Let there be light

new progress in photostimulation apparatus

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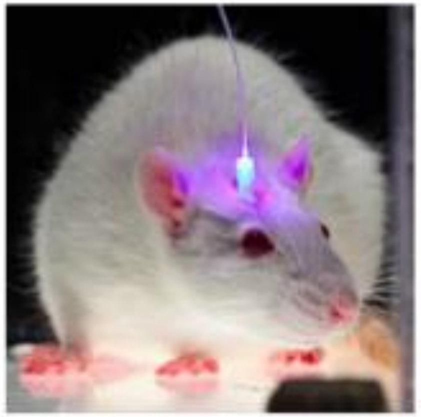
1 Theory

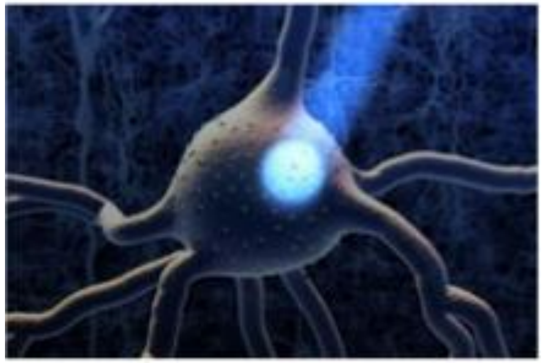
Introductions of Optogenetics, Methods of Genetic Modification, Photosensory Molecules, Controls of Cell Functions, Mechanism of Stimulation

1.1 Introductions of Optogenetics



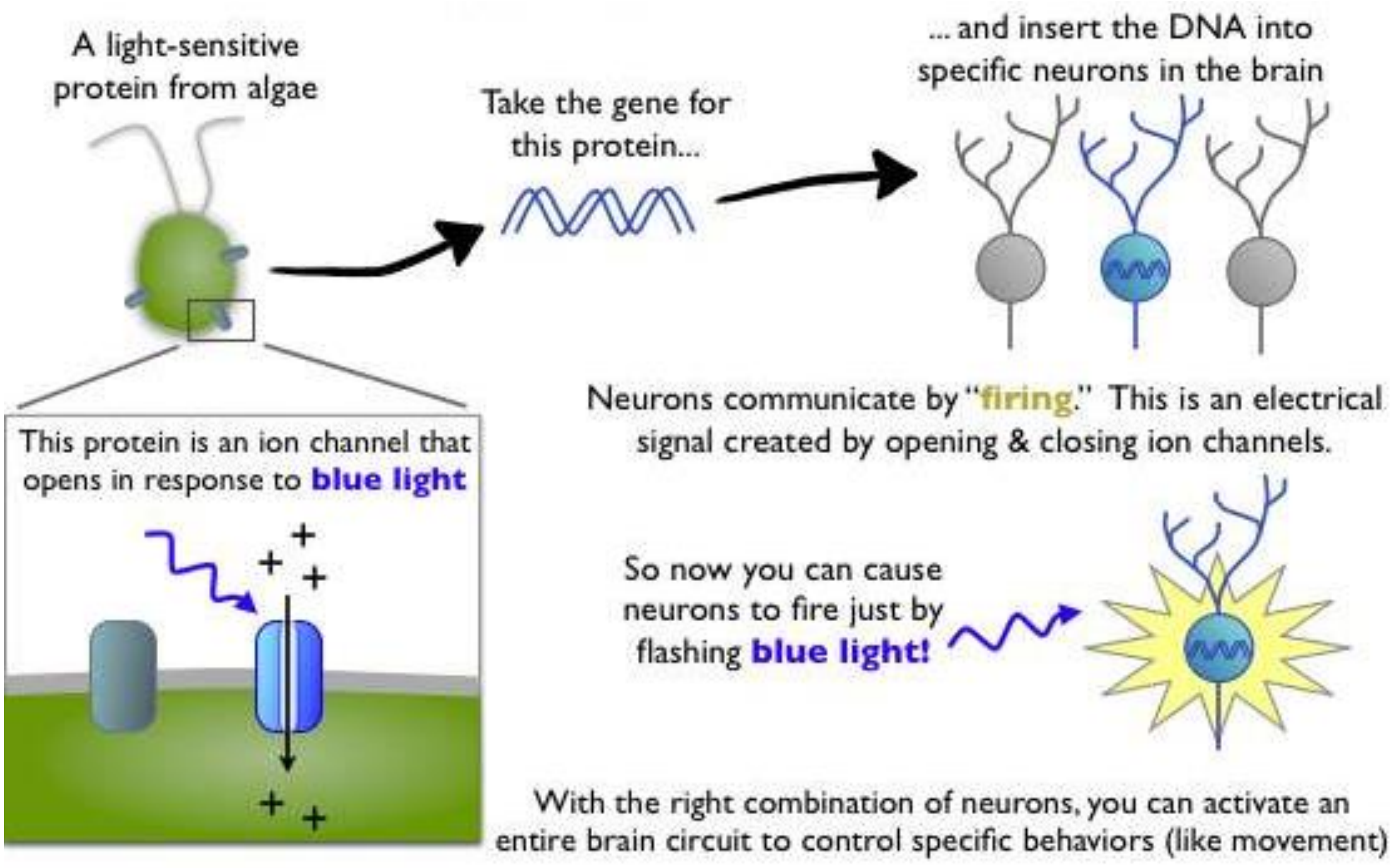
- Optogenetics is a branch of biotechnology which combines genetic engineering with optical methods
- Research tool to obtain insights into complex tissue function such as Parkinson's disease

- Optogenetics is subdivided into:
  - Sensors: monitor neural circuits
  - Effectors: manipulate neural circuits



- Basic concept: expressing a light activated ion channel in a specific group of cells such as neurons then illuminating the cells to control activity

1.2 Methods of Genetic Modification

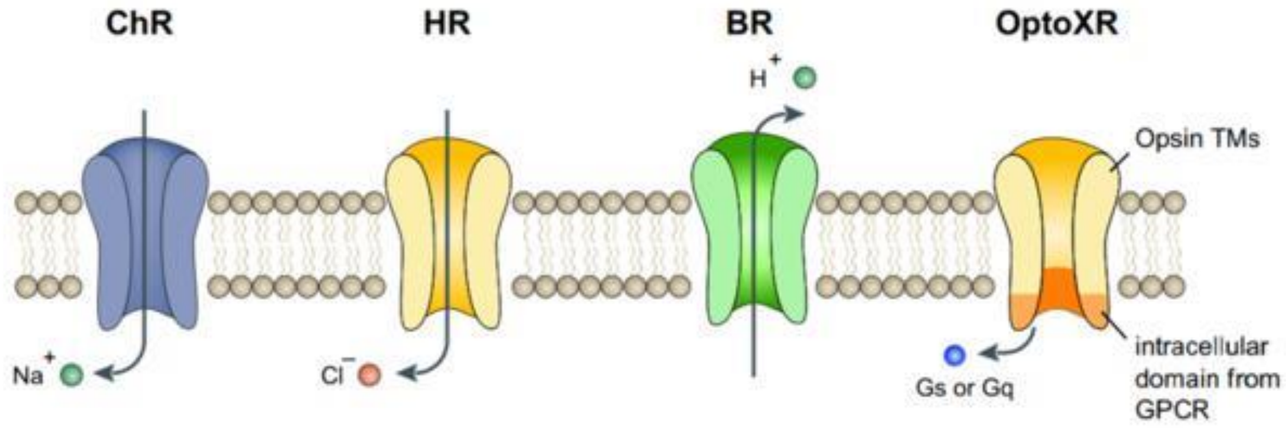


1.3 Photosensory Molecules

- Molecules that convert light into electricity
- Can be naturally occurring or chemically modified

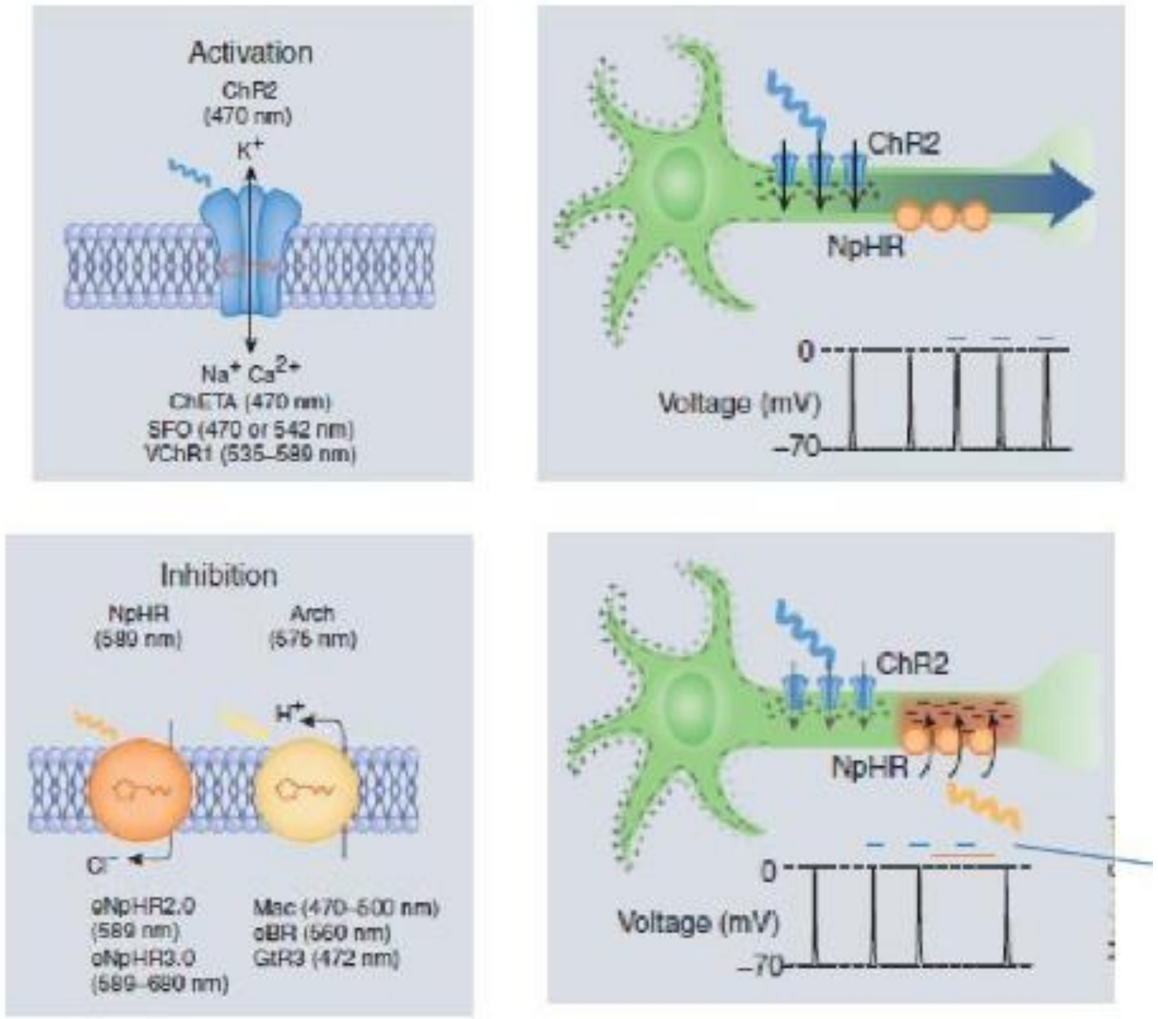
光敏感通道蛋白 — Channelrhodopsin (ChR2) - found in algae *Chlamydomonas reinhardtii*

嗜盐视紫红质 — Halorhodopsin (NpHR) – found in archaeon *Natronomonas pharaonic*



- Genes that code for these molecules can be delivered by:
  - Transfection (introducing nucleic acids into cells, non-viral methods in eukaryotic cells)
  - Viral transduction
  - Creation of transgenic animal lines

1.4 Controls of Cell Function



Channelrhodopsin

- Cation channel
- Activated by blue light (470nm)
- Allows Na^+ influx across the membrane and depolarizes the neuron, thus activating it
- Acts as the on switch

Halorhodopsin

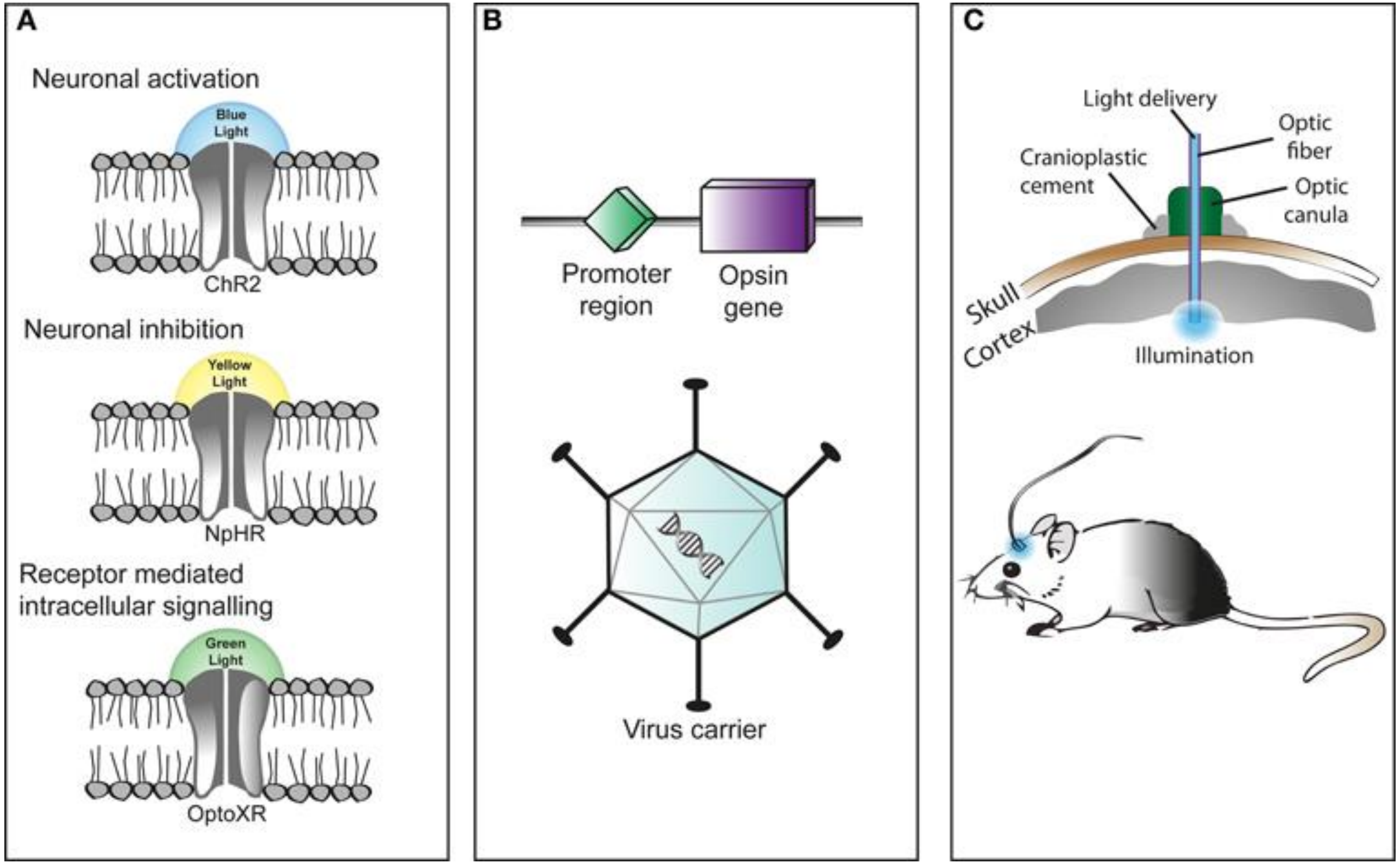
- Chloride pump
- Activated by yellow light (580 nm)
- Triggers influx of Cl^- which hyperpolarizes the cell and inhibits the neuron
- Acts as the Off switch

1.5 Mechanism of Stimulation

(A) : light-responsive proteins called opsins， reacts differently to light stimulation of particular wavelengths

(B) express of microbial opsins in mammalian cells : virus injection, transgenic animals, use of Cre-driver animals, Cre-dependent viruses or *in utero* electroporation

(C) Light can be delivered straight into the brain through an optical fiber, using a chronically implanted cannula that is affixed to the skull.



2 Optrode

Design and Fabrication

2.1 Optrode

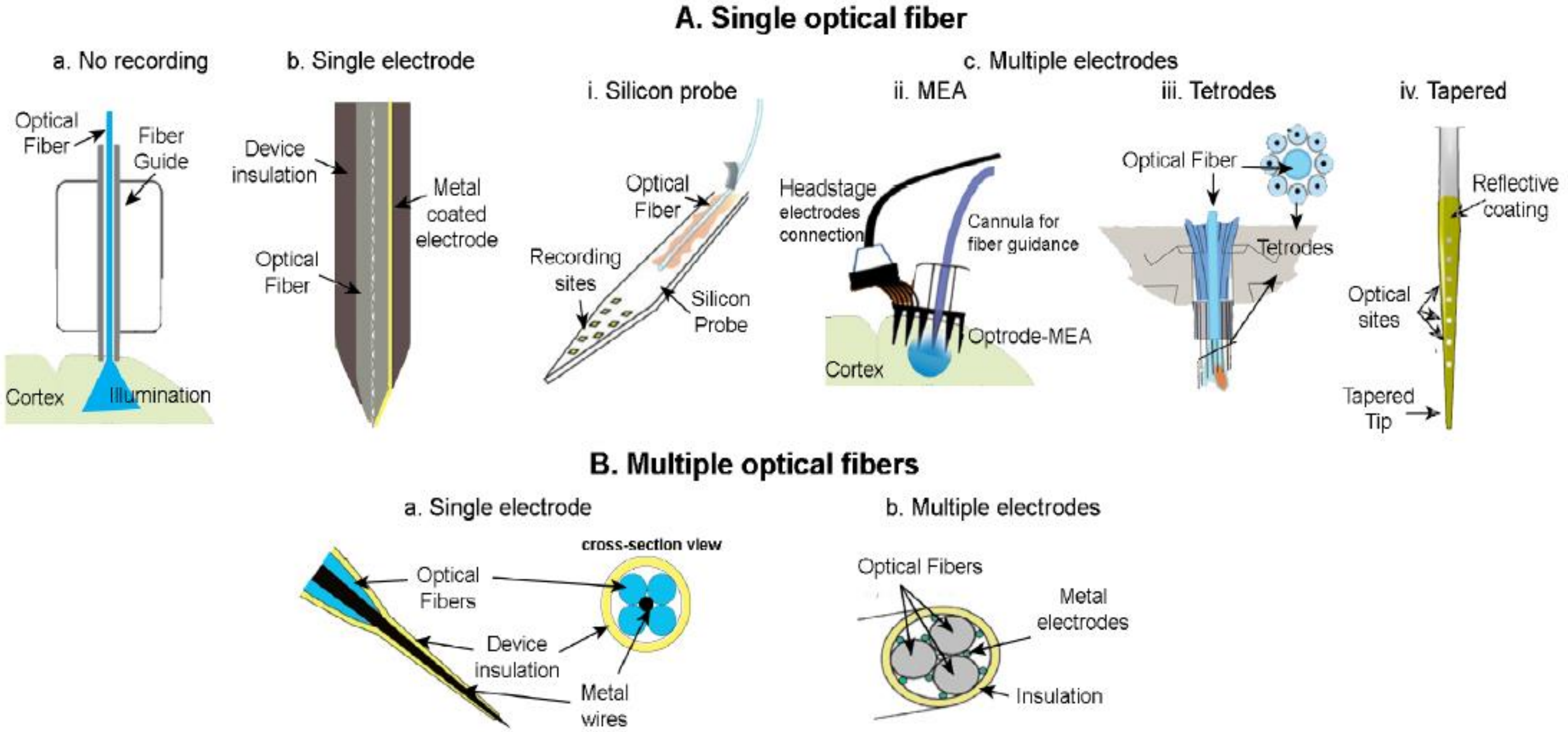
- A light source: activate photosensitive proteins in neurons
- Electrical recording sites: simultaneous electrophysiology studies
- A rigid or flexible platform: fixation
- Data acquisition, transmission and processing

2.2 Challenges

- Electrical devices’ chronical performance
- Minimize tissue damage and displacement
- Small cross-section and overall dimensions
- Effective light intensity
- Multi-site optrodes- homogeneous distribution of light
- Thermal properties
- Stimulation artifacts
- Compatibility with other technologies
- Reliable signal transfer and data acquisition

2.3.1 Optical Fiber

- State-of-the-art optical fiber optrode designs



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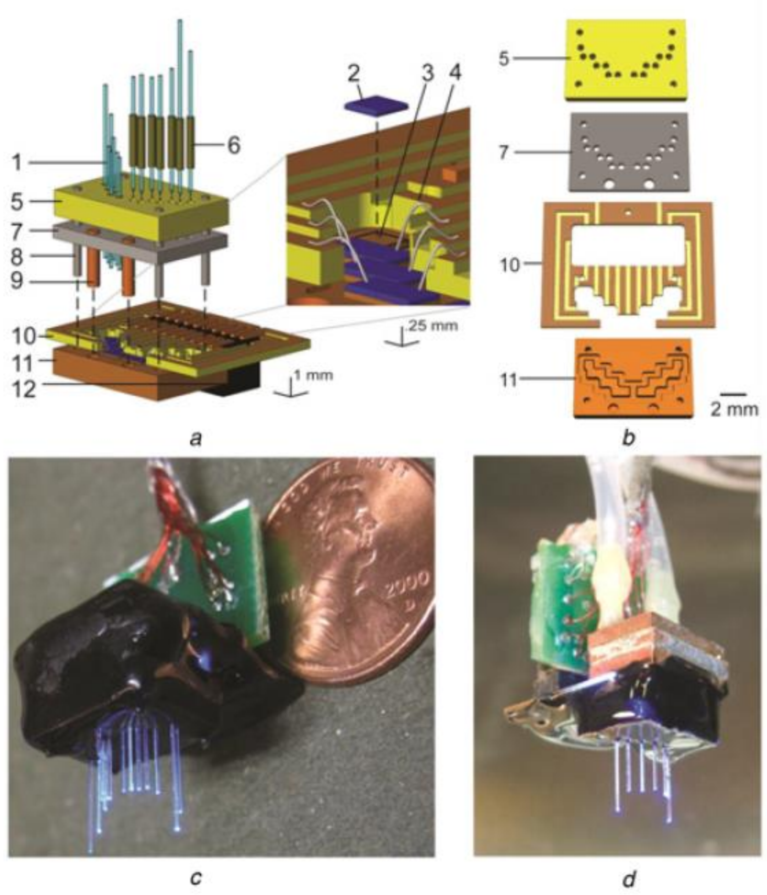


Fig. 1 *Design and fabrication of optical fibre arrays*

1 Optical fibers

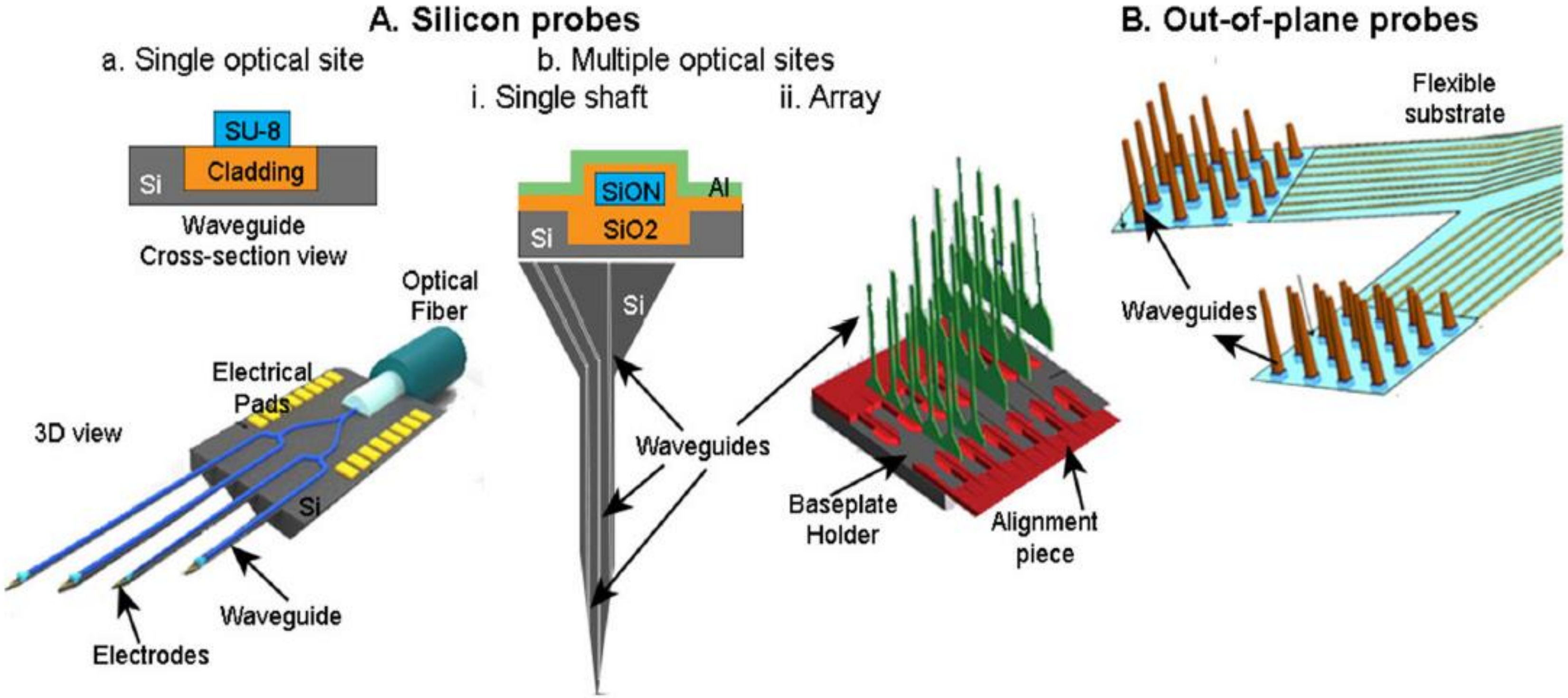
2 LED

- A 3D fiber array optrode
- A stiff silicon housing
- A flexible substrate with integrated LEDs
- Two sets of special cables

Bernstein, J. G., Allen, B. D., Guerra, A. A., Boyden, E. S. (2015). Processes for design, construction and utilisation of arrays of light-emitting diodes and light-emitting diode-coupled optical fibres for multi-site brain light delivery., 2015(5), 177-184.

2.3.2 Waveguide

- State-of-the-art waveguide optrode designs



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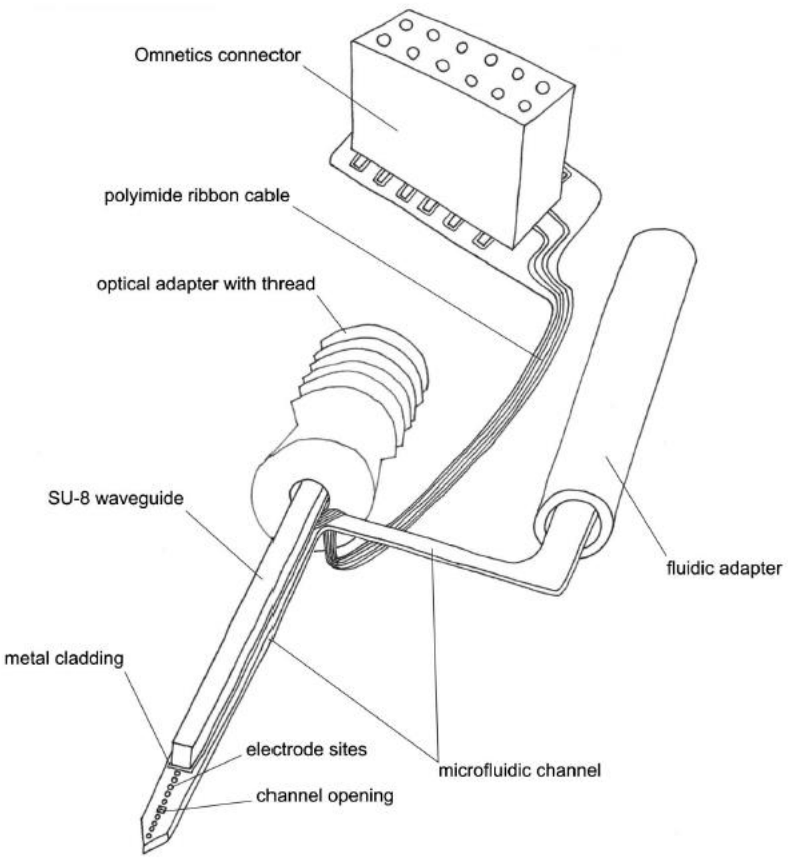
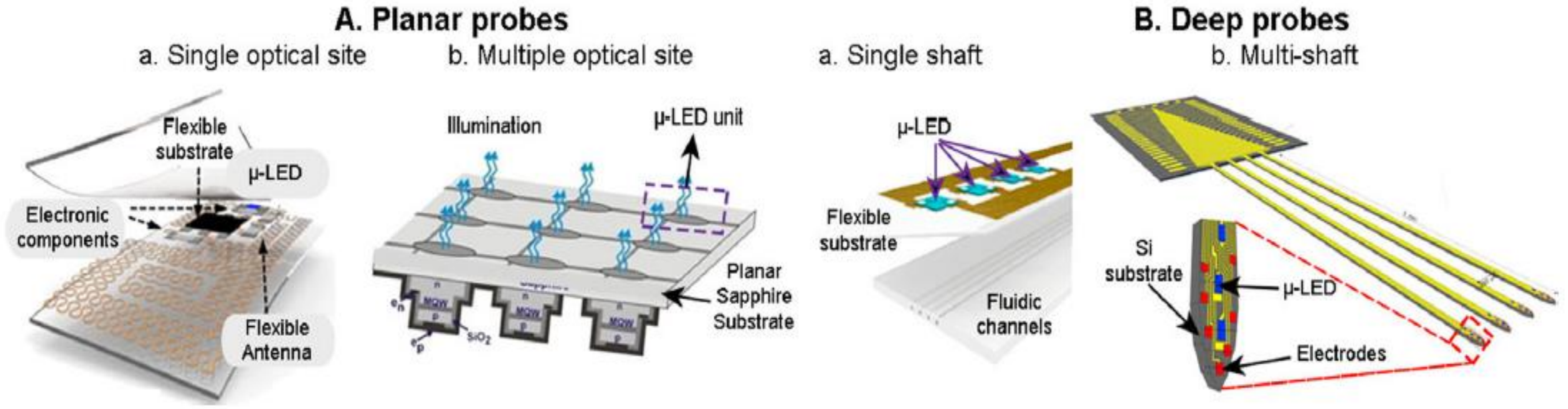


- A microfluidic channel
- An optical waveguide
- Microelectrodes

Rubehn, B., Wolff, S. B. E., Tovote, P., Lüthi, A., & Stieglitz, T. (2013). A polymer-based neural microimplant for optogenetic applications: design and first in vivo study. Lab on a Chip, 13(4), 579-588.

2.3.3 μ-LEDs

- State-of-the-art μ-LEDs optrode designs



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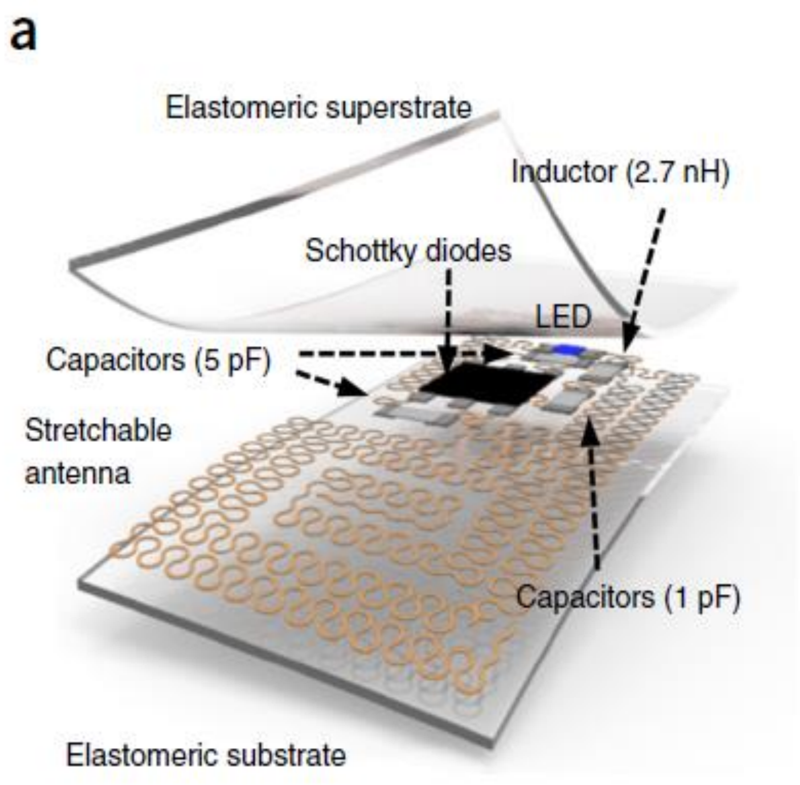
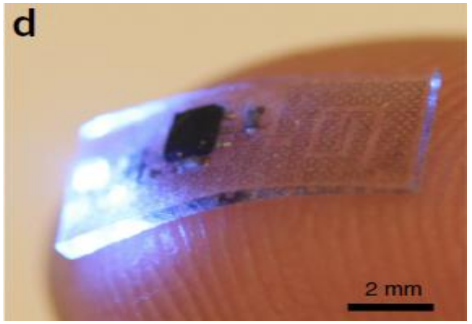


- Flexible, lightweight
- capable of implantation into challenging anatomical shapes
- A stretchable RF harvesting unit



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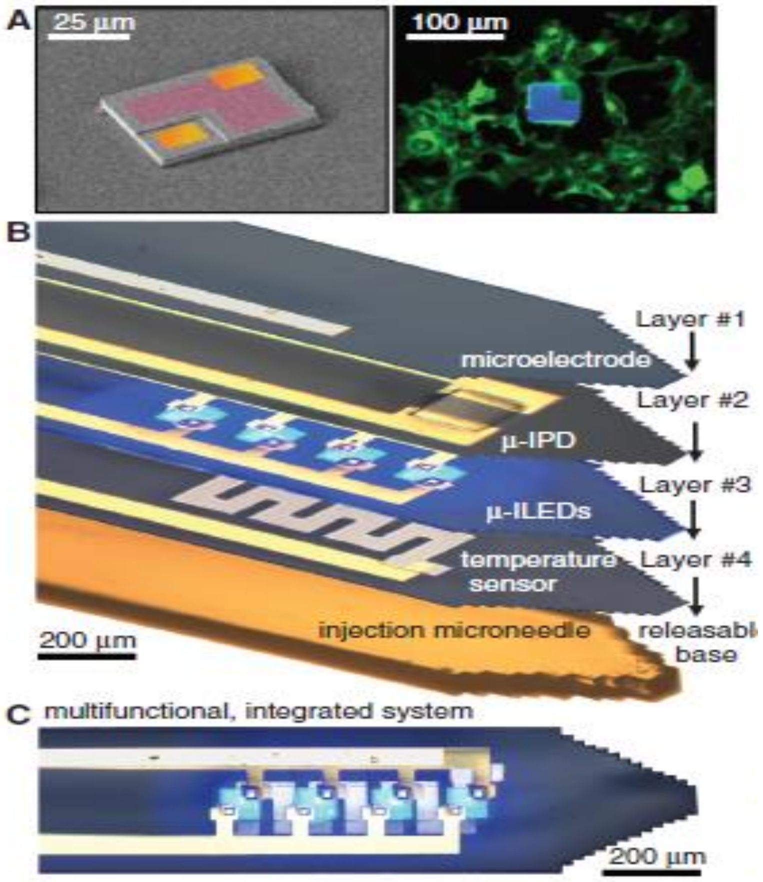
2.4 Multifunctional Integrated System



- Releasable injection needles for insertion
- Temperature sensors/microheaters: determine the degree of local heating
- µ-ILEDs: spatially precise
- µ-IPD: measure the intensity of light
- Microelectrodes

Kim, T., McCall, J. G., Jung, Y. H., Huang, X., Siuda, E. R., Li, Y., Bruchas, M. R. (2013). Injectable, Cellular-Scale Optoelectronics with Applications for Wireless Optogenetics. Science, 340(6129), 211.

2.4 Multifunctional Integrated System

- A Hybrid Neural Interface With Transparent μECoG Electrode Array and Integrated LEDs

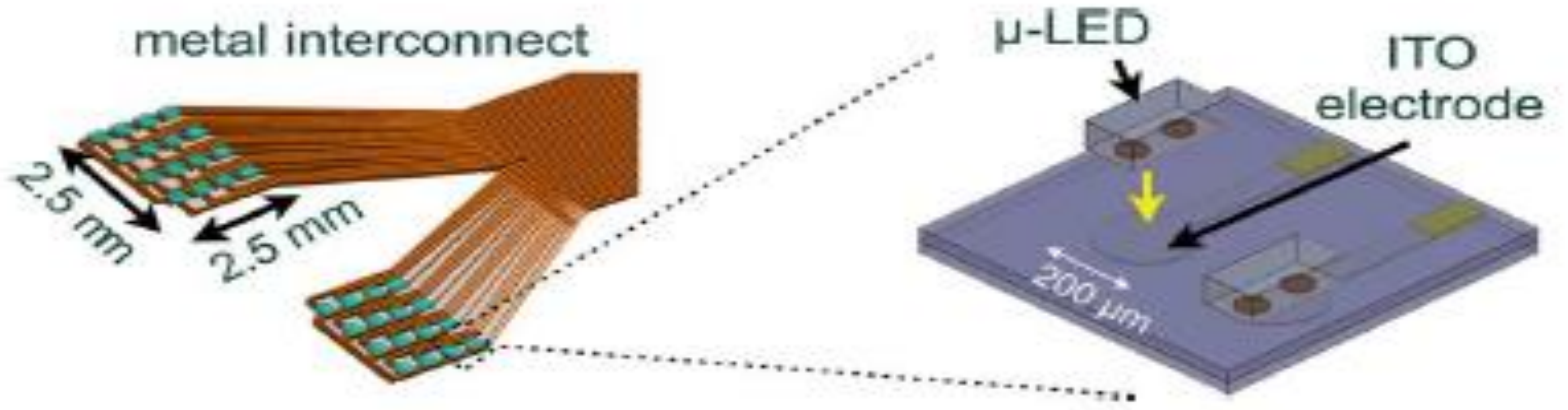


Fig. 2. Concept illustration of the proposed Opto-μECoG array.

K. Y Kwon, B. Sirowatka, A. Weber, W. Li (2013). Opto-μECoG Array: A Hybrid Neural Interface With Transparent μECoG Electrode Array and Integrated LEDs for Optogenetics. IEEE Transactions on Biomedical Circuits and Systems, 7(5), 593-600.

3 Application

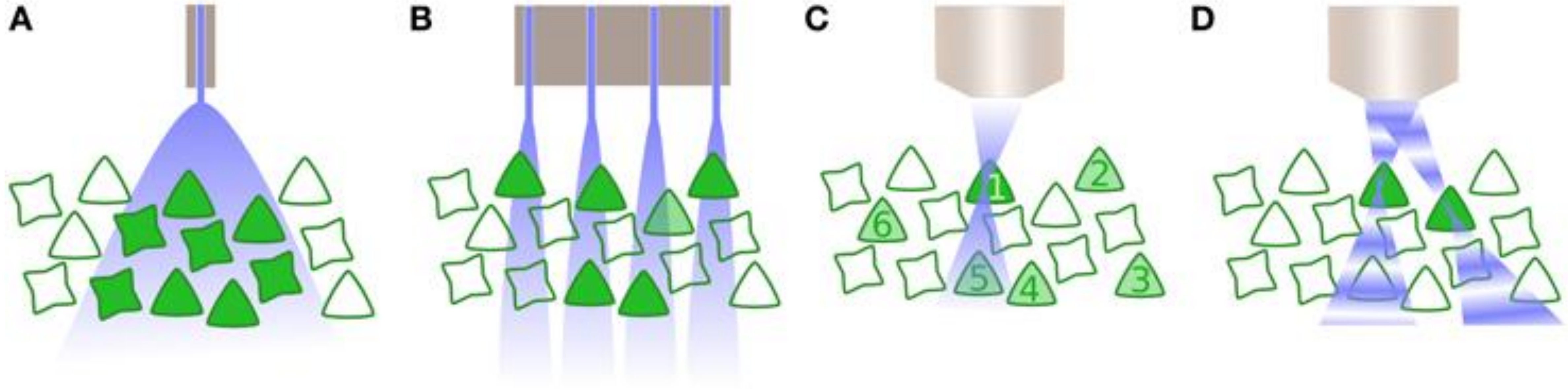
optogenetics, NIRS, and NIS

3.1 Applications

- 1、Optogenetics
- 2、Further Applications of Optical Neural Probes
- 3、Near-infrared spectroscopy (NIRS)
  - Functional near-infrared spectroscopy (fNIRS)
  - A commercial apparatus

3.2 Optogenetics

- Mechanisms underlying coding of cognitive information within the brain
- How can a large number of neurons within a population be driven with precise spatial, and defined temporal, resolution?



(a) Whole field illumination (b) An array of photodiodes (c) Multiphoton excitation (d) Digital holography

Figure 3.1 Activating neurons to drive activity (Jarvis & Schultz, 2015)

3.3 Optical Neural Probes

- 3D light-targeted photostimulation

(A) SLM-based multiplexing strategies allow to target opsin-expressing neurons over axial and lateral fields of excitation
(B) The spatial resolution
(C) The temporal precision
(D) The temporal resolution

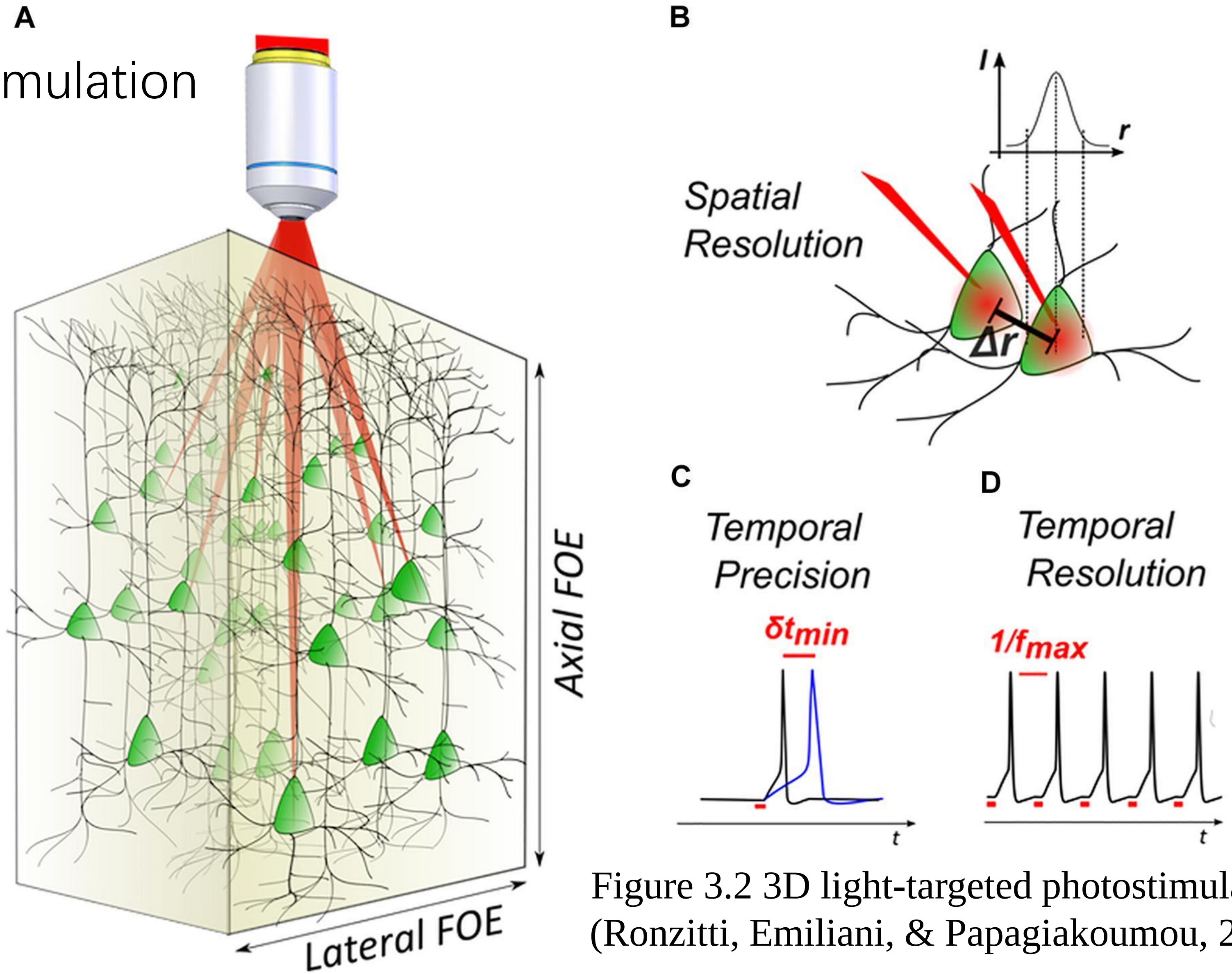


Figure 3.2 3D light-targeted photostimulation (Ronzitti, Emiliani, & Papagiakoumou, 2018)

3.4 NIRS

- Functional near-infrared spectroscopy (fNIRS)

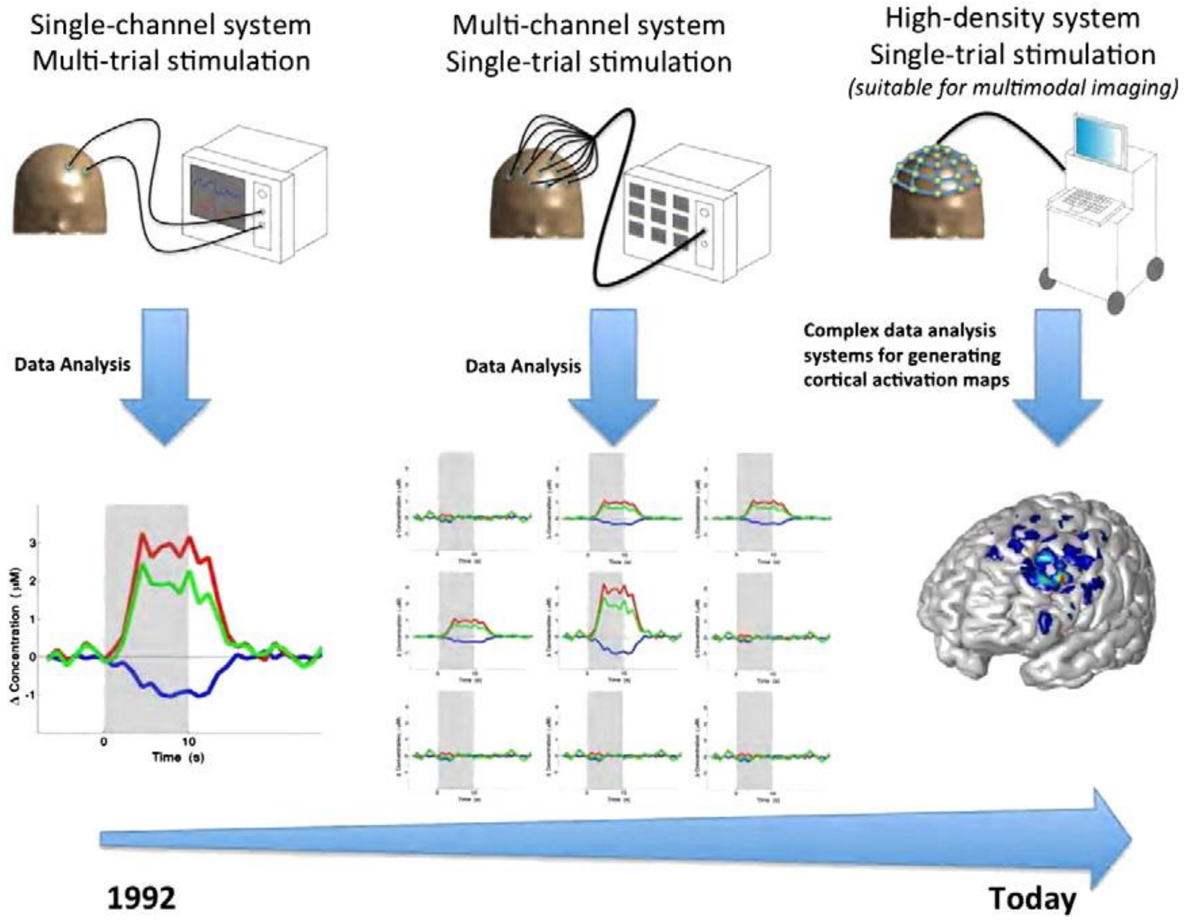
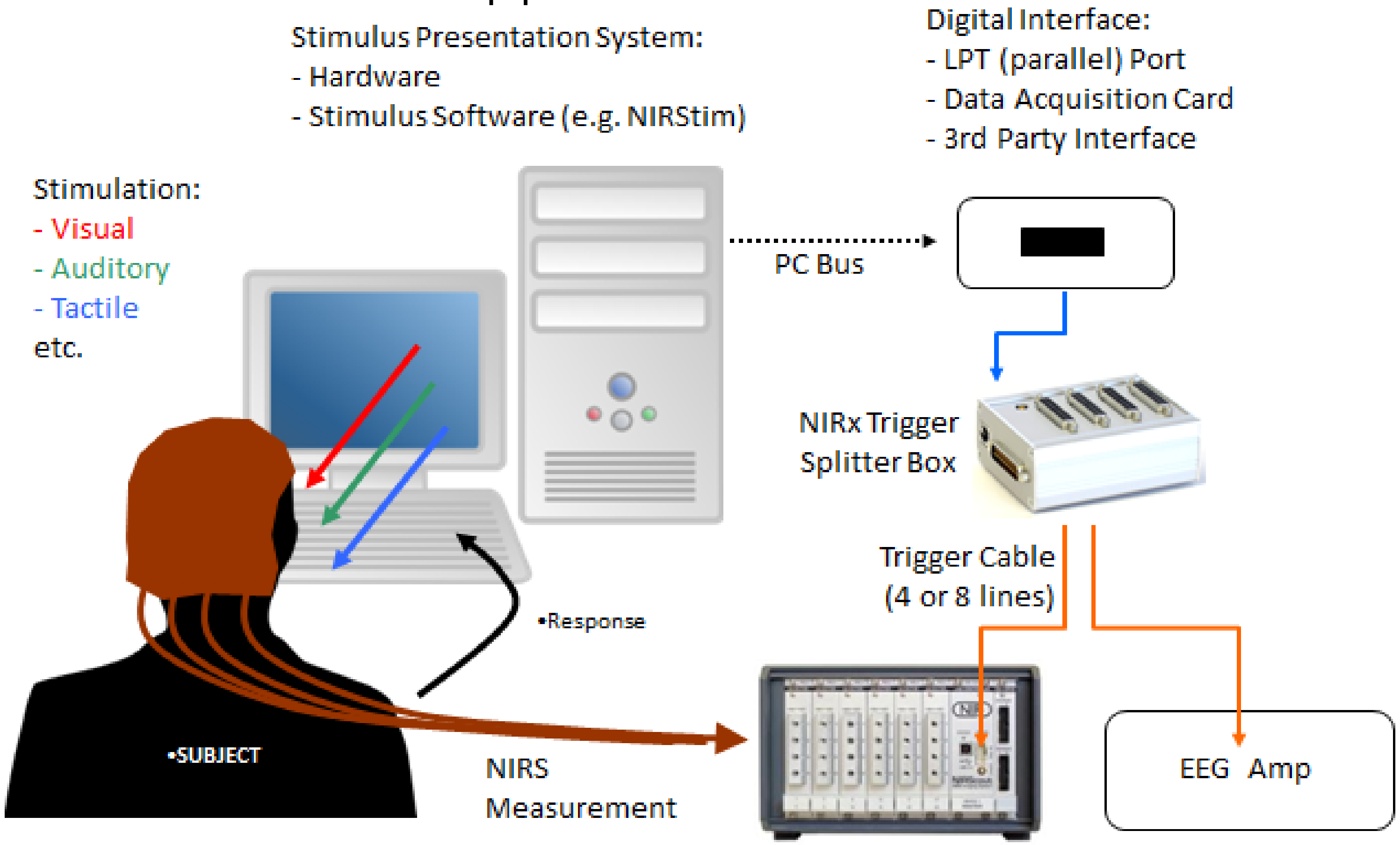


Figure 3.3 Sketch of the development of fNIRS instrumentation (Ferrari & Quaresima, 2012)

The present high temporal resolution multi-channel systems, using the three different NIRS techniques and complex data analysis systems, provide simultaneous multiple measurements and display the results in the form of a map or image over a specific cortical area.

3.4 NIRS

- A commercial apparatus



(a) Example of NIRSport 2 + EEG Data Integration

(b) NIRSport 2 with back strap for mobile applications

https://nirx.net/nirsport

Figure 3.4 An Example of commercial NIRS measurement

4 Vision of the Future

limitations &Possibilities of optogenetic

4.1 Clinical Application

- **1. Parkinson's disease**

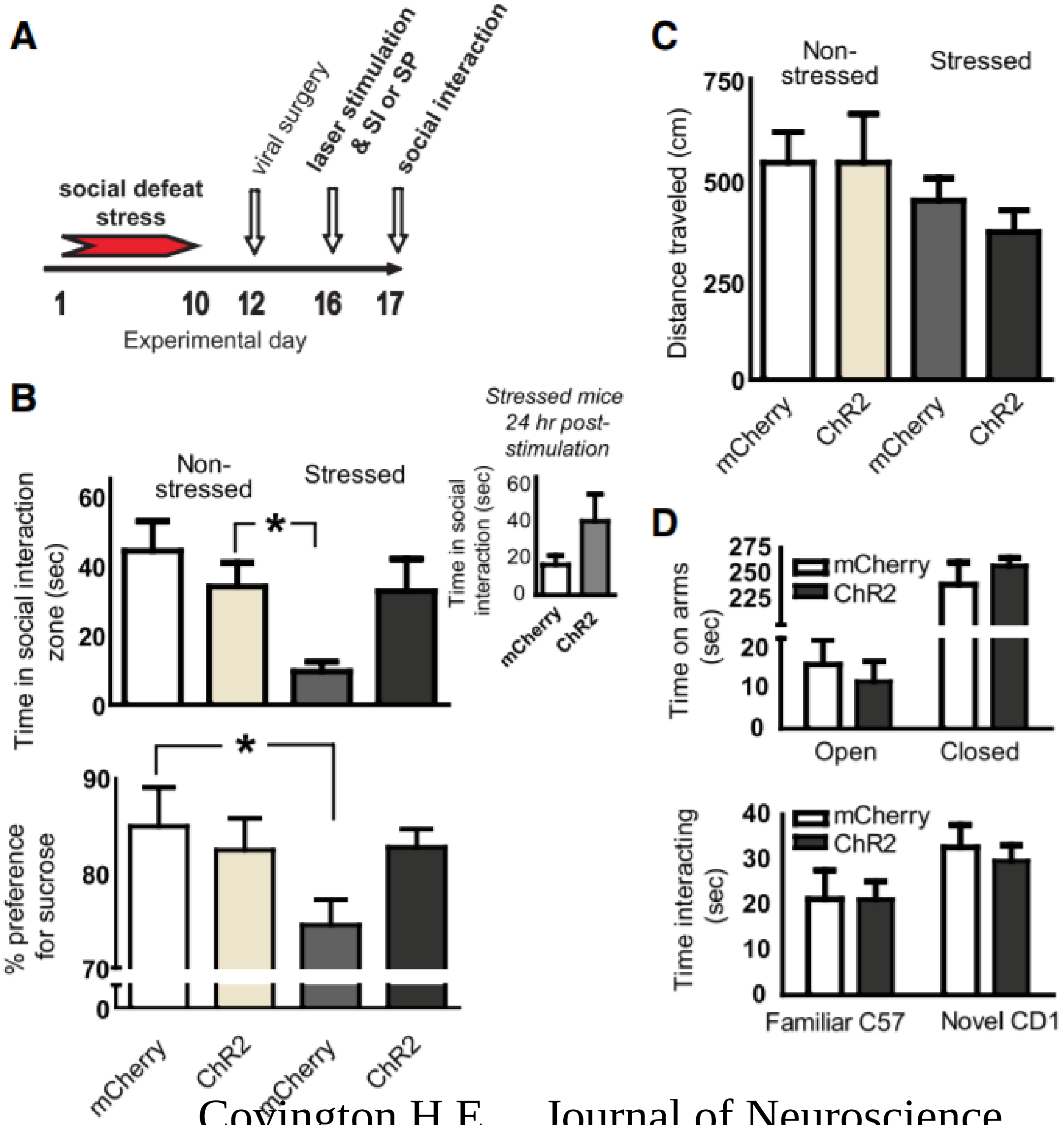
The loss of LC-NE is the basis of the early cognitive dysfunction of Parkinson's disease, which can be targeted and controlled by optogenetic technology.

Vazey E M , . Frontiers in Behavioral Neuroscience, 2012, 6.

4.1 Clinical Application

- **2. Depression**

Light stimulation of the medial prefrontal cortex (MPFC) can reduce depressive behavior, but optogenetics can target specific cell subsets, making it possible to further study the substrates and treatment strategies for many diseases, including depression.



Covington H E , . Journal of Neuroscience, 2010, 30(48):16082-16090.
Carter M E , Yizhar O , Chikahisa S , et al. Nature Neuroscience, 2010, 13(12):1526-1533.

4.1 Clinical Application

- **3. Retinal degeneration disease**

In retinal degenerative diseases, optogenetics can restore the vision of patients to some extent by injecting opsin gene and activating opsin by external light.

Thyagarajan S , et al. Journal of Neuroscience, 2010, 30(26):8745-8758.

4.3 Limitations

1. Risks of Virus transfectionand ;

2. Selection of target cells ;

3. Immunogenicity.

4.3 Possibilities

1. Noninvasive light stimulation ;

2. Miniaturization and portability;

3. Biomaterial ;

4. More clinical areas: blood sugar, cardiac function, muscle.

THANK YOU!

Q&A

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