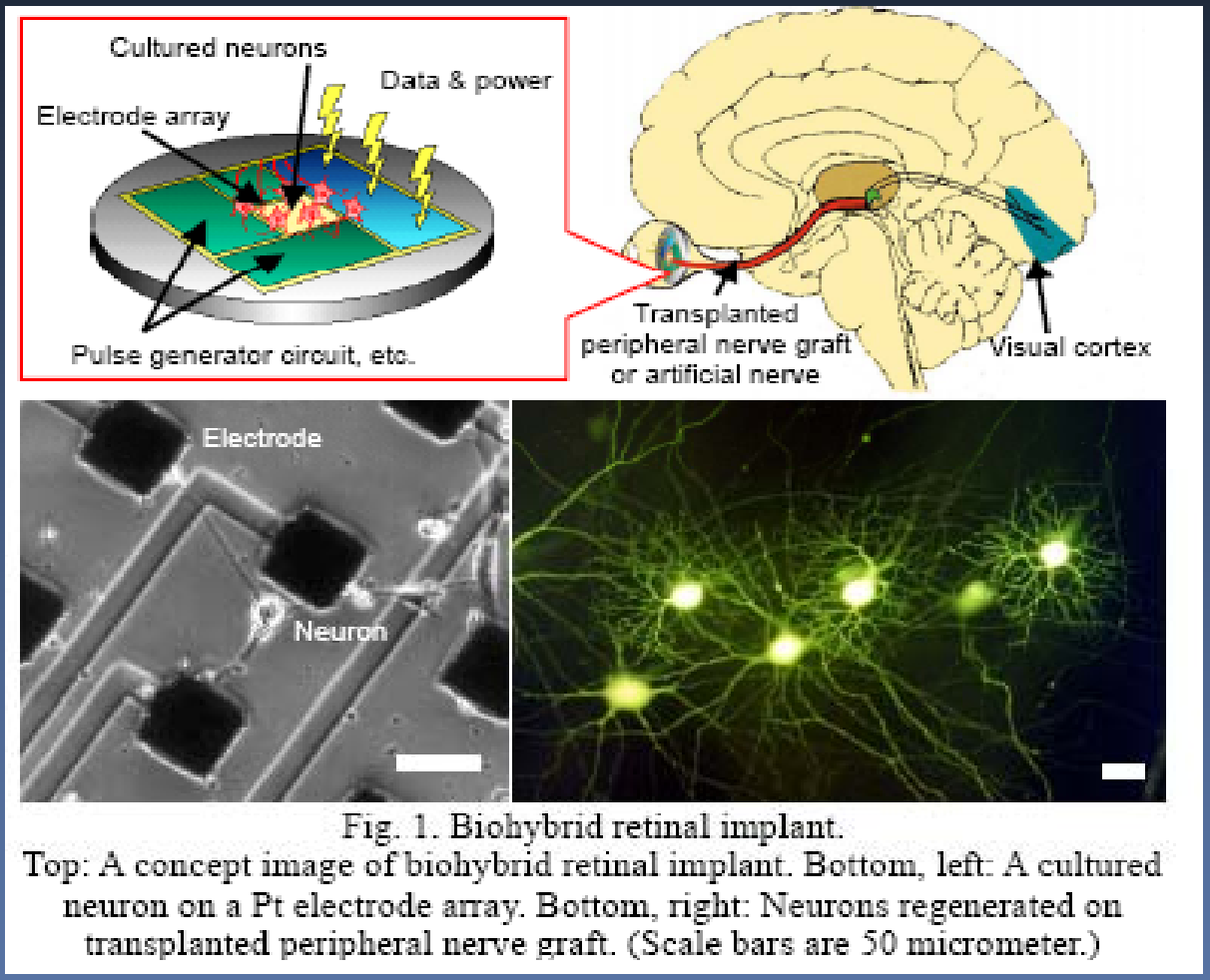


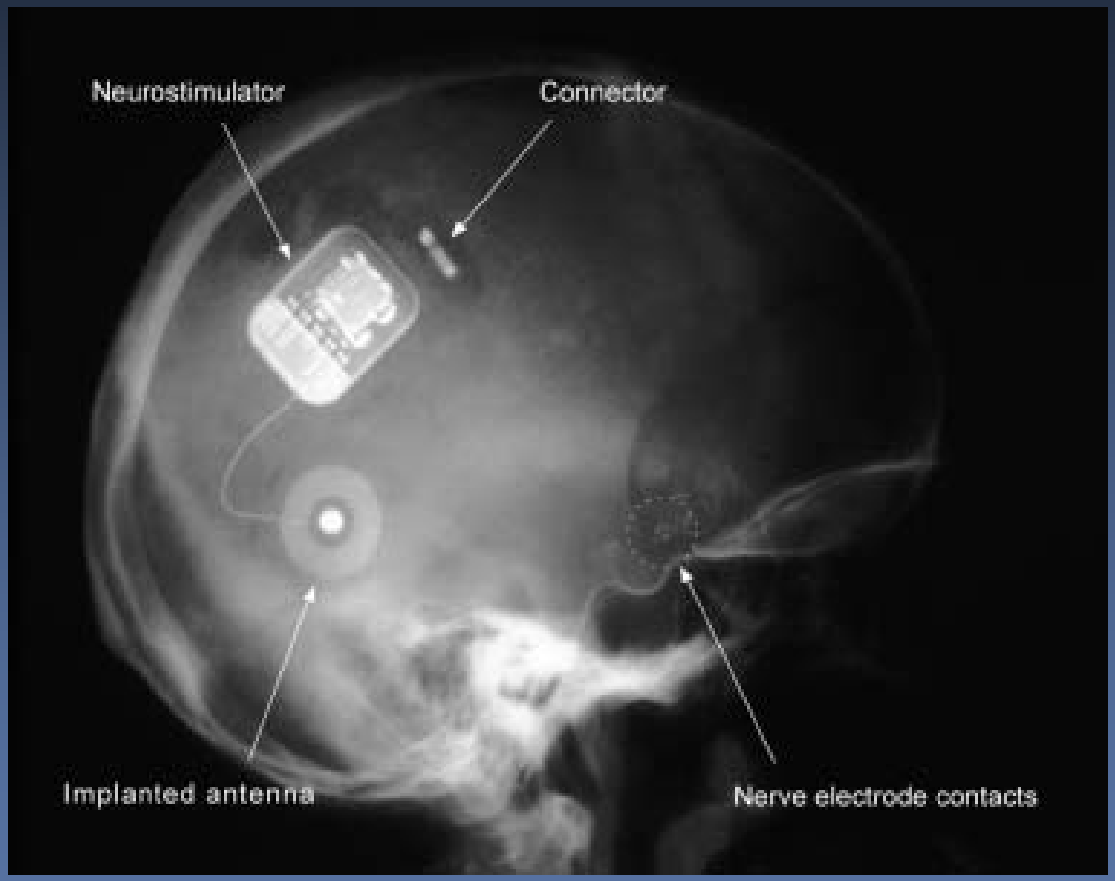
Fig. 1. Biohybrid retinal implant.
Top: A concept image of biohybrid retinal implant. Bottom, left: A cultured neuron on a Pt electrode array. Bottom, right: Neurons regenerated on transplanted peripheral nerve graft. (Scale bars are 50 micrometer.)

- Both biological and electronic components
- Not into Clinical Trials
- Only *In vivo* exp.

Source (Yagi,2005)

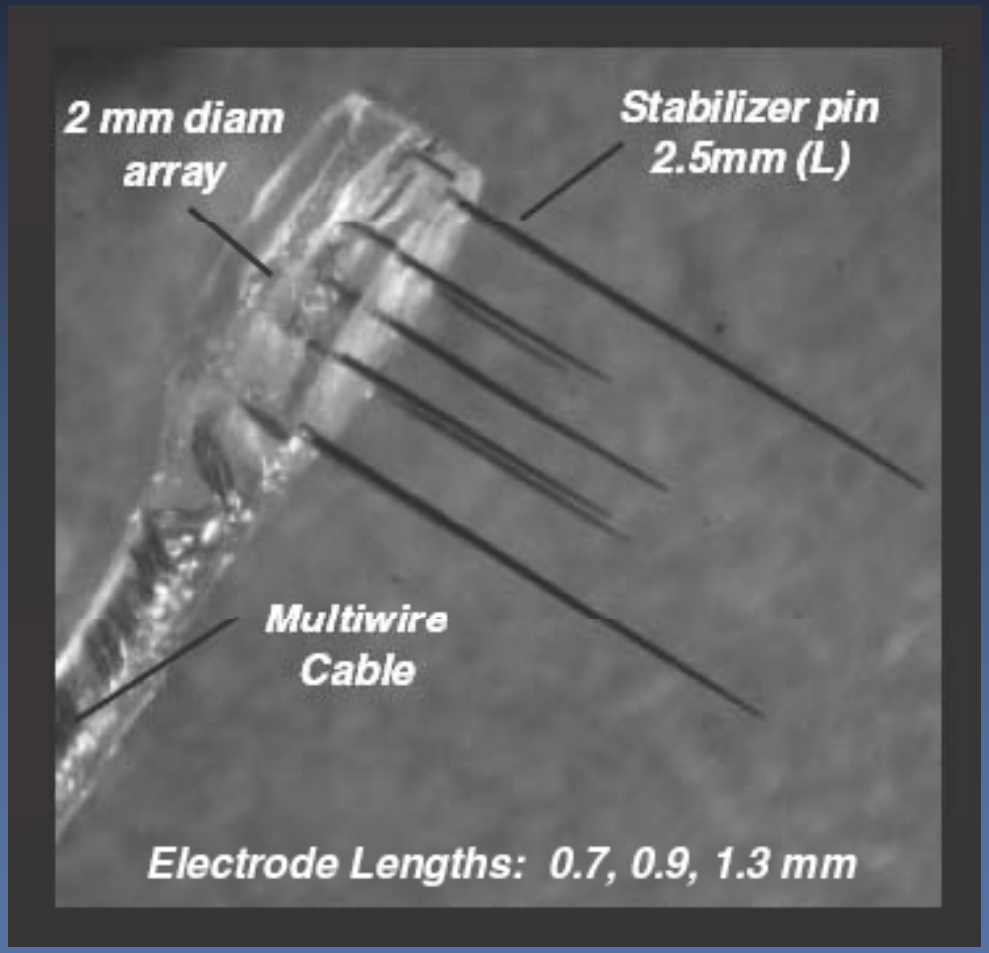
Ex: Optic Nerve Prosthesis

- Cuff Spiral electrodes
- Into Clinical Trials



Source (Veraart,2003)

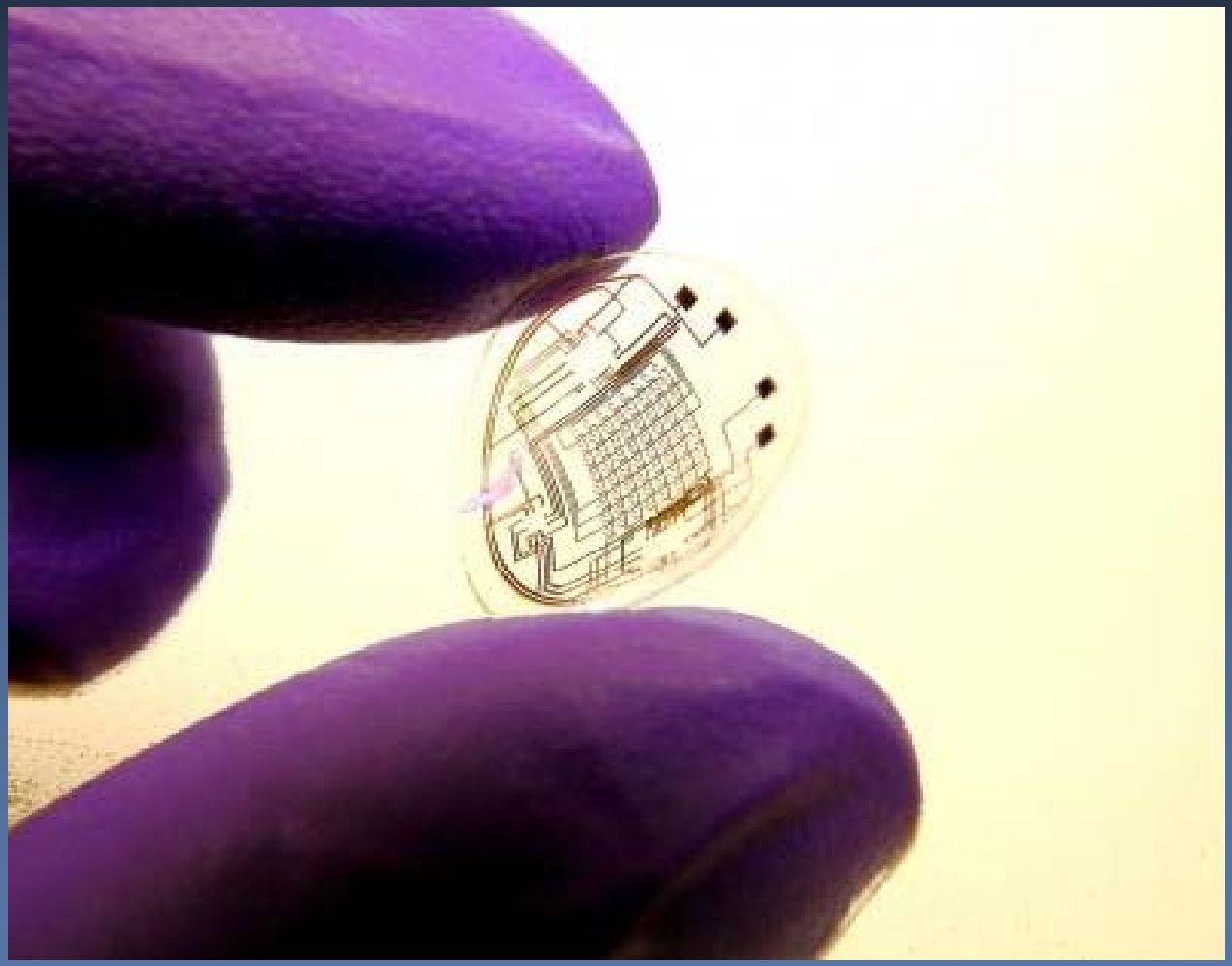
Ex: Intracortical Visual Prosthesis



- Developed at HMRI
- In vivo studies in Monkeys

Source (Troyk,2003)

Bionic Vision: Electronic lens



Source
http://www.sciencentral.com/articles/view.php3type=article&article_id=218393067

Future work

- Better understanding of biocompatibility of electrodes
- Behavioural experiments in primates

  (determine the stability of the stimulation thresholds and evoked visual perceptions)
- Short term experiments in human volunteers

  (evaluate stimulation parameters for optimal phosphenes generation)

Unanswered Questions

- Will plasticity in the visual system be a major/minor factor?
- Does patterned electrical stimulation of the visual pathway result in a patterned visual perception?
- How do closely spaced electrodes in either the retina/cortex interact to produce lines/complex shapes from multiple phosphenes?

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