Implantable Micro- and Nanophotonic Devices: Toward a New Generation of Neural Interfaces for Brain–Machine Communication and Neuroprosthetics

Dr. Jonathan Miller[1]*

[1]Massachusetts Institute of Technology (MIT), Department of Bioengineering and Neural Engineering, Cambridge, USA

Abstract:

This review focuses on the role that micro and nanotechnologies are having in the development of a new generation of optical neural interfaces for deep brain regions. The advent of optical methods to control and monitor neural activity has indeed raised neuroscientists' demand for small, soft and multifunctional devices to interface with sub-cortical structures. These are indeed widely inaccessible with microscopy-based approaches, and the scientific community has proposed complementary methods based on integrated photonics, implantable micro LEDs and engineered optical fibers. After discussing advantages and drawbacks of these methods, the manuscript closes with an overview on the emerging field of optical neural interfaces based on colloidal nanoparticles.

1 Introduction:

New advances in understanding how the brain works have been historically accompanied by important technological developments. From electrophysiology to optical methods, micro and nanotechnologies are playing a key role in allowing neuroscientists to get a better picture of how neurons coordinate to generate the extraordinary functions our brains can afford [1,2]. With this perspective, optical approaches to access neural structures are one of the major tools employed in neuroscience labs, with the goal of getting a more detailed picture on how information is codified and elaborated [3] and on the mechanisms behind neural diseases [4]. These approaches are mostly enabled by optogenetic methods, which encompass the use of genetically encoded optical actuators (OAs) and fluorescent indicators (FIs) of neural activity expressed on specific sub-populations of neurons, enabling unprecedented molecular specificity in studying functional connections [5,6]. OAs are ion channels or ion pumps that upon absorption of light generate cell depolarization or hyperpolarization, triggering or inhibiting neural activity [5]. Commonly employed proteins for this application are Channelrhodopsin2 (ChR2) [7], which can generate action potentials by absorbing trains of blue light pulses, and Halorhodopsin (Halo) [8], which absorbs light at ~590nm and inhibits neural activity. Instead, FIs change their fluorescence intensity in response to neural activity, with the most used being indicators of calcium concentration [9,10], voltage sensitive dyes [11,12] and indicators of neurotransmitters concentration [13].

The brain is, however, a highly scattering tissue and getting excitation light to OAs and FIs and collecting back fluorescence represent challenging tasks [14]. Both single and two-photon microscopy can be used in combination with genetically-encoded OAs and FIs in shallow regions of the brain [15–18], while getting visible light to and from depths higher than 1mm requires the use of implantable systems. This review is placed in this latter framework, focusing on recent micro and nanotechnologies developed to get optical access to deep brain regions. The common thread of these methods is the need of reducing the overall tissue reaction to the implant decreasing its size and stiffness, while integrating multiple functionalities in the same device. In the following, we will describe how integrated photonics, optoelectronics devices and optical fibers are being engineered to reach these goals, with the last paragraph discussing the emerging field of optical neural interfaces based on quantum confinement in colloidal nanoparticles.

2 Planar waveguides and integrated photonics

The use of solid-state optical waveguides to deliver light in multiple points of the brain is one of the first applications of integrated photonic devices for optogenetic applications. The main components of these systems are depicted in Figure 1A: a light source that stays outside the brain (i) is directed by a coupler (ii) and a switcher (iii) to a set of waveguides (iv), whose guided light is outcoupled into the brain by a light redirecting element (v). Since 2010, several devices have been proposed following this scheme, with the main goal to achieve full integration of blocks (i)-(v) in a single probe.

In its earliest implementation, this approach was proposed by Zorzos et al [19,20] by realizing multiple ridge multimodal waveguides on a silicon shank, with blocks (i)-(iii) implemented on an optical table by using optical scanning systems and blocks (iv) and (v) realized on the shank. Each waveguide was built of a Silicon Oxynitride (SiON) core with SiO_2/Al claddings and ended with a mirror at 90°, directing light away from the shank in a two- or three-dimensional array (Figure 1B). After this seminal work, more complex photonic elements have been integrated with the main goal to optimize outcoupling efficiency into the brain and to integrate on-chip light sources and beam routing. In ref [21] Shim and colleagues proposed light redirection elements (block (v)) based on diffraction gratings receiving light from a mainstream waveguide (Figure 1C). The waveguide and the gratings were realized with stoichiometric Silicon Nitride Si_3N_4 to reduce absorption at 473nm and patterned with electron-beam lithography and reactive ion etching, achieving a propagation loss of the waveguide of 1.4dB/cm. A second grating was realized at the waveguide input, to optimize coupling with an external single-mode optical fiber. Although this work represents one of the first integrated switcher for this application, all the emitting points available along the shank were activated simultaneously. This issue was addressed by Seveg and coworkes in ref [22]. A micro-prism was used to inject light into a phototonic microcircuit realized onto the shank (Figure 1D), and an integrated arrayed waveguide grating (AWG) was exploited to demultiplex sub-portions of the multispectral light source into each Si_3N_4 waveguides. With a proper design of the AWG and of the outcoupling gratings, the authors were able to independently emit light from nine different points along the shank with spectral shifts of a few nanometers, well within the absorption spectra of ChR2. Selection of the active pixels was instead performed by off-probe circuits which, together with the bulk source, remain the only non-integrated parts. Very recently, Mohanty et al [23] proposed an elegant strategy to integrate block (iii), realizing on-chip light routing by electrically-driven interferometric switches (Figure 1E). These switches were implemented by co-fabricating the waveguides with microheaters that locally change the temperature and therefore the refractive index of the light-guiding material. In a two-output ports configuration, the resulting phase change allows to control the interference and the routing of light into the waveguides and the activated delivery points that, also in this case, exploit outcoupling gratings. The intrinsic compatibility of photonic microcircuits with planar microfabrication technologies also allows these systems to host multiple electrodes to record extracellular activity [24–27]. These can be realized in conjunction with polymeric [24] or semiconductor [25] waveguides (Figure 1F) and can also host on-chip laser diode sources [26] (Figure 1G). In this latter work Schwarzle and coworkers realized SU-8 waveguides bringing light close to Ti recording electrodes and used flip-chip bonding to couple a laser diode to each waveguide, avoiding the use of bulk light sources.

The use of integrated waveguides and photonic elements therefore represents one of the roads to realize fully integrated “optrodes” devices able to trigger and record neural activity from multiple points of the brain simultaneously. The possibility of exploiting planar nano- and micro-fabrication makes indeed this approach scalable, and very recent approaches to record from thousands of individual cells have been proposed using active CMOS electrodes [28,29]. Optical stimulation techniques/performances are, however, still limited by the maximum number of integrated waveguides the shank can host and by the minimum waveguide size necessary to carry a sufficient amount of power. This will be one of the main challenges that the field will be facing in coming years, with multiplexing approaches being a possible solution.

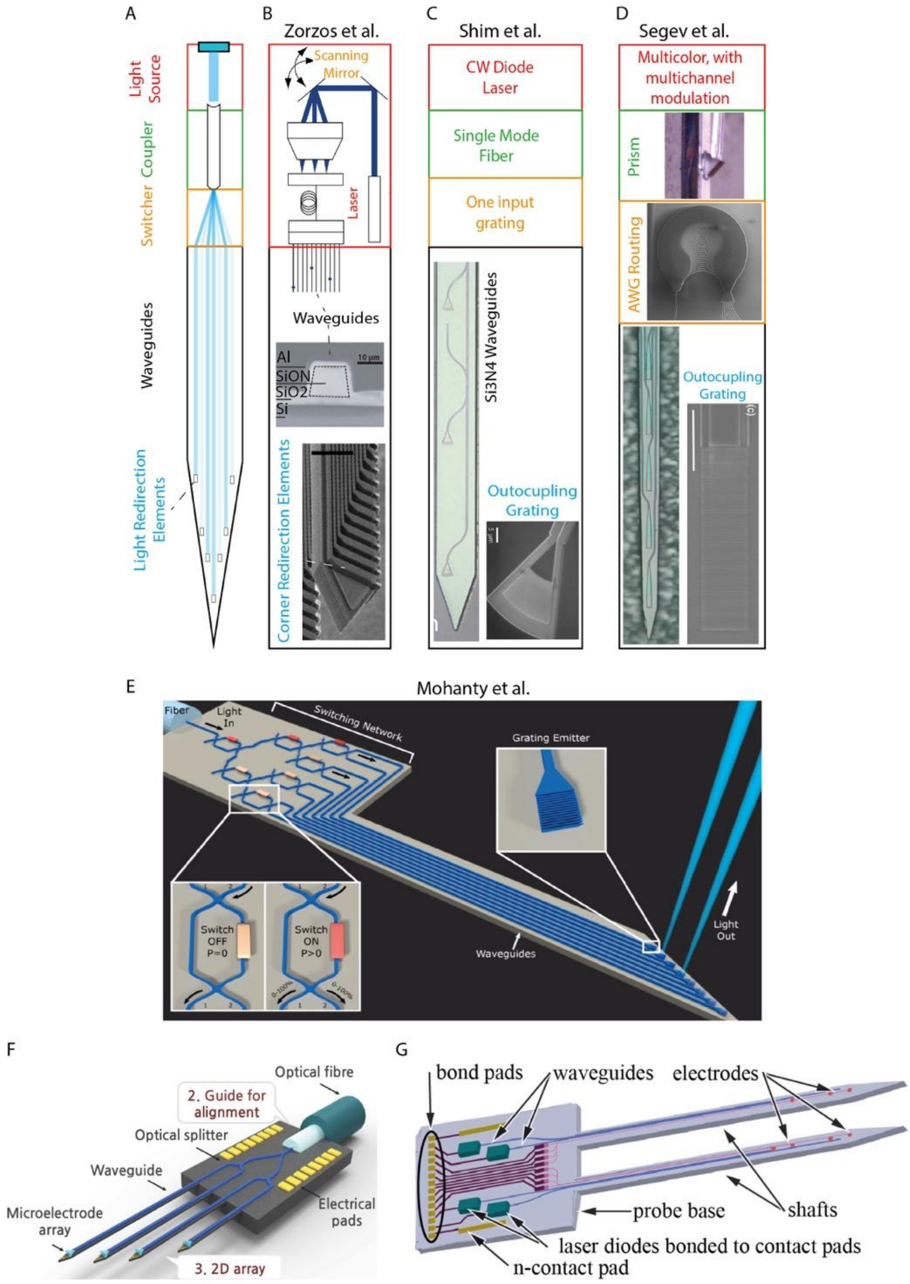

Figure 1: Optical neural interfaces based on integrated photonics. (A) *Schematic representation of the different blocks composing implantable optical neural interfaces based on solid-state waveguides.* ***(B)*** *Block diagram summarizing the works by Zorzos et al, in which switcher, coupler and light source are implemented out-of-probe, while redirecting elements are constituted by 90° integrated mirrors (figures are reproduced from ref.s* [19,20]*).* ***(C)*** *Diffraction-gratings approach proposed by Shim and coworkers. Gratings are implemented both at the outputs and at the input of the waveguide (images are reproduced from ref* [21]*).* ***(D)*** *AWG routing approach implemented by Segev and collaborators to independently and selectively activate different emission sites along the shank (images are reproduced from ref.* [22]*).* ***(E)*** *Integrated interferometric switches developed by Mohanty et al (panel E is reproduced from ref.* [23]*). (F), (G) Examples of integrated waveguides paired with electrodes for extracellular recoding of neural activity, integrating a fiber/waveguide coupler (panel F) or laser diodes on-probe (panel G). Panels F and G are reproduced from refs* [24,26]*, respectively.*

3 Implantable Micro Light Emitting Diodes

Opposite to waveguides, the light sources are implanted directly in the brain in the case of micro light emitting diodes (µLEDs) probes. An approach to obtain arrays of µLEDs for optical neural interfaces was proposed in 2013 by McAlinden and co-workers, who realized multiple and independently driven GaN emitters on a Sapphire substrate[30]. μLEDs were covered with p-metal in order to mask one side of the emission and direct light toward the sapphire substrate. This resulted in a Lambertian emission profile, which represents one of the main limitations of the spatial resolution achievable with this approach. The final probe containing up to four emitters was shaped and released by laser dicing, and used to excite neurons at different depths in the mouse neocortex [31]. Although Sapphire represents a widely used substrate for integrating GaN emitting devices by virtue of the low density of defects at the GaN-Sapphire interface, it has the important issue of not allowing for the integration of extracellular recording sites besides the μLEDs. Across 2015 and 2016, two different works [32,33] overtook this limitation by realizing implantable micro emitters directly on Silicon substrates, realizing also recording pads for neural activity readout. Wu et al [32] fabricated InGaN μLEDs on Si with quantum wells emission centered at 460nm; on the same substrate a Ti/Al/Ti/Au stack was used to form interconnection lines, while the portion of the electrodes exposed to the electrolyte was coated with Ti/Pt/Ir layers. The full stack view and typical images of the device are shown in Figure 2A, with the final probe featuring four different shanks (each hosting three μLEDs and eight electrodes) used to trigger neural activity of pyramidal cells in the CA1 of the mouse hippocampus. Scharf et al [33] used a similar approach to scale up the process, obtaining a probe hosting 96 μLED on six shanks (16 emitters per shank, Figure 2B), interfaced with a Universal Serial Bus (USB). In their work they also provide an interesting study based on a Monte-Carlo method to study heat dissipation of GaN-over-Si μLEDs and the achievable spatial resolution. If on one hand the GaN/Si interface presents a higher density of defects with respect to the more canonical GaN/Sapphire stack and results in lower internal quantum efficiency, the Si substrate dissipates much better the heating generated by the μLED and allows to reach up to 150mW/mm^2 and 5 ms stimulation pulses with temperature increase ≤1°C. This evaluation was performed through Monte-Carlo simulations of light distribution, and the same approach was implemented to assess the achievable optical resolution limit. Due to the Lambertian emission, decreasing the size of the emitters and their pitch on the probe allows improving spatial resolution but reduces the penetration depth of light in the direction perpendicular to the shaft, highlighting an important trade-off for experimental design.

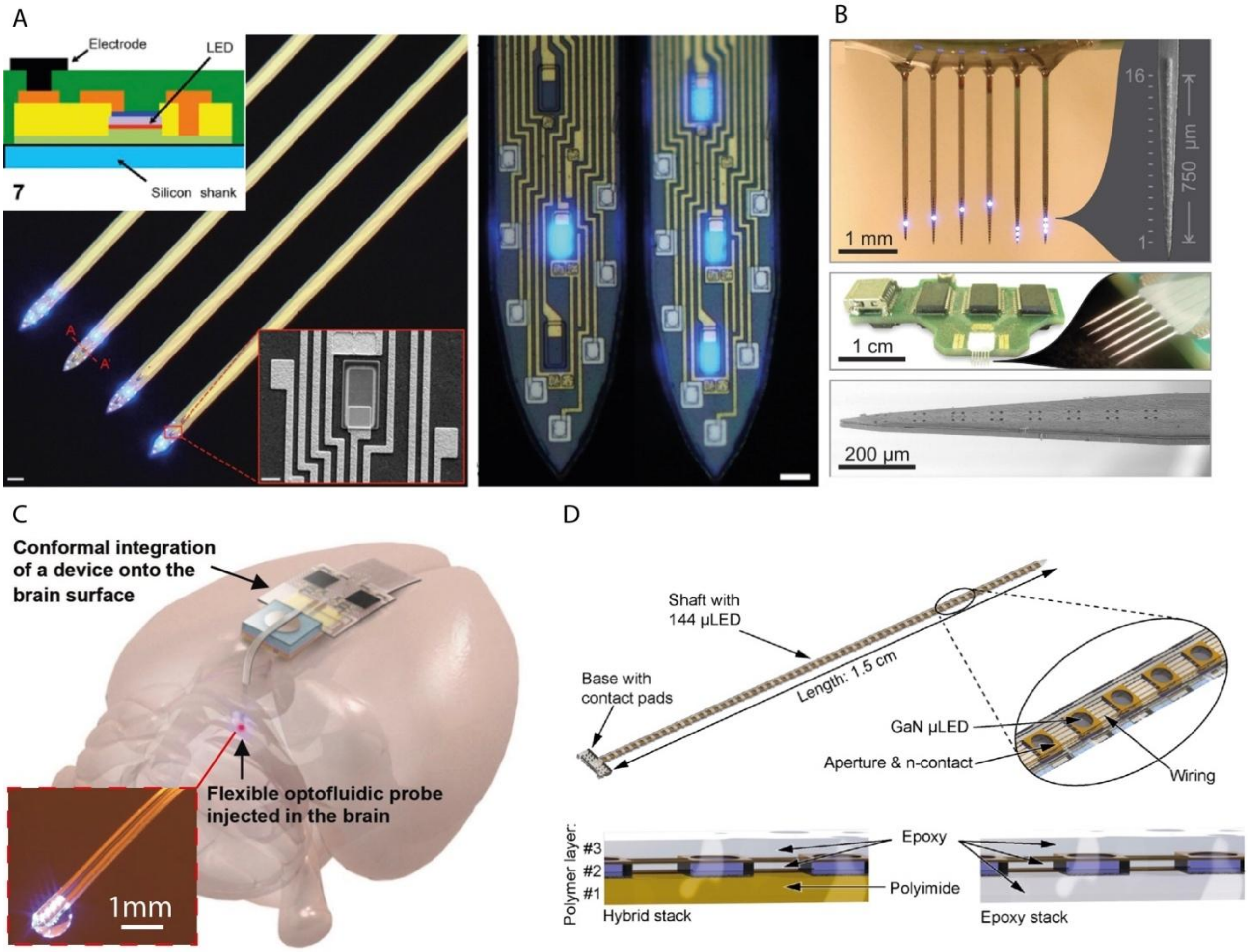

Figure 2: Implantable μLEDs technology. ***(A)*** *Monolithic integration of μLEDs on silicon substrate together with electrodes for extracellular recording of neural activity (images reproduced from ref.* [32]*)* ***(B)*** *High-density probes for optical stimulation with 16 μLEDs on 6 shanks for a total of 96 emitters (panels are reproduced from ref.* [33]*).* ***(C)*** *Flexible optofluidic probes with implanted μLEDs and drug-delivery channels (reproduced from ref.* [34]*).* ***(D)*** *Flexible high-density μLEDs probe for optical control of auditory functions in the cochlea (reproduced from ref.* [35]*).*

An alternative method to integrate μLEDs is represented by the pick-and-place approach. In 2013 Kim and collaborators [36] used a laser-based method to release the μLED emitters from a sapphire substrate and to place them on a flexible shank together with other implantable micro devices (Figure 2C) including temperature sensors, extracellular electrodes and, later in time, also reservoirs and microchannels for drug delivery [34]. The use of flexible materials allows to better match the stiffness of the implant with the mechanical properties of the brain, strongly reducing astrocyte and glial accumulation around the implant [36,37]. The driving electronic is placed between the skull and the skin (Figure 2C) and driving is obtained with wireless communication. The low power consumption of μLEDs makes, indeed, these light sources highly suitable for use in free-moving mice experiments, and the single mice can host complex implanted radiofrequency (RF) circuits. The same group showed that multiple RF stretchable antennas operating in the range of a few GHz can be designed by exploiting a scheme based on serpentines and capacitive coupling, implanted under the skin, and used to independently drive multiple μLEDs [38]. The technology can be used both in the brain as well as in the peripheral nervous system [39] and can host both lumped and distributed circuits to obtain dynamic control of the emission power to correct for variations in RF power transfer due to different orientations of the antenna(s) while the animal moves [40]. Very recently, flexible electronics has been also used to obtain shanks featuring a μLED beside an integrated photodetector, paving the way for wireless optical readout of neural activity with genetically-encoded fluorescent indicators [38]. As a further application of pick-and-place μLEDs probes, high density arrays of emitters on very long flexible shaft are being implemented to exploit optogenetics to restore auditory functions by optogenetic light delivery in the cochlea (Figure 2D). Laser lift-off of μLEDs was employed by Goßler and collaborators in 2014 to release multiple emitters simultaneously and place them on a polyamide-on-Si substrate [41]. This was done with a two-step laser lift-off, with the first step used to release all μLED and the second one to release the entire Sapphire wafer. In its latest development the resulting probe can host up to 144 emitters, over a total length up to 1.5cm, and is realized with a full epoxy encapsulation that reduces mechanical stress induced by high temperatures during processing [35].

μLEDs therefore present several advantages for optical neural interfaces: (i) can be integrated on both flexible and rigid shafts, (ii) can be driven and powered wirelessly, (iii) can achieve high-density and a spatial resolution comparable to the size of a few neurons, and (iv) can be integrated with several other microdevices to build multifunctional implants. In addition, chronic implants have been demonstrated for periods up to 9 months [40], although an intrinsic limitation of the technology remains: in case of failure of a single emitter, the entire probe needs to be substituted. Another drawback concerns the temperature gradient induced by μLEDs, which can easily overtake 1°C when operating for long periods, either with polymeric, silicon or Sapphire substrates. This constraint prompted the generation of another class of devices in which long stimulation times and low temperature increase are required: micro emitters are placed just outside the brain and light is guided downwards in the region of interest by optical waveguides. Also in this case μLEDs can be aligned to the waveguides with pick-and-place approach [42] or monolithically fabricated on a substrate in correspondence to the waveguide's input [43], and are fully compatible with integrated extracellular recording systems and wireless driving and powering [44]. Although these latter approaches bring light sources in a distal site and the overall device structure is similar to the one described in paragraph 2, these works highlight that a strong interaction between the integrated photonics and μLEDs community can help developing implantable devices that can better meet experimental needs.

4 Engineered Optical fibers

Implanted fiber optics were the first waveguides used for optogenetic applications for acute and chronic experiments [45,46], and still represent the most diffused method to deliver light into the brain, in particular in free-moving animal experiments. A single fiber optic implant has, however, several disadvantages if compared with photonic or μLEDs implants: it is quite invasive (implant cross-section is ~200μm on average), can interface with a single, small volume of tissue [5,47], and it requires the implantation of a separate device to readout neural activity [48]. In last few years, most of these limitations have been overcome by employing micro and nanotechnologies to exploit the photonic properties of optical fibers and to structure their surface. This is giving birth to new generations of implantable optical fibers for neurophotonics, that can be catalogued as: (i) polymeric multifunctional fibers (PMFs) hosting light delivery channels, electrodes for extracellular recording of neural activity as well as drug delivery channels, and (ii) tapered optical fibers (TFs), which exploit mode-division demultiplexing operated by the fiber taper to deliver (collect) light to (from) multiple points of the brain.

PMFs [49] are constituted by different layers of soft polymers, including poly(etherimide), poly(phenylsulfone), polycarbonate, cyclic olefin copolymer, and a polymer composites, stacked in a cylindric preform and pulled with a thermal drawing process (Figure 3A). The use of soft polymers allows to better match the mechanical properties of the implant with the stiffness of the nervous system, greatly reducing tissue reaction over time and improving biocompatibility over long time implants [49,50]. By layering the different polymers in a cylindric symmetry, it is possible to engineer the cross-section of the device and build flexible fiber optics able to integrate multiple functionalities. An example of this approach was given in 2017 by Park and coworkers [50], who realized devices containing microfluidic channels, light-delivery waveguides and electrodes for extracellular recording with a flexible geometrical disposition that can be arranged depending on the specific experimental needs. The waveguides were realized using polycarbonate as core, while cyclic olefin copolymer was used as cladding. The conductive electrodes were made by a composite containing graphite (5%wt) in conductive polyetilene and the entire structure pulled down to a diameter between 180µm and 200µm.

PMFs allows reducing the misalignment of virus and light delivery that is unavoidable in conventional optogenetic experiments where: (i) an adeno associated virus (AAV) is injected in the brain region of interest to express ChR2 in the target neurons; (ii) the fiber optics is implanted separately, inducing an unavoidably misalignment between the virus injection and the fiber implant site. PMFs merge together the two steps: the fiber can be chronically implanted and the microfluidic channels used to deliver the AAV. After the expression of ChR2 is complete, the same implant can be used to deliver light and record neural activity exactly in the same brain volume where the virus was delivered. The versatility of the fabrication and the use of soft polymers enable the use of these devices in the brain as well as in the spinal cord [51] (Figure 3A), making PMFs a unique solution for integrated and simultaneous drug and light delivery in tissue. Optical monitoring of neural activity instead has not been demonstrated yet with MPFs, with the autofluorescence properties of the employed polymers that could represent an important obstacle to be overtaken to this end.

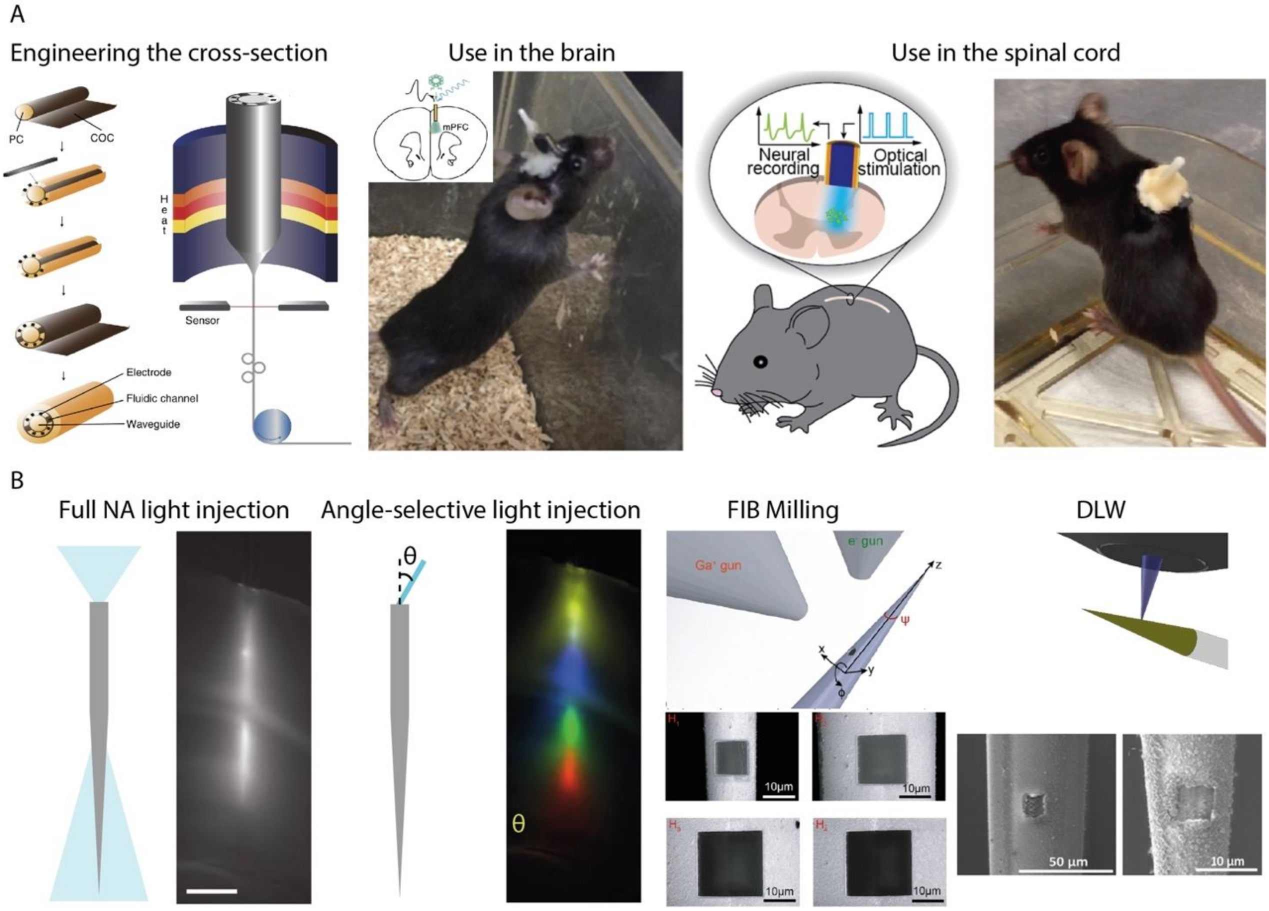

Figure 3: Optical neural interfaces based on fiber optics. *(A) Multifunctional polymeric optical fibers and their use in the brain and in the spinal cord (panels reproduced from refs.* [50,51]*). (B) Tapered optical fibers used for wide volume or site-selective light delivery. Panels on the right show two different methods to structure the fiber taper.*

A second class of optical fibers for optogenetic applications is represented by tapered fibers (TFs), displayed in Figure 3B [52,53]. TFs exploit the modal properties of the narrowing waveguide to control light emission along the taper: when the diameter of the waveguide reduces, modes of decreasing orders are outcoupled in the environment, resulting in a uniform emission along the fiber taper [54] (Figure 3B-Left). Selecting the input angle of light within the total NA of the fiber instead allows conveying optical radiation in a subset of guided modes, generating emission in a specific portion of the taper (Figure 3B-Center). This latter approach works with pure a dielectric waveguide as well as with TFs featuring a patterned metal layer along the taper [52,55]. Structuring the metal coating enables a customize light-emission geometry that can be tailored with the anatomy of the brain region of interest [56–58]. Structuring the metal cladding around the taper represents a challenging task, due to the highly non-planar surface of the taper, which features a reduction of the radius of curvature while it narrows. Patterning can be realized by either Focused Ion Beam Milling or Direct Laser Writing, with both methods operating in a “quasi-planar” condition when removing metal at different sections of the waveguide as writing spots are much smaller than the taper radius of curvature [56,59]. TFs have been used *in vivo* in free-moving animals [53], can be coupled with wirelessly-triggered light delivery systems [60], and as for MPFs they reduce tissue reaction over several days of implant [53]. All these features make TFs an important complement to μLEDs or integrated photonics approaches, in particular for implementing multipoint control of neural activity along the implant axis. In a recent preprint, the possibility to obtain multipoint fluorescence collection has been proposed exploiting localized fluorescence excitation in a laser-scanning system along the taper [61]. If this latter point represents an important advantage with respect to polymeric flexible fibers, at the present date the integration of electrodes for extracellular recordings and drug delivery channels along the taper has not been demonstrated yet.

5 Nanoparticles as optical neural interfaces

A promising alternative to implantable devices for neurophotonics is the use of colloidal nanoparticles (NPs). NPs have been suggested for both optical control and optical readout of neural activity as their small size allows for an interaction at the single cell level exploiting peculiar optical properties induced by quantum confinement. Figure 4 summarizes some of the NPs-based approaches, including the use of up-conversion nanoparticles (UCNPs), plasmonic gold nanocolloids and semiconductor nanocrystals (NCs).

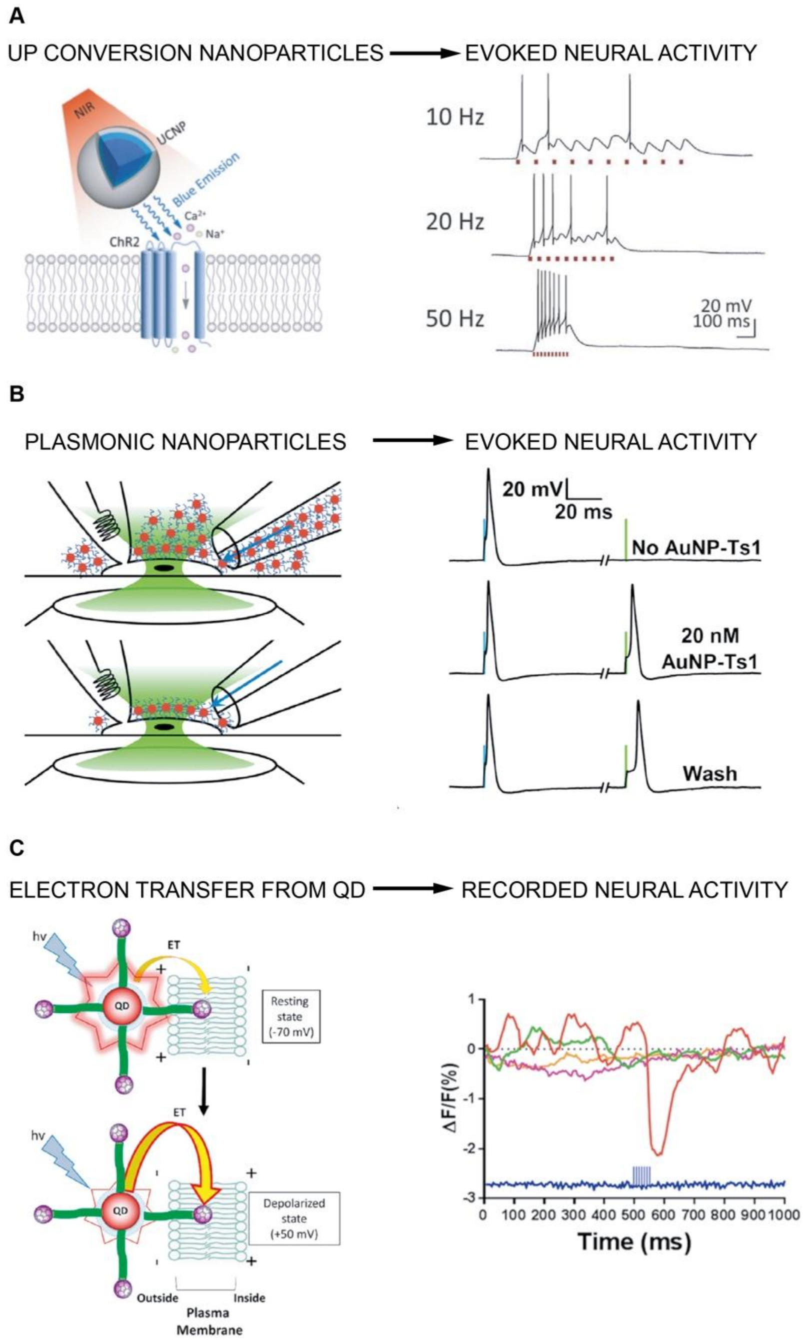

Figure 4: Nanoparticles-based optical neural interfaces. *(A) Use of up-conversion nanoparticles to control neural activity (reproduced from ref.* [62]*). (B) Plasmonic-assisted optical triggering of action potentials (reproduced from ref.* [63]*). (C) Colloidal quantum dots (QDs) and fullerene exploited to monitor neural activity exploiting electron transfer (reproduced from ref.* [64]*)*

In ref [62] Chen and co-workers used near-infrared (NIR) light to excite core/shell NPs with NAYF4:Yb/Tm core and NaYF4-SiO2 shells injected in deep brain regions. The composition of the particles was engineered to tune the emission spectrum with the maximum absorption of ChR2, and transcranial NIR light (930nm) was employed to trigger neural activity using a 2W continuous wave laser that was guided into an optical fiber (200µm core) which was not implanted, but instead was placed above the mouse head. With respect to the 473nm light commonly employed to excite ChR2, tissue absorption and scattering have a much lower influence on the 930nm light used by Chen et al., that can therefore easily reach sub-cortical areas. Blue light is then locally emitted by nanoparticles very close to the target neurons, and can readably trigger neural activity with an average power density of 0.34mW/mm^2. By changing the core composition to NAYF4:Yb/Er, the same approach can be used to engineer green-emitting nanoparticles to inhibit neural activity [62], making UCNPs a promising tool to optically access cellular events in deep-brain regions with cell-type specificity and without using implanted probes. An alternative approach to trigger neural activity exploits the plasmonic properties of gold nanocolloids. Carvalho-De-Souza and collaborators [63] enabled photosensitivity of neurons both *in vivo* and *in vitro* by functionalizing Au nanoparticles on the cell membrane. Green light was used to excite the plasmonic resonance on the single particles and generate local heat, which resulted in local change of membrane potential therefore in the generation of action potentials. Although the functionalization proposed in ref. [63] was not cell-type specific, targeting specific receptors on the cell membrane would allow the application of plasmonic neural stimulation to sub-populations of neurons. With respect to UCNPs, the plasmonic approach has the advantage of not requiring any genetic modification to the tissue, and spectral shift of the plasmonic resonance toward the NIR could potentially allow plasmonic control of neural activity with trans-cranial light delivery.

At the same time, recent proposals have instead focused on the exploitation of charge dynamics in semiconductor nanoparticles [65] to detect neural activity, trying to take advantage of several important features: a very high internal quantum efficiency [66,67], the higher two-photon absorption cross section with respect to other genetically encoded fluorescent indicators of neural activity [68–70], and their resistance to photodamage [71]. A first approach is based on the use of the quantum confined stark effect (QCSE) [72], consisting in a red shift of the emission spectra directly proportional to the square of an electric field gradient across the nanoparticle. Both theoretical and experimental works have shown that the time dynamics of this shift and the intensity of the electric fields required to produce a detectable QCSE are compatible with action potentials temporal evolution and trans-membrane potential [73–75]. On the other hand, a nanocrystal staying outside the neural membrane could hardly be used to optically monitor neural activity through QCSE [73–76]. This still represents one of the main limitations for the practical implementation of this method, since placing either spherical or elongated nanoparticles across the plasma membrane still represents a challenging task [65,73,77,78], with only a proof-of-concept demonstration to date [76]. An approach to keep the nanoparticle outside the plasma membrane and outside the cell relies in exploiting Foster energy transfer (FET) between the NC and an acceptor placed in the intracellular part of the lipid bilayer. Acting as the donor, the nanoparticle would decrease its photo luminescence (PL) intensity upon depolarization. Although approaches based on both FET and QCSE were not implemented yet, monitoring of neural activity has been instead demonstrated with electron transfer (ET) between a CdSe/CdS/Zns nanocrystal and fullerene (C60) in the configuration displayed in Figure 4C [64]. The nanoparticles engage ET with C60, with this latter being within the plasma membrane and linked to the NP with a peptide connection. When the cell depolarizes, the energy transfer is less effective and fluorescence intensity decreases [64]. Also plasmonic resonances have great potentialities to readout neural activity, exploiting the possibility to sense very small variations of refractive index induced by the electric field dynamics in the proximity of the plasma membrane. These were preliminary employed both *in vivo* and *in vitro* some years ago, although these works mostly focused on patterned substrates and implantable probes [79,80]. This sub-field could highly benefit by recent developments in targeting cell membranes with nanoparticles, and could lead to high-sensitivity optical readout of neural activity without the need of genetically-encoded indicators.

6 Conclusions and future directions

Micro and nanotechnologies are greatly contributing to a new generation of optical neural interfaces, with different and complementary approaches based on integrated photonics elements, implanted optoelectronic emitters and engineered fiber optics. All these methods are now facing the challenge of integrating multiple functionalities in the same implant, to get a dynamic picture of both electrical and chemical information codified by neural circuitry.

Although several approaches have been proposed so far for optical stimulation exploiting optogenetics, technologies for optical readout of neural activity are still at their embryonal stage [61,81]. More sensitive and spatially resolved systems to detect functional fluorescence from deep brain regions will not only allow to detect electrical signals through voltage sensitive dyes, but will also represent a major advance in monitoring neurotransmitters concentration exploiting newly developed fluorescent molecules [13]. To reach this goal, existing technologies have important advantages to exploit and drawbacks to circumvent. Integrated photonics is scalable and compatible with planar fabrication methods based on silicon technology, while implanted μLEDs can exploit flexible substrates to better match with the stiffness of central nervous system and to reach regions with a peculiar anatomy like, for example, the cochlea. In both cases, however, the access cost to the approach is still relatively high, with μLEDs presenting the additional drawback of local heat generation. On the other hand, approaches based on polymeric or tapered fibers are low cost and represent an efficient base to realize multifunctional implants, although high-resolution and high-density stimulation or recording has not been demonstrated yet. In addition, the scientific community is exploring the possibility of using the unique optical properties of colloidal nanoparticles, whose quantum confinement and light-matter interaction at the nanoscale could represent next frontier for optical neural interfaces.

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