Optogenetic visual cortical prosthesis

Conflicts of interest: I have filed a number of patents and CANDO may have commercial impact. But currently no commercial interests.

Dr. Patrick Degenaar

Reader in Neuroprosthesis

Newcastle University

Neuroprosthetics @ Newcastle

Epilepsy brain prosthesis

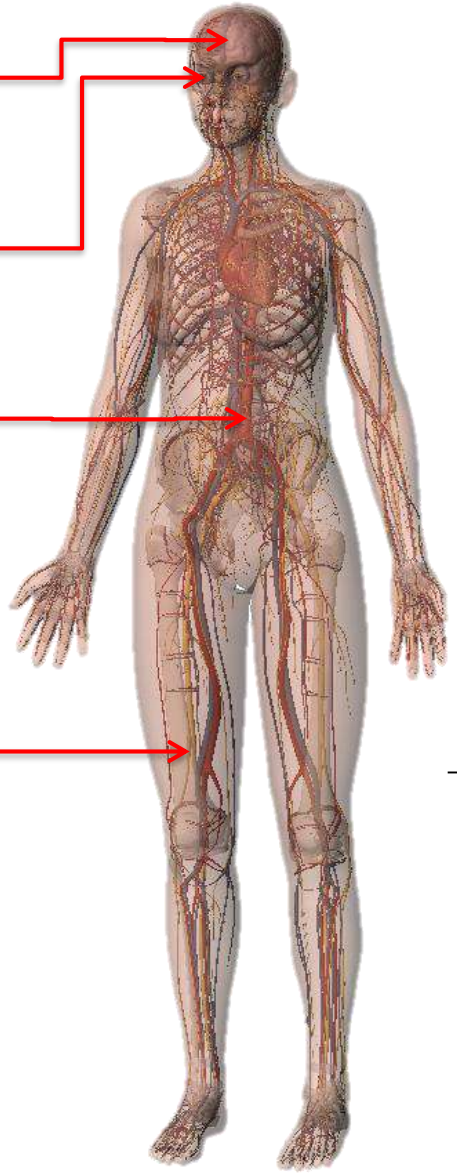
http://www.cando.ac.uk

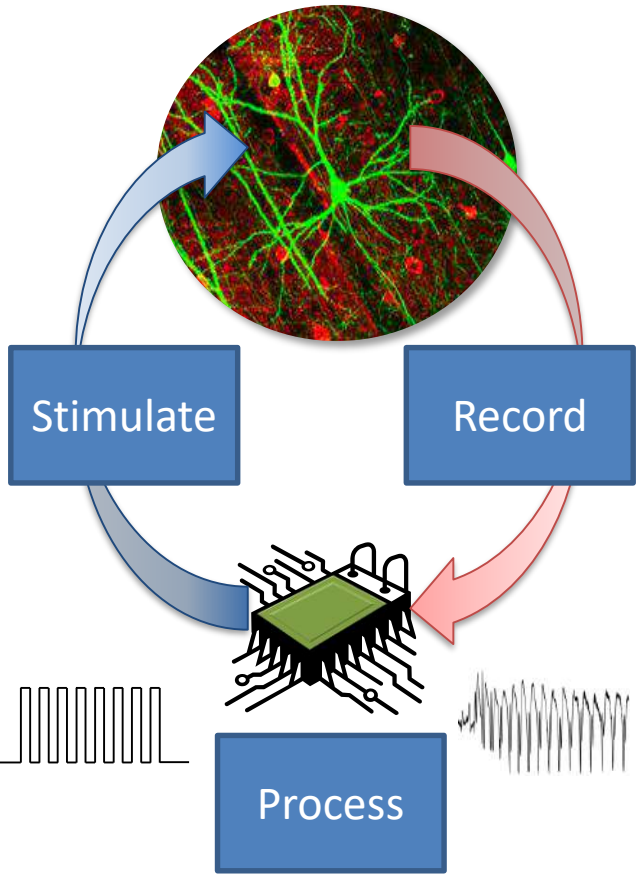
Visual prosthesis

http://www.optoneuro.eu

Spinal cord injury

Hand/Leg bionics





Electrodiagnostics

Multi-EMG recording

Closed loop neural interfaces!!

SEVENTH FRAMEWORK PROGRAMME

EPSRC

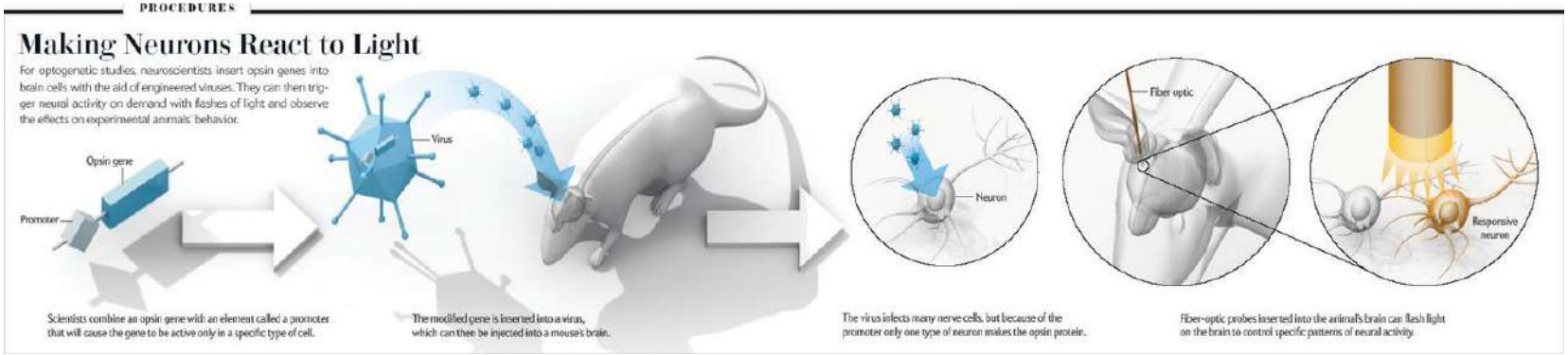
wellcome trust

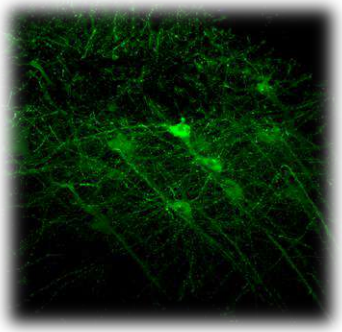
Newcastle University

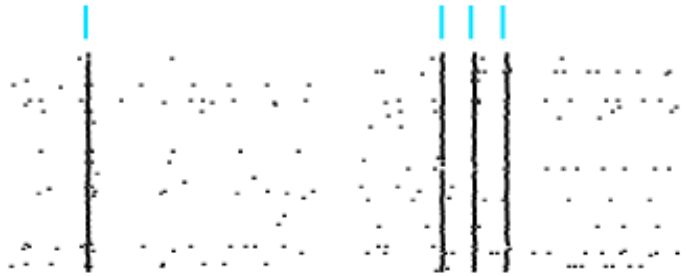
CANDO

Controlling Abnormal Network Dynamics using Optogenetics

The optogenetics revolution

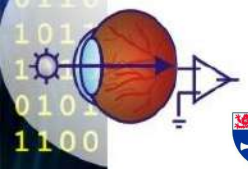






Blue light is used to activate neurons expressing channelrhodopsin. Other opsins can silence activity

Optogenetic control of behaviour. Gradinaru et al. *J Neurosci* (2007)



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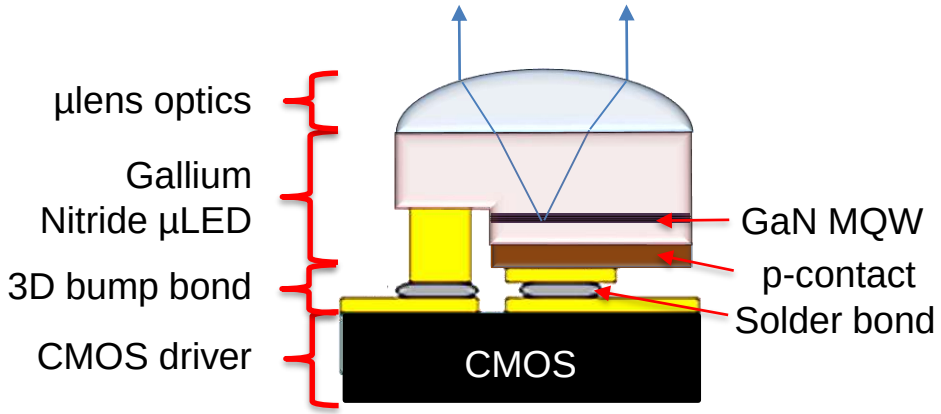
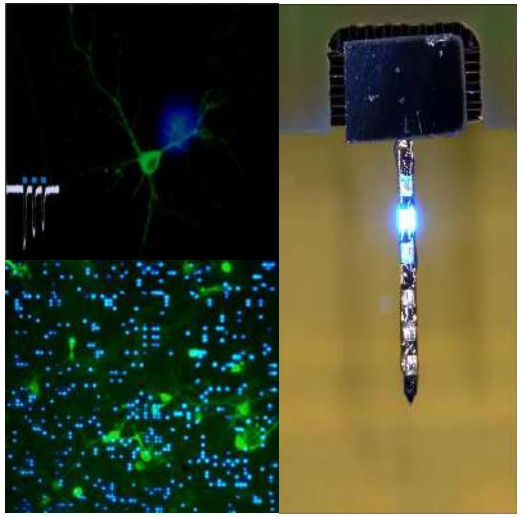
Optoelectronics for optogenetics





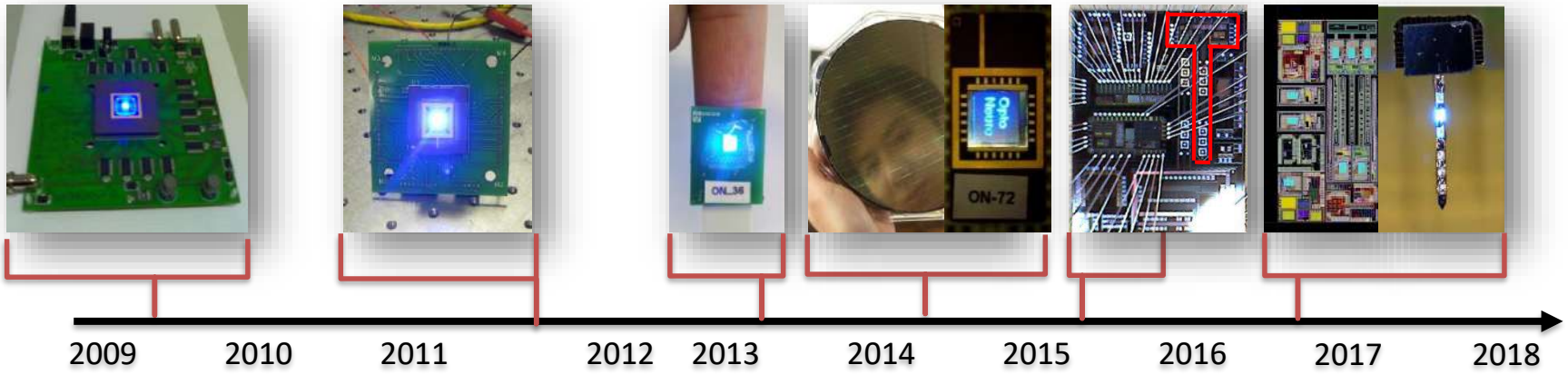
64x64, 64x1 passive µLED arrays

16 x 16 MPW CMOS chip driven µLED arrays

90x90 Retina wafer

CANDO 1 Optrode

CANDO 3 Wafer



High radiance optoelectronics for optogenetics:

Grossman N et al. IEEE TBME 2011, 58(6), 1742-1751.

McGovern B et al IEEE TBCAS 2010, 4(6, part 2), 469-476.

Grossman N et al, J. Neural Engineering 2010, 7(1), 016004.

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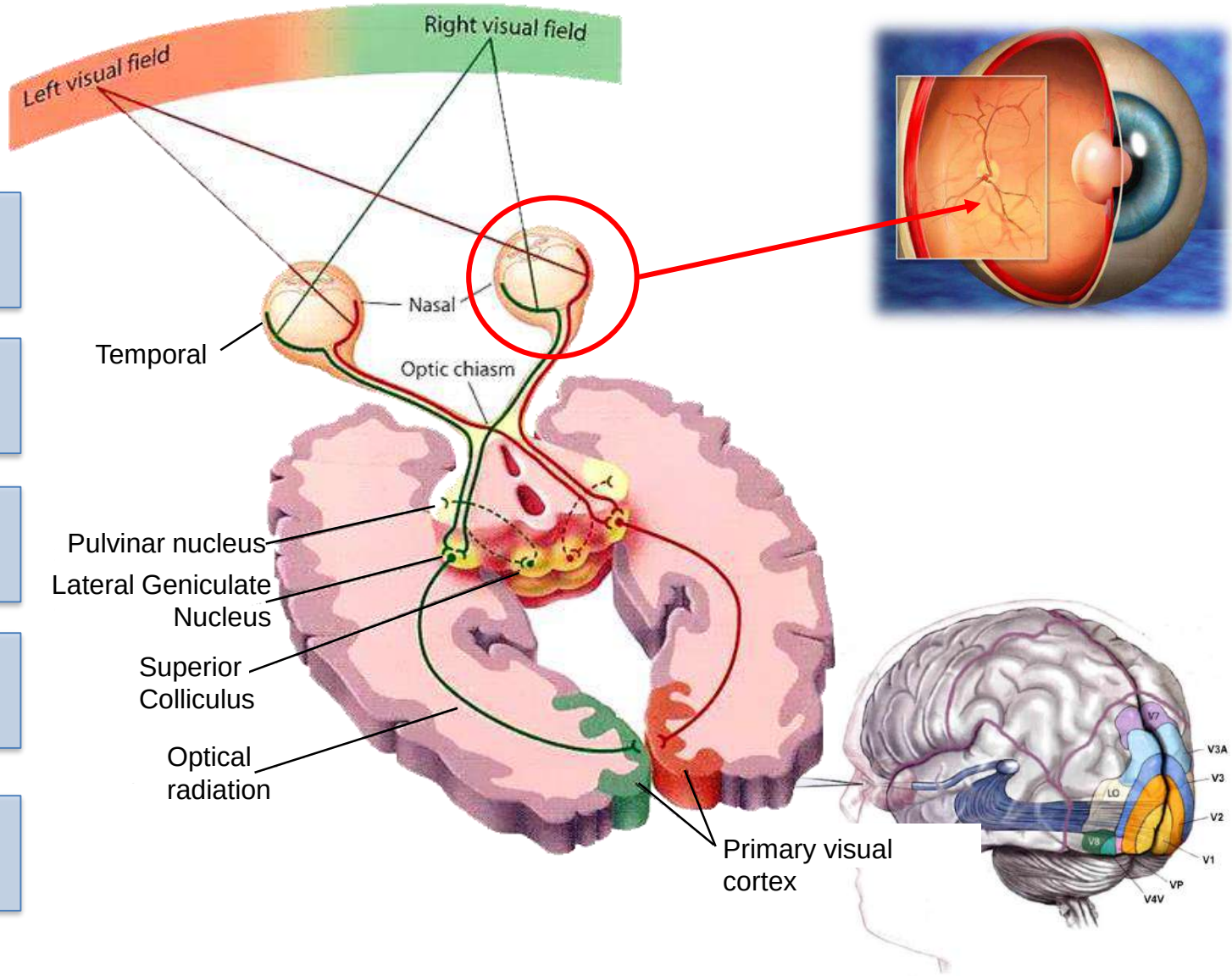
The visual system

- Optics (cornea/lens)
- Sense/code (retina)
- Transmission (Optic Nerve)
- Sorting (Thalamus)
- Interpretation (Visual Cortex)

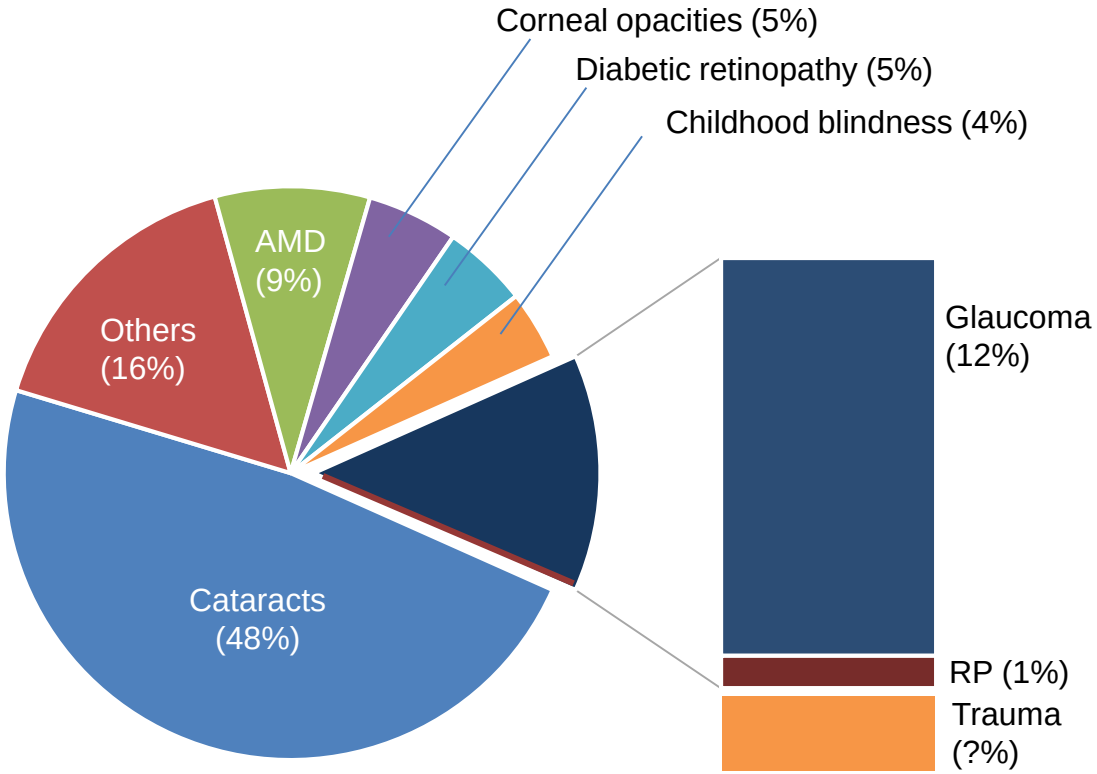


Visual loss: statistics

According to WHO, about 180 million people worldwide have a visual impairment

Legal blindness:

“medically diagnosed central visual acuity of 20/200 or less in the better eye with the best possible correction, and/or a visual field of 20 degrees or less”



From: WHO

Primary visual prosthesis target conditions

Drugs and gene therapy becoming increasingly useful.. But cannot restore lost vision

Disorders of the visual system

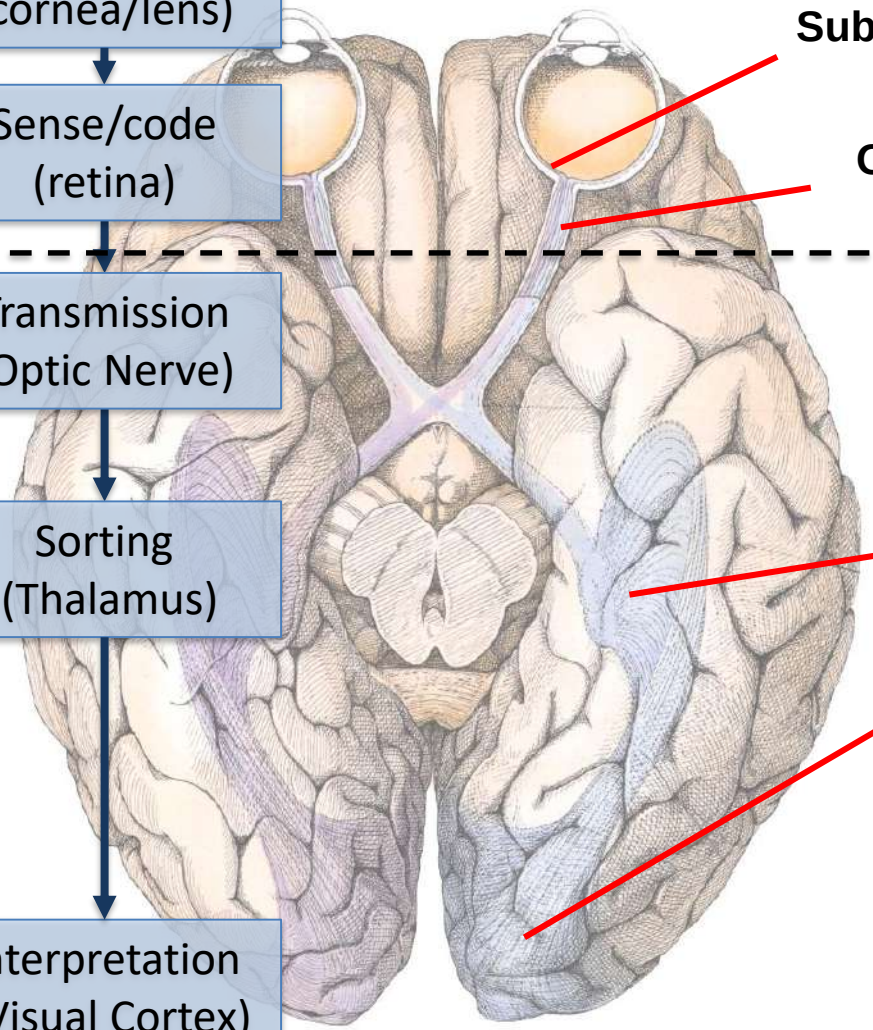
Optics (cornea/lens)

Sense/code (retina)

Transmission (Optic Nerve)

Sorting (Thalamus)

Interpretation (Visual Cortex)



Sub/epi retinal prosthesis

Optic nerve prosthesis

Retinitis Pigmentosa

(<1% of blindness)

LGN prosthesis

Cortical prosthesis

Glaucoma

Trauma

Other severe blindness

(~30% of blindness)

For invasive procedures only!
Very expensive!
Will be enormously difficult!
But can treat much larger cohort

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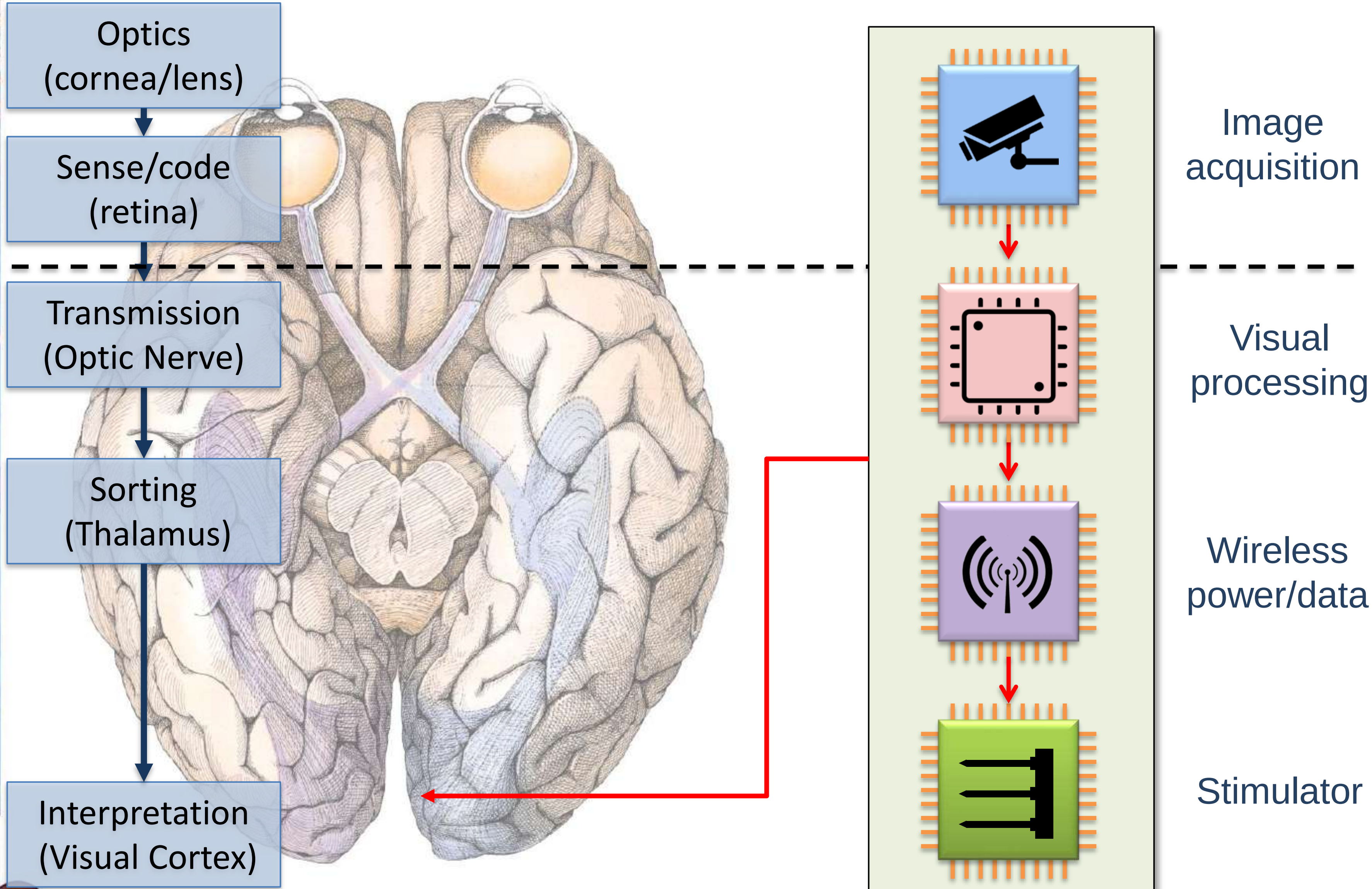
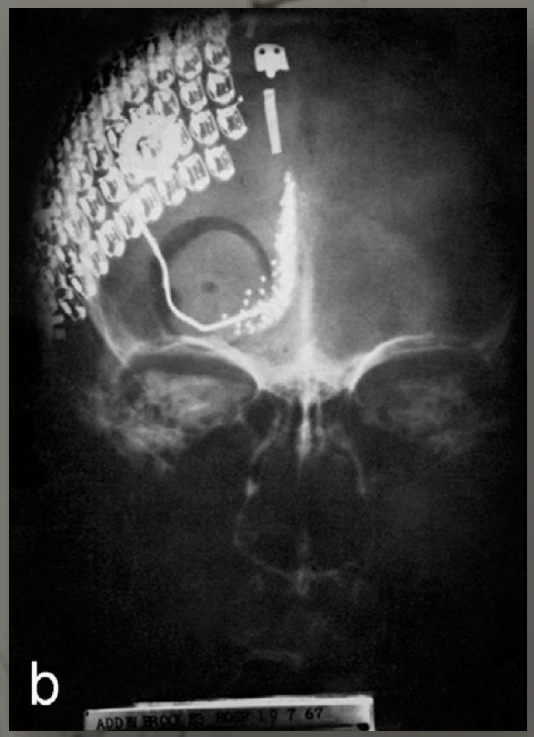
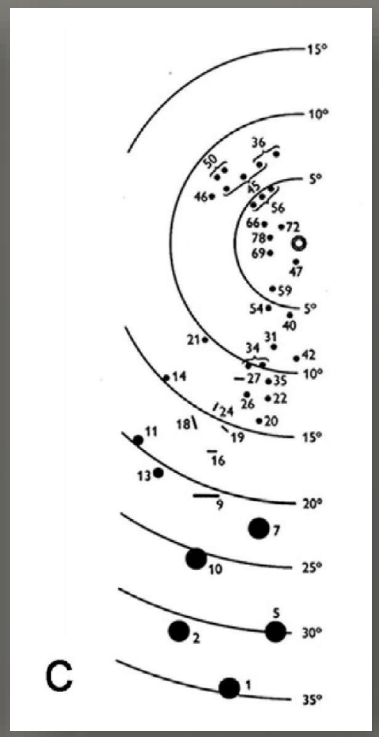
Implementing a visual prosthesis



Easy??





Brindley and Lewin did it in 1968!!!

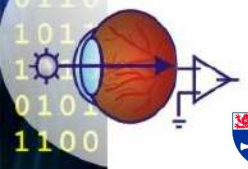
- Brindley,G.S.,Lewin,W.S.,1968.The visual sensations produced by electrical stimulation of the medial occipital cortex. J Physiol.19454-5P.
- Brindley,G.S.,Lewin,W.S.,1968.The sensations produced by electrical stimulation of the visual cortex.J.Physiol.196,479–493.

Challenge 1: Sheer scale of challenge

1960's: You could build a device on a Monday and put it in a patient on a Friday

Now: A project to create an active implantable device requires £10-50M and 5-10 years worth of regulatory effort to demonstrate safety before implantation is allowed

As such, almost the entire field moved to retinal prosthesis in the 1990's as it was a much easier target!!



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Challenge 2: Visual acuity

Normal vision

山登り

Asian/pictographic scripts:

~ 1000 pixels

Hillwalking

European/phonetic scripts:

~ 5000 pixels

k

European/phonetic characters:

~ 100 pixels

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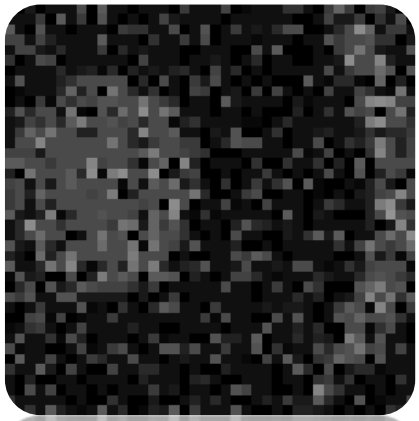
Lessons from retinal prosthetics



1500 electrodes – but only a few dozen can be on at any moment in time.

From Retina AG

Eberhard-Karls-Universität
UKT
Universitätsklinikum Tübingen

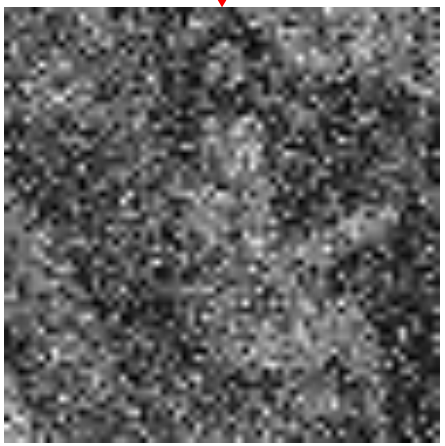
Challenge 3: Effective contrast

Original image

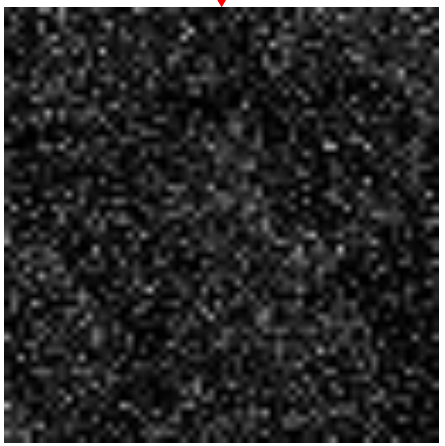
Assume greyscale retina @ 64 x 64 resolution

Add noisy retina effect

With insufficient stimulus contrast it is like whispering through a typhoon!

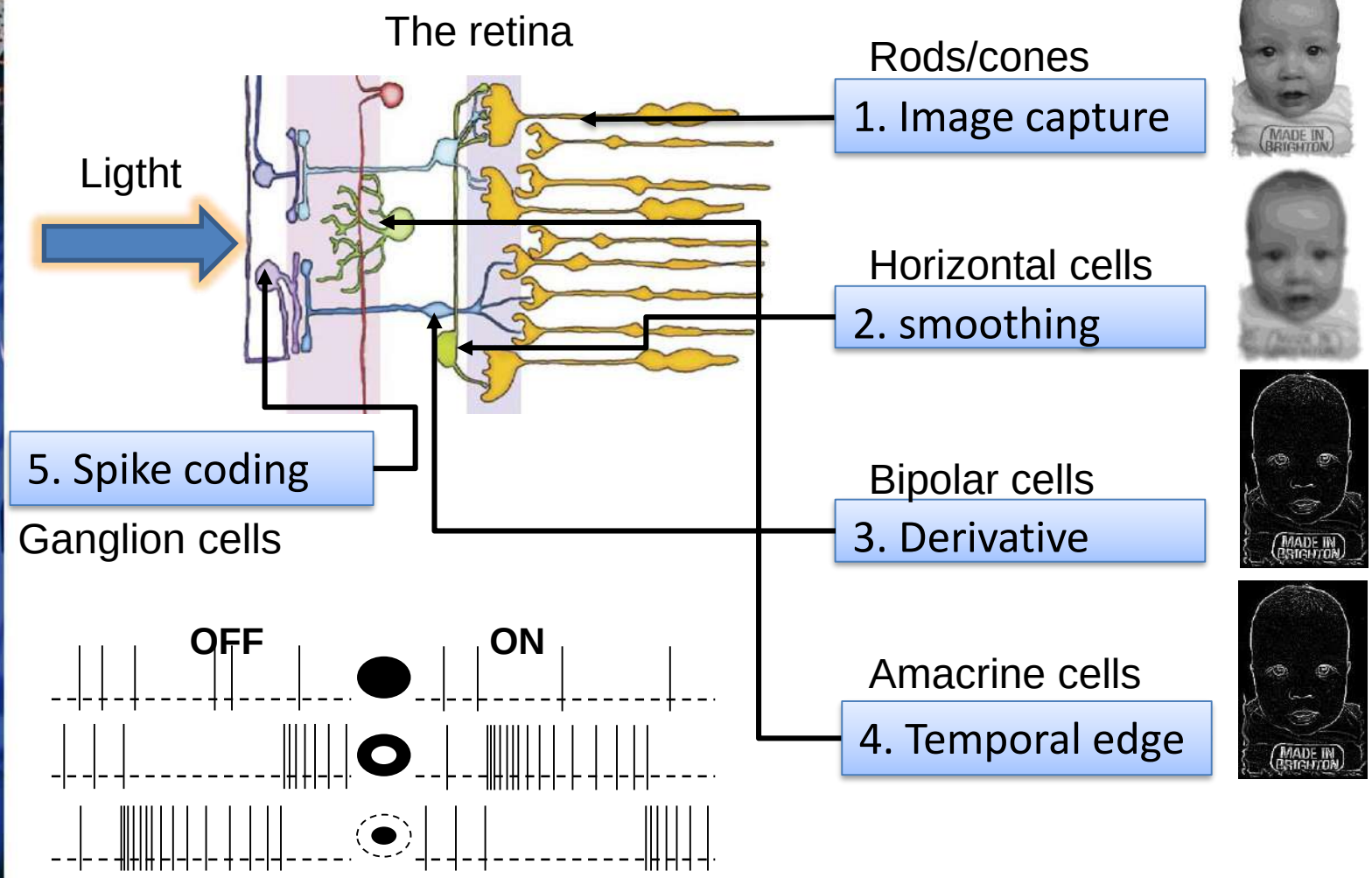


100:1 contrast ratio



50:1 contrast ratio

Challenge 4: The eye is not a camera!



The retina has 60 different cell types. If we are bypassing the natural processing, we need to replicate the key features!

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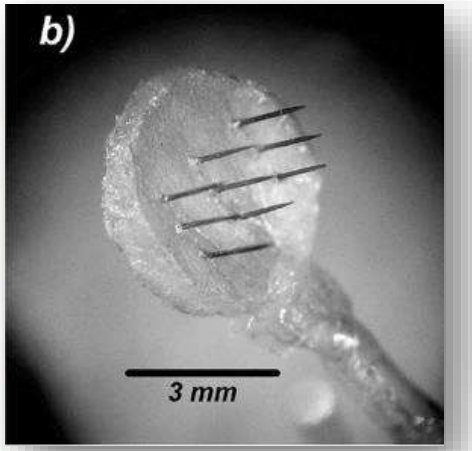
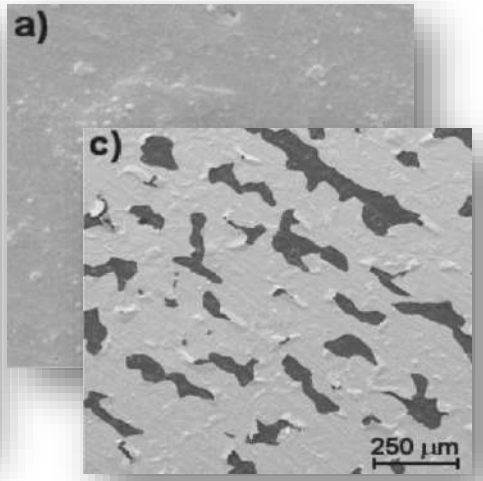
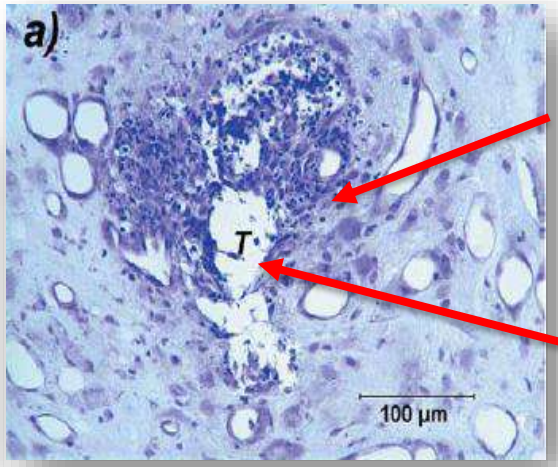
Challenge 5: Biocompatibility







Glial scarring

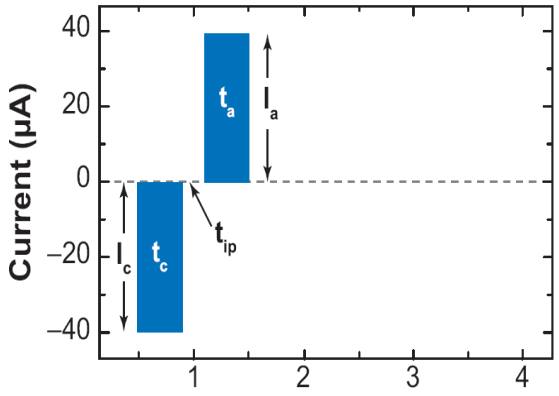
Electrode insertion point

Journal of The Electrochemical Society, ***152 (7) J85-J92 ~2005!***

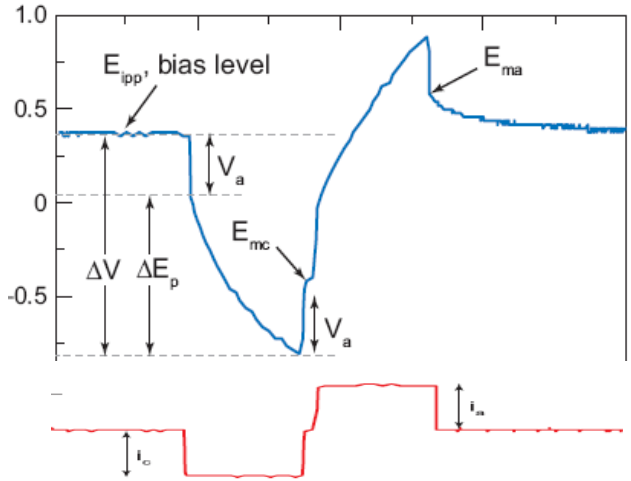
Accelerated ageing, 1000 cycles at 1.7V/s

IEEE Transactions on Neural Systems and Rehabilitation , Vol. 12, No. 2, June 2004

Ideal



Real



Electrode degradation and adverse tissue reactions are a major issue for smaller stimulating electrodes because of high charge density requirements

Annu. Rev. Biomed. Eng. 10:275–309, 2008

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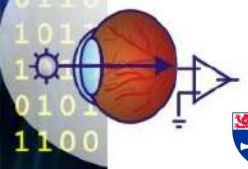
Where to start?



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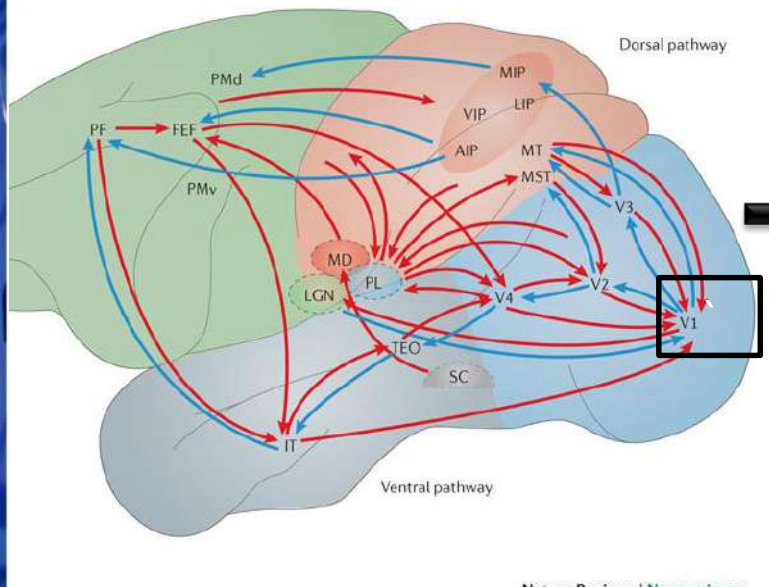
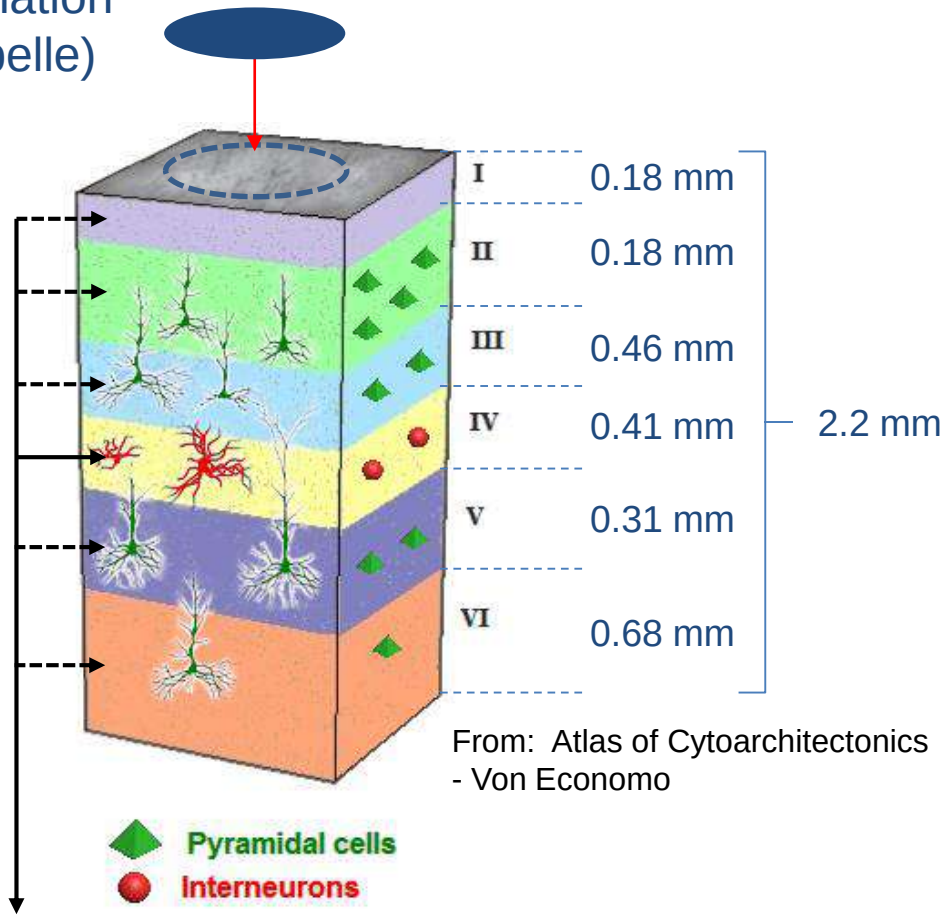
Developing the stimulator

Surface stimulation
(Brindley, Dobelle)





From: Atlas of Cytoarchitectonics - Von Economo

Penetrating stimulation

Can we make the communication bi-directional?
Can we treat communication as a control problem?

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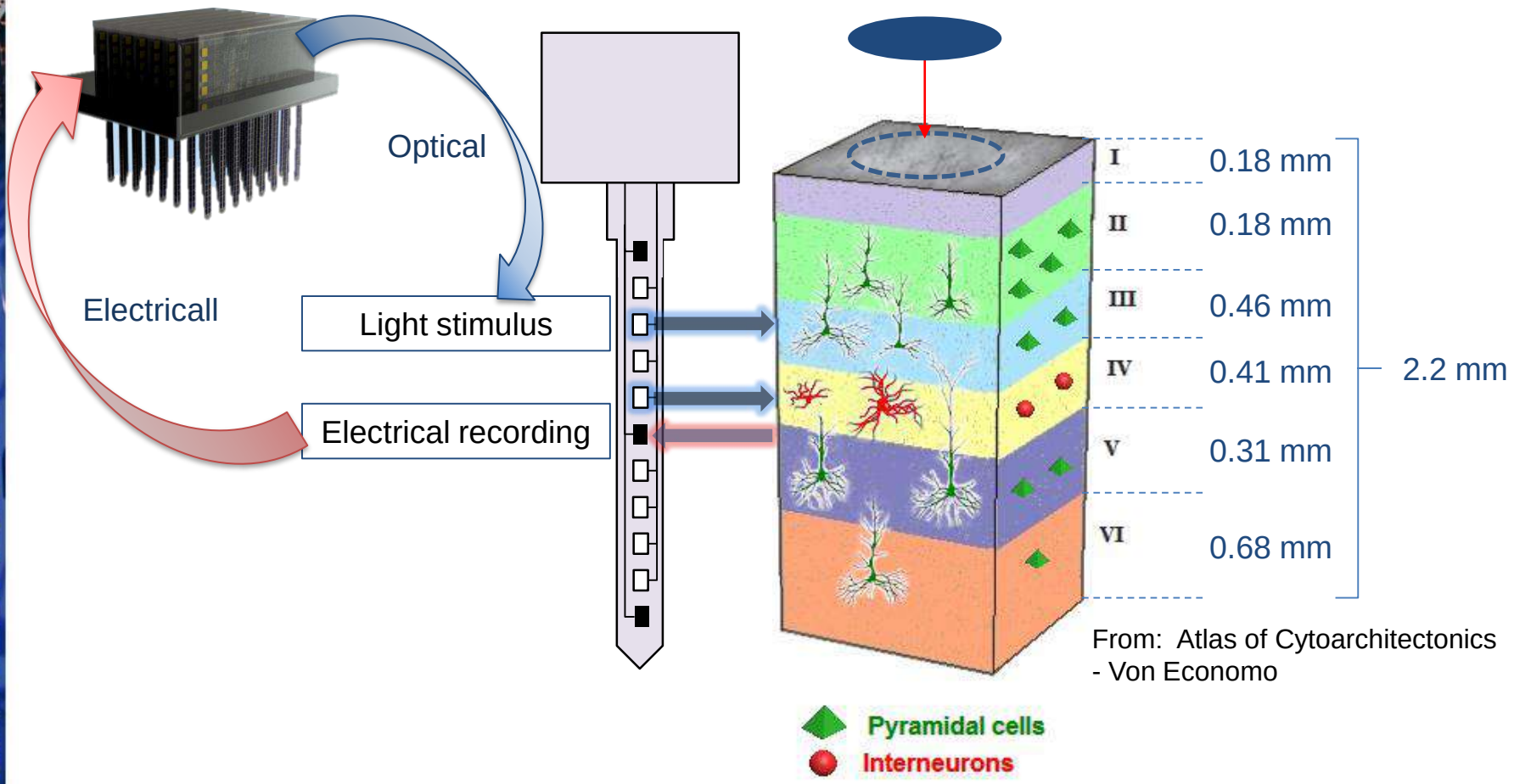
Optogenetics & closed loop control



Penetrating stimulation

Can we make the communication bi-directional?
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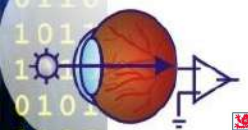

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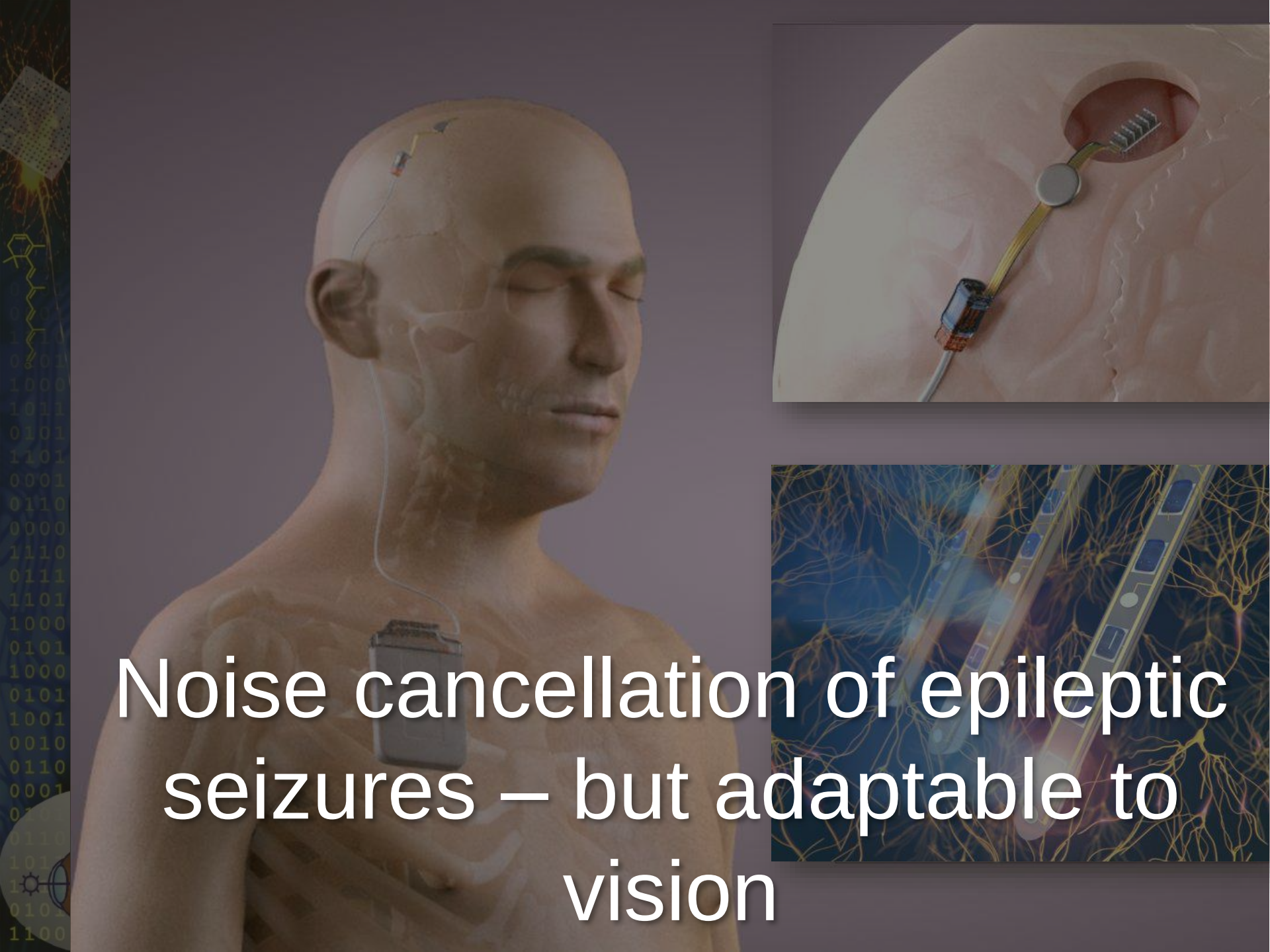
Controlling Abnormal Network Dynamics with Optogenetics

Lighting the Way to a New Epilepsy Treatment

£10M project: Clinical trials aimed for 2021

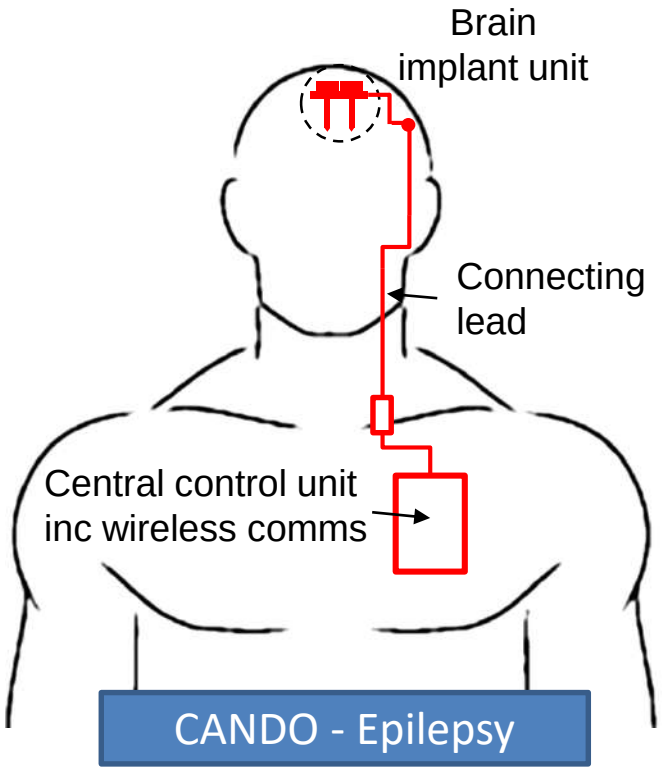
ION The Institute of Neuroscience
Newcastle University
The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust
Imperial College London
UCL

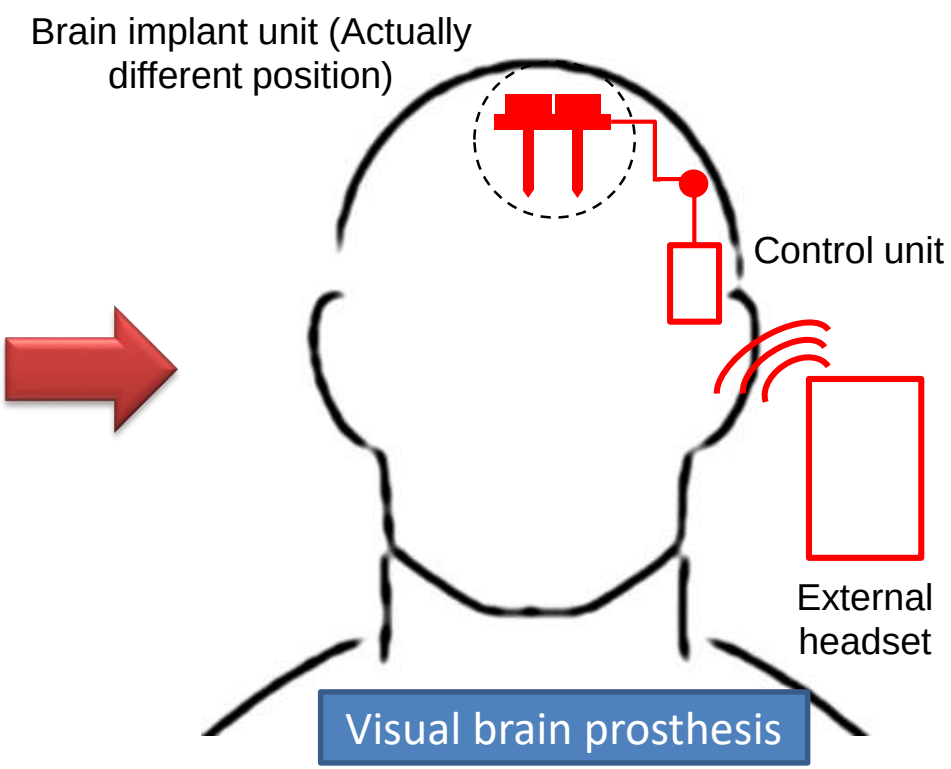
EPSRC Engineering and Physical Sciences Research Council
wellcome trust



Noise cancellation of epileptic seizures – but adaptable to vision

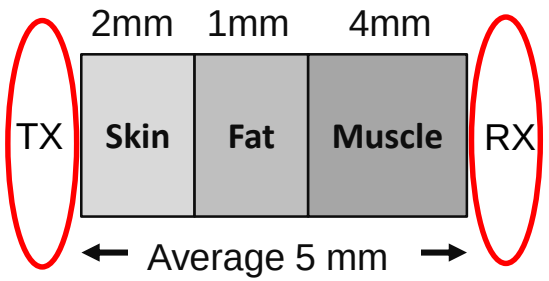
Adapting to visual brain prosthetics

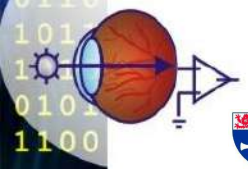




Principles:

1. Custom brain implant starting as 4 x 4 x 4 LEDs can be utilised
2. The control unit is quite different – higher power, no battery
3. Cabling can be simpler





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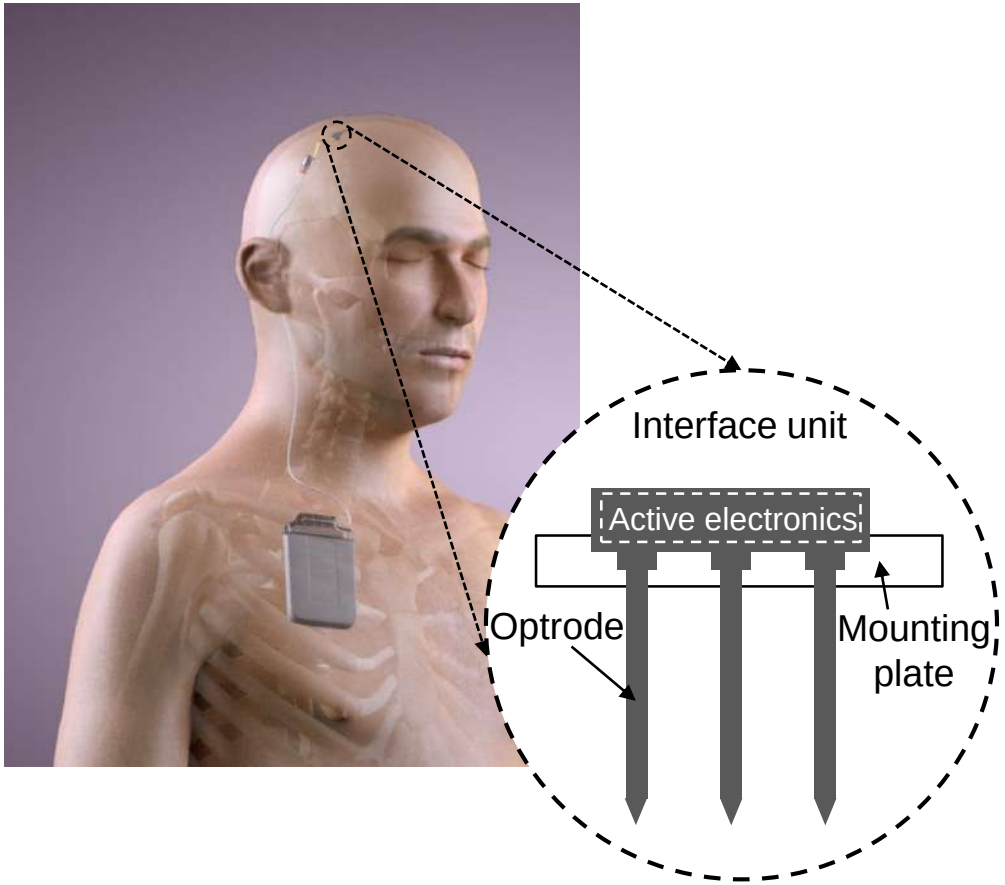
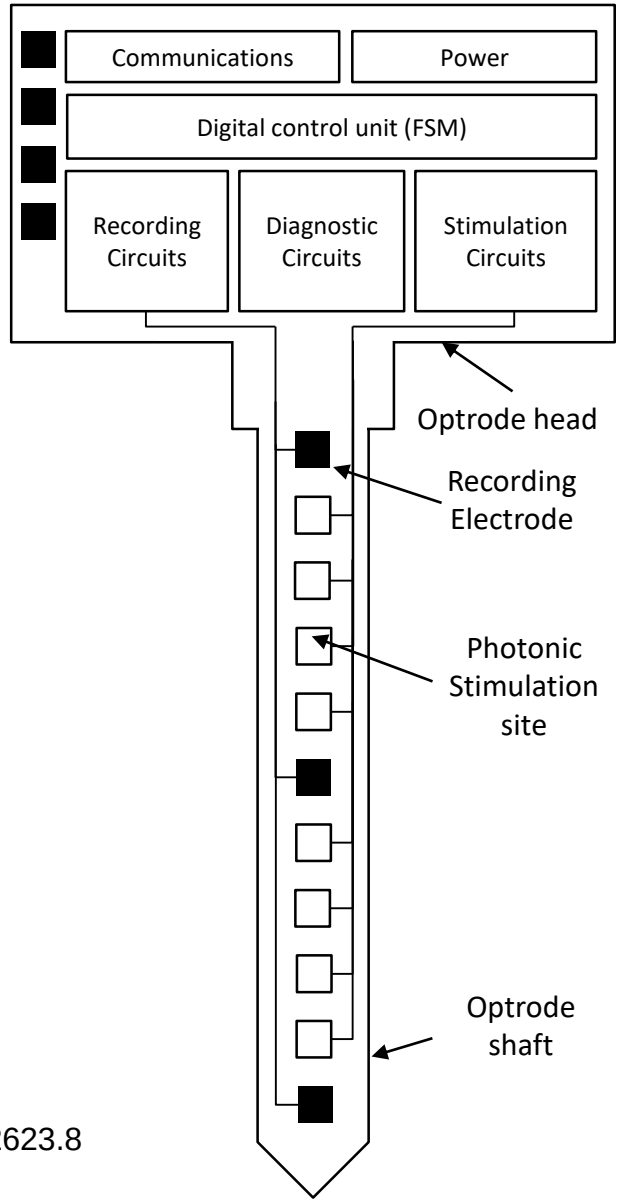
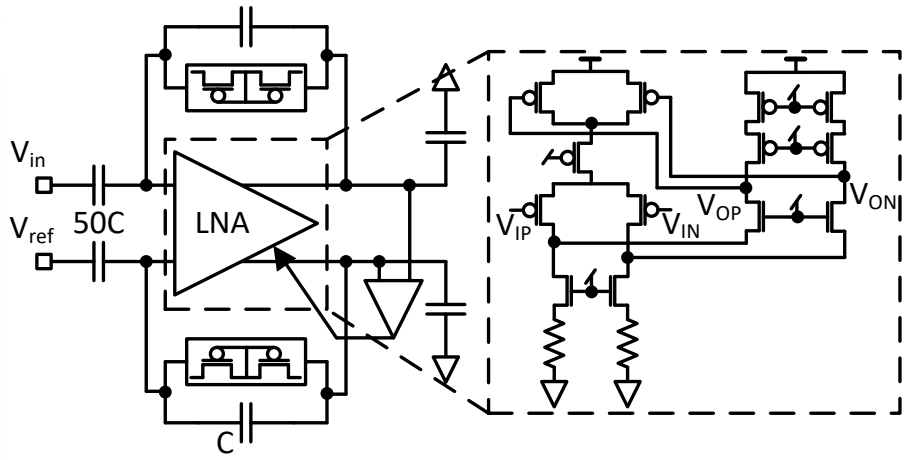
Brain stimulator unit



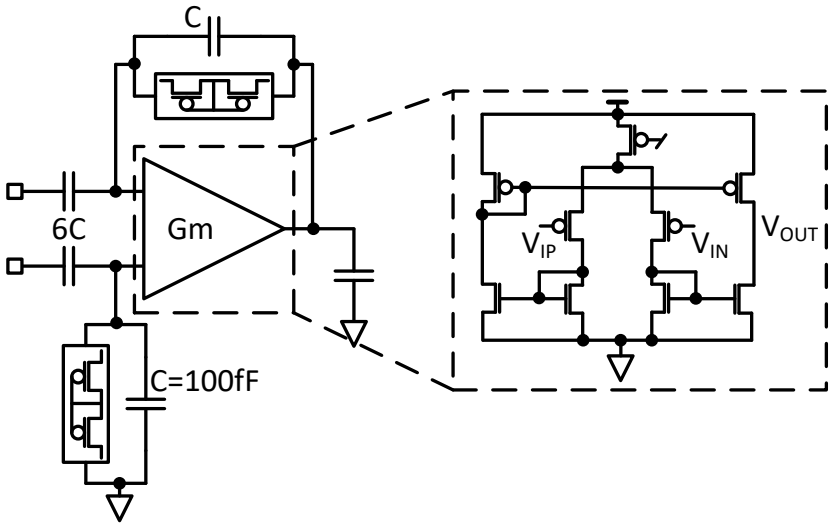


1. Ramezani et al. submitted to IEEE TCAS-I, June 2017
2. Zhao et al. Implantable optrode GB1410886.4
3. Dekhoda et al. Temperature sensor GB1522790.3
4. Degenaar Optical stimulation arrangement GB1616725.6
5. Constandinou et al On Chip Random ID generation GB1702623.8

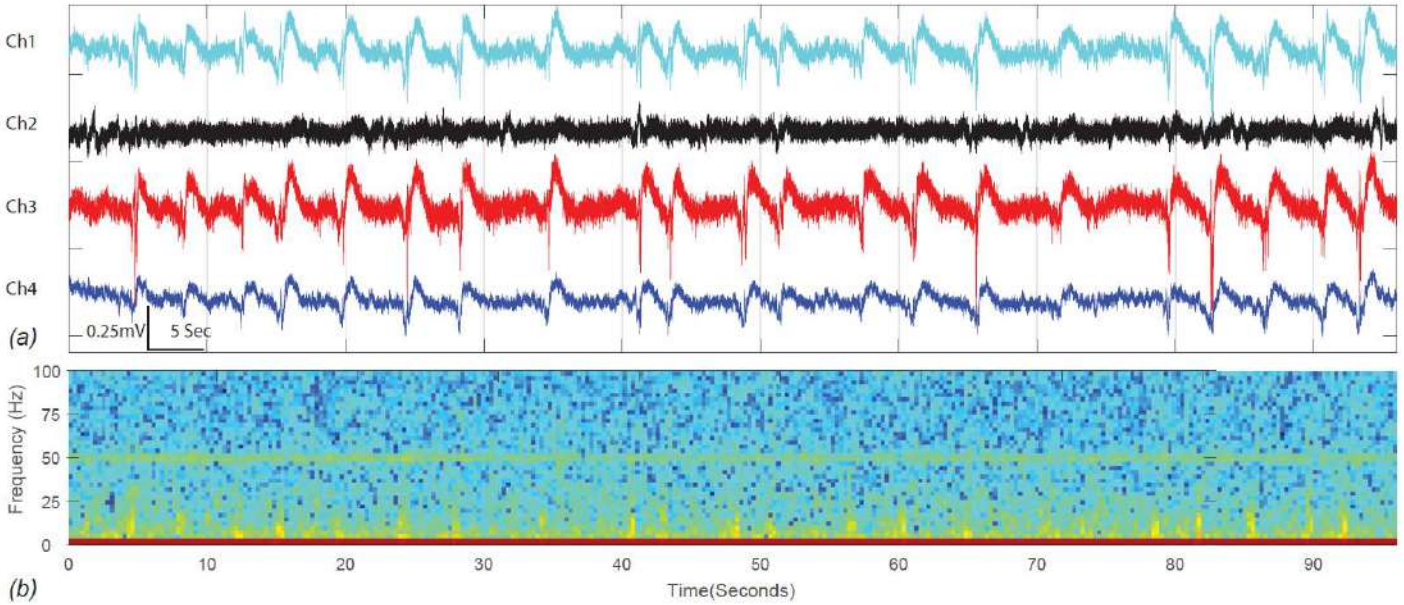
Recording microelectronics



Front end amplifier



Programmable gain amplifier



Recordings from non-human primate brain

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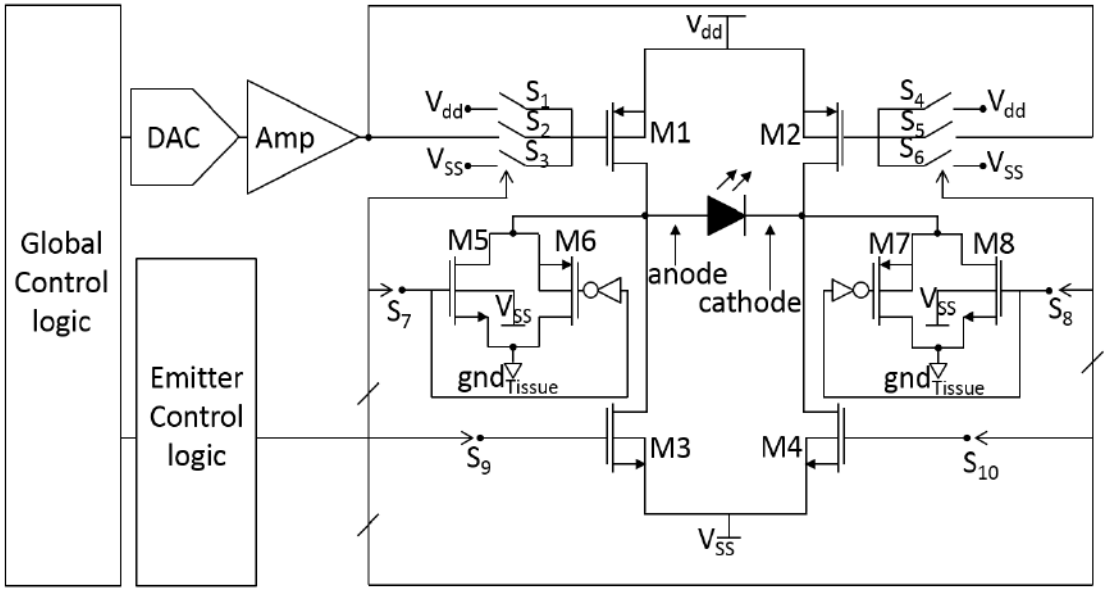
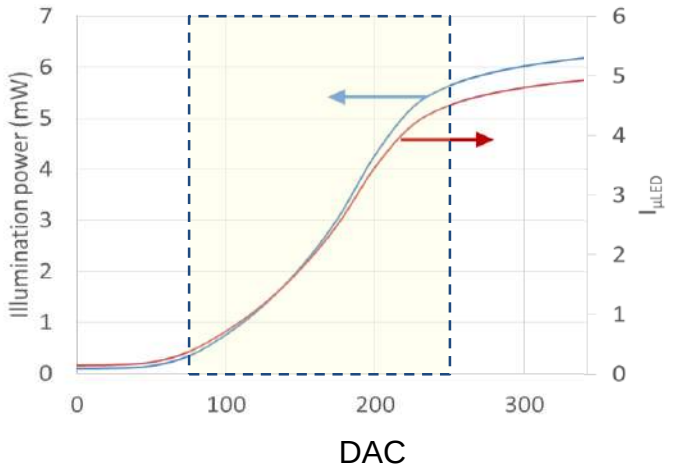
LED driver circutry

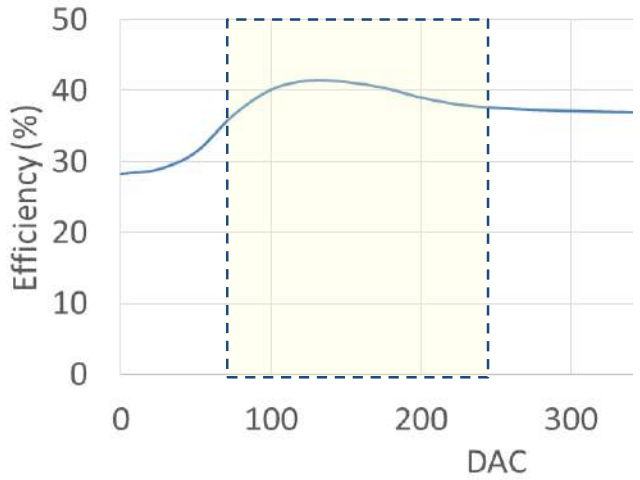


- Amplitude modulation
- PWM modulation
- Diagnostic and methods

LED drive power



LED efficiency



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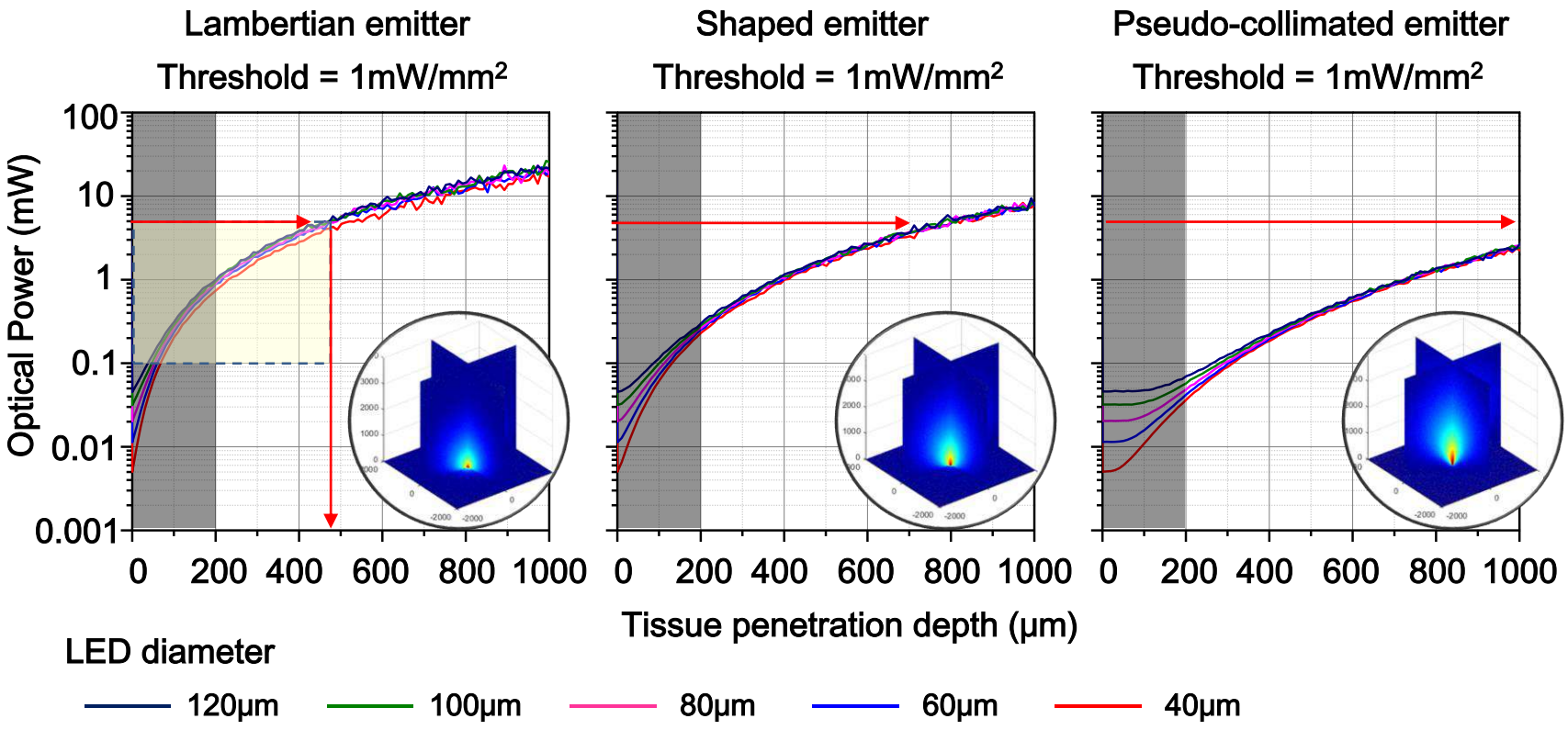
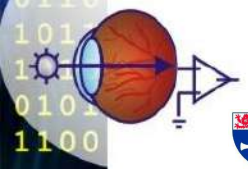
How much light do we need?



Key take home message:

1. Size doesn't matter to penetration depth!
2. Need to penetrate at least 100-200μm for long term implantables due to gliosis
3. More collimated light will give better penetration



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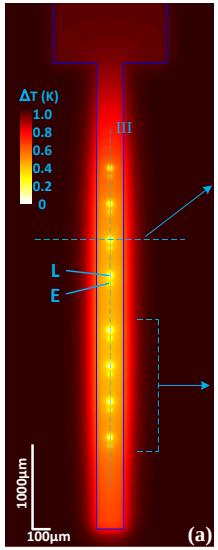
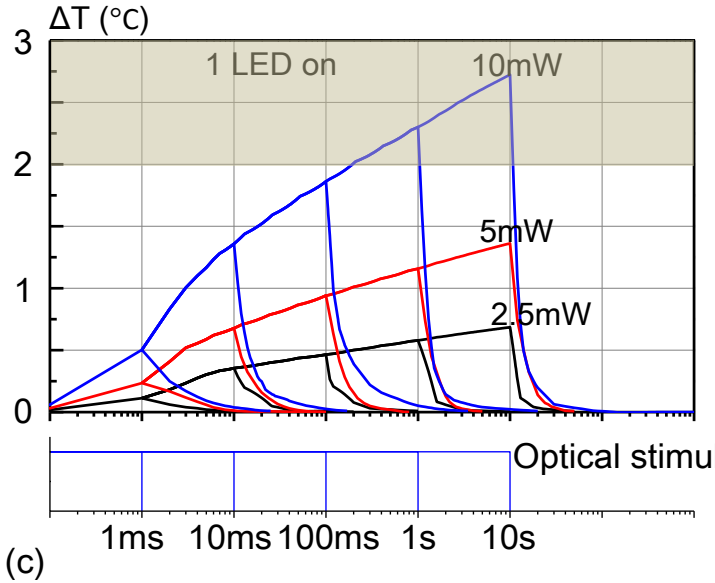
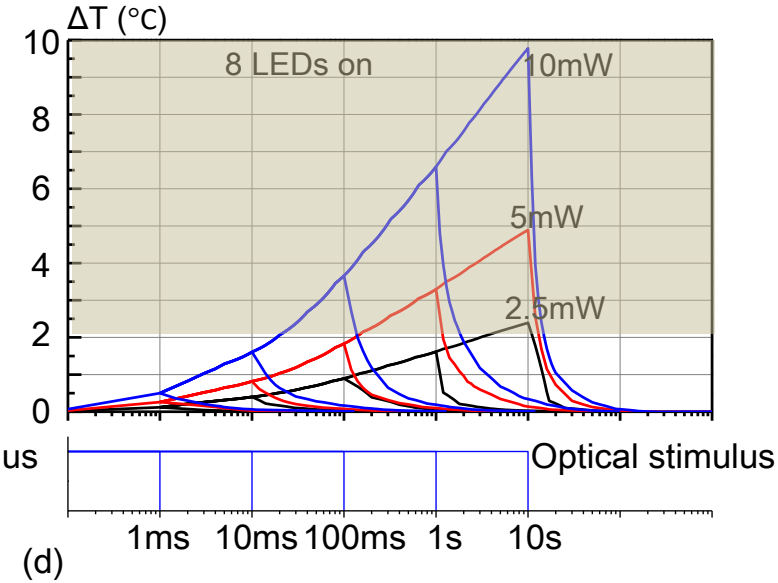
Dong et al. For submission to J. Biomedical Photonics 2017

LED thermal impact







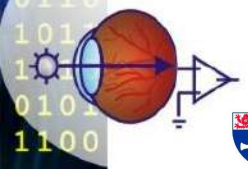
Target LED characteristics:

Driving current: 1mA
Driving voltage: 4-5V

Light requirement: 1mW
Efficiency: >20%

Typical micro-LED efficiencies from literature ~ 1-5%

Wu et al. Neuron 2015:	0.8%
Kim et al. Science 2013:	0.2%
McAlinden al: Opt Lett 2013:	5%
McGovern et al: PLOS ONE 2013:	5%
McGovern et al: IEEE TBCAS 2010:	1%



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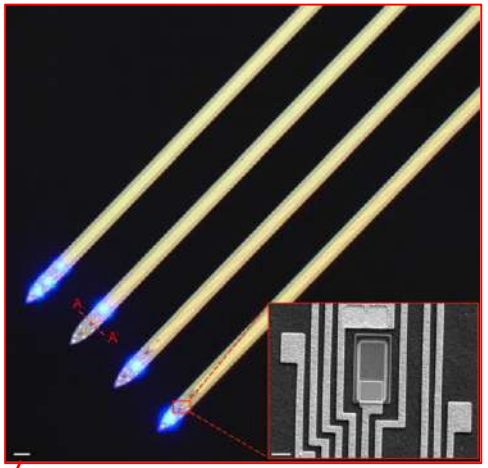
Dong et al. For submission to J. Biomedical Photonics 2017

LED efficiencies



Wu et al Neuron 2015

Dong et al. For submission to J. Biomedical Photonics 2017

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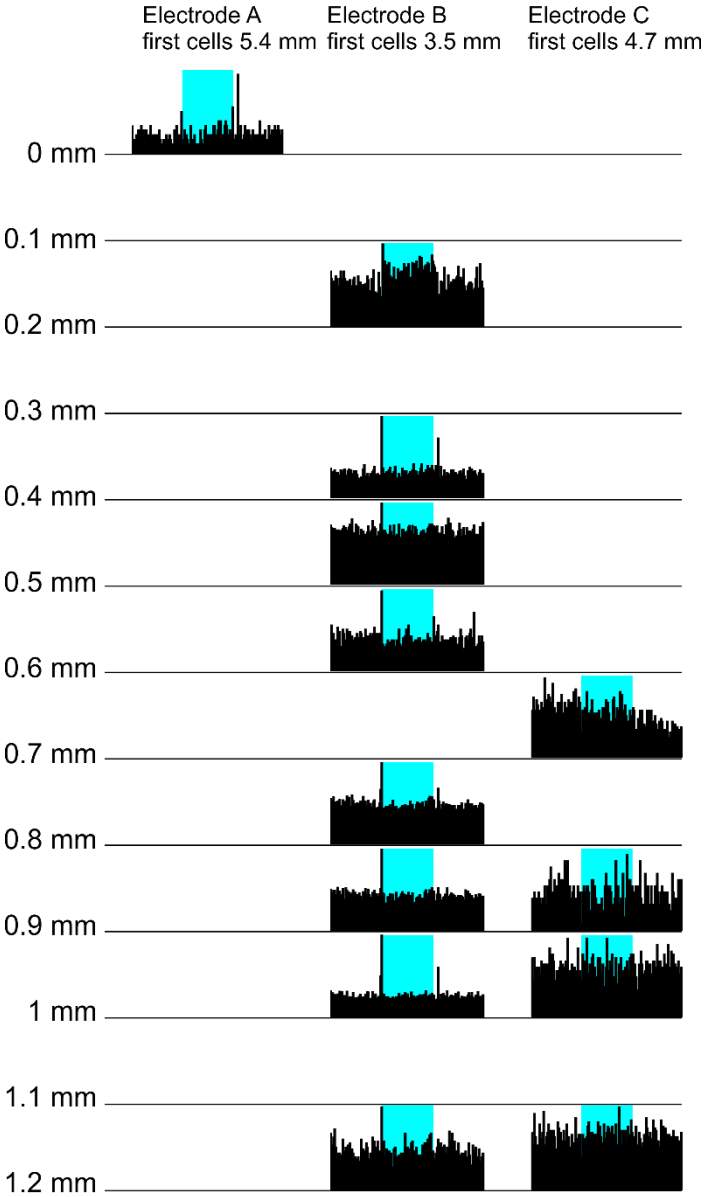
Light requirement in-vivo



"Official" threshold is 0.7mW/mm^2 for dissociated culture. But what about in practice???

In NHP experiments, We saw responses at 1mm with emission intensities of only 0.5mW. i.e. At that depth the irradiance << 0.1mW/mm^2

Caveat: we cannot separate neural transmission!

Modelling indicates a lower effective threshold of 0.1 - 0.3 mW/mm^2

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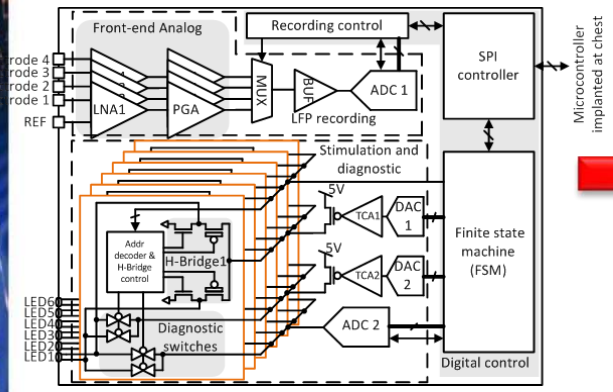
Currently Unpublished work

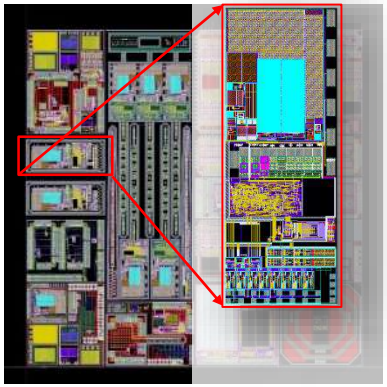
Luo et al. Submitted to JNE 2017

Assembling the optrodes

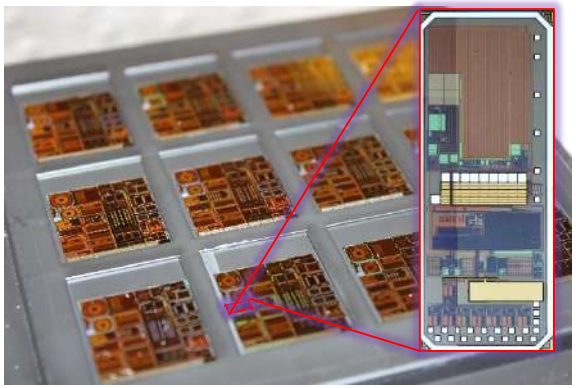
Schematic design



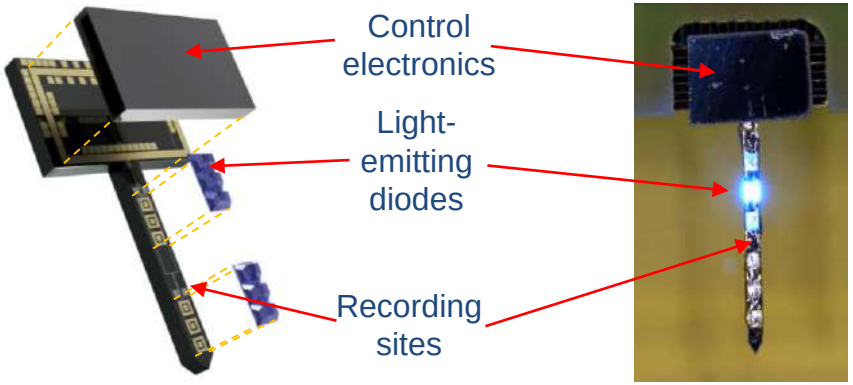
CAD layout



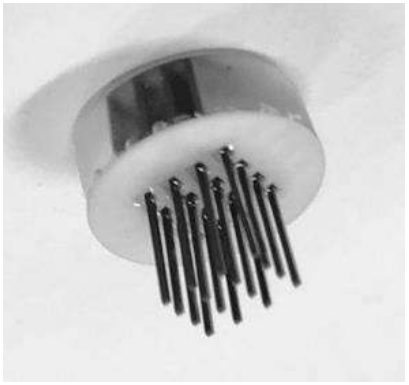
Wafer fabrication



Probe assembly



3D assembly



We are developing a fully manufacturable implant!!

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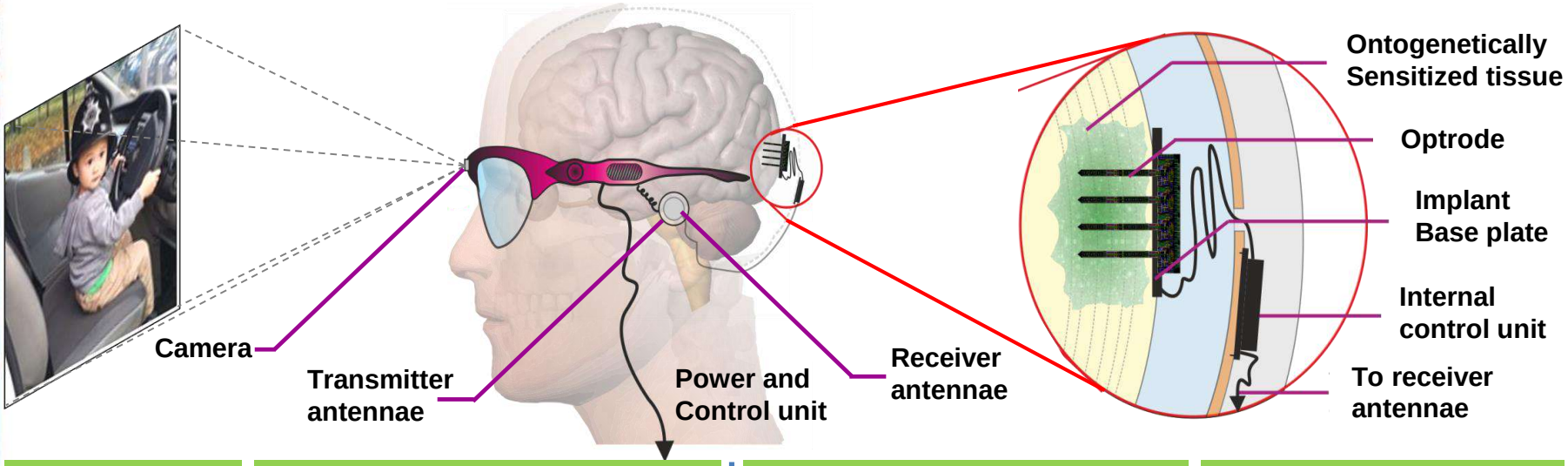
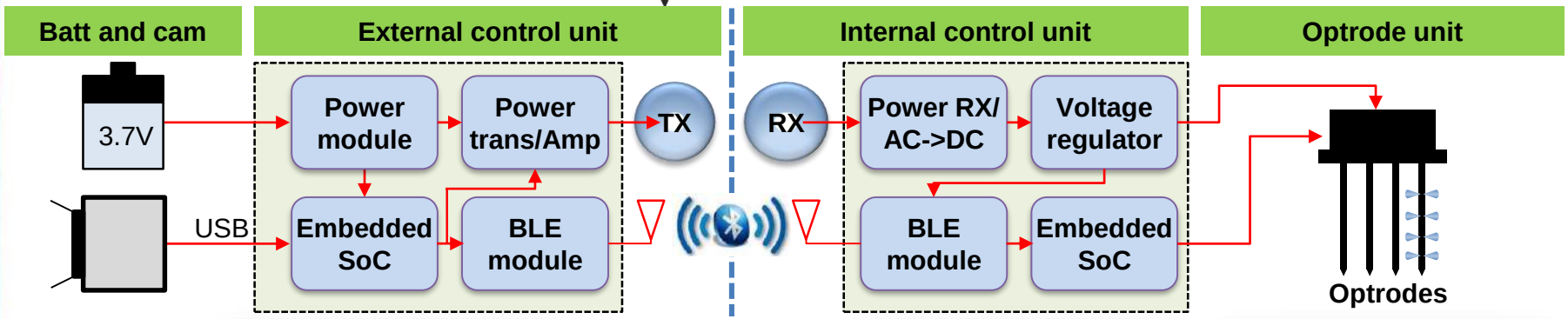
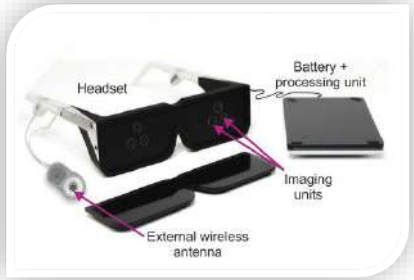
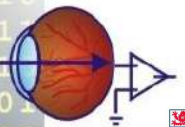
Developing the control system









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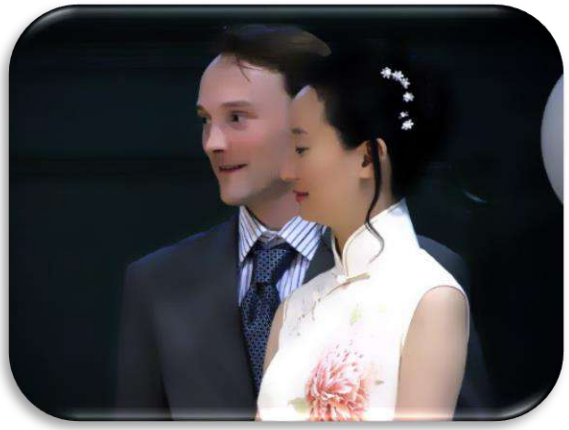
Fattah & Soltan et al. in preparation for IEEE TBME submission

System software - preprocessing

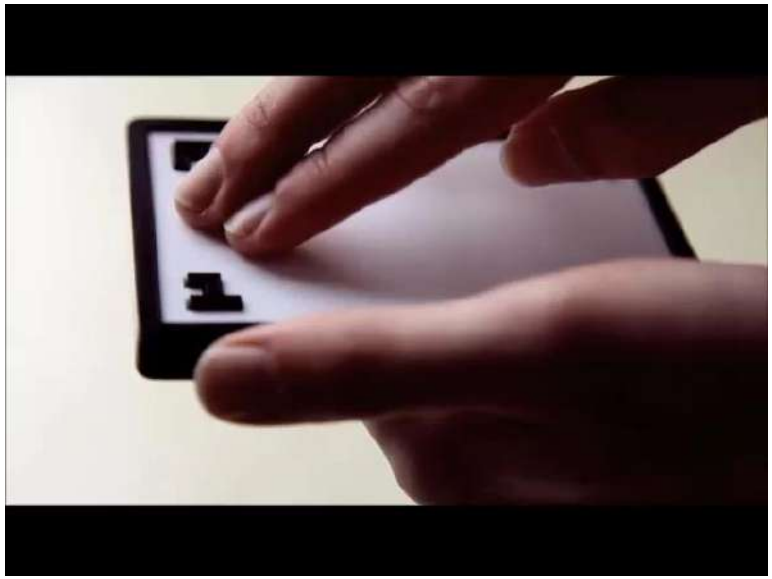


Simplification

Cartoonization

Visual augmentation

The vision that we will return to patients with visual prosthesis will be rudimentary. We are therefore using patients with partially degenerate vision as a simulation of what can be achieved.



Song of the Machine!

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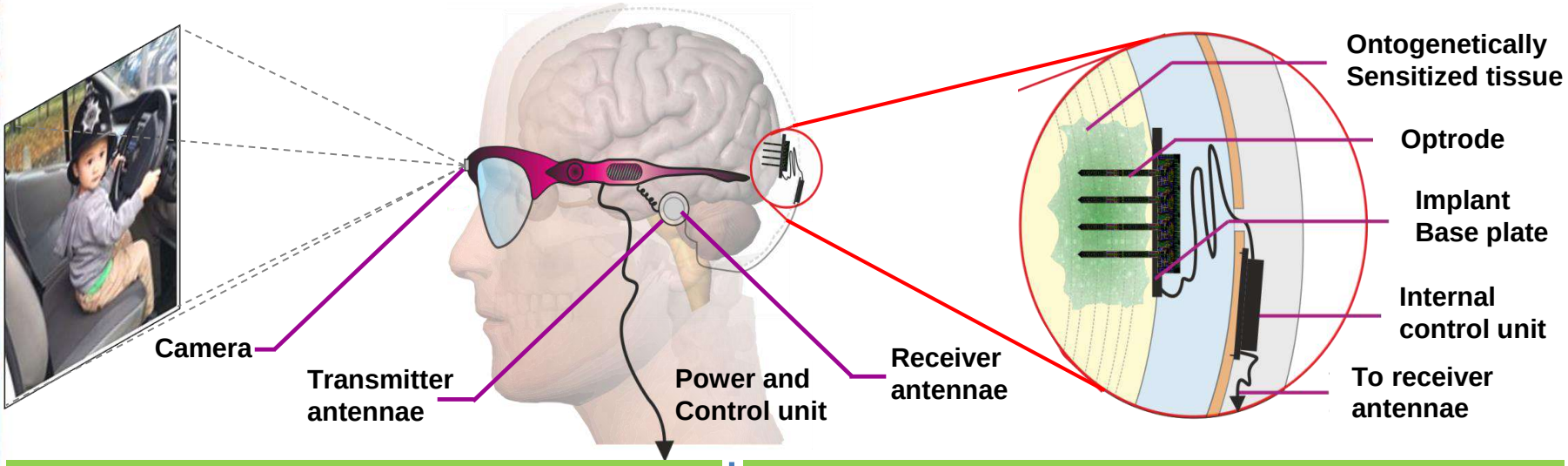
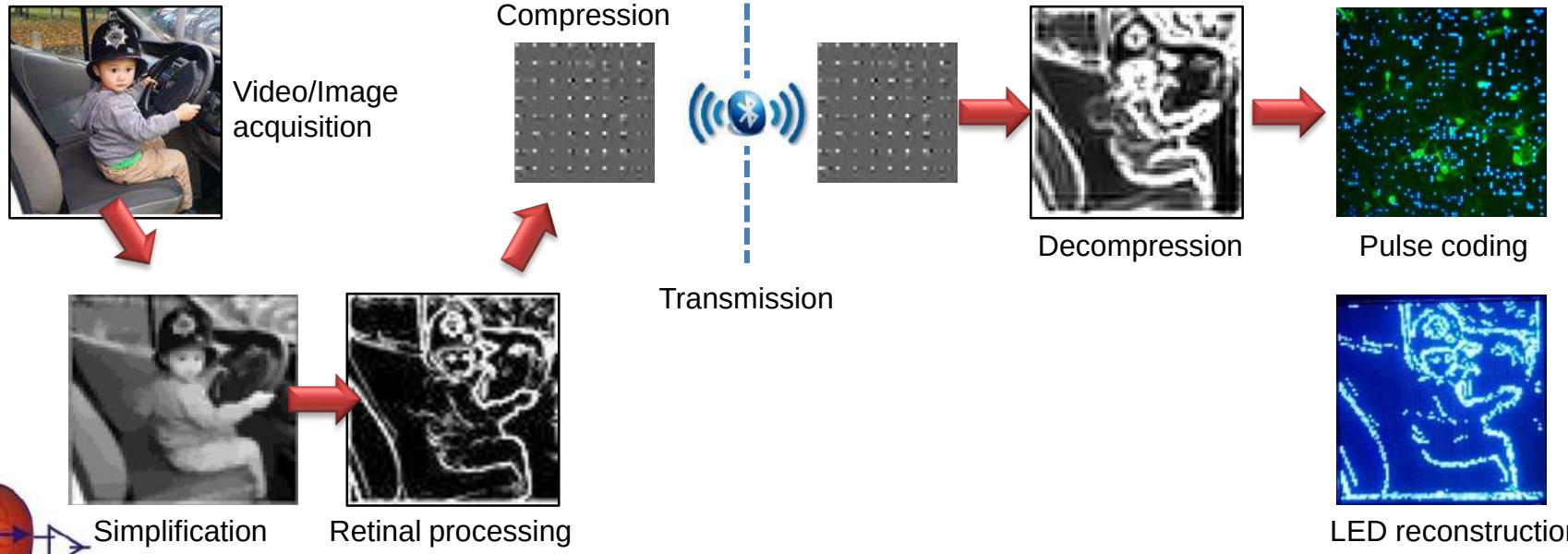
superflux | सुपरफ़्लक्स

Full software process



External control unit | **Internal control unit**



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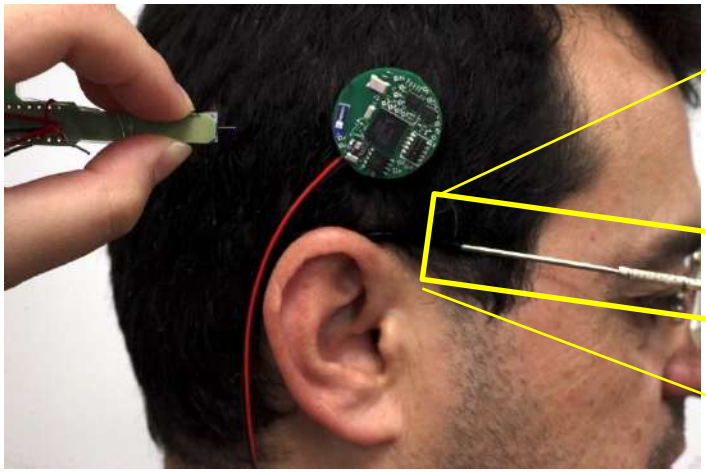
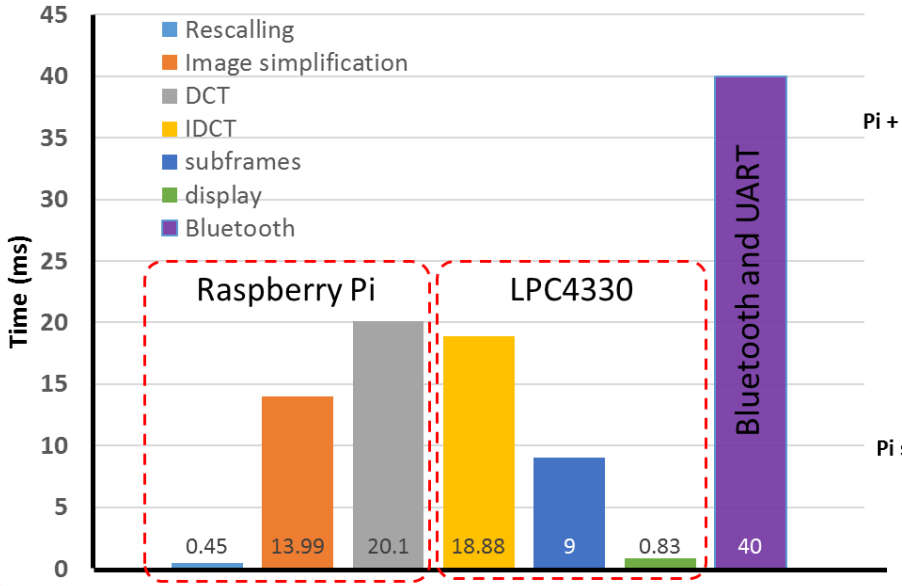
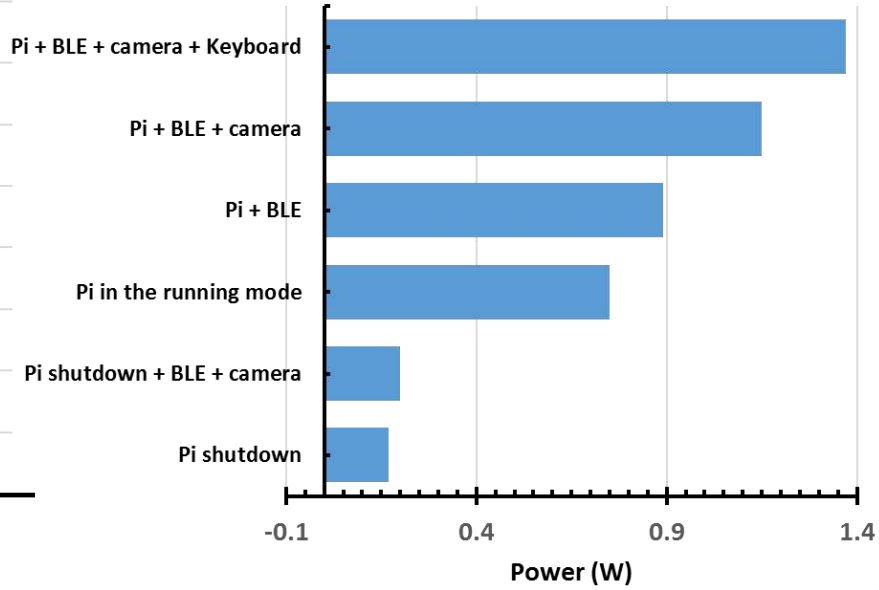
Fattah & Soltan et al. in preparation for IEEE TBME submission

Visual cortical Headset







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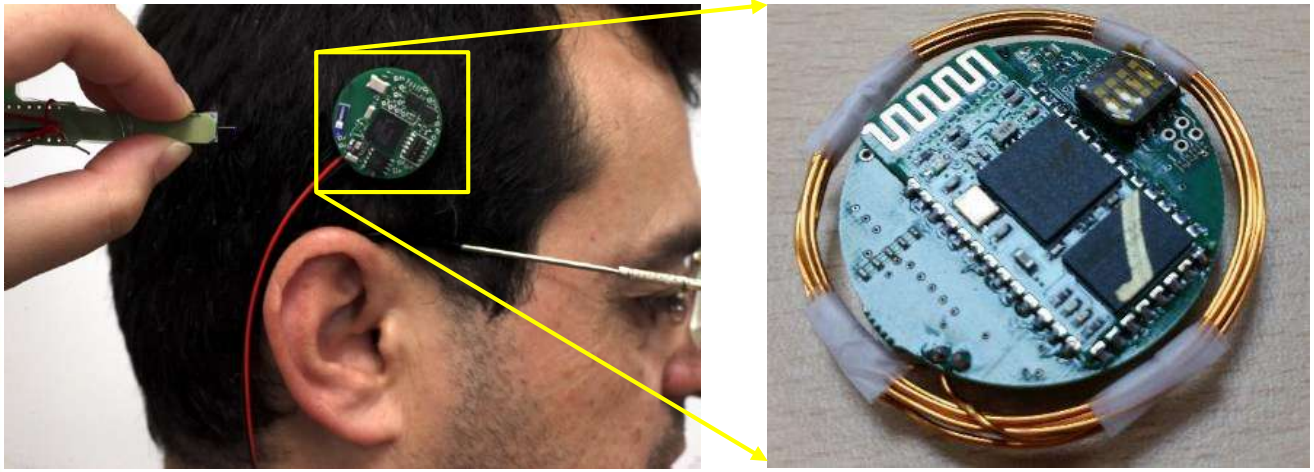
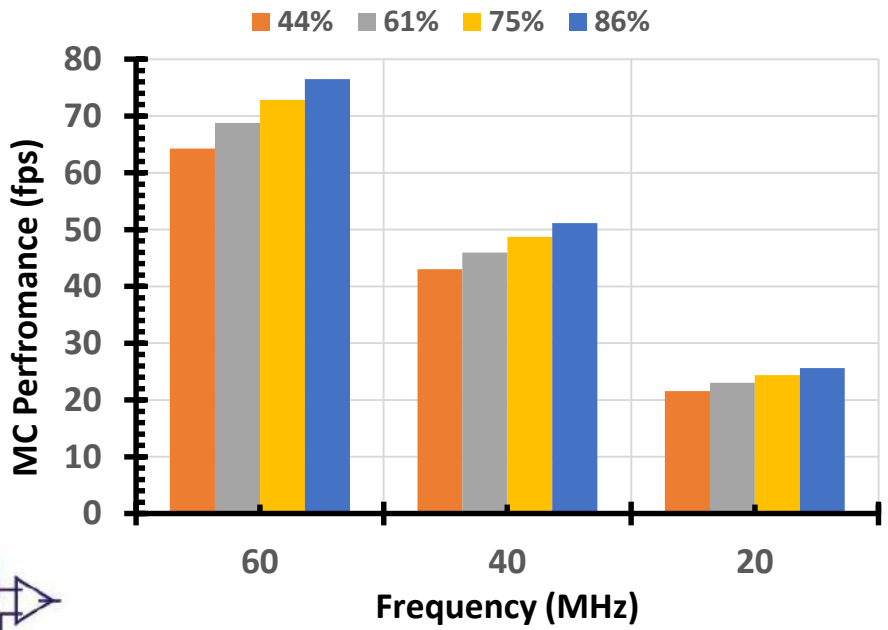
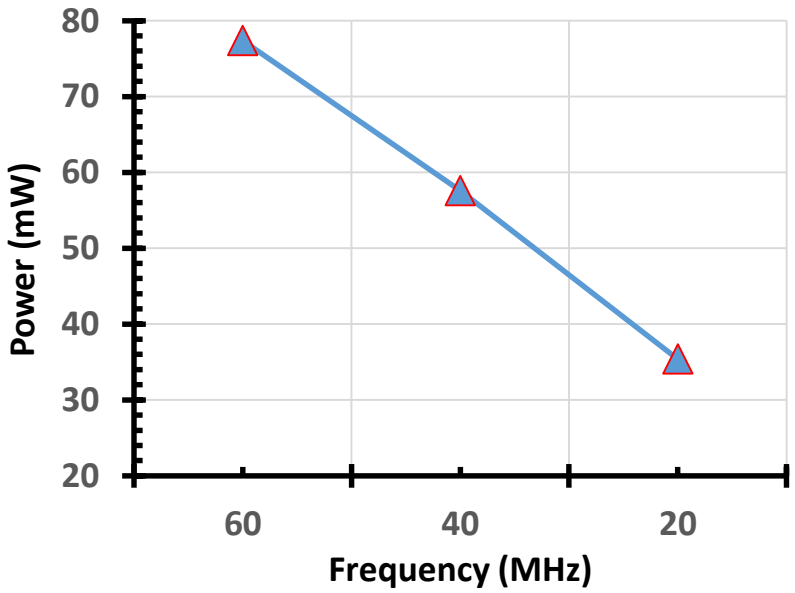
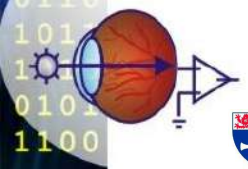
Implantable control unit









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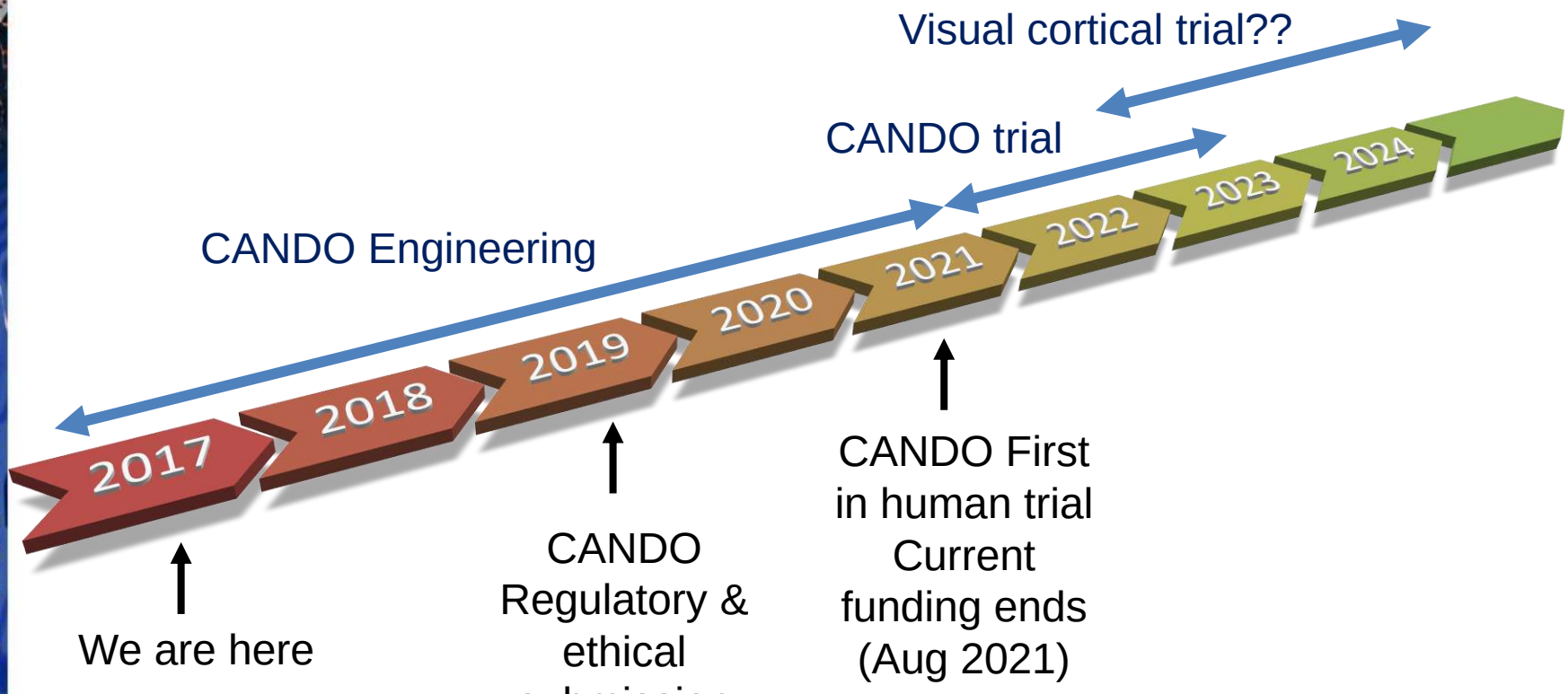
Timeline


Visual cortical trial??
CANDO trial
CANDO Engineering
2017
2018
2019
2020
2021
2022
2023
2024
We are here
CANDO Regulatory & ethical submission
CANDO First in human trial Current funding ends (Aug 2021)

CANDO
Controlling Abnormal Network Dynamics using Optogenetics

Acknowledgments

CANDO project

Tim Constandinou *(Imperial College)*, Nick Donaldson *(UCL)*, Andrew Sims *(Newcastle RVI (NHS))*, Andrew Jackson *(Newcastle IoN)*, Mark Cunningham *(Newcastle IoN)*, Anthony O'Neil *(Newcastle EEE)*, + Others:

OptoNeuro FP7 project

Mark Neil *(Imperial College)*, Ernst Bamberg *(Max Planck Institute)*, Christian Bamann *(Max Planck Institute)*, Botond Roska *(FMI, Switzerland)*, Pleun Maaskant *(Tyndall Institute)*, David Rogerson *(Scientifica)*, Mark Johnson *(Scientifica)*

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Macular Society