

Hybrid Electrical and Optical Neural Interfaces

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Abstract

Neural interfaces bridge the nervous system and the outside world by recording and stimulating neurons. Combining electrical and optical modalities in a single, hybrid neural interface system could lead to complementary and powerful new ways to explore the brain. It has gained robust and exciting momentum recently in neuroscience and neural engineering research. Here, we review developments in the past several years aiming to achieve such hybrid electrical and optical microsystem platforms. Specifically, we cover three major categories of technological advances: transparent neuroelectrodes, optical neural fibers with electrodes, and neural probes/grids integrating electrodes and microscale light-emitting diodes. We discuss examples of these probes tailored to combine electrophysiological recording with optical imaging or optical neural stimulation of the brain and possible directions of future innovation.

Keywords: neural interfaces, hybrid, transparent electrodes, optical fibers, LED

1. Introduction

Understanding the brain has always been challenging yet rewarding. Over the past centuries, our knowledge on our own brain has exploded from both studying the brain mechanisms and exploring therapeutic interventions for neurological disorders like epilepsy and Parkinson's disease [1]. Concomitantly, various neural interface technologies have been developed, including optical and electrical methods, to probe and interrogate the brain [2-5]. Historically, Ramón y Cajal pioneered modern neuroscience by elucidating and recognizing the fundamental neuron-based microscopic structure of the brain in the late 19th century through improved Golgi staining and microscopy [6]. Observed by du Bois-Reymond though first in animal nerves [7], action potential was found to be the information carrier for cell-to-cell communication, which was later established by Nobel laureates Adrian Edgar and Charles Sherrington in the early 20th century [8, 9]. After that, the establishment of the ion-permeation-based mechanism by Hodgkin and Huxley in the 1950s has laid the foundation for the most of our knowledge of neuronal signaling [10, 11]. Measuring and interrogating neuronal signals therefore are crucial to the reverse engineering of the brain to understand normal or pathological dynamics of underlying neural circuits.

The brain, however, is extremely complex, containing networks of billions of neurons with different types, shapes, and complicated connections surrounding them. Conventional neuroelectrodes have proven their ability to probe the electrical activity from the brain with high temporal resolution but intrinsically lacks the spatial precision, while existing optical methods have established as the workhorse to reveal the finest spatial intricacies in brain tissue though they are still catching up in recording fast neuronal activities [12]. Combining these two modalities, in a single, hybrid platform could lead to complementary and powerful new ways to explore the brain and has gained much exciting momentum recently in neuroscience and neural engineering research [13]. As the device technology developed, biological aspects have also taken into consideration to minimize the damage of the brain and to maximize the device performance in terms of engineering perspective. During device implantation, it is crucial to understand the reaction of tissues in terms of cellular and molecular level to mitigate tissue damage, which would otherwise degrade the performance of devices in terms of signal sensitivity and longevity [14]. To reduce the footprint of the device implantation, developments in both materials and device designs have also been made to use softer materials to have better mechanical compliance with the brain and smaller devices to decrease the insertion footprint [15].

In this paper, we review developments in the past several years aiming to achieve such hybrid electrical and optical microsystem platforms. Specifically, we cover three major categories of technological advances, namely (i) transparent neuroelectrodes, (ii) optical neural fibers with electrodes, and (iii) neural probes/grids integrating electrodes and micro-light-emitting diodes (μ -LEDs). In the first category, transparent electrodes enable high spatiotemporal resolution of brain activity mapping since they are capable of recording/stimulating electrical neural activity, and allow optical imaging and interrogation of the neurons simultaneously. The combination of high temporal resolution from the electrophysiology recording and superior spatial resolution from optical imaging will bridge the fast neuronal networks to the underlying molecular and cellular structures in detail. For example, this method revealed spontaneous firing activity of single neurons in the brain network dynamics with corresponding spatial patterns in the cortical area [16]. The second and third categories are both related to optogenetics, a powerful new optical method that can deliver cell-type-specific stimulation of neurons [17], and modulates and controls the neural activity by light stimulating genetically modified neurons with light-sensitive opsins, such as channelrhodopsin-2 (ChR2) and halorhodopsin (NpHR). Significant improvements have been made recently for optogenetic tools in neurobiology including optical fibers and implantable probes [18-20]. The use of optical fiber has drawn considerable attention for effective light delivery in optogenetics due to its well-established optical waveguide property and miniaturized footprint [21]. Fiber-optic based hybrid platforms could offer various properties such as being compact, light-weight, immune to large dynamic range, electromagnetic interference, and their chemical and biological inertness in nature [22, 23]. On the other hand, μ -LEDs have emerged as the other popular means for localized light sources in optogenetics. Systems integrating electrodes with light stimulation capability has also been demonstrated, which incorporated μ -LED on a single or multiple shanks. Together, these hybrid electrical and optical neural interfaces, and their future developments will pave promising pathways for next-generation brain research.

2. Transparent neuroelectrodes

There has been tremendous progress in developing transparent electrodes in recent years, due to their capabilities of simultaneous electrical and optical recordings [24]. The state-of-the-art of microelectrode arrays (MEAs) have achieved high-density microelectrodes for recording and/or modulating of brain signals with electrical stimulation with high sensitivity and selectivity. However, electrode recording alone intrinsically lacks high-level of spatial resolution compared

to optical imaging, which is critical as it allows to differentiate cell types, shapes, and complicated neural network connections among the brain cells. In the past, there have been the usage of optical imaging techniques to examine tissue surrounding electrode sites [25]. However, an exact correlation of neural signals with imaging data has been difficult. The development of completely transparent neuroelectrode devices is critical for next-level neural research, allowing both cortical imaging and optogenetic interventions concurrently with electrical recording. Over the past decade, a large number of studies aiming to integrate electrodes with optical imaging methods resulted in many different types of transparent electrodes to meet this need, which can be loosely categorized by the transparent electrode materials in use.

2.1 Indium tin oxide neuroelectrodes

Having high conductivity and transparency over the entire visible spectrum, transparent conductive oxides like indium tin oxide (ITO) have been utilized in numerous industrial applications. ITO has long been used in transparent and flexible applications, including displays, LEDs, solar cells and more recently in neural microelectrodes (**Fig. 1a-d**), due to its outstanding optical properties, such as extremely high transmittance and low auto-fluorescence. **Figure 1a** presents a 49-ch MEA using sputtered ITO as electrodes, gold (Au) as its interconnect and Parylene C as substrate [26]. It demonstrated 90% transparency and impedance of 30 k Ω with an electrode size of 250 μm in diameter. Parylene C is a widely used polymer for transparent and flexible neural devices, due to its biostability, biocompatibility, durability, lubricity, transparency, corrosion resistance, flexibility and surface consolidation, thus evading flaking or dusting [27]. Although ITO provides excellent electrical conductivity and transparency at the same time, it intrinsically has a brittle property [28]. To mitigate the brittleness, a hybrid structure of ITO and Au has been developed by confining ITO only to the electrodes while the long interconnect traces and bonding pads are fabricated with ductile Au (**Fig. 1b**) [29]. This opto-array showed 94% transparency and impedance of 1 ~ 5 k Ω with an electrode size of 200 μm in diameter, and utilized integrated LEDs for optical stimulation and simultaneous electrical recording. More about LED-integrated electrodes will be discussed in Section 4 of this review. Another ITO electrode array had 93% transparency and impedance of 345 k Ω with an electrode size of 100 μm in diameter and was able to facilitate two-photon imaging of Ca^{2+} signals and simultaneous electrical recording of cortical electroencephalogram (EEG) (**Fig. 1c**) [30]. They were able to perform the imaging without noticeable distortion of detected neuronal structures. Two-photon combines energy from two light

sources, so excitation light arising from near-infrared wavelength range (700 ~ 1000 nm) will be less scattered in the tissues and penetrates deeper [31]. In chronic settings, it showed that fluorescent Ca^{2+} signals from individual neurons could be collected after 51 days. ITO has also been made into penetrating electrodes for spatial mapping and broader functionality of ITO-based electrodes (**Fig. 1d**) [32]. This type of electrode is fabricated similarly to the Utah array but with a ZnO crystal, which is an optically transparent, electrical highly conductive semiconductor and the electrode tip is made with ITO-coated ZnO. It demonstrated 90% transparency and impedance of 300 k Ω with an electrode size of $\sim 10,000 \mu\text{m}^2$. This electrode successfully validated intracortical acute neural recording in an *in vivo* mouse model. Its recorded spike amplitude was comparable to commercial products from their Si counterpart. Rapid progress has been made recently to overcome the relative brittleness, moderate conductivity, and capacitive nature of ITO-based neuroelectrodes.

2.2 Graphene neuroelectrodes

Graphene has also been deployed as a material for transparent neuroelectrodes recently. Due to its high transparency and conductivity, graphene serves as an excellent candidate for transparent and flexible neuroelectrodes. Graphene's advantages include broad-spectrum transparency, flexibility, transferability, strength, and tunable electronic properties [33, 34]. Park *et al.* were among the first to demonstrate graphene-based neuroelectrodes with also 16 individual channels, showing 90% transparency and 243 k Ω with an electrode size of 200 μm in diameter (**Fig. 1e**) [35]. The impedance characteristics of graphene electrodes were found to be similar to those of conventional platinum electrodes. By using four-layer graphene films, they showed having more graphene layers could increase electrical conductivity to minimal transparency loss. Any transparent conductor film has inherent trade-offs between transparency and conductivity, where a thicker material increases conductivity but decreases the transparency. They chose four layers of graphene to achieve the lowest sheet resistance to have $\sim 90\%$ transmittance, and better yield and mechanical strength than fewer-layered graphene. Through *in vivo* experiment, the device recorded evoked potentials with stimulation to both ipsilateral and contralateral, showing electrophysiological responses of $\sim 100 \mu\text{V}$ evoked potentials. This result demonstrates that graphene electrodes can record both spontaneous baseline activities and evoked signals similarly to conventional platinum electrodes. Another seminal work in graphene neuroelectrodes demonstrated doping of graphene increases electrical performance of the graphene electrodes

(**Fig. 1f**) [36]. Through doping, it achieved a significant improvement of signal to noise ratio (SNR) and decreased electrical interference noise compared to Au electrodes. This 16-ch graphene neuroelectrode showed 90% transparency and impedance of 541 k Ω with an electrode size of 50 $\times$ 50 μm^2 . It also demonstrated simultaneous electrophysiology measurement and calcium imaging, which was performed with confocal or two-photon microscopy setups, having small laser-induced artifacts. The combination of both modalities revealed temporal and spatial characteristics of the high-frequency bursting activities and synaptic potentials. Another work on graphene microelectrodes has been conducted to reduce the artifact during local field potentials recordings, optogenetics and deep 2-photon imaging. They developed a new fabrication process to avoid crack forming during conventional graphene transfer process [37]. More recently, there has been exciting progress in improving the impedance and charge stimulation capabilities of graphene neuroelectrodes while not substantially degrading their transparency.

2.3 Functional nanomesh neuroelectrodes

Functional nanomesh is also emerging as a contender for transparent neuroelectrode material [38]. Stacked layers of conventional metal (*e.g.*, Au) and low-impedance coating (*e.g.*, poly(3,4-ethylenedioxythiophene) polystyrene sulfonate, PEDOT:PSS) of the same nanomesh pattern results in transparency with significant electrical performance increase due to faradaic interfacial layer [39]. A 32-ch bilayer nanomesh MEA with Au and PEDOT: PSS demonstrated comparable electrical performance to non-transparent, commercial Michigan arrays, having an impedance of 130 k Ω and electrode size of 20 μm in diameter with 73% transparency (**Fig. 1g**) [40]. This array presented concurrent electrical recordings of visual-evoked activities *in vivo* along with two-photon imaging of individual neurons from the visual cortex of awake mice. More recently, penetrating probes with nanomesh neuroelectrodes demonstrated the measuring of single-unit action potentials in the brain (**Fig. 1h**) [41]. These 32-ch probes demonstrated 67% transparency and impedance of 149 k Ω with electrode size of 15 $\times$ 15 μm^2 , and was able to detect single-unit electrophysiological neuronal activities. During *in vivo* experiment, they recorded spontaneous and evoked neuronal single-unit activities across the visual cortex of mice with high yield. For the penetration, the soft Parylene C shanks were temporarily stiffened with PEG for better insertion. Because of the ability to include the low-impedance coatings, which typically are opaque, functional nanomesh offers high electrode performance and great scalability, which could enable high-channel-count transparent neuroelectrode arrays for large-scale brain mapping.

2.4 Neuroelectrodes from other nanostructures

Other types of nanomaterials can also be great candidates for transparent neuroelectrodes, and nanowires (NWs) are one of them. For example, a 16-ch transparent MEA fabricated from Au NWs on polydimethylsiloxane (PDMS) showed 90% transparency and electrical impedance of 1 k Ω with electrode size of 94,200 μm^2 (**Fig. 1i**) [42]. It was chronically stable *in vivo* for weeks, suitable for 2-photon calcium imaging, and performed multiple sessions of electrophysiological recording in awake and anesthetized animals. A post-mortem histology study revealed that there was no qualitative difference between implanted and non-implanted regions after 6 weeks. From the concurrent imaging and electrical recording, the calcium signal demonstrated a correlation in positive and negative peaks with electrocorticography (ECoG) signals. Neto *et al.* used combination of silver nanowires (AgNWs) and indium-doped zinc oxide (IZO) as their transparent material (**Fig. 1j**) [43]. Its performance showed 60% transparency and electrical impedance of 20 k Ω with an electrode size of 500 μm in diameter. These metal nanowire networks maintained the properties of patterned metal films with simple fabrication using solution-based deposited techniques. Also, IZO coating increased adhesion between the substrate and nanowires, preventing corrosion of AgNW film over time, thus improving conductivity of the NWs. The electrodes recorded electrical neural activities *in vivo* from the surface of the rat cortex under anesthesia. Another similar approach is to use nanonetwork (NN) (**Fig. 1k**) [44]. A 16-ch Au NN MEA had 81% transparency and electrical impedance of 34 k Ω with an electrode size of 200 μm in diameter. Patterning Au films and polymer nanofibers together helped microelectrodes to achieve high transparency and low sheet resistance. It also has tunability by controlling the density of Au NN. This device recorded multi-channel *in vivo* neural activities with high SNR and minimal photoelectric artifacts. Fast and accurate responses from the optically stimulated neurons were measured by the microelectrodes. Simultaneous *in vivo* recording with optogenetics also achieved efficient and precise visualization of neural activities, spreading from the light-stimulated neurons to interneurons, interpreting neural dynamics accurately and precisely. Finally, polymer conductors can also serve as transparent neuroelectrodes. **Figure 1l** showed a 15-ch transparent, flexible, and active electrode, which consisted of transparent and organic electrochemical transistors (OECTs) with PEDOT:PSS as low-impedance coating and transparent Au grid interconnects [45]. This device demonstrated 69% transparency and electrical impedance of 10 k Ω with an electrode size of 1,400 μm^2 in diameter. The active electrodes demonstrated mapping of

evoked responses *in vivo* with an amplitude of 800 μ V at the same region where the surface of cortex is optogenetically modulated by a laser beam. This effort also presented the spatial mapping of EEG recordings from an optogenetic rat with low light-induced artifacts. The field of transparent neuroelectrode is growing rapidly to not only facilitate concurrent electrophysiology and optical approaches, but also achieve large-throughput devices for brain mapping with high spatiotemporal resolution.

3. Optical fibers with electrodes

Achieving better optical interfaces with the brain needs new technologies to deliver light in a more spatially resolved fashion to precisely illuminate the target brain structures. In many studies, it is required to deliver wide-field illumination over a large area of the brain, while for other applications, focused illumination to small brain areas is better. Due to optical fiber's preservation of energy, it has long been used in many applications such as communications, biomedical technology, and imaging [46-48]. The versatility of optical fiber-based devices is becoming more widely leveraged for *in vivo* applications [49]. For example, light collection from deep brain regions using fiber-photometry techniques has enabled neural activity recording [50-52]. In addition, multiphoton microscopy through Gradient Index (GRIN) lenses has established as a minimally invasive optical method for imaging of deep structures and subcellular resolution to several millimeters in intact animals. GRIN lenses are needle-like dimension that have been utilized for fiber bundle which is coupled with confocal microscopy [53, 54]. With the advent of optogenetics, optical fibers have become the primary tool for light delivery in neuroscience experiments. Integrating microelectrodes with optical fibers can therefore enable simultaneous electrical recording and optogenetic stimulation to allow cell-type-specific neuronal circuit investigations.

3.1 Materials to form optical fibers

Optical fiber is a flexible filament, like a hair, made of a molten glass or an appropriate polymeric material. Generally, inorganic glasses such as vitreous silica dioxide materials are used in the preparation of optical fiber. Researchers have extended the usage of glass fibers in neuroscience by adding extra functionalities [55-57] or combining them with the neural recording systems [58-63]. To improve mechanical compliance with the brain and optical fibers [64-66], several polymers are used including polymethylmethacrylate (PMMA), polystyrene (PS),

polycarbonates (PC), cyclic olefin copolymer, and amorphous fluoropolymer [67-72]. These polymer-based fibers are flexible and biocompatible [73, 74]. However, trade-offs have to be considered in thermal expansion and thermo-optic coefficients, photosensitivity, glass transition temperature, moisture absorption, and refractive index stress-optic coefficient [75, 76]. In this regard, various groups have improved optical fibers by different chemical and physical modifications [77-79].

Fibers can be manufactured into complex structures with multiple classes of materials including metals, semiconductors, and insulators. Optoelectronic devices are formed by conducting and semiconducting domain integration, which is manufactured by utilizing standard wafer based processes [80]. Although these devices are small and also low-cost, they have mechanically rigid substrates and restriction to planar geometries. The unique integration of metals, semiconductors, and insulators into one-dimensional (1D) fibers made optoelectronic functionalities in large-scale and soft substrates (flexible and stretchable) [80, 81]. These types of multi-material fibers are integrated tools to sense and deliver multiple signals into and from the nervous tissue. Various examples of fibers made from multi-material have been reported across multiple applications in several engineering fields [63, 82-85]. Multi-material fibers have developed an easy solution to combine optogenetics with other nervous interrogation devices while decreasing the elastic mismatch between the rigid implanted devices and the soft tissue [22, 86-88].

3.2 Optical fiber designs

In many optogenetic experiments, an optical fiber is inserted into the brain tissue to transmit light to the brain for activating or silencing neurons. One end of the fiber is coupled to the light source, and the opposite end serves as the photo-stimulation site. Light sources can be xenon lamps [89], LED [90, 91], and mostly laser diodes due to their high light intensity, coherence with narrow bandwidth, and low light beam divergence [61, 92-94]. Optical fibers with long, light-weight, and flexible structures are capable of reaching deep neural layers. Dimensions and shapes of the devices play the main role in chronic external body response of the neural tissue, as well as the implantation techniques. To shrink their implantation footprint, optical fibers tolerate mechanical stripping [90] or chemical etching process [95], or simply attain a tapered profile at the end of the fiber for smoothly penetrating into the tissue during the implantation.

Optical fiber-based devices demonstrated several designs (**Fig. 2**). Aravanis, *et al.* reported the first approach to improve photo-stimulation in an animal, in which to deliver light to the neural tissue using a single optical fiber attached to an outer light source [96]. In this work, the optical fiber was embedded by using a cannula mounted on the animal skull for spatial guidance (**Fig. 2a**). A multimode fiber to have simultaneous activation and inhibition [97], neural probes combined electrophysiological recordings and optical channels based on optical fibers arrays [90], and an array of 3D optical fiber for optogenetics along with integrated LEDs and flexible substrate [98] were also reported. Although they can study a large number of neurons, array-based solutions need more complex designs and confront more challenges. Indeed, optical sites were simultaneously transformed with conventional electric recording sites for electrophysiology studies.

3.3 Hybrid systems from integrating optical fibers with neuroelectrodes

Over the years, several optical-fiber-based system designs have been reported, integrating one or more optical fibers with different numbers of electrodes. **Fig. 2b** indicated a single optical fiber with a single electrode [99], and a combination of single optical fibers with multiple electrodes is shown in **Figs. 2c-k**. For electrophysiology recordings, the single electrode fabrication process includes a thin-film metallic layer deposition over the body of the fiber [95] or simply a metallic wire coupled to the fiber [62, 100]. Also, glass-based optical fiber has been introduced to prevent undesired photoelectric artifacts in the metal electrodes [62, 86]. In contrast, optical fiber designs along with various sites electrode include hybrid solutions which are depending on a single fiber unit integration into simply tetrodes (**Fig. 2c**) [101], and tapered optical fiber (**Fig. 2d**) [102], *etc.* **Fig. 2d** presents the fabrication flow of such device that has multipoint optical stimulation sites for *in vivo* mouse striatum and cerebral cortex where the tapered fiber is attached to planar microelectrode array that carries out extracellular recordings.

Recording and stimulation at large scale and with great spatial and temporal accuracy are major prerequisites to study the real-time dynamics of neuronal networks. With high-density electrodes, the large-scale of individual neurons can be monitored. For example, optical fibers integrated with silicon MEA [92] can attain a good spatial resolution of optical stimulation by delivering light adjacent to the probe recording sites (**Fig. 2e**). High-density electrodes can gather clinical data in the proximity of photo-stimulation focus and in other targets of neural circuits simultaneously. In the optical fiber coupled with 6×6 MEA, in which the pitch between neighboring electrodes is 400 μm and the length of electrode shank is 1 mm approximately (**Fig. 2f**), the extracellular neural

activity can be recorded [103]. This technique provided accurate optical stimulation and electrophysiological neural response monitoring simultaneously, both close and distant from the stimulation site. On the contrary, both the electrodes and optical fibers have a drive mechanism to certify careful guidance and alignment in the optical electrode method [101]. **Fig. 2g** illustrates an integrated device with MEA attached to an optical fiber to optically stimulate and record electrical signals from the deep brain. This device design is a suitable tool for the acquisition of neural signals in optogenetics and other neuroscience fields [104].

An interfacing implantable optical fiber with *in vivo* electrophysiological arrays is presented to manipulate neural circuit elements with minimal tissue damage or change in light output over time (**Fig 2h**). In this optical fiber coupled with MEA, selective control of neural circuit elements with simultaneous recording of spike activities and local field potentials is achievable [105]. Microfabrication approaches which depend on optical fibers to deliver light to neural cells have been illustrating successful photo stimulation results. Also, optical fibers coupled with LEDs can pattern the delivery of light to the deep targets in the brain (**Fig. 2i**) [90]. To have better accessibility to neural populations, a tapered optical fiber with a 16-ch electrode neural probe is introduced. Optical fibers can be applied to deliver light to deep targets, and LEDs can be spatially arranged in places in order to deliver light into a pattern. Integration of arrays and LED-coupled optical fibers can also enable patterned light delivery to deep targets in the brain (**Fig. 2j**) [106].

Recent approaches of neural interrogation depend on flexible and multifunctional devices that need the spatiotemporal resolution, selection of cell-type, and long-term stability. Due to urgent needs for understanding and treatment of nervous system disorders, different types of multifunctional tools have been constructed to record and also control the neural activity [86]. Furthermore, thermal drawing (TD), three-dimensional (3D) printing [107], lithographic processes [108], and molding [74] are all techniques to fabricate implantable fiber and waveguides. Generally, TD is a technique used for silica and other inorganic material-based optical fibers [109, 110] or multifunctional polymer fibers [86]. Recent attempts have been made with respect to a light-guiding probe to provide a bigeminal functionality, such as concurrent recordings of potentials and light guidance [32]. A multifunctional probe with optical waveguide and electrical recording capability is considered for bidirectional communication with neural circuits, allowing simultaneous optical stimulation, electrophysiological recording, and drug delivery at high spatial resolution *in vivo* [111]. A multifunctional fiber probe proportionate with an optical ferrule, an

injection tube, and an electrical connector is presented in **Fig. 2k** [87]. This device is made of an optical waveguide, two microfluidic channels, and six electrodes made with fiber drawing which comforted injections of viral vectors taking opsin genes while supplying optical stimulation and collocated neural recording.

To increase the range of spatial coverage, more advanced optical fiber design emerges, including multicore through bunching multiple single cores of optical fibers [112], with a single (**Fig. 2l**) [93] or several electrode sites for recording (**Fig. 2m**) [113]. The integration of several recording sites relies on processes of assembly between the optical fiber and metallic recording wires that are manually inserted into the guide tubes later. The binding of light sources to any optical fiber core becomes a more intricate process and can reduce its energy link efficiency. Minimize brain tissue damage is another key consideration for these hybrid fibers and achieving multifunctionality on a coaxial optrode through micro-nanofabrication coupled fiber manufacturing demonstrates a promising direction for future system miniaturization [99]. The future of optical-fiber-based hybrid neural systems will enjoy continuous advances on performance development and expansions in neuroscience applications.

4. Neural probes/grids integrating electrodes and μ -LEDs

Another important approach to combine optical stimulation and electrophysiology is to integrate μ -LEDs and electrodes [114]. These probes use integrated μ -LEDs to provide individually controllable optical excitation sites, each of which stimulates a local, specific region of the tissue. Over the past years, several probes have been introduced for these purposes [89, 115-117]. The most popular approach has been leveraging probes of Michigan types [118, 119]. Other approaches were also reported, such as through integrating carbon-based transparent ECoG grids with μ -LEDs in which the electrical recording and optical stimulation can be carried out [120, 121]. μ -LEDs directly produce light on site instead of piping light from external sources, and they allow multiple light sources with different stimulation wavelengths [119]. These LEDs typically are of sizes from 10 to 100 μm resulting in successful integration of the light delivery in neural probes monolithically [119, 122]. The commercial availability of μ -LEDs with diverse features in terms of output power, wavelength, configuration and size [123-125] make this approach a promising pathway towards functional hybrid systems.

4.1 Stiff, penetrating probes integrating electrodes and μ -LEDs

Due to absorption of light and light scattering in the brain, silicon-based stiff, penetrating probes have been developed to deliver the light into the brain with small insertion footprints. Also, to reduce the heat dissipation from μ -LEDs, which could result in tissue damage when used for long-term, the good thermal conductivity of silicon can dissipate the heat effectively. Scharf, *et al.* presented an optoelectronic neural interface consisting of 6 silicon-shanks with 16 μ -LEDs per shank (**Fig. 3a**) [126]. In this work, all 96 μ -LEDs were easily controlled by readily available integrated circuits. During *in vivo* validation, they captured a distinct spatiotemporal population induced by μ -LED stimulation. The other neural probe provided spatially limited optical stimulation of monitored neurons in dealing with animals simultaneously (**Fig. 3b**) [127]. This probe with 4-shank had 32 recording electrodes and 12 μ -LEDs, which were integrated monolithically at the tip of the probes to cover a 200 mm vertical area. In deep structures of animals, this configuration will allow for multiscale manipulation of neural circuit behavior in an unprecedented spatiotemporal resolution. Furthermore, complex analysis of the brain requires high-density of both μ -LEDs and recording electrodes, which inevitably causes high stimulation artifact. This 4-shank device with 8 recording electrodes and 3 μ -LEDs per shank incorporated a substrate with heavily doped silicon by boron to eliminate the photovoltaic effect from the LED illumination (**Fig. 3c**) [128]. As a result, during the *in vivo* validation, this system demonstrated stimulation-artifact-free electrical recording without any signal degradation.

4.2 Soft probes integrating electrodes and μ -LEDs

Having flexible or soft neural probes can alleviate micromotion-induced tissue damage [129-134]. While traditional silicon probes have been widely used, soft polymer materials are recently getting attention due to their flexibility and biocompatibility. For chemical sensing of the deep-brain and agent delivery, a flexible and multifunctional neural probe using liquid metal provided ultra large tunable stiffness [135]. There are several efforts on implantable flexible neural probes [122, 136-142], their biodegradable materials covering [143-147], and their usage *in vivo* validation.

Ji, *et al.* demonstrated a flexible PI-based hybrid optoelectric neural interface integrated with 16 μ -LEDs and 16-ch IrO_x -modified electrodes (**Fig. 3d**) [148]. They showed stability of the device with 3-month soaking tests, and extensive research on thermal and electrochemical properties to show usefulness of this device for an optogenetic tool. **Figure 3e** presents a flexible

probe array with multi-channel μ -LEDs and wireless-enabled, for bidirectional wireless neural interface [149]. For accurate delivery of light and recording of neural signals in multiple cortical layers altogether, the array integrated wirelessly addressable μ -LED chips with an inclined polymer probe array. *In vivo* tests on the brains of the rats found that the μ -LEDs could be powered inductively and controlled by utilizing a stimulator of wireless switched capacitor. A light induced neural activity was recorded simultaneously using integrated recording electrodes.

The development of the III-V compound semiconductor μ -LEDs enabled a dramatic improvement of optical and electrical performance compared to conventional LEDs due to their miniaturization [150]. Among many different compound semiconductors, GaN has a long history in LEDs to produce blue, violet, and ultra-violet (UV) laser diodes [151]. The major parameter of binary and ternary III-Nitride alloys is their bandgap energy value, which directly affects the output light wavelength on optoelectronic applications of the material. **Figure 3f** introduces a flexible, multifunctional, and wireless system, integrated with GaN-based μ -LEDs, having injectable capability [119]. In this work, ultra-small "cellular-scale" μ -LEDs with a size of $50 \times 50 \mu\text{m}^2$ and thickness of $6.45 \mu\text{m}$ were utilized, having attenuated tissue damage, effective thermal management, and minimal inflammation for chronic uses. This multifunctional integrated system was mainly divided into four different layers, consisted of recording electrodes, photodetectors, μ -LEDs, and temperature sensors. This demonstration analyzed optical, thermal, and electrophysiological extensively, as well as chronic *in vivo* validation, including cell-type-specific expression of ChR2, electrical signal detection and real-time thermal sensing.

Utilizing elastomeric materials can create probes which are flexible and also remarkably softer, which can tolerate local stretching. Elastomeric probes are usually slightly thicker than flexible ones, but they have better mechanical compliance with the brain. A PDMS probe consisting of metallic structures with serpentine-shaped and off the shelf components along with embedded μ -LEDs is fabricated (**Fig. 3g**) [152]. It is a soft optoelectronic neural system for wireless optogenetics, controlling different cells and field oscillations in mobile mice with a unique spatial resolution. Another stretchable optoelectronic neural interface was reported, having 4 μ -LEDs and 9 recording electrodes (**Fig. 3h**) [153]. This device used Dragonskin as substrate and encapsulation layers and incorporated serpentine-shaped interconnects for enhanced stretchability. They also successfully demonstrated ECoG signals with optogenetic stimulation of ChR2 from focal cortical areas of the awaked mouse *in vivo* recording.

In addition to optogenetic stimulation, implantable μ -LEDs can also be used for neural recording and imaging. Lee, *et al.* introduced an interesting approach combining the merits of electronics (CMOS for recording, signal amplification and encoding) and of optics (μ -LED for power and data uplink) by using microscale opto-electrically transduced electrodes (MOTEs) [154, 155]. These devices recorded *in vivo* neural activities in a tether-less fashion when implanted into the brain. While not demonstrated yet, MOTEs hold the potential to perform dual-modal optogenetic stimulation and electrical recording. Another example was an implantable single-photon imager integrated monolithically in the form of a complementary metal-oxide-semiconductor Integrated Circuit (CMOS IC) and optical image sensor array based on shank [156]. It could localize the fluorescent objects beyond conventional systems depth with a minimal tissue displacement. The other approach was an implantable lens-less, shank-based image sensor array and optical-filter-less allowing cellular-resolution recording at the arbitrary depths along with excitation which is provided by an outer laser light source [157].

Utilizing μ -LEDs can also realize three or more modalities (*e.g.*, optical, chemical, fluidic, and electrical) integrated together by downscaling the component and developing creative fabrication methods with microfabricated polymer probes [86, 158]. These integrated systems often incorporate various tools and components, including implantable waveguides, control electronics, light sources, power supply, tools for implantation, and electrical interfaces [159]. Multiple components can be applied with microfabrication technology as a result of the small size of the μ -LEDs. Generally, combining optical and electrical techniques provides an exciting opportunity to examine the stimulation effect on organ-level activity. The combination of magnetic modality with both optogenetic stimulation and electrical recording to consider how optogenetic stimulation affects the extensive brain activities is another great approach [160]. This technique has recently been demonstrated as an effective tool to study depression and schizophrenia which are related to neural circuits in awake rats [161].

5. Conclusion and outlook

Neural interface with hybrid electrical-optical modalities consisted of new sets of circuits and sensors represents unique tools to understand the brain [162]. Especially, transparent electrodes allow simultaneous electrical recording and optical approaches especially imaging, converging complementary information on neuronal dimensions, types, and their activities. In addition to imaging, the invention and rapid development of optogenetics subsequently spurred the birth of a

cohort of neural probes for light delivery, enabling cell-type-specific brain stimulation. Today, optical fiber-based probes are widely used in neuroscience studies, some even with compact and wireless devices for brain mapping. In parallel, hybrid probes with μ -LEDs have been developed significantly in the recent years, allowing optical stimulation with increased spatial resolution and stimulation with various wavelengths. Combining optical fibers or μ -LEDs with electrodes have therefore been enabling closed-loop interrogation of the brain and its underlying network. On the other hand, combining electrical and optical modalities could create new challenges where photo stimulation causes light-induced artifact due to photovoltaic effects that interfere with electrical signals from the brain. Great efforts have been made and will continuously be to reduce such artifacts by using different materials with low photovoltaic effects or developing new shielding strategies.

Looking ahead, a natural evolution of hybrid electrical-optical systems is also to scale up in a way that is minimally invasive. A variety of system functionalities, including signal multiplexing, data processing, signal digitalization, pattern recognition, and even data classification, may also be implanted in the brain altogether, permitting multipurpose interactions and reducing latency dramatically. Furthermore, the possibility of constructing hybrid electrical and optical systems on a chip still remains largely unexplored. Such an advanced hybrid system could greatly facilitate the acquisition of spatial data around the stimulation site and allow researchers to understand the area to area interaction and propagation of the brain signaling. Finally, it is also necessary to reduce the cost of manufacturing for widespread applications. Achieving these milestones will significantly advance fundamental neuroscience research as well as enable biomedical devices for clinical purposes.

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Figure Captions

Figure 1. State-of-the-art transparent electrodes. *ITO*: (a) 16-ch hybrid Au-ITO ECoG array [26], (b) Opto- μ ECoG array [29], (c) ITO-based array [30], (d) 16-ch penetrating ITO array [32], *Graphene*: (e) 16-ch graphene-based device [35], (f) doped-graphene 8-electrode hippocampal slice array [36], *Nanomesh*: (g) 32-ch Au/PEDOT:PSS nanomesh MEA [40], (h) 32-ch penetrating nanomesh electrode [41], *Nanostructure*: (i) Opto-e-Dura [42], (j) AuNW-based electrodes [43], (k) Au NN ECoG devices on a mouse brain and the single microelectrode from SEM [44], and *Organic transistor*: (l) 3×5 transparent electrophysiology organic electrochemical transistors array [45].

Figure 2. State-of-the-art optical neural fibers with electrodes. (a) Close-up view of how an optical fiber neural interface coupled on rodents [96]. (b) Cross sectional (on the top) and side view coaxial probe photograph displaying main parts (on the bottom). The center of the optical fiber with a 10 micrometer diameter optical aperture leads to have highly and directional light output [99]. (c) Single optical fibers and 16 electrodes with 64 channels [101]. (d) Schematic demonstration of a tapered optical fiber [102], (e) Multi-array(MA) silicon probes with integration of optical fibers [92]. (f) optical fiber coupled to MEA (bottom), detailed structure of the probe (top). Light can be delivered through the tapered optical fiber aperture locally, while the nearby cells neural activities are recorded simultaneously [103]. (g) The integrated multi-electrode array coupled with fiber optic [104]. (h) Interfacing implantable optical fibers by *in vivo* electrophysiological [105]. (i) LED array and LED-coupled optical fibers [90]. (j) Tapered Fibers composed with a Multi-Electrode Array [106]. (k) A multifunctional fiber probe be equipped with an optical ferrule, an injection tube, and electrical connector [87]. (l) Optical fibers are tightly limit to the tungsten shank without a notable gap [93]. (m) Multiple optical fibers with multiple electrode combination [113].

Figure 3. State-of-the-art neural probes/grids integrating electrodes and μ -LEDs. *Stiff*: (a) 6-shank μ -LED probe with 16 μ -LEDs per shank [126], (b) 4-shank probe with 3 μ -LEDs and 8 electrodes per shank [127], (c) Minimal-stimulation-artifact μ -LED optoelectrodes [128], *Flexible*: (d) The front side (left) and back side (right) of the flexible hybrid optoelectric neural interface based polyimide with 16 channels of both electrodes and μ -LEDs [148], (e) Probes array coupled with 16 μ -LEDs and 16 electrodes [149], (f) The ultra-flexible probe by the blue light-on μ -LED. The inset image display the integrated device concluding a wireless radio frequency scavenger [119], *Stretchable*: (g) soft, stretchable, fully implantable optoelectronic system integrated with μ -LEDs [152], and (h) Stretchable opto-electronic neural interface with 4 μ -LEDs and 9 recording electrodes (right) and schematic (left) [153].

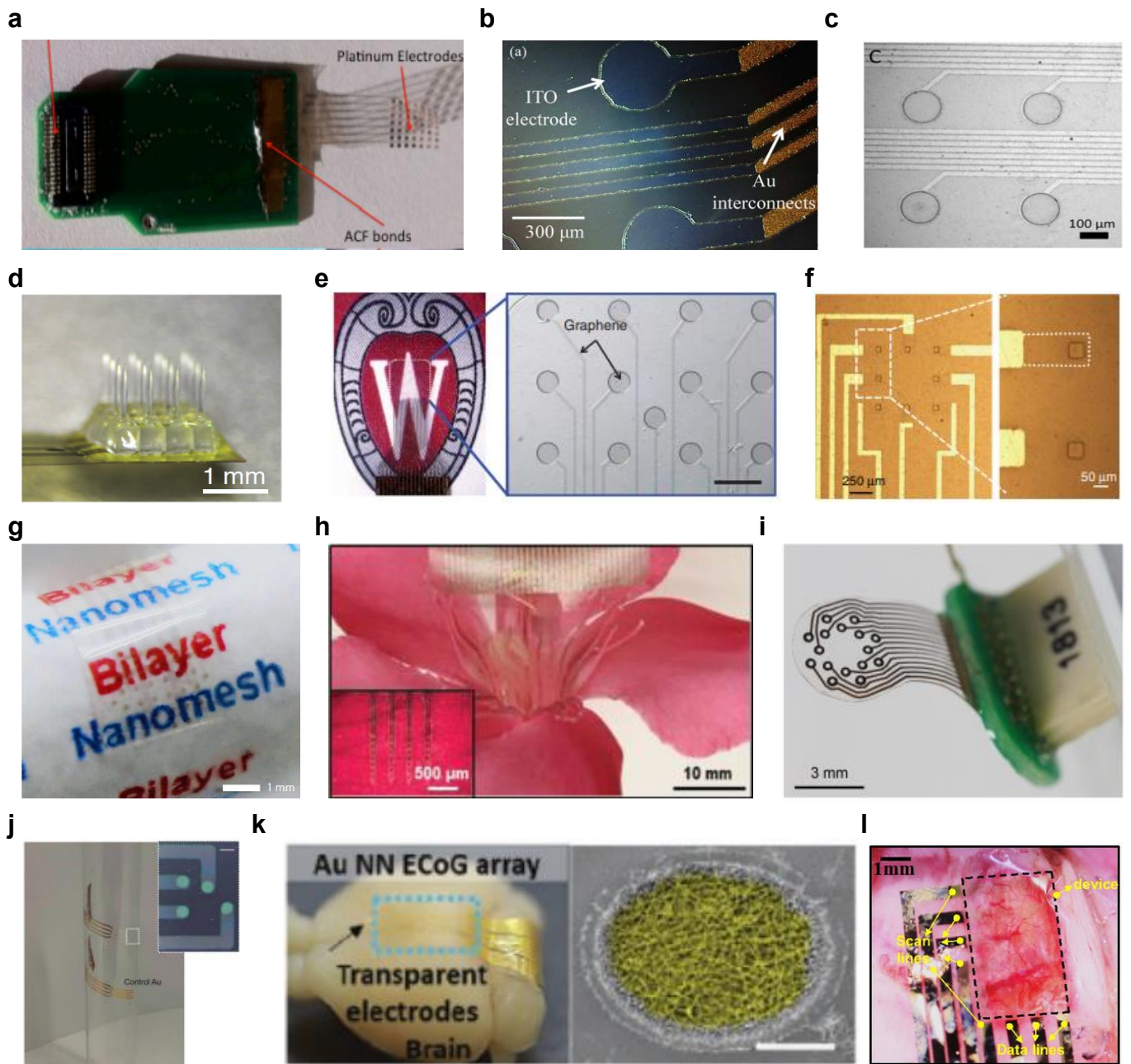


Figure 1

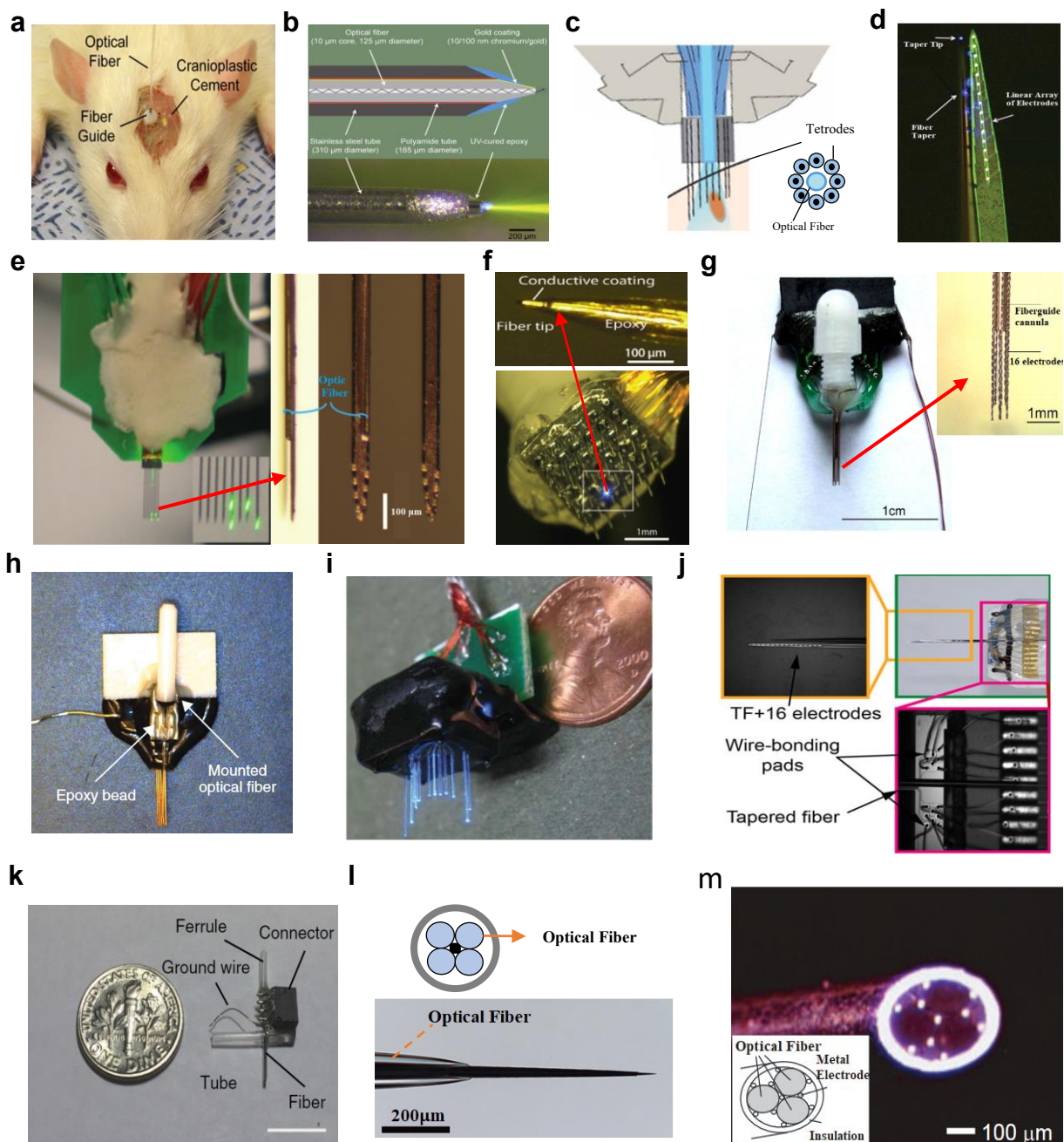


Figure 2

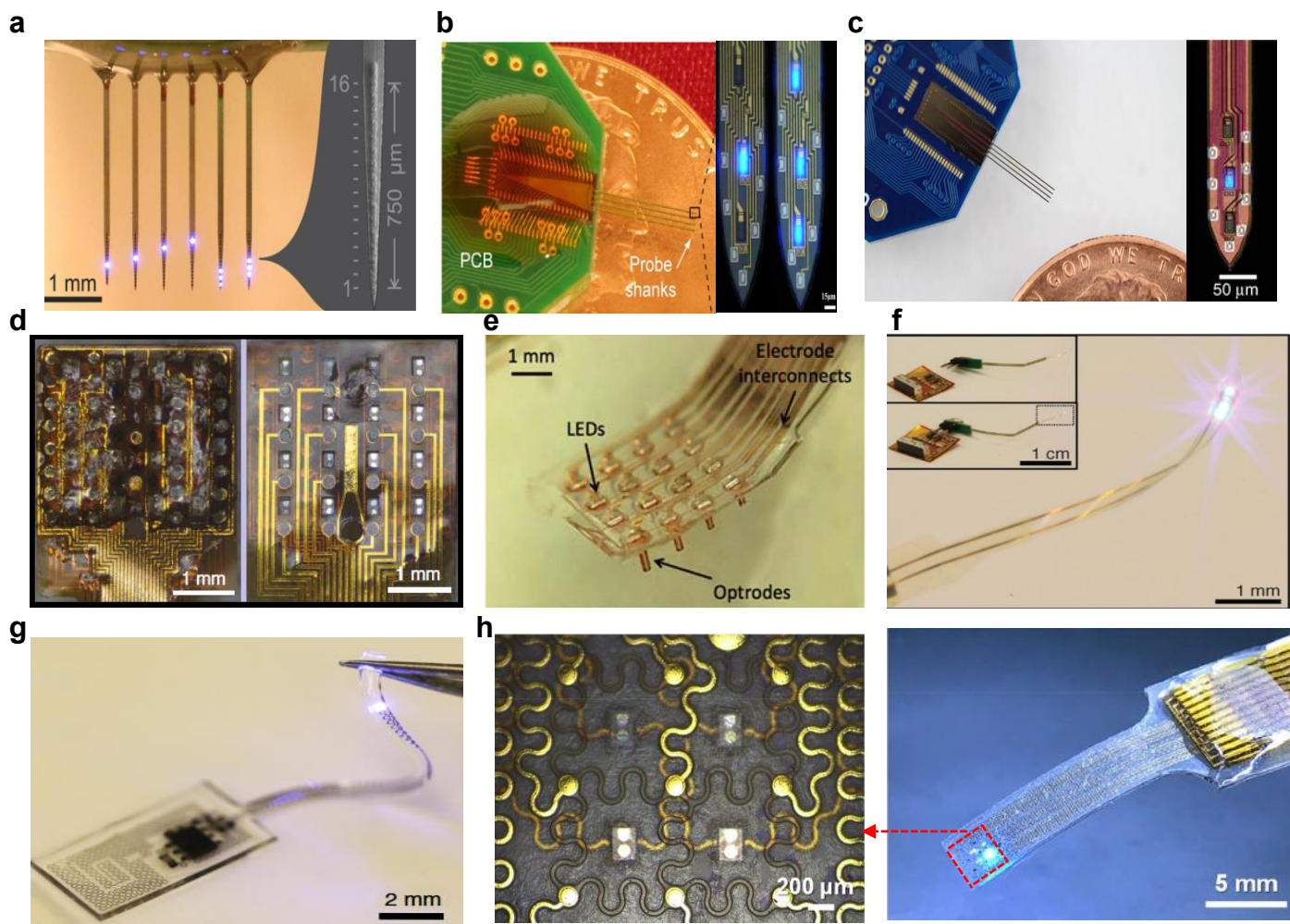


Figure 3

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