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REVIEW

Emerging Applications of Optical Fiber-Based Devices for Brain Research

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Abstract

Research in neuroscience and neuroengineering has attracted tremendous interest in the past decades. However, the complexity of the brain tissue, in terms of its structural, chemical, mechanical, and optical properties, makes the interrogation of biophysical and biochemical signals within the brain of living animals extremely challenging. As a viable and versatile tool for brain studies, optical fiber based technologies have provided exceptional opportunities to unravel the mysteries of the brain and open the door for clinical applications in the treatment, diagnosis, and prevention of neurological diseases. Typically, optical fibers with diameters from 10 to 1000 μm are capable of guiding and delivering light to deep levels of the living tissue. Moreover, small dimensions of such devices along with their flexibility and light weight paved the way for understanding the complex behaviours of living and freely moving mammals. This article provides a review of the emerging applications of optical fibers in neuroscience, specifically in the mammalian brain. Representative utilities, including optogenetics, fluorescence sensing, drug administration and phototherapy, are highlighted. We also discuss other biological applications of such implantable fibers, which may provide insights into the future study of brain. It is envisioned that these and other optical fiber based techniques offer a powerful platform for multi-functional neural activity sensing and modulation.

Keywords Optical fibers · Neuroscience · Optogenetics · Biosensing

Introduction

The human brain, which contains hundreds of billions of neurons and glial cells, manages an entire range of activities of the body from breathing and perception to thinking and moving [1]. Systematic understanding of the brain structures and functionalities is crucial for advancing neuroscience and improving clinical therapeutics. Nevertheless, such a critically important organ is difficult to investigate due to its complicated structural, mechanical, optical, electrical and chemical properties. To resolve the functional structure of brain in vivo, various materials, devices and systems have been exploited to interrogate neural activities, by stimulating and detecting biophysical and biochemical signals in the living systems. In particular, along with the rapid developments of genetically encoded optical actuators and indicators, optical based methods have been widely used to sense and modulate brain activities, which notably impacted the brain studies. Optical techniques are suitable for brain research because light can penetrate through brain tissue at a moderate depth in a minimally invasive way, helping us understand neural circuits at high spatial, temporal and spectral resolutions with desirable cell specificity. However, there remain a variety of main challenges in this area, including: (1) how to guide light to the targeted region while the penetration depth of visible and near-infrared light is limited, (2) how to collect and transmit the light emission, (3) how to reach the

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targeted area within living tissue in a less invasive manner, and (4) how to simultaneously modulate and detect multimode (optical, electrical, chemical, etc.) brain signals [2, 3].

To overcome these challenges, various optical materials and devices have been introduced, such as integrated microscale light emitting diodes (μLEDs) [4], planar waveguides and integrated photonics [5, 6], engineered optical fibers [7–9] and nanoparticles [10]. Among them, optical fibers have attracted considerable attention in biomedical fields due to their optical transparency, mechanical flexibility, ideal biocompatibility, as well as mature manufacturing feasibility that can easily be adopted from silica fibers used for telecommunications [11, 12]. Specifically, optical fiber-based devices have also exhibited intense potential as advanced neural interfaces for brain studies. Current literature has witnessed that fibers made of different materials, including conventional silica and flexible, stretchable, and biodegradable nature-derived materials, have been extensively explored as optical neural interfaces [5, 6]. Furthermore, devices made from these fibers with various functions, have also been acknowledged as having prevalent usage in optical instrumentation of brain-related studies and clinical applications [13].

With the flourishing of research on optical fibers for brain studies, various kinds of fibers for different applications, such as sensing, stimulating and treatment, have been developed. Correspondingly, light over the wavelength range of visible and near infrared (NIR) is used for different applications. For instance, in a typical optogenetics experiment, neurons can undergo depolarization and hyperpolarization when exposed in 480 ± 10 nm (blue) and 580 nm (yellow) light stimuli, respectively, when using Halorhodopsin (NpHR) and channelrhodopsin-2 (ChR2) opsins [14]. Moreover, photodynamic therapy widely uses wavelengths between 600 and 800 nm (red), where longer wavelengths show better tissue penetrations [15]. A conceptual sketch illustrated in Fig. 1 (left) illustrates the various applications of optical fibers utilizing different wavelengths in brain studies. Accordingly, Fig. 1 (right) provides an example of optical fiber implanted in brain of animals and coupled to blue light for delivering optical signals.

Previous reviews [13, 16–18] have overviewed implantable optical waveguides and fibers focusing on the materials and fabrication methods together with their applications in imaging, biosensing, surgery, therapy and optogenetics. Differing from them, the present article provides a comprehensive review of fiber-optic based devices with various applications particularly in brain, not only including optogenetics and fluorescence photometry, but also highlighting other recently reported sensing capabilities, for example, tracking the temperature, pressure and oxygen of the brain, photodynamic therapy (PDT) for curing brain tumors, and delivering drugs and neurotransmitters [19–24]. We also incorporate the discussion of fibers with other biological applications, like glucose, strain, and chemical sensing, currently used in non-brain tissues, which may provide insight into the future development of brain-related biomedical applications.

Optogenetics

To understand how brain neural circuits work, as well as how they become dysfunctional in particular disease states, methods to break down the complexity of brain with a proper precision level are required. The emergence of optogenetic tools has made it possible to dissect nervous system with highest degree of specificity [25, 26]. This groundbreaking technology has emerged as a potential approach in neuroscience research, not only capable to enrich our understanding of brain functions, but also capable to offer methods for neuroglial brain disorder diagnostics (e.g., Alzheimer [27], Parkinson [28], Epilepsy [29] and depression-related disorders [30]).

The emerging and powerful optogenetic method uses the combination of light and genetically modified microbial rhodopsins or animal/vertebrate opsins to manipulate neural activities [31–33]. The major optogenetic tools "Opsins" are transmembrane proteins whose conformation changes upon

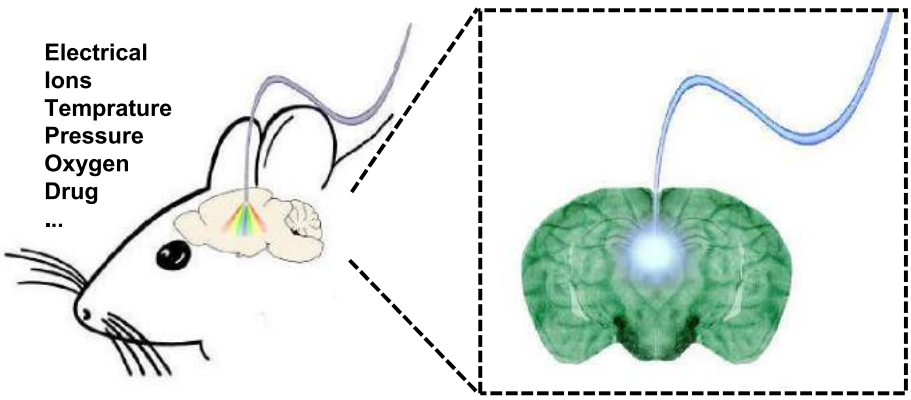


Fig. 1 Schematic illustration of an implantable fiber for applications in brain research

being exposed to light. Accordingly, opsin-expressing cells also experience a change in its membrane potential when illuminated. Up to now, there are different types of excitatory opsins, including channelrhodopsin-2 (ChR2) which depolarizes neurons in response to light. Inhibitory opsins that hyperpolarize neurons upon lighting have also been proposed, e.g., halorhodopsin and archaerhodopsin [26, 33, 34]. These opsins typically present excitation spectra within the visible range, where the scattering and absorption properties of the tissue result in limited penetration depth of light in living tissue. Over the last decades, wide varieties of opsins with various absorption spectra have been established [15, 35]. In addition to opsins, the success of optogenetics would also benefit significantly from the development of neuron probes. In light of these, a desirable optogenetics implant to link the complicated nervous system and the external world shall comply with the following requirements: capability to deliver light deep to the brain tissue, light weight and biocompatibility.

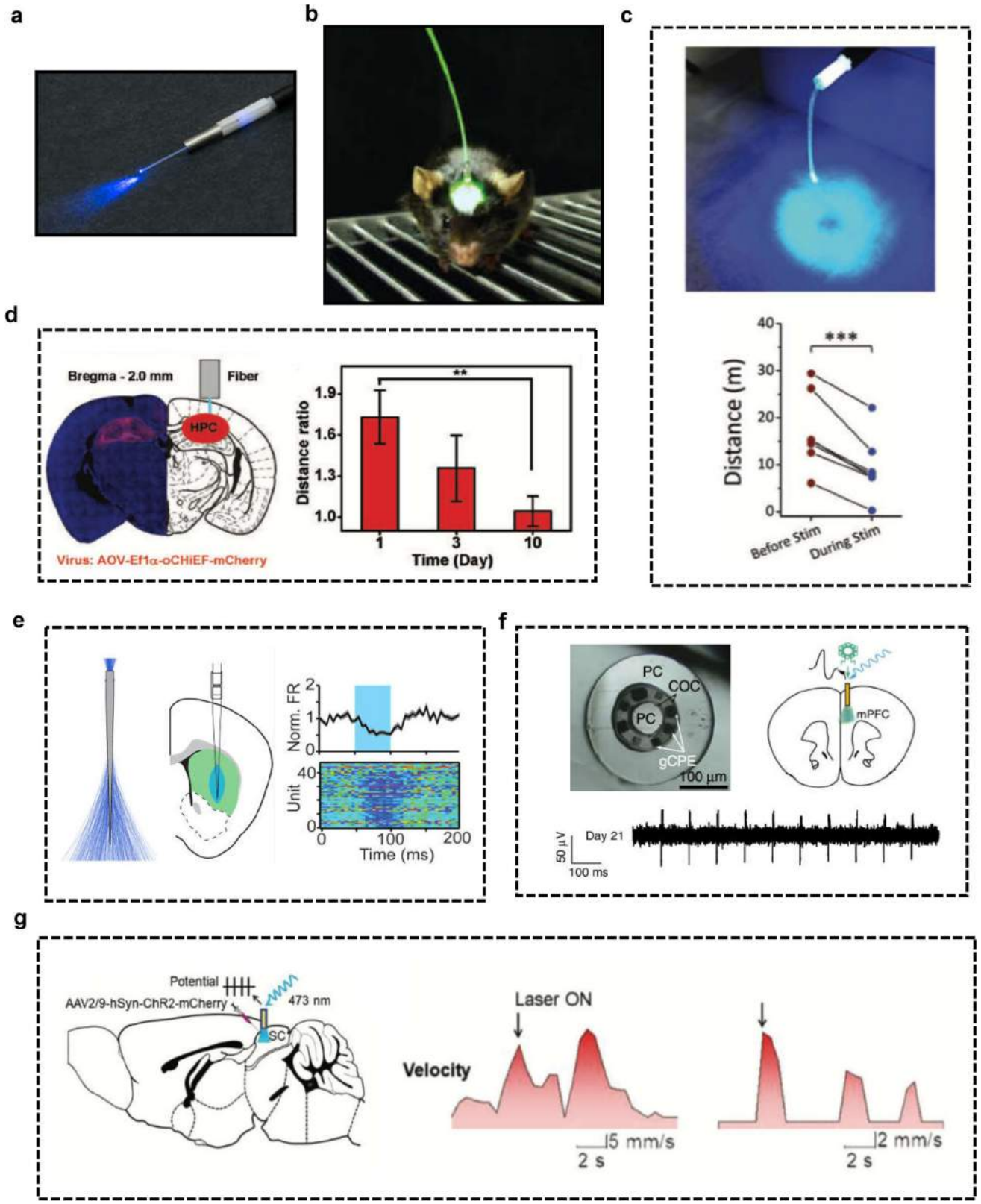
Implantable optical fibers are the first devices applied in optogenetics experiments and still are the best option for transmitting light into the deep brain region, especially in free-moving mammals. Primarily, these optical fibers were made of silica (Fig. 2a) [13]. A representative image of an early optogenetic experiment in free-moving mouse utilizing silica fiber is shown in Fig. 2b. Furthermore, these optical fibers can be integrated with classical recording electrodes like Utah and Michigan probes, for simultenous optogenetic stimulation and electrophysiological recording [36, 37].

Such optical fibers not only have a high optical transparency in a wide range of wavelengths, but also have a very low propagation loss (as low as 0.2 dB/km) within the near-infrared range [13]. However, in contrast to above advantages, silica fibers are rigid and brittle with an average Young's modulus (10–100 GPa), which is several orders of magnitude larger than that of neural tissue (~ 1 kPa) [38].

Such mechanical properties cause them to easily damage the surrounding tissues, which confronted scientists with an inevitable challenge. To alleviate this problem, scientists considered soft, biocompatible, and biodegradable polymers or bio-derived materials such as silk in order to realize more biocompatible fibers [39–42]. Recently, several soft and elastic polymeric materials have been used to fabricate optical fibers, with a reduced immune reaction and steady performance during chronic implantations. An example of this approach was given in 2018 by Lu and co-workers, who developed a novel alginate-PAM hydrogel optical fiber with an extremely efficient and effective transmission, as well as exceeding stretchability and low modulus (from a few to thousands of kPa) [39]. This optical fiber was built through the cross-linking and one-step polymerization process of the alginate-PAM precursors in tube molds in a variety of sizes. Figure 2c illustrates blue light-emitting diode coupled with mentioned hydrogel optical fiber along with uniform irradiation. The optogenetic stimulation by implanted hydrogel fibers in the early motor cortex could highly modulate the behavior of the animal, whose results are presented in Fig. 2c. However, fully biodegradable and bioresorbable optical fibers were still desired within the domain of optogenetics. In this regard, Fu et al. [41] offered another approach, in which a biodegradable optical fiber with poly (L-lactic acid) (refractive index $n = 1.47$) as a key material was developed to deliver light deep to the tissue and spare the secondary surgery damage throughout the implantation. The thermal drawing method was applied to fabricate the PLLA biodegradable fiber (bending stiffness ~ 1.5×10^4 N/m) using similar geometry (e.g., diameter 220 μm) with standard silica fibers (bending stiffness ~ 2.4×10^5 N/m). The PLLA fiber implanted in the hippocampus (HPC) of free moving mice and connected to a blue light source is presented in Fig. 2d. Whenever light is transmitted to HPC through PLLA fiber, a seizure is induced in response that triggers the mice and increases its distance of travel. The ratio of such distances without and with optical stimulation is shown in Fig. 2d. The decrease in ratio of distance reflects that the aforementioned fiber degraded within 10–15 days.

As a matter of fact, in typical optical fibers, light travels along their axes and exits as a single light point from the tip of the fiber. Hence, it is useful to embrace numerous optical stimulation sites together with a single fiber. To achieve this, tapered optical fibers (TFs) have been introduced to illuminate focal or large brain region and enable simultaneous and selective optical stimulation [9, 43, 44]. Tuning the input light angle allows the optical modes exiting at variant vector positions along the tapered fiber. The technique is displayed in Fig. 2e. Researchers have demonstrated that by using optical fibers with tapered tips specific groups of cells could be targeted in the motor cortex such that dorsal neurons could be exempted from stimulation [44].

By combining polymer and other components, multimaterial multifunctional fibrous devices with both optogenetic and other applications (such as electrophysiological recording) have been proposed and fabricated [8, 45]. Such fibers are composed of various layers of polymers such as polycarbonate (PC), cyclic olefin copolymer (COC), conductive poly etherimide (CPE), and composites of polymers with elastic moduli (1–10 GPa) lower than that of glasses (10–100 GPa) and fabricated through the thermal drawing process (TDP) [22]. These polymers have desirable mechanical properties matching the brain tissue, which make them less likely to cause tissue damages and more compatible with long-time implant. Park et al. [46] have manifested an example of this approach and integrated polymeric materials together with a waveguide, electrodes and microfluidic channels into a single tool. In their work, fibers with a bending stiffness of ~ 80 N/m were accomplished by selecting the



PC as the core and COC as the cladding. When combined with brain tissue-like soft matters like hydrogels, multimaterial fibers can achieve an even lower bending stiffness, futher reducing the stress field in the brain tissue surrending them. Park and co-workers have used polyacrylamide-alginate (PAAm-Alg) hydrogel to combine with traditional

◂**Fig. 2** Optogenetics. **a** Photograph of a silica optical fiber connected to a blue laser source. **b** Image of a mouse model with an implanted fiber for optogenetic experiments. Reproduced with permission [35]. Copyright 2015, Nature Publishing Group. **c** Light transmission through a soft hydrogel optical fiber (top) and distances of mice travelling during optogenetic stimulations (bottom). Reproduced with permission [39]. Copyright 2018, Wiley–VCH. **d** Left: Schematic showing a PLLA based biodegradable fiber inserted to HPC; Right: Ratio of traveling distances for mice with and without optical stimuli. Reproduced with permission [41]. Copyright 2018, Wiley–VCH. **e** Left: Light distribution around a tapered optical fiber; Middle: A tapered fiber implanted into the mouse brain for optogenetics; Right: results of optogenetic manipulation. Reproduced with permission [44]. Copyright 2017, Nature Publishing Group. **f** A hybrid multifunctional fiber allowing for optogenetic stimulation, electrophysiology recording and virus injection. Top-left: cross-sectional view of the multifunctional probe; Top-right: schematic showing the probe implanted into mPFC of the mouse brain; Bottom: electrophysiological signals recorded with a multifunctional fiber probe. Reproduced with permission [46]. Copyright 2017, Nature Publishing Group. **g** Left: A multimodal and flexible polymeric optical fiber implanted to the brain of a mouse for simultaneous optogenetics and electrophysiology; Right: Measured velocity of movement of a behaving animal under optical stimuli. Reproduced with permission [52]. Copyright 2020, Wiley–VCH

multimaterial fibers and obtained a tissue-like fiber with a bending stiffness of 0.42 N/m in hydrated state [47]. The hydrogel also endows the fiber with hydration-induced adaptive modulus, which enables its direct insertion into the brain in dried state. This fibrous device was implanted to brains of mice to track isolated single-neuron action potentials for over 6 months.

With multiple materials and layered structures, the functions of these fibers are not limited to light delivery [14]. Coupled with metal connectors and hollowed tubes, such fibers are also able to deliver chemicals and record electric signals simultaneously [48–52]. This allows combination of electrophysiological recording and optogenetic stimulation, allowing feedback-based control of optogenetics [53]. With chemcial-delivering tubes, viral vector delivery and optical stimulation could be accomplished by a single multifunctional fiber, achieving one-step optogenetics [46]. Figure 2f depicts a functional probe consisting of an electrical connector, an optical ferrule, and a tube for injection. The device maintained reliable and accurate performance for optical stimulation for up to several months as presented in Fig. 2f [46]. This technology permits one-step optogenetics and provides a persistent alternative to the current practices of optogenetics. In the present scenario, as another approach, a flexible and small thermally drawn multi-material fiber has been developed [52], which was composed of embedded metal electrodes and a double-clad waveguide for optical stimulation. Such an arrangement highly improved the mechanical properties, enhanced the optical transmission, and minimized the impedance of probes more efficiently. Such properties also enabled a long-term simultaneous optical stimulation for at least 10 weeks along with neural recording at a single cell level in awake and behaving animal with high signal-to-noise ratio (SNR) of about 30 dB. As shown in Fig. 2g, such fiber probe together with distinct electrodes bearing 50 µm of diameter was implanted to superior colliculus of mice, and ultimately the success of mice behavioral manipulation was presented. It is expected that these newly developed fibers are capable to make a great change in neuroscience field. Owing to their complex structures, multimaterial fibers also have high design versatility which helps them meet more needs from applications. For example, with the guidance of a designed helica scaffold, multisite optogenetics, electric recording and drug delivery are achieved with a spatially expandable multimaterial fiber [48]. This device is capable to conduct electrical recording and optical/chemical modulation across multiple distant regions in deep brain, suitable for study of more complex brain circuits and functions.

Fluorescence Photometry

Besides exploitation of optical fibers in investigating the brain through optogenetics, these tools have exhibited a great potential for incorporation of numerous functionalities which make them employable in many other applications, including fluorescence sensing of ion indicators via fiber photometry. Fiber photometry is a gold standard technique of optically stimulating and recording fluorescence signals from genetically targeted calcium indicators (GECIs) like GCaMPs and the most recently genetically encoded voltage indicators (GEVIs) in behaving animals [21, 54–56]. Using these indicators, fiber photometry provides cell-type information and reports the behavior of neuron population. In the photometry system, stimulation light is coupled into a tiny flexible optical fiber which delivers the excitation light into the targeted brain region to interact with the fluorescent activity indicators. Fluorescence emission from excited neurons will be collected by the same fiber and then guided to the other end of the fiber, where it is separated from the excitation light instantly via a dichroic mirror. Eventually, the fluorescence reaches a detector, where neural activities are recorded. Figure 3a illustrates the primary fiber photometry system used to record activities of brain during mammalian behaviors [21]. In their work, they demonstrated that a typical silica fiber simultaneously delivered excitation light (475 nm) and collected the dynamic calcium signal emitted by the indicators in the targeted region. As depicted in the Fig. 3a, the intensity of the emitted fluorescence is highly correlated with the period of licking sucrose. Up till now, most of these experiments have relied on traditional flat-cleaved optical fibers out of silica with the diameter of 200–400 µm. Silica is used due to its lower losses in

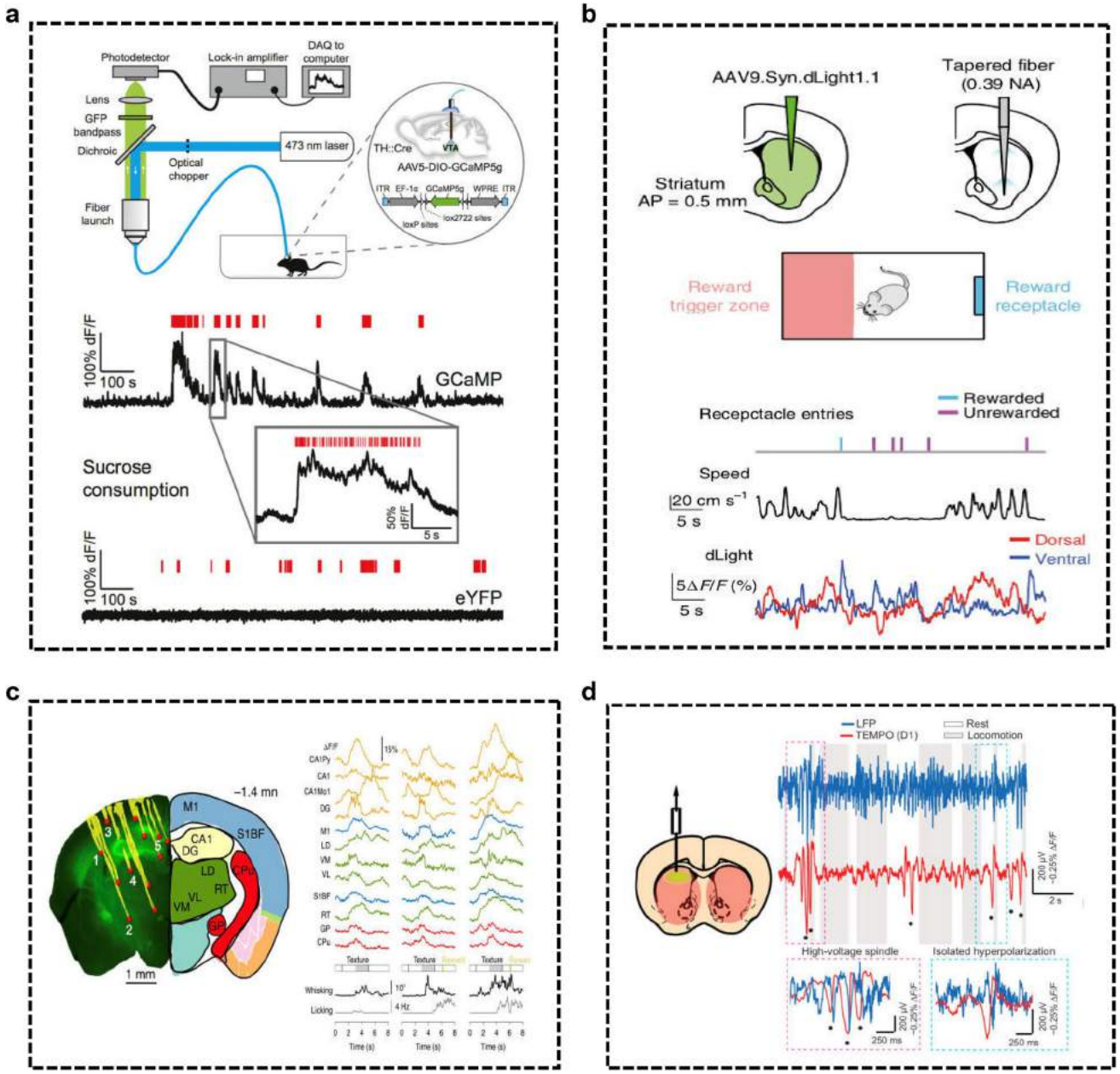


Fig. 3 Fluorescence Photometry**. a** Scheme of the primary fiber photometry system (top) and recorded calcium signals from the mouse brain expressing GCaMP (middle) and eYFP (bottom). Reproduced with permission [21]. Copyright 2014, Elsevier. **b** In vivo fiber photometry using tapered optical fiber. Top: Schematic of experimental setup and multi-site illumination via TF. Bottom: Recorded calcium signals from a mouse with an implanted TF. Reproduced with permission [7]. Copyright 2019, Nature Publishing Group. **c** Left: Fiber photometry for recording fluorescence signals at multiple regions. Right: Simultaneously recorded calcium signals from 12 different regions using multi-array fibers. Reproduced with permission [58]. Copyright 2019, Nature Publishing Group. **d** Left: Schematic illustration of an fiber-optic voltage sensor implanted to a brain. Right: Recorded voltage signals from targeted regions in an awake mouse. Reproduced with permission [56]. Copyright 2016, Elsevier

comparison with polymers. Nonetheless, recently optical fibers out of biodegradable polymers such as PLLA were also successfully utilized as photometry interfaces [14].

Despite the advantages of single fiber photometry, such as flexibility, light weight and deeper penetration depths in brain tissues, it sacrifices the cellular resolution due to limited size of the fiber core. To overcome this limitation, many research efforts have been devoted. For example, researchers have developed an ideal multi-channel fiber photometry capable to simultaneously record neural activities from several different regions of a mammalian brain (up to seven regions) or from various animals [57]. Accordingly,

a multi-brain-region fiber photometry for both head-fixed and freely moving animals has been recently manifested by *Helmchen et al*. They obtained parallel fluorescence recordings from 12 to 48 brain regions by allowing up to 48 fibers to be placed into the grooves (Fig. 3c) [58]. Moreover, researchers have designed a spectrometer-based fiber photometry system to simultaneously measure the neuron activities from both direct- and indirect-pathways by using green and red GECIs [59].

In addition to widely used flat-cleaved optical fibers, TFs have also been employed in fiber photometry systems recently to create a depth-resolved fiber photometry based on mode-division demultiplexing [7]. As stated earlier in the optogenetics section, the tapered tips enable simultaneous and selective illumination, so that such tools are also capable for multisite signal collections via galvanometric mirror in fiber photometry systems. Figure 3b shows a practical example of such technique.

Study in this field has also addressed a few disadvantages with respect to GECIs. Ca^{2+} activity performs well in reflecting behaviors of animals, but reflects the spiking activity in cells poorly and cannot trace voltage waveform in time-scales finer than 25–100 ms. Thus, in 2016 researchers reported a non-CEGI fiber-optic technique to record voltage dynamics of genetically particular cells using opsin-FRET indicators within behaving mice as shown in Fig. 3d [56]. In this technique, a silica based multimodal fiber (diameter ~ 400 µm) is utilized as the implant, which couples to external laser sources and photoreceivers for optical excitation and recording. Trans-membrane Electrical Measurements Performed Optically (TEMPO) method was used to facilitate the removal of physiologically induced noise and made the device approximately tenfold more sensitive than conventional fiber-optic method with respect to Ca^{2+} sensing. This sensitivity enhancement allowed a lower illumination power and recording of an hour long. Figure 3d states the validated results of TEMPO with consideration of hippocampal and cortical oscillations in behaving mice.

Temperature Sensing

It is crucial for neuroscience researchers to determine the temperature of brain, an organ highly sensitive to temperature change [60]. The temperature of the brain might be influenced by distinct factors such as immunological, toxicological, and environmental ones [61]. Moreover, any moderate change may cause cell toxicity, alternation of cell functions and dramatic variation in behaviors. For brain temperature sensing, fiber optic sensors have been regarded as one of the best candidates because of their high sensitivity, small dimensions, chemical inertness, and rapid response for real-time monitoring. The most traditional and common optical fiber adapted for sensing temperature of deep brain tissue contains a Bragg grating in the core called fiber Bragg grating sensor (FBG) [23, 62]. Figure 4a shows a recent example regarding FBG sensors for tracking temperature in brain. FBG sensors are capable of tracking the temperature by monitoring the specific wavelength of the light reflected back from the grating. However, such fiber sensors do not resolve small temperature fluctuations, as well as need complex fabrication process and a long length of fiber.

As a matter of fact, when measuring the brain temperature, high level of precision as well as temperature resolution less than 0.5 °C are needed [63]. To reach such targets, researchers developed a portable optical fiber sensor (OFS) based on a rare earth glass deposited on the tip of typical silica optical fibers and implanted it to the targeted region of brain of rats. Figure 4b states the validated results of temperature measurement through portable optical fiber sensor. However, despite many advantages these sensors possessed, effectively using the fiber sensors in free-moving animals was once a challenge. Therefore, the portable optical fiber temperature sensor discussed above was subsequently improved by the same research group in order to measure the deep structure of the brain of free moving rodents [64]. They demonstrated, for the stereotaxic implantation, the standard microdialysis guide cannula could be used in the fiber-optic temperature probe in order to minimize the risk of fiber breakage before and during the measurements. The enhanced structure of the probe allowed the optical fiber to be inserted and removed as single piece. The sensor achieved 0.1–0.3 °C temperature resolution and successfully sensed the brain temperature in an awake and free-moving rat (Fig. 4c).

Furthermore, Rogers and co-workers have successfully established innovative designs for multifunctional bioresorbable devices that monitor multiple signals including temperature, oxygenation, and pressure of mammalians in a continuous manner [65, 66]. The proposed design facilitated minimally invasive implantation through injection and the entire constituent materials could be resorbed after a well-elaborated operational time [66]. The region of active sensing with PLGA as the substrate consisted of three main parts including a photodetector, electrodes and a PLGA fiber. The thermal resistance determined by Si nanomembrane photodetector granted the sensation of cerebral temperature with a resolution around 0.1 °C. Obtained data are plotted in Fig. 4d.

Oxygen Sensing

Oxygen consumed in the activities of brain is transported through hemoglobin (Hb) in red cells of the blood. Consequently, activities of brain lead toward vascular responses,

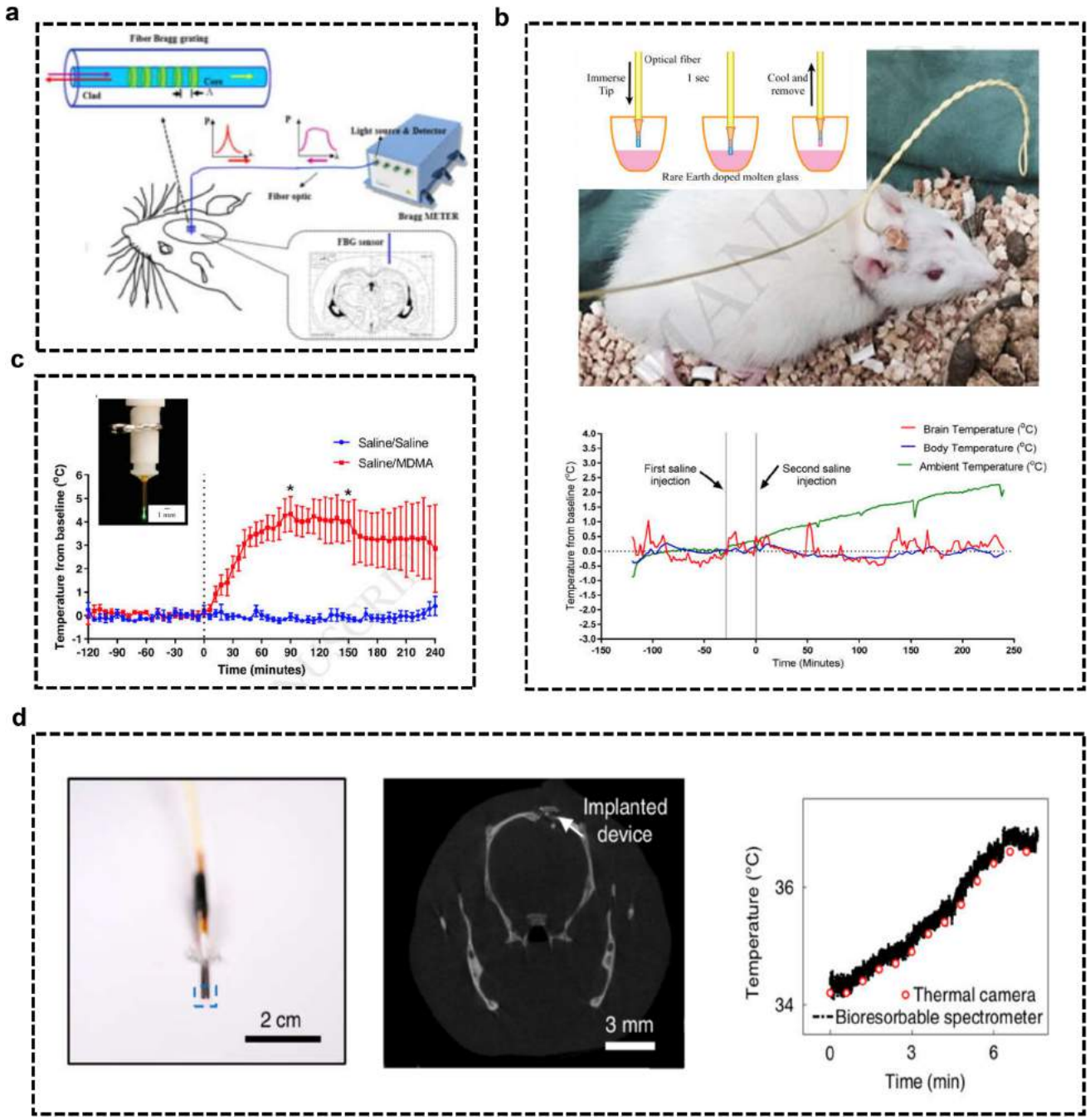


Fig. 4 Temperature Sensing**. a** Scheme of a fiber optic Bragg grating sensor to measure the brain temperature. Reproduced with permission [62]. Copyright 2017, IEEE. **b** Fabrication and functioning of a portable optical fiber sensor (top) and measured temperature from the brain (bottom). Reproduced with permission [63]. Copyright 2016, Optical Society of America. **c** Photograph of a improved temperature sensor using a guide cannula (inlet) and tracked temperature by the probe. Reproduced with permission [64]. Copyright 2018, Elsevier. **d** Left: Photo of a bioresorbable spectrometer for temperature sensing; Middle: axial view of the device implanted into the brain; Right: temperature of the brain obtained by the bioresorbable device. Reproduced with permission [66]. Copyright 2019, Nature Publishing Group

so that any variation in parameters related to blood can be utilized as surrogates for investigating functions of the brain [67]. Hemoglobin is known to have different absorption behaviors for near-infrared and visible lights depending on whether it carries oxygen or not. Therefore, to measure the hemodynamic parameters (e.g., oxygen saturation, sO_2) as indicators of neural activities within the cerebral cortex, intrinsic optical signals (IOSs) have

been extensively used. On the basis of this, diffuse reflectance spectroscopy (DRS) and near-infrared spectroscopy (NIRS) have been widely applied to hemodynamic parameter measurements, including sO_2 [68, 69]. However, when interrogating the activity of the brain, optical methods suffer from a limited penetration depth owing to scattering of tissues. Using the near infrared wavelength decreases the effect of scattering, which enables light to reach deep structure of brain. However, the spatial resolution of NIRS is quite low. Moreover, due to the weight and size of the components, traditional optical systems cannot be applied in free-moving animals [69]. Considering the factors mentioned above, a single optical fiber system is the best option for measuring deep brain activities within both unconstrained and free-moving animals. Such systems were also employed to examine the hemodynamics parameters, including sO_2.

As a proof of concept, a single fiber system was introduced by Yu et al. in order to measure sO_2 from the deep brain region by adopting continuous-wave reflectance spectroscopy within visible range [70]. In such a region, due to strong absorption of Hb the optical interrogation volume became smaller. Accordingly, in their work, through Monte-Carlo simulations the estimated volume of the tissue probed by the system was about 0.02–0.03 mm^3. In addition, they have also demonstrated *in-vivo* experiment within anesthetized mice to testify the feasibility and accuracy of the system in monitoring cerebral oxygenation under deep brain stimulation. Figure 5a shows the experimental set up as well as calculated sO_2 obtained by abovementioned single

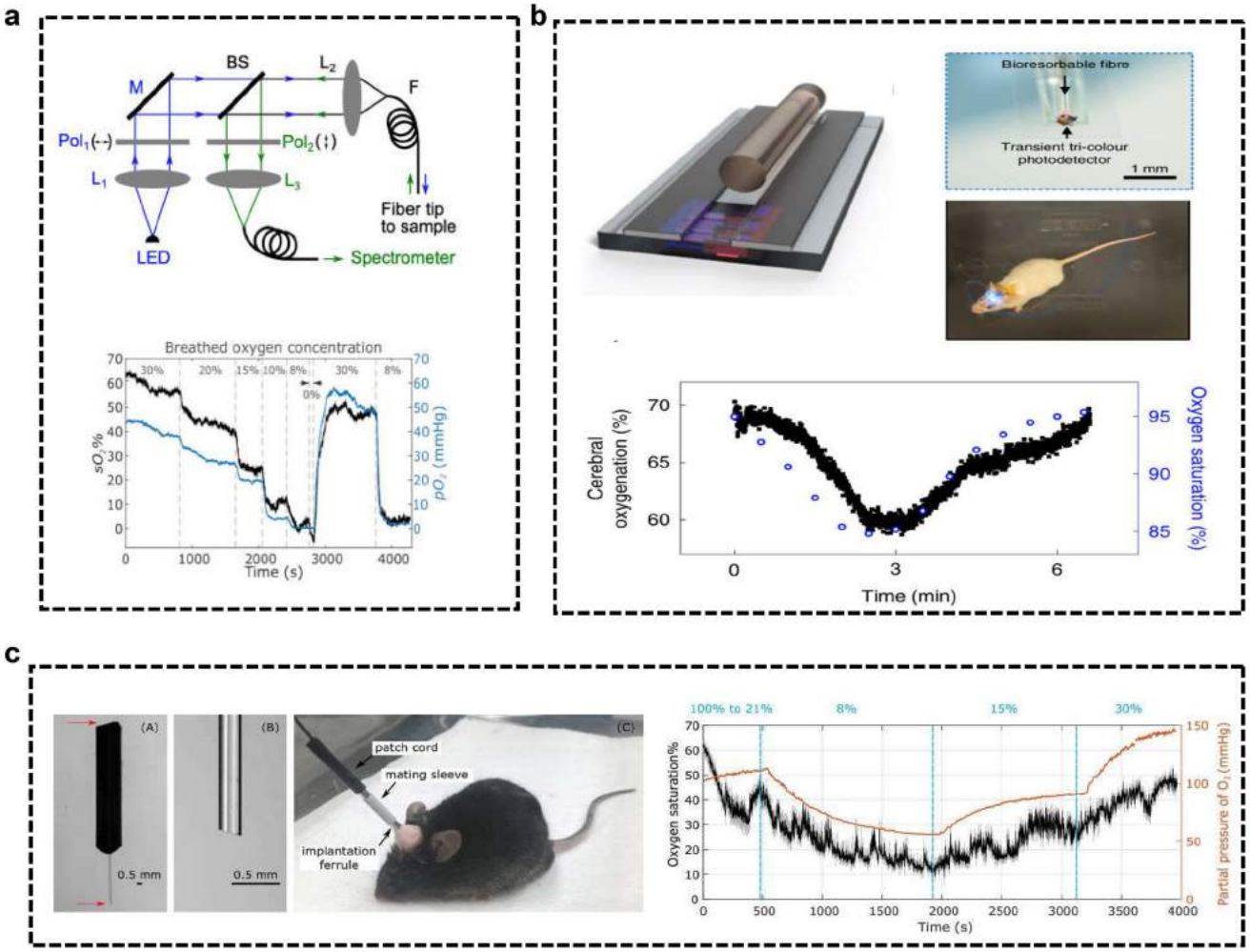


Fig. 5 Oxygen saturation measurement. **a** Scheme of a fiber optic set-up to measure the oxygen saturation (top), and obtained oxygen curve by the fiber system (bottom). Reproduced with permission [68]. Copyright 2016, Optical Society of America. **b** Schematic illustration and image of a bioresorbable fiber optic probe implanted in a free-moving animal (top) and tracked cerebral oxygen by the bioresorbable sensor (bottom). Reproduced with permission [66]. Copyright 2019, Nature Publishing Group. **c** Image of a designed fiber ferrule implanted to a free moving mouse (left) and measured oxygen saturation (right). Reproduced with permission [71]. Copyright 2020, Optical Society of America

fiber system. However, the fiber birefringence is highly sensitive to the fiber movement; therefore, such system cannot be utilized in awake rodents. In order to overcome such limitation, researchers improved previous SFS (single fiber spectroscopic) system in 2020. They used an optical fiber with customized ferrule and patch cable to monitor cerebral oxygen saturation in highly-localized deep brain regions within behaving animals for the first time [71]. In this system, a multimode optical fiber with 200 μm of core diameter and 0.39 of numerical aperture was employed to deliver and collect the light to and from the brain. The oxygen saturation was measured in both in vitro and in vivo experiments. In in vivo measurements, they monitored oxygen saturation from targeted brain region for 31 days as well as from a behaving animal for more than an hour continuously, as shown in Fig. 5c.

The current development in real-time monitoring in vivo through bioresorbable spectroscopic photonic devices also enables the quantification of oxygenation in brain. Such a novel tool was constructed with Si membrane detector electrodes, filter layers of SiO_x and SiN_y, a PLGA optical fiber, and a SiO_2 thin film encapsulation [66]. Functioning of the device is totally reliant on spectral response of Si nanomembranes positioned at the tip of the optical fiber. The device exhibited its potential in sensing cerebral oxygen saturation and cerebral temperature in live animals (Fig. 5b).

Intracranial Pressure Sensing

There are two types of pressure in our body. One is isotropic pressure (e.g., blood pressure and intracranial pressure), and the other is contact pressure (e.g., intra vertebral pressure). The excess of pressure within body's internal cavities may result from several diseases or from the responses toward physical injuries. Therefore, to monitor pressure is usually an important aspect in evaluating the health of a patient. Specially, measuring the brain pressure is crucial in diagnosis of the injury of traumatic brain. Intracranial pressure varies according to fluctuations in circulatory dynamics of the cerebrospinal fluid and cerebral blood. To monitor the pressure in such a domain requires an invasive transducer that can be inserted through surgery [72–74]. Additionally, various fiber based sensors incorporating Bragg gratings or Fabry-Pérot interferometers (FPI) have been employed for isotropic pressure measurements in the animal body [75–78]. Figure 6 presents an example of such an intracranial pressure sensor, incorporationg an bioresorbable implanted FPI sensor coupling to a PLGA fiber [65]. This device was implanted in the intracranial region of animals to sense intracranial pressure, which provides promises in clinical uses. In order to obtain detailed information of the brain, direct attachment of the electrode array on the brain could be utilized to record and map electrophysiological signals with a high resolution.

Photodynamic Therapy

Photodynamic therapy (PDT) is a modern form of phototherapy that destroys tumor cells in a minimally invasive manner. This technique combines the usage of special drugs called photosensitizing (PS) agents, oxygen, and light sources such as light-emitting diodes (LEDs), lasers or fluorescent lamps [79]. Nowadays, such a therapeutic method is a well-established treatment employed to treat diverse kinds of cancers such as brain, lung, bladder, ovarian, esophageal, skin, and breast cancers. It is reported that through light irradiation, a particular photosensitizer preferentially accumulated within the abnormal cells, reactive oxide species (ROS), as well as toxicity of singlet oxygen that limits nutrient and oxygen supply could be generated to kill cancer cells without destroying healthy ones [80]. Several optical methods have been used clinically to overcome the weakness of low light penetration depth (< 1 cm) via biological tissues [19, 80–82]. It is noteworthy that the biocompatible optical fibers with ideal optical properties such as low optical loss and high level of transparency may be used to transmit the light to deep targeting regions of biological tissues.

GBM (glioblastoma multiforme) is a most aggressive kind of brain tumor with a median survival of about 14.6 months for adults. In previous studies, PDT has been proposed as a potential treatment of GBM. Moreover, PDT highly relies on ROS generation in microenvironment of the tumor, which is related to the concentration of PS and oxygenation. Hence, ROS generation can be controlled by localizing the PS and confinement of light in targeting microenvironment of the tumor, as shown in Fig. 7a [83].

Researchers not only have shown that the photodynamic anticancer of mitochondrial-targeted photosensitizer-loaded albumin nanoparticles (PS@chol-BSA NPs) is efficacious, but also have demonstrated the high capability of PS@chol-BSA NPs in targeting the brain tumor. Hence, this mitochondria-targeted photosensitizer paved the way for several promising therapeutic methods based on photodynamic therapy. Furthermore, in the recent studies, it was found that PDT effect of PS@chol-BSA NPs was improved by the light confinement induced by fiber optic cannula in the mouse brain. Use of optical fibers increases the dose of light and decreases the phototoxicity in targeted and non-targeted brain regions. Kang and Ko reported in vivo inhibition of brain tumor when using fiber without and with the cannula, as shown in Fig. 7a [83]. Tumors in mice were treated with PS@chol-BSA NPs as well as irradiated via optical fiber. The results indicate that the brain tumor became much smaller with the help of the cannula.

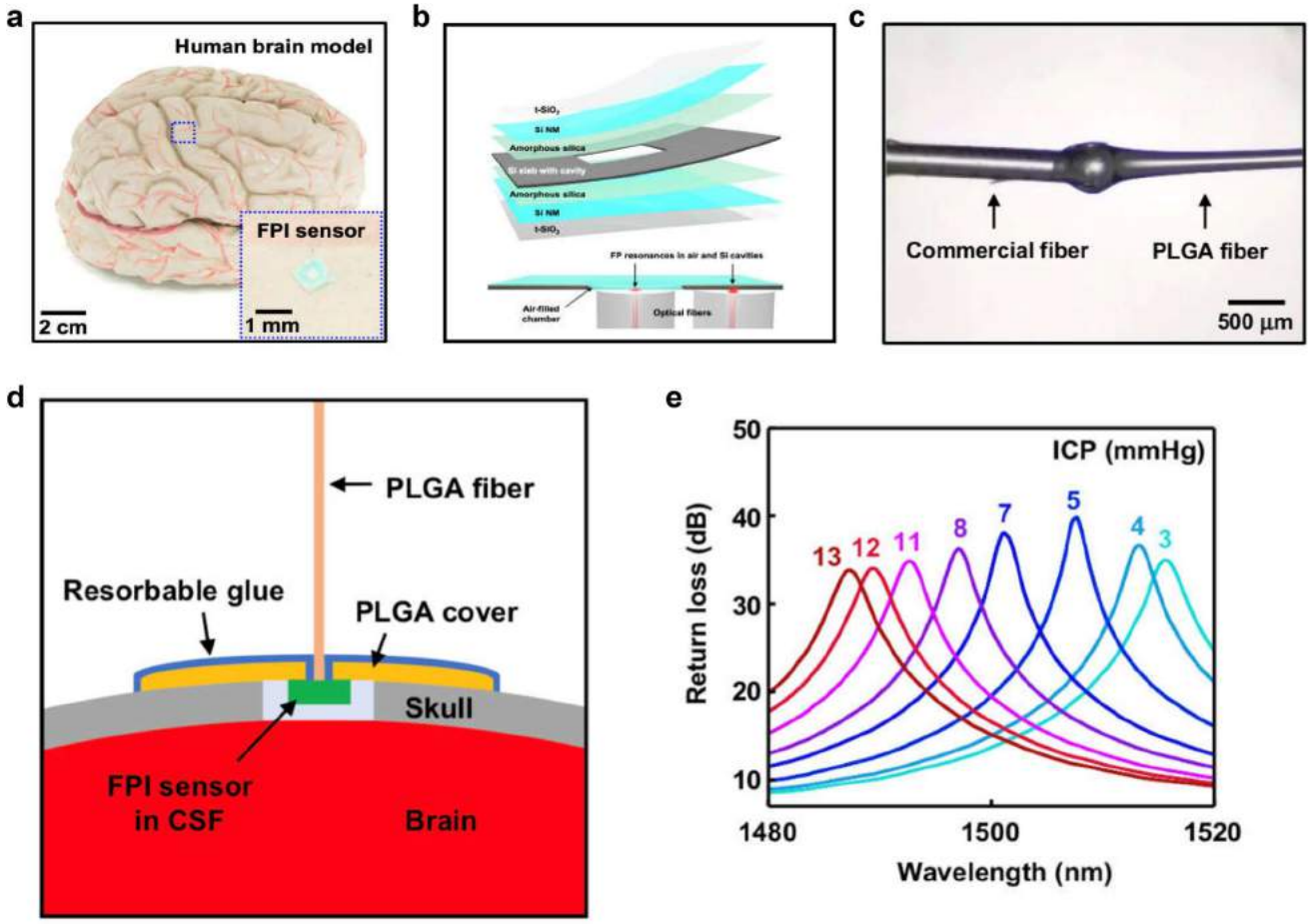


Fig. 6 Intracranial pressure sensing. **a** Image of a Fabry-Pérot interferometer (FPI) based pressure sensor placed on human brain model. **b** Scheme of the bioresorbable FPI pressure sensor. **c** Image of a PLGA optical fiber formed at the tip of a single-mode fiber. **d** Cross-sectional view of the device set up during animal experiment. **e** Optical spectra at different pressures obtained by the FPI pressure sensor. Reproduced with permission [65]. Copyright 2019, AAAS

Besides wired PDT devices, wireless devices for chronic PDT in deep tissues have also received considerable attention. In some of these devices, NIR light with high penetrating property was used to transmit light power to deep regions, while upconversion nanoparticles (UCNPs) were used to convert NIR to light with a shorter wavelength, which the photosensitizers response to. To restrain the movement of these nanoparticles and prevent potential drop in light delivery property, optic fibers have been used to sequester these UCNPs. Teh et al. have reported an upconverting implant consisting of UCNPs encapsulated by an optic fiber with poly(ethylene glycol) diacrylate (PEGDA) as core and fluorinated ethylene propylene (FEP) as cladding [84]. With this flexible and biocompatible device and photosensitizer 5-ALA, chronic PDT therapy for as long as 16 days was conducted in a deep brain region of mice with GBM. It was observed that, when treated with the upconversion fiber, NIR input and photosensitizers, the tumor regressed over time, as shown in Fig. 7b.

Delivery of Neurotrasmitters and Drugs

Multifunctional fibers can also serve as a powerful tool for delivering drug and neurotransmitters into the brain in a controllable manner. The neurotransmitters are important chemicals with the ability of transmitting information between neurons. Moreover, they are also vital for brain to work properly and any abnormalities in them cause mental disorders. Recently, Park et al. [85] designed an electrocatalytic sensor with an implantable multi-material fiber made of PC and COC fabricated through thermal drawing with three hollow channels. This sensor platform achieved controlling the NO generation correlated with neuronal signaling in the mouse brain. An illustration of this implantable probe is shown in Fig. 8a.

The above-mentioned features led scientists to develop a flexible optical fiber out of polymers through TDP, which was thinner than human hair [44, 51]. Furthermore, microfluidic channels were implemented into such fibers in order

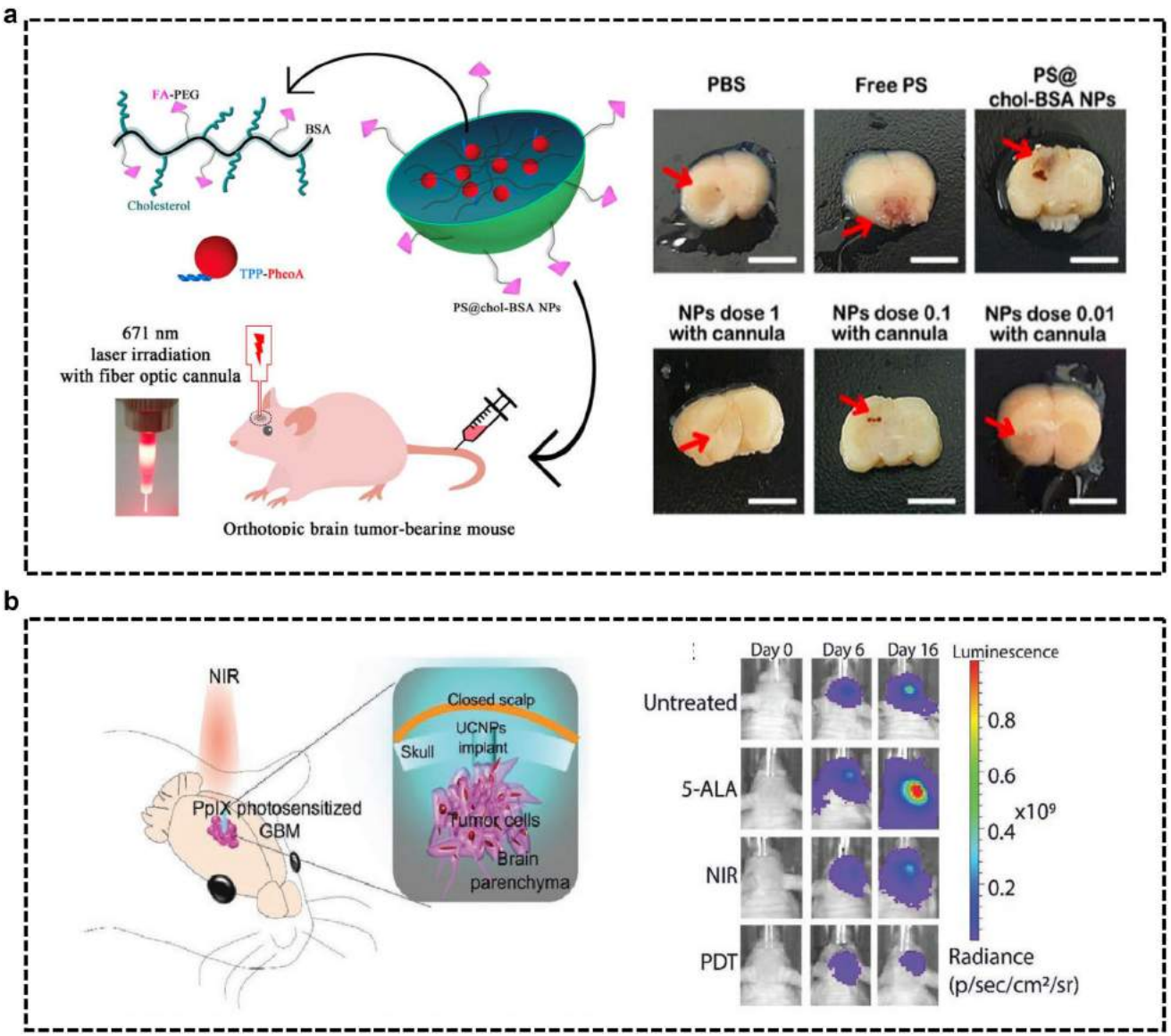


Fig. 7 Photodynamic therapy. **a** Left: Schematic diagram of a dual-selective photodynamic therapy by a fiber cannula and mitochondria-targeted photosensitizer, Right: Comparison of braintumor treatment with (bottom) and without (top) fiber optic cannula. Reproduced with permission [83]. Copyright 2019, Royal Society of Chemistry. **b** Left: Scheme of a wireless upconversion fiber implant for chronic deep region photodynamic therapy, Right: Comparison of brain tumor treatment over time of photodynamic therapy and control. Reproduced with permission [84]. Copyright 2020, Wiley–VCH

to transmit a set of optical, chemical, and electrical signals. On the basis of the idea that the materials used should have similar mechanical and thermal properties, researchers selected various polymers with different refractive indices. During certain tests, through the integrated microfluidic channels in fiber, the drug was transmitted successfully to the deep structure of brain tissue. Figure 8b shows such a device tested within a mouse brain [51].

Using multifunctional fiber with drug delivering tube, switchable photopharmacology can also be achieved. Recently, Frank et al. [86] used a multifunctional fiber to deliver a photoswitchable capsaicin analog, *red*-AzCA-4, to control the TRPV1 ion channel in a targeted region of mouse brain. The *red*-AzCA-4 isomerizes between the cis/trans forms with light of different wavelength, and its cis form activates TRPV1 more strongly than trans. Therefore, they could control the nueral circuits by delivering such light-controllable ligand and different light with a single mutifunctinoal fiber through photopharmacology, which is meaningful for investigating underlying molecular mechanisms of brain activities.

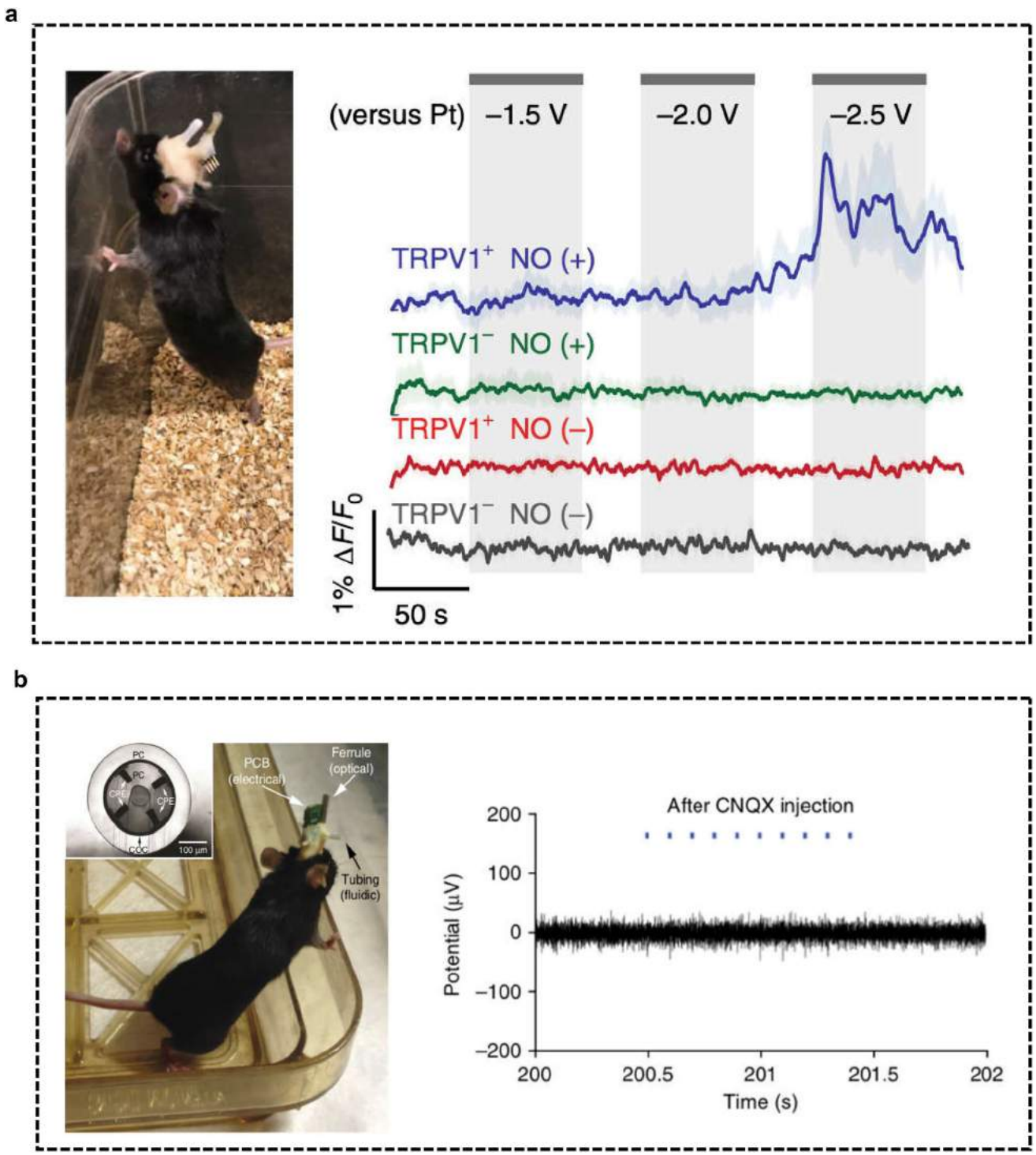


Fig. 8 Neurotransmitter and drug delivery**. a** Left: An NO generation-controlling fiber implanted into a mouse brain; Right: Normalized fluorescence signals through different conditions. Reproduced with permission [85]. Copyright 2020, Nature Publishing Group. **b** Left: Photo of a mouse with an implanted multifunctional fiber; Right: Drug-delivery capability of a multifunctional probe. Reproduced with permission [51]. Copyright 2015, Nature Publishing Group

pH Sensing

Another possible way of understanding the complex brain function in health and disease is high spatial and temporal resolution analysis of chemical signals in the brain. In maintaining normal brain functions, pH is one of the most important factors. To date, different technologies such as nuclear magnetic resonance (NMR) [87], fluorescent-based chemical probes [88], and electrochemical techniques [89] are used to sense the pH changes of brain tissue and detect abnormal physiological activities of the brain in a timelier manner. Recently, Guo et al. have developed a class of fiber-based probe that is capable of capturing the changes of pH at multiple pixels in deep brain regions with high spatial (250 um) and temporal (30 Hz) resolutions (Fig. 9) [90]. This miniaturized probe relies on a light-addressable potentiometric sensor (LAPS) linked to a convergence multimodal PC/PMMA fiber.

Possibilities for Future Applications

In this section, we present a brief summary of the applications of optical fibers in body parts other than the brain. From these works, we may borrow some concepts for future fiber-optic devices for brain.

As stated earlier, increasingly more optical fibers made of stretchable, soft, biocompatible, and biodegradable materials have been developed for biomedical applications and personal health care, several of which are discussed in detail here [91]. For instance, an optical fiber for strain sensing has been fabricated. Figure 10a shows the process and results of strain sensing with an optical fiber composed of ionic and covalent polymers. Such hydrogel fibers were capable of enduring the motions of the body and elasticity of skins [92]. Using hybrid alginate-polyacrylamide, stretchable and tough step-index hydrogel based optical fibers were fabricated through dip-coating and modeling process and were able to endure strain of up to 700%. Moreover, the levels of glucose in blood play a key role in measuring the amount of blood sugar secreted within a body. Yetisen et al. demonstrated a hydrogel fiber made of poly (acrylamide-co-poly(ethylene

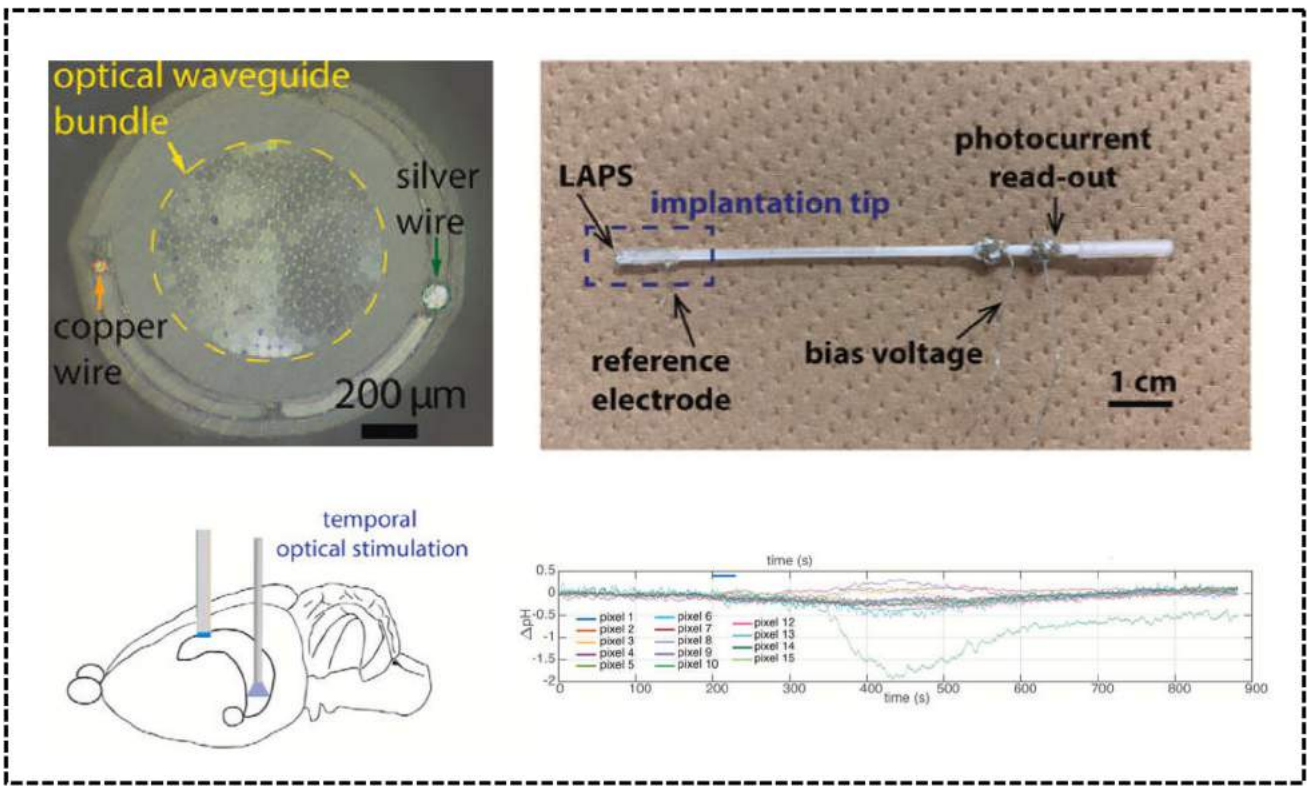


Fig. 9 pH sensing**.** Top-left: Cross-sectional view of the multi-material based fiber structure used for in vivo pH sensing in the brain; Top-right: Photograph of the fiber structure; Bottom-left: Scheme for working principles of simultaneous optical stimulation and pH recording; Bottom-right: Optically recorded pH signals in response to optogenetic activation. Reproduced with permission [90]. Copyright 2021, Elsevier

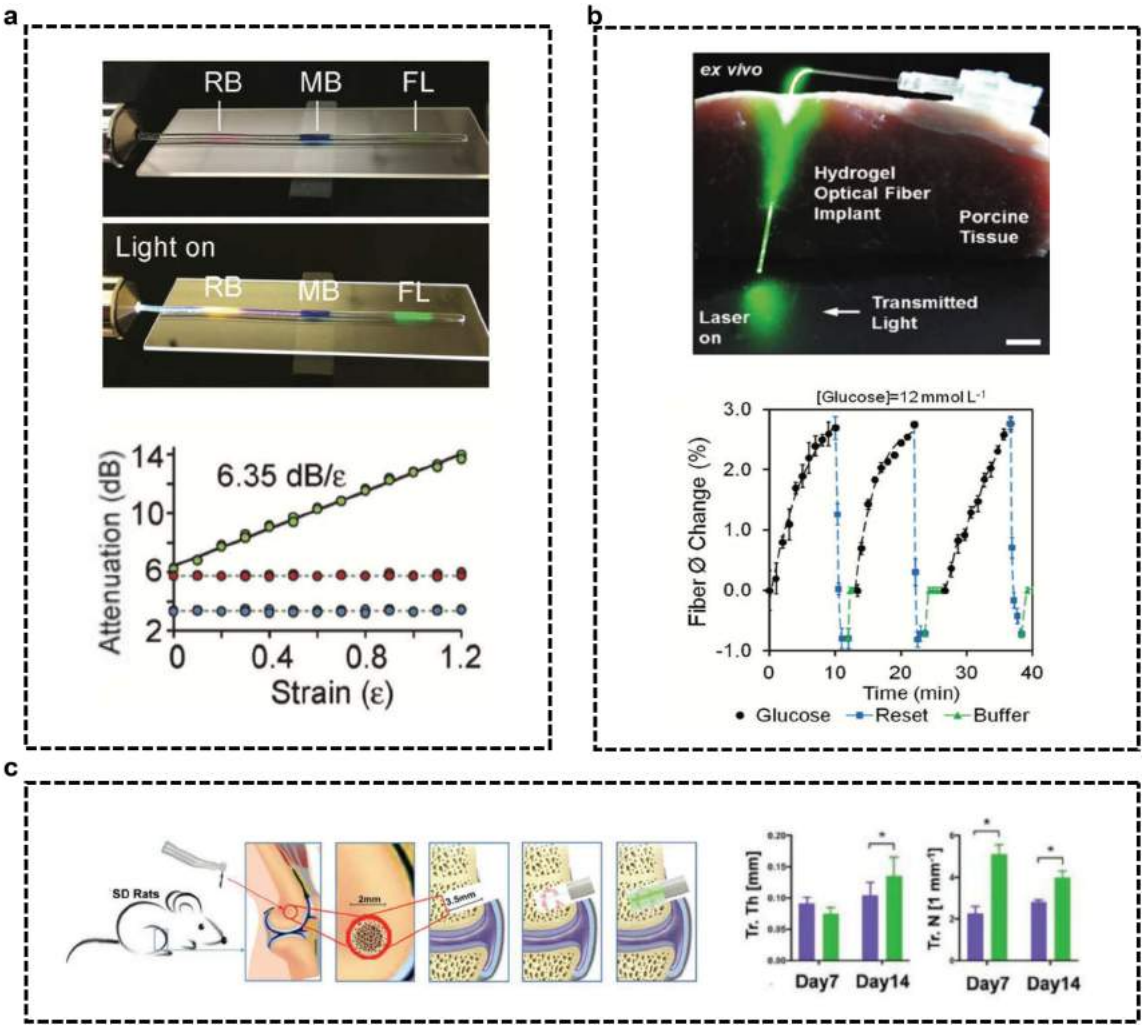


Fig. 10 Other possible applications that can possibly be adopted for brain research in the future. **a** Top: Photo of an optical fiber containing three sensors with light (bottom) and without light (top) illuminations; Bottom: The fiber attenuation at varied strain. Reproduced with permission [83]. Copyright 2016, Wiley–VCH. **b** Top: An optical fiber made of hydrogel implanted in tissue to measure the glucose; Bottom: Measured fiber diameter change (related to glucose concentration) dependent on pH. Reproduced with permission [84]. Copyright 2017, Wiley–VCH. **c** Left: Schematic illustration of a rat bone defect model treated via a biodegradable fiber guiding green light; Right: Estimated bone morphological structures within time. Reproduced with permission [100]. Copyright 2020, Wiley–VCH

glycol) diacrylate) functionalized with phenylboronic acid as core and Ca-crosslinked alginate as cladding. Phenylboronic acid integrated in the core served as a glucose-sensitive chelating agent for sensing glucose [93]. A variation in hydrogel density alters the refractive index of the aforesaid hydrogel fiber and consequently influence the propagation of light through it. Therefore, change in RI of the fiber core helps to determine glucose concentrations. Results of such fibers implanted to a porcine tissue for sensing glucose are shown in Fig. 10b.

Neurotransmitters are crucial markers of neural activities. Compared to traditional methods such as microdialysis that requires subsequent separation and detection [24, 94] and electrochemical methods such as fast scan cyclic voltammetry [95, 96], optical fiber-based devices can accomplish in-situ sensing with high selectivity. For example, Haghparast and co-workers applied a tapered optical fiber immobilized with dopamine-binding aptamer to perform label-free dopamine sensing. When combined with dopamine, the conformation of the aptamer changes and induces refractive index change around fiber surface, which can be detected with the tapered fiber. The limit of detection of this device reached 37 nM, with minimized interferences with epinephrine and ascorbic acid [97].

Surface plasmon resonance (SPR) is a commonly used method to detect chemical substances with optical fiber. In a typical SPR sensor, there is a metal film in contact with the core of a fiber, whose dielectric constant changes along

with its molecular absorption, which is related to the concentration of specific molecules. By measuring the dielectric constant, concentration information can be obtained. To improve the sensitivity of SPR, researchers modified the metal film by adhering colloidal substances and proteins to its surface. *Ribaut et al.* used plasma fiber Bragg grating to detect healthy lung tissue and tumor tissue with the help of CK17 markers, which can better identify tumor tissue in in vitro biopsy [98]. Multimaterial fibers have also been used in localized SPR sensing [99].

Another approach that has attracted noticeable attention is using fibers made of biodegradable materials. The tools fabricated out of these materials are very useful in healthcare due to their full biodegradability. The PLLA biodegradable fibers used as neural interfaces discussed earlier also have been applied in bone regeneration with the mid-wavelength light (green) [100]. Figure 10c shows an example of such application. Though these works are from non-brain studies, these functionalities are also highly demanded in brain studies. Therefore, these devices could inspire novel fiber-optic devices for brain in the future, or even be used directly in brains after proper modification. For example, the sensor for lung tumor detection using tiled fiber Bragg grating can be used in brain therapeutics if the markers are replaced with those sensitive to brain tumors. However, it is noteworthy that the mechanical and optical properties of brain are different from those of other organs. Thus, when transforming these devices to devices for brain, modifications like replacing with soft materials and tuning the wavelength are necessary.

Advanced material, structure and processing designs have been continuously developed, especially in multimaterial fibers. By combining them with waveguides, new multifunctional optical fibers could be produced and used for more diverse applications. For example, semiconductors have been used in optoelectronic multimaterial fibers for all-fiber-integrated devices [101, 102]. Besides, nanoscale metallic glass fiber has been used in multimaterial fiber for deep-brain electrical stimulation and recording [103]. Microstructured fibers have also been fabricated, such as cantilever-like strucutre for pressure sensing [104] and hierarchical textured surface for nerve regenaration [105]. Additionally, structures and processing techniques used in other structural fiber sensors can also be used in optical fibers [106–108]. These designs could also provide new functions and opportunities if used in brain research.

Summary

To conclude, here we review the applications of advanced optical fiber systems for brain research, including widely used optogenetic and fluorescence recording tools, as well as the most recent progresses in the sensing of other brain activities and biochemical interrogations. Some applications including strain, glucose sensing and tissue regeneration have not been reported in brain studies yet, but it is envisioned that these directions would become viable in the future. With their unique advantages, it is expected that optical fiber-based devices for brain will keep flourishing in the future, with more new applications demonstrated and existing applications moving towards clinical uses. Using softer, more biocompatible and bioresorbable materials, increasing the number of sensing sites, integrating multiple functionalities and enhancing movement stability will still be the trend of this field. We anticipate that these and other optical fiber-based techniques will not only be helpful in fundamental brain research, but also provide a viable platform for future diagnostics and therapeutics in neurological diseases.

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Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Lindboe CF. Brain weight: what does it mean? Clin Neuropathol. 2003;22(6):263–5.
2. Jacques SL. Optical properties of biological tissues: a review. Phys Med Biol. 2013;58(11):R37.
3. Keiser G, Xiong F, Cui Y, Shum PP. Review of diverse optical fibers used in biomedical research and clinical practice. J Biomed Opt. 2014;19(8):080902.
4. Li L, Liu C, Su Y, Bai J, Wu J, Han Y, Hou Y, Qi S, Zhao Y, Ding H, Yan Y, Yin L, Wang P, Luo Y, Sheng X. Heterogeneous Integration of microscale GaN light-emitting diodes and their electrical, optical, and thermal characteristics on flexible substrates. Adv Mater Technol. 2018;3(1):1700239.
5. Shim E, Chen Y, Masmanidis S, Li M. Multisite silicon neural probes with integrated silicon nitride waveguides and gratings for optogenetic applications. Sci Rep. 2016;6:22693.
6. Mohanty A, Li Q, Tadayon MA, Roberts SP, Bhatt GR, Shim E, Ji X, Cardenas J, Miller S, Kepecs A, Lipson M. Reconfigurable nanophotonic silicon probes for sub-millisecond deep-brain optical stimulation. Nat Biomed Eng. 2020;4(2):223–31.
7. Pisano F, Pisanello M, Lee SJ, Lee J, Maglie E, Balena A, Sileo L, Spagnolo B, Bianco M, Hyun M, De Vittorio M, Sabatini BL, Pisanello F. Depth-resolved fiber photometry with a single tapered optical fiber implant. Nat Methods. 2019;16(11):1185–92.
8. Sung C, Jeon W, Nam KS, Kim YJ, Butt H, Park S. Multimaterial and multifunctional neural interfaces: from surface-type and implantable electrodes to fiber-based devices. J Mater Chem B. 2020;8(31):6624–66.

9. Pisano F, Pisanello M, Sileo L, Qualtieri A, Sabatini BL, De Vittorio M, Pisanello F. Focused ion beam nanomachining of tapered optical fibers for patterned light delivery. Microelectron Eng. 2018;195:41–9.
10. Chen S, Weitemier AZ, Zeng X, He L, Wang X, Tao Y, Huang AJY, Hashimotodani Y, Kano M, Iwasaki H, Parajuli LK, Okabe S, Teh DBL, All AH, Tsutsui-Kimura I, Tanaka KF, Liu X, McHugh TJ. Near-infrared deep brain stimulation via upconversion nanoparticle-mediated optogenetics. Science. 2018;359(6376):679–84.
11. Shabahang S, Seonghoon K, Seok HY. Light-guiding biomaterials for biomedical applications. Adv Funct Mater. 2018;28(24):1706635.
12. Xu H, Yin L, Liu C, Sheng X, Zhao N. Recent advances in biointegrated optoelectronic devices. Adv Mater. 2018. https://doi.org/10.1002/adma.201800156.
13. Nazempour R, Zhang Q, Fu R, Sheng X. Biocompatible and implantable optical fibers and waveguides for biomedicine. Materials. 2018;11(8):1283.
14. Canales A, Park S, Kilias A, Anikeeva P. Multifunctional fibers as tools for neuroscience and neuroengineering. Acc Chem Res. 2018;51(4):829–38.
15. Fenno L, Yizhar O, Deisseroth K. The development and application of optogenetics. Annu Rev Neurosci. 2011;34:389–412.
16. Zhang Y, Ding J, Qi B, Tao W, Wang J, Zhao C, Peng H, Shi J. Multifunctional fibers to shape future biomedical devices. Adv Funct Mater. 2019. https://doi.org/10.1002/adfm.201902834.
17. Guo J, Yang C, Dai Q, Kong L. Soft and stretchable polymeric optical waveguide-based sensors for wearable and biomedical applications. Sensors. 2019;19(17):3771.
18. Quandt BM, Scherer LJ, Boesel LF, Wolf M, Bona GL, Rossi RM. Body-monitoring and health supervision by means of optical fiber-based sensing systems in medical textiles. Adv Healthcare Mater. 2015;4(3):330–55.
19. Kim MM, Darafsheh A. Light sources and dosimetry techniques for photodynamic therapy. Photochem Photobiol. 2020;96(2):280–94.
20. Warden MR, Cardin JA, Deisseroth K. Optical neural interfaces. Annu Rev Biomed Eng. 2014;16:103–29.
21. Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, Lammel S, Mirzabekov JJ, Airan RD, Zalocusky KA, Tye KM, Anikeeva P, Malenka RC, Deisseroth K. Natural neural projection dynamics underlying social behavior. Cell. 2014;157(7):1535–51.
22. Jia X, Froriep U, Lu C, Wei L, Hou C, Tringides C, LaVine JD, Fink Y, Anikeeva P. Multimodality flexible fiber neural probes for in vivo simultaneous optical stimulation, electrical neural recording, and drug delivery. In: Abstracts from the 41st Neural Interfaces Conference. International Neuromodulation Society; 2014. pp. 10
23. Li J, Ebendorff-Heidepriem H, Gibson BC, Greentree AD, Hutchinson MR, Jia P, Kostecki R, Liu G, Orth A, Ploschner M, Schartner EP, Warren-Smith SC, Zhang K, Tsiminis G, Goldys EM. Perspective: biomedical sensing and imaging with optical fibers—innovation through convergence of science disciplines. APL Photonics. 2018. https://doi.org/10.1063/1.5040861.
24. Niyonambaza SD, Kumar P, Xing P, Mathault J, De Koninck P, Boisselier E, Boukadoum M, Miled A. A review of neurotransmitters sensing methods for neuro-engineering research. Appl Sci. 2019;9(21):4719.
25. Guru A, Post RJ, Ho YY, Warden MR. Making sense of optogenetics. Int J Neuropsychopharmacol. 2015;18(11):pyv079.
26. Joshi J, Rubart M, Zhu W. Optogenetics: background, methodological advances and potential applications for cardiovascular research and medicine. Front Bioeng Biotechnol. 2020;7:466.
27. Baldermann JC, Hardenacke K, Hu X, Köster P, Horn A, Freund HJ, Zilles K, Sturm V, Visser-Vandewalle V, Jessen F, Maintz D, Kuhn J. Neuroanatomical characteristics associated with response to deep brain stimulation of the nucleus basalis of Meynert for Alzheimer's disease. Neuromodulation. 2018;21(2):184–90.
28. Gardner J. A history of deep brain stimulation: technological innovation and the role of clinical assessment tools. Soc Stud Sci. 2013;43(5):707–28.
29. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM. Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia. 2002;43(6):603–8.
30. Levinson DF. The genetics of depression: a review. Biol Psychiatry. 2006;60(2):84–92.
31. Deisseroth K, Feng G, Majewska AK, Miesenböck G, Ting A, Schnitzer MJ. Next-generation optical technologies for illuminating genetically targeted brain circuits. J Neurosci. 2006;26:10380–6.
32. Deisseroth K. Optogenetics. Nat Methods. 2011;8(1):26–9.
33. Lee SH, Kwan AC, Zhang S, Phoumthipphavong V, Flannery JG, Masmanidis SC, Taniguchi H, Huang ZJ, Zhang F, Boyden ES, Deisseroth K, Dan Y. Activation of specific interneurons improves V1 feature selectivity and visual perception. Nature. 2012;488(7411):379–83.
34. Montagni E, Resta F, Mascaro ALA, Pavone FS. Optogenetics in brain research: from a strategy to investigate physiological function to a therapeutic tool. Photonics. 2019;6(3):92.
35. Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. Nat Neurosci. 2015;18(9):1213–25.
36. Sebastien R, Zemelman BV, Mladen Barbic M, Attila Losonczy A, György Buzsáki G, Jeffrey C, Magee JC. Multi-array silicon probes with integrated optical fibers: light-assisted perturbation and recording of local neural circuits in the behaving animal. Eur J Neurol. 2010;31(12):2279–91.
37. Zhang J, Farah Laiwalla F, Jennifer A, Kim JA, Hayato Urabe H, Rick Van Wagenen R, Yoon-Kyu Song YK, Barry W, Connors BW, Feng Zhang F, Karl Deisseroth K, Arto V, Nurmikko AV. Integrated device for optical stimulation and spatiotemporal electrical recording of neural activity in light-sensitized brain tissue. J Neural eng. 2009;6(5):055007.
38. Chen R, Canales A, Anikeeva P. Neural recording and modulation technologies. Nat Rev Mater. 2017;2(2):1–16.
39. Wang L, Zhong C, Ke D, Ye F, Tu J, Wang L, Lu Y. Ultrasoft and highly stretchable hydrogel optical fibers for *in vivo* optogenetic modulations. Adv Opt Mater. 2018. https://doi.org/10.1002/adom.201800427.
40. Jackman SL, Chen CH, Chettih SN, Neufeld SQ, Drew IR, Agba CK, Flaquer I, Stefano AN, Kennedy TJ, Belinsky JE, Roberston K, Beron CC, Sabatini BL, Harvey CD, Regehr WG. Silk fibroin films facilitate single-step targeted expression of optogenetic proteins. Cell Rep. 2018;22(12):3351–61.
41. Fu R, Luo W, Nazempour R, Tan D, Ding H, Zhang K, Yin L, Guan J, Sheng X. Implantable and biodegradable poly (L-lactic acid) fibers for optical neural interfaces. Adv Opt Mater. 2018;6(3):1700941.
42. Zhang Y, Li X, Kim J, Tong Y, Thompson EG, Jiang S, Feng Z, Yu L, Wang J, Ha DS, Sontheimer H, Johnson BN, Jia X. Thermally drawn stretchable electrical and optical fiber sensors for multimodal extreme deformation sensing. Adv Opt Mater. 2021;9(6):2001815.
43. Sileo L, Bitzenhofer SH, Spagnolo B, Pöpplau JA, Holzhammer T, Pisanello M, Pisano F, Bellistri E, Maglie E, De Vittorio M, Ruther P, Hanganu-Opatz IL, Pisanello F. Tapered fibers combined with a multi-electrode array for optogenetics in mouse medial prefrontal cortex. Front Neurosci. 2018;12:771.

44. Pisanello F, Mandelbaum G, Pisanello M, Oldenburg IA, Sileo L, Markowitz JE, Peterson RE, Della Patria A, Haynes TM, Emara MS, Spagnolo B, Datta SR, De Vittorio M, Sabatini BL. Dynamic illumination of spatially restricted or large brain volumes via a single tapered optical fiber. Nat Neurosci. 2017;20(8):1180–8.
45. Park S, Loke G, Fink Y, Anikeeva P. Flexible fiber-based optoelectronics for neural interfaces. Chem Soc Rev. 2019;48(6):1826–52.
46. Park S, Guo Y, Jia X, Choe HK, Grena B, Kang J, Park J, Lu C, Canales A, Chen R, Yim YS, Choi GB, Fink Y, Anikeeva P. One-step optogenetics with multifunctional flexible polymer fibers. Nat Neurosci. 2017;20(4):612–9.
47. Park S, Yuk H, Zhao R, Yim YS, Woldeghebriel EW, Kang J, Canales A, Fink Y, Choi GB, Zhao X, Anikeeva P. Adaptive and multifunctional hydrogel hybrid probes for long-term sensing and modulation of neural activity. Nat Commun. 2021;12:3435.
48. Jiang S, Patel DC, Kim J, Yang S, Iii WAM, Zhang Y, Wang K, Feng Z, Vijayan S, Cai W, Wang A, Guo Y, Kimbrough IF, Sontheimer H, Jia X. Spatially expandable fiber-based probes as a multifunctional deep brain interface. Nat Commun. 2020;11(1):6115.
49. Guo Y, Werner CF, Canales A, Yu L, Jia X, Anikeeva P, Yoshinobu T. Polymer-fiber-coupled field-effect sensors for label-free deep brain recordings. PLoS One. 2020;15(1):e0228076.
50. Kilias A, Canales A, Froriep UP, Park S, Egert U, Anikeeva P. Optogenetic entrainment of neural oscillations with hybrid fiber probes. J Neural Eng. 2018;15(5):056006.
51. Canales A, Jia X, Froriep UP, Koppes RA, Tringides CM, Selvidge J, Lu C, Hou C, Wei L, Fink Y, Anikeeva P. Multifunctional fibers for simultaneous optical, electrical and chemical interrogation of neural circuits *in vivo*. Nat Biotechnol. 2015;33(3):277–84.
52. Du M, Huang L, Zheng J, Xi Y, Dai Y, Zhang W, Yan W, Tao G, Qiu J, So K, Ren C, Zhou S. Flexible fiber probe for efficient neural stimulation and detection. Adv Sci. 2020;7:2001410.
53. Lu C, Park S, Richner TJ, Derry A, Brown I, Hou C, Rao S, Kang J, Moritz CT, Fink Y, Anikeeva P. Flexible and stretchable nanowire-coated fibers for optoelectronic probing of spinal cord circuits. Sci Adv. 2017;3(3):e1600955.
54. Liu S, Nie J, Li Y, Yu T, Zhu D, Fei P. Three-dimensional, isotropic imaging of mouse brain using multi-view deconvolution light sheet microscopy. J Innovative Opt Health Sci. 2017;10(5):1743006.
55. Chen TW, Wardill TJ, Sun Y, Pulver SR, Renninger SL, Baohan A, Schreiter ER, Kerr RA, Orger MB, Jayaraman V, Looger LL, Svoboda K, Kim DS. Ultrasensitive fluorescent proteins for imaging neuronal activity. Nature. 2013;499(7458):295–300.
56. Marshall JD, Li JZ, Zhang Y, Gong Y, St-Pierre F, Lin MZ, Schnitzer MJ. Cell-type-specific optical recording of membrane voltage dynamics in freely moving mice. Cell. 2016;167(6):1650–62.
57. Guo Q, Zhou J, Feng Q, Lin R, Gong H, Luo Q, Zeng S, Luo M, Fu L. Multi-channel fiber photometry for population neuronal activity recording. Biomed Opt Express. 2015;6(10):3919–31.
58. Sych Y, Chernysheva M, Sumanovski LT, Helmchen F. High-density multi-fiber photometry for studying large-scale brain circuit dynamics. Nat Methods. 2019;16(6):553.
59. Meng C, Zhou J, Papaneri A, Peddada T, Xu K, Cui G. Spectrally resolved fiber photometry for multi-component analysis of brain circuits. Neuron. 2018;98(4):707–17.
60. Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperthermia. 2003;19(3):267–94.
61. Schiff SJ, Somjen GG. The effects of temperature on synaptic transmission in hippocampal tissue slices. Brain Res. 1985;345(2):279–84.
62. Zibaii MI, Latifi H, Karami F, Ronaghi A, Nejad SC, Dargahi L. *In vivo* brain temperature measurements based on fiber optic Bragg grating. In: 2017 25th optical fiber sensors conference (OFS). IEEE; 2017. pp. 1–4
63. Musolino S, Schartner EP, Tsiminis G, Salem A, Monro TM, Hutchinson MR. Portable optical fiber probe for *in vivo* brain temperature measurements. Biomed Opt Express. 2016;7(8):3069–77.
64. Musolino ST, Schartner EP, Hutchinson MR, Salem A. Improved method for optical fiber temperature probe implantation in brains of free-moving rats. J Neurosci Methods. 2019;313:24–8.
65. Shin J, Liu Z, Bai W, Liu Y, Yan Y, Xue Y, Kandela I, Pezhouh M, MacEwan MR, Huang Y, Ray WZ, Zhou W, Rogers JA. Bioresorbable optical sensor systems for monitoring of intracranial pressure and temperature. Adv Sci. 2019. https://doi.org/10.1126/sciadv.aaw1899.
66. Bai W, Shin J, Fu R, Kandela I, Lu D, Ni X, Park Y, Liu Z, Hang T, Wu D, Liu Y, Haney CR, Stepien I, Yang Q, Zhao J, Nandoliya KR, Zhang H, Sheng X, Yin L, MacRenaris K, Brikha A, Aird F, Pezhouh M, Hornick J, Zhou W, Rogers JA. Bioresorbable photonic devices for the spectroscopic characterization of physiological status and neural activity. Nat Biomed Eng. 2019;3(8):644–54.
67. Vo-Dinh T. Biomedical photonics handbook: biomedical diagnostics. Boca Raton: CRC Press; 2014.
68. Rejmstad P, Zsigmond P, Wårdell K. Oxygen saturation estimation in brain tissue using diffuse reflectance spectroscopy along stereotactic trajectories. Opt Express. 2017;25(7):8192–201.
69. Hillman EM. Optical brain imaging *in vivo*: techniques and applications from animal to man. J Biomed Opt. 2007;12(5):051402.
70. Yu L, Wu Y, Dunn JF, Murari K. *In-vivo* monitoring of tissue oxygen saturation in deep brain structures using a single fiber optical system. Biomed Opt Express. 2016;7(11):4685–94.
71. Yu L, Thurston EM, Hashem M, Dunn JF, Whelan PJ, Murari K. Fiber photometry for monitoring cerebral oxygen saturation in freely-moving rodents. Biomed Opt Express. 2020;11(7):3491–506.
72. Singh R, Bathaei MJ, Istif E, Beker L. A review of bioresorbable implantable medical devices: materials, fabrication, and implementation. Adv Healthc Mater. 2020;9(18):e200070.
73. Clausen I, Glott T. Development of clinically relevant implantable pressure sensors: perspectives and challenges. Sensors. 2014;14(9):17686–702.
74. Correia R, James S, Lee SW, Morgan SP, Korposh S. Biomedical application of optical fibre sensors. J Opt. 2018;20(7):073003.
75. Poeggel S, Tosi D, Duraibabu D, Leen G, McGrath D, Lewis E. Optical fibre pressure sensors in medical applications. Sensors. 2015;15(7):17115–48.
76. Kanellos GT, Papaioannou G, Tsiokos D, Mitrogiannis C, Nianios G, Pleros N. Two-dimensional polymer-embedded quasi-distributed FBG pressure sensor for biomedical applications. Opt Express. 2010;18(1):179–86.
77. Ahmad H, Chong WY, Thambiratnam K, Zulklifi MZ, Poopalan P, Thant MMM, Harun SW. High sensitivity fiber Bragg grating pressure sensor using thin metal diaphragm. IEEE Sens J. 2009;9(12):1654–9.
78. Islam M, Ali MM, Lai MH, Lim KS, Ahmad H. Chronology of Fabry-Perot interferometer fiber-optic sensors and their applications: a review. Sensors. 2014;14(4):7451–88.
79. Sarbu MI, Matei C, Mitran CI, Mitran MI, Caruntu C, Constantin C, Neagu M, Georgescu SR. Photodynamic therapy: a hot topic in dermato-oncology. Oncol Lett. 2019;17(5):4085–93.

80. Wang J, Dong J. Optical waveguides and integrated optical devices for medical diagnosis, health monitoring and light therapies. Sensors. 2020;20(14):3981.
81. Liu H, Daly L, Rudd G, Khan AP, Mallidi S, Liu Y, Cuckov F, Hasan T, Celli JP. Development and evaluation of a low-cost, portable, LED-based device for PDT treatment of early-stage oral cancer in resource-limited settings. Lasers Surg Med. 2019;51(4):345–51.
82. Song D, Chi S, Li X, Wang C, Li Z, Liu Z. Upconversion system with quantum dots as sensitizer: improved photoluminescence and PDT efficiency. ACS Appl Mater Interfaces. 2019;11(44):41100–8.
83. Kang JH, Ko YT. Dual-selective photodynamic therapy with a mitochondria-targeted photosensitizer and fiber optic cannula for malignant brain tumors. Biomater Sci. 2019;7(7):2812–25.
84. Teh DBL, Bansal A, Chai C, Toh TB, Tucker RAJ, Gammad GGL, Yeo Y, Lei Z, Zheng X, Yang F, Ho JS, Bolem N, Wu BC, Gnanasammandhan MK, Hooi L, Dawe GS, Libedinsky C, Ong W, Halliwell B, Chow EK, Lim K, Zhang Y, Kennedy BK. A flexi-PEGDA upconversion implant for wireless brain photodynamic therapy. Adv Mater. 2020. https://doi.org/10.1002/adma.202001459.
85. Park J, Jin K, Sahasrabudhe A, Chiang PH, Maalouf JH, Koehler F, Rosenfeld D, Rao S, Tanaka T, Khudiyev T, Schiffer ZJ, Fink Y, Yizhar O, Manthiram K, Anikeeva P. In situ electrochemical generation of nitric oxide for neuronal modulation. Nat Nanotechnol. 2020;15(8):690–7.
86. Frank JA, Antonini MJ, Chiang PH, Canales A, Konrad DB, Garwood IC, Rajic G, Koehler F, Fink Y, Anikeeva P. In vivo photopharmacology enabled by multifunctional fibers. ACS Chem Neurosci. 2020;11:3802.
87. Magnotta VA, Hye-Young Heo HY, Brian J, Dlouhy BJ, Nader S, Dahdaleh NS, Robin L, Follmer RL, Daniel R, Thedens DR, Michael J, Welsh MJ, John A, Wemmie JA. Detecting activity-evoked pH changes in human brain. Proc Natl Acad Sci USA. 2012;109(21):8270–3.
88. Mathew T, Yin Pun Hung YP, Gary Yellen G. Imaging intracellular pH in live cells with a genetically encoded red fluorescent protein sensor. J Am Chem Soc. 2011;133(26):10034–7.
89. Takmakov P, Matthew K, Zachek MK, Richard B, Keithley RB, Elizabeth S, Bucher ES, Gregory S, McCarty GS, Mark R, Wightman RM. Characterization of local pH changes in brain using fast-scan cyclic voltammetry with carbon microelectrodes. Anal Chem. 2010;82(23):9892–900.
90. Guo Y, Carl Frederik Werner CF, Shoma Handa S, Mengyun Wang M, Tomokazu Ohshiro T, Hajime Mushiake H, Tatsuo Yoshinobu T. Miniature multiplexed label-free pH probe in vivo. Biosens Bioelectron. 2021;174:112870.
91. Yu X, Zhang S, Olivo M, Li N. Micro- and nano-fiber probes for optical sensing, imaging, and stimulation in biomedical applications. Photonics Res. 2020;8(11):1703–24.
92. Guo J, Liu X, Jiang N, Yetisen AK, Yuk H, Yang C, Khademhosseini A, Zhao X, Yun SH. Highly stretchable, strain sensing hydrogel optical fibers. Adv Mater. 2016;28(46):10244–9.
93. Yetisen AK, Jiang N, Fallahi A, Montelongo Y, Ruiz-Esparza GU, Tamayol A, Zhang YS, Mahmood I, Yang SA, Kim KS, Butt H, Khademhosseini A, Yun SH. Glucose-sensitive hydrogel optical fibers functionalized with phenylboronic acid. Adv Mater. 2017. https://doi.org/10.1002/adma.201606380.
94. Kennedy RT, Watson CJ, Haskins WE, Powell DH, Strecker RE. In vivo neurochemical monitoring by microdialysis and capillary separations. Curr Opin Chem Biol. 2002;6(5):659–65.
95. Phillips PEM, Wightman RM. Critical guidelines for validation of the selectivity of in-vivo chemical microsensors. Trends Anal Chem. 2003;22(9):509–14.
96. Keithley RB, Takmakov P, Bucher ES, Belle AM, Owesson-White CA, Park J, Wightman RM. Higher sensitivity dopamine measurements with faster-scan cyclic voltammetry. Anal Chem. 2011;83(9):3563–71.
97. Zibaii MI, Latifi H, Asadollahi A, Bayat AH, Dargahi L, Haghparast A. Label free fiber optic apta-biosensor for in-vitro detection of dopamine. J Lightwave Technol. 2016;34(19):4516–24.
98. Ribaut C, Loyez M, Larrieu J, Chevineau S, Lambert P, Remmelink M, Wattiez R, Caucheteur C. Cancer biomarker sensing using packaged plasmonic optical fiber gratings: towards *in vivo* diagnosis. Biosens Bioelectron. 2016;92:449–56.
99. Jiang S, Song J, Zhang Y, Nie M, Kim J, Marcano AL, Kadlec K, Mills WA, Yan X, Liu H, Tong R, Wang H, Kimbrough IF, Sontheimer H, Zhou W, Jia X. Nano-optoelectrodes integrated with flexible multifunctional fiber probes by high-throughput scalable fabrication. Acs Appl Mater Interfaces. 2021;13(7):9156–65.
100. Jiang Y, Qi W, Zhang Q, Liu H, Zhang J, Du N, Nazempour R, Su Y, Fu R, Zhang K, Lyu P, Dong F, Yin L, Sheng X, Wang Y. Green Light-based photobiomodulation with an implantable and biodegradable fiber for bone regeneration. Small Methods. 2020. https://doi.org/10.1002/smtd.201900879.
101. Yan W, Qu Y, Das Gupta T, Darga A, Dang Tung N, Page AG, Rossi M, Ceriotti M, Sorin F. Semiconducting nanowire-based optoelectronic fibers. Adv Mater. 2017;29(27):1700681.
102. Yan W, Richard I, Kurtuldu G, James ND, Schiavone G, Squair JW, Nguyen-Dang T, Das Gupta T, Qu Y, Cao JD, Ignatans R, Lacour SP, Tileli V, Courtine G, Loffler JF, Sorin F. Structured nanoscale metallic glass fibres with extreme aspect ratios. Nat Nanotechnol. 2020;15:875–82.
103. Yan W, Tung ND, Cayron C, Das Gupta T, Page AG, Qu Y, Sorin F. Microstructure tailoring of selenium-core multimaterial optoelectronic fibers. Opt Mater Express. 2017;7(4):1388–97.
104. Tung ND, Page AG, Qu Y, Volpi M, Yan W, Sorin F. Multimaterial micro-electromechanical fibers with bendable functional domains. J Phys D Appl Phys. 2017;50(14):144001.
105. Tung ND, de Luca AC, Yan W, Qu Y, Page AG, Volpi M, Das Gupta T, Lacour SP, Sorin F. Controlled sub-micrometer hierarchical textures engineered in polymeric fibers and microchannels via thermal drawing. Adv Funct Mater. 2017;27(10):1605935.
106. Sordo F, Janecek ER, Qu Y, Michaud V, Stellacci F, Engmann J, Wooster TJ, Sorin F. Microstructured fibers for the production of food. Adv Mater. 2019;31(14):1807282.
107. Dong C, Page AG, Yan W, Nguyen-Dang T, Sorin F. Microstructured multimaterial fibers for microfluidic sensing. Adv Mater Technol. 2019;4(10):1900417.
108. Lee Y, Canales A, Loke G, Kanik M, Fink Y, Anikeeva P. Selectively micro-patternable fibers via in-fiber photolithography. ACS Cent Sci. 2020;6(12):2319–25.