The retina: What can go wrong and how can we make it better?

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Two leading causes of blindness/vision loss

- **Diabetic Retinopathy**
  - rises from 2% to 8% between 40 and 74 years

- **Age Related Macular Degeneration**
  - rises from 3% to 11% between 75 and 80 years

*images from the National Eye Institute of NIH*
Retina

~100 million photoreceptors

~1 million axons
Parallel pathways in the retina

OFF pathway
- Cone
- Bipolar
- Ganglion

Increases spike rate in response to *decrements* of light

ON pathway
- Cone
- Bipolar
- Ganglion

Increases spike rate in response to *increments* of light

together: increase the dynamic range (allow to distinguish more subtle variation in light intensity)
Diabetic Retinopathy

diabetes causes blockage of retinal blood vessels

deprived retinal neurons ask for more nutrients

new, abnormal, blood vessels grow

new blood vessels leak

leakage kills retinal neurons
Diabetic Retinopathy

retinal blood vessels are blocked

deprived retinal neurons ask for more nutrients

cannot kill some retinal neurons to delay the distress signal

new, abnormal, blood vessels grow

new blood vessels leak

leakage kills retinal neurons
Photocoagulation

human retina after photocoagulation
Selective photoreceptor photocoagulation

barely visible lesion

1 hour rabbit reina

100 μm

532 nm

GANGLION CELLS
BIPOLAR CELLS
PHOTORECEPTORS

1 week

GANGLION CELLS
BIPOLAR CELLS
PHOTORECEPTORS

4 months

GANGLION CELLS
BIPOLAR CELLS
PHOTORECEPTORS

Selective photoreceptor photocoagulation
Methods

multielectrode array recording

512 electrodes spaced at 60 \( \mu \text{m} \)

SCIPP
AGH UST, Krakow, Poland
Salk Institute
Starthclyde U., Scotland
Methods

spike triggered average response of the detected cells
Methods

ON and OFF retinal ganglion cells
Methods

ON and OFF retinal ganglion cells

200 ms

400 μm

time to spike
Methods

retina on the electrode array
Methods

RPE abnormality zones
Methods

receptive fields of recorded RGCs
Methods

400 μm
Visual sensitivity is restored

1 day

RPE

receptive fields

example OFF RGC

example ON RGC

2 month

400 m
Visual sensitivity is restored

all RGCs
OFF RGCs
ON RGCs

relative sensitivity

lesion age (days)
Rewiring

light-responsive RGCs

1 day

no rewiring

rewiring

2 month

relative density of RGCs at the lesion site from two preparations
Conclusions

• Visual sensitivity restoration occurs both in ON and OFF retinal pathways.

• Migrating photoreceptors rewire to deafferented bipolar cells, bringing retinal circuitry closer to normal and demonstrating restorative plasticity.

• Selective ablation of photoreceptors avoids side effects that accompany conventional (more severe) burns, while reducing the metabolic load by killing photoreceptors. It also allows for repeated treatment.
Age related macular degeneration

photoreceptors in the central retina (macula) start to break down causing blurring and potentially blind spots
Age related macular degeneration

photoreceptors in the central retina (macula) start to break down causing blurring and potentially blind spots

But the processing and output retinal neurons are still there!

Activate them using electrical currents
Subretinal photovoltaic prosthesis

Each photodiode pixel consists of 3 diodes in series.

Peripheral vision is often preserved in AMD patients, which helps maintain their visual acuity at the level of about 20/400, a small retinotomy, while tiling permits expansion of the 'window' (electrode polarization between active and return electrodes), thus avoiding water electrolysis and simplifying the surgical procedure; an external camera allows decoding electronics box connected to the retinal stimulation circuitry and requires high-frequency stimulation to elicit burst responses.

The nerve fibre layer and axonal stimulation thresholds are similar 20/1,260 (ref. 7). As epiretinal electrodes are positioned on top on successful implantation in 30 patients with a best visual acuity of up to 20/550 (ref. 16), still significantly lower than would be reported visual acuity of up to 20/1,200 (ref. 8), and more recently in each pixel, to stimulate the retina.

Power is provided via a cable in a cochlear implant14,15. In the first clinical trial, the company Macmillan Publishers Limited. All rights reserved.

Transdermal magnetic coupler delivers the power to the receiver, as that exits the eye, and is routed under the skin to behind the ear. A transscleral cable is rather complex, with 30% of implants only allowing power to be transmitted to a limited dynamic range of ambient light. The device includes a complex surgery involving many structures of the eye, the orbit and the skull and a limited dynamic range of ambient illumination and provides a small retinotomy, while tiling permits expansion of the 'window' (electrode polarization between active and return electrodes), thus avoiding water electrolysis and simplifying the surgical procedure; an external camera allows decoding electronics box connected to the retinal stimulation circuitry and requires high-frequency stimulation to elicit burst responses.

Recently, an epiretinal implant with 5 electrodes positioned on the epiretinal surface bypasses inner retinal neurons (inner nuclear and ganglion cell layers) that are stimulated with single epiretinal electrodes. Current studies are aiming at development of selective targeting of ganglion cells.

Each photodiode pixel consists of 3 diodes in series.

Each photodiode pixel consists of 3 diodes in series.
Photovoltaic prosthesis activates ganglion cells

- Ganglion cells can be activated with a safe amount of infrared light.
- Activation occurs not directly, but through the bipolar cells.

*Matheison, et al, Nature Photonics, 2012*
Implantation procedure

video courtesy of D. Palanker
Brain visual areas get activated through the prosthesis

Optical Coherence Tomography image of the photodiode array chronically implanted under the rat retina.

Visually Evoked Potentials recorded from the rat implanted with the photodiode array.


What is the spatial resolution?
Stimulus Spread: Electrical and Retinal
Methods

- **Visible light stimulation of wild-type rat retina:**

- **Photodiode stimulation of RCS degenerate retina:**
  - Lacking photoreceptor layer
  - Photodiode pixel
  - NIR light pulse ~880nm

**Multielectrode recording array with 512 electrodes, spaced at 60 microns**
Mapping the Spread of Stimulation

Radial spread: defined as distance at which stimulation drops to 50% of its maximum.
Conclusions

• Photovoltaic retinal prosthesis provides for safe stimulation of the retina that is relayed to the brain.

• Measured spatial spread of photovoltaic stimulation is comparable to the spread of visual stimulation measured in the healthy rat retina.

• It remains to be seen if this prosthesis design can provide spatial resolution needed by ARMD patients.
Thank you!

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