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Invited article

(INVITED)Review of Optical Fiber Technologies for Optogenetics

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ABSTRACT

Research in the field of Optogenetics has matured to the extent that *in vivo* implementations are more frequent in the literature. The majority of these employs different variants of optical fibers, including standard optical fibers, fiber bundles and tapered fibers. In the present contribution we review the application of optical fibers in optogenetics, in terms of critical requirements (biocompatabiliy, minimal invasiveness, spatial accuracy, etc) for *in vivo* demonstrations.

1. Introduction

The human brain, through its complex organization, is the controller of behavior, the interpreter of senses and the initiator of movement. Overall it defines who we are. It is justifiably argued that the human brain is the most complex entity we know. Research advances in neurological and behavioral science and the development of new research techniques (Vázquez-Guardado et al., 2020) have led to a more profound comprehension of the operation of the brain. Despite the remarkable research breakthroughs in brain research of the last decade (Kriegeskorte et al., 2008), the full decoding brain operation is still elusive. To this end, brain research is intensified and it is supported by major collective research efforts worldwide (Insel et al., 2013; Amunts et al., 2019). This is reflected in the plethora of research methods and tools developed that include Electroencephalography (EEG) (Biasiucci et al., 2019), functional Magnetic Resonance Imaging (fMRI) (Matthews and Jezzard, 2004) and Positron Emission Tomography (PET) (Berger, 2003). Optogenetics is a fairly new addition to the portfolio of brain neuromodulation methods that unlike others offers unprecedented spatiotemporal precision in the activation of neurons. Optogenetics (Deisseroth et al., 2006) combines genetic engineering and optical technology to activate and control neurons that are previously modified to express light-activated proteins, called opsins (Deisseroth et al., 2006; Yizhar et al., 2011).

The multidisciplinary nature of optogenetics involves intense research in areas such as preparation of light-sensitive proteins (Berndt and Deisseroth, 2015), gene delivery and expression, light illumination of genetically-modified neurons and recording of induced brain activity (Carter and de Lecea, 2011; Kravitz and Kreitzer, 2011). For the efficient optical stimulation of neurons, several light delivery strategies (Papagiakoumou, 2013) have emerged in the field of optogenetics (Packer et al., 2013).

Beam directing is the most straightforward approach for photostimulation of opsin-expressing neurons by focusing a light beam through a microscope objective or an optical fiber into the brain region of interest. Yet, this approach lacks in terms of speed of light beam steering over the targeted illumination area. The galvo-based scanning method (Ji et al., 2016) overcomes this limitation by shifting the light beam to various regions of interest using galvanometric mirrors. The position and orientation of the galvanometer-driven mirror system is displaced in the kilohertz frequency range and as a result it is feasible to illuminate a few regions of interest within millisecond intervals. However, the galvo-based scanning method is not capable of generating complex illumination patterns or stimulate a large number of regions of interest at once.

Direct and holographic projection methods employ optoelectronic devices known as Digital Micromirror Devices (DMDs) and Spatial Light Modulators (SLMs) respectively. These devices modulate intensity or phase of the incident light field, in order to create a complex patterned beam for simultaneous excitation of multiple brain regions thus providing a holistic view of brain function.

The bulk of the optogenetics literature concerns *in vitro* experimental demonstrations of the aforementioned light delivery strategies, with remarkable contribution towards the understanding of the underlying mechanisms of the brain. These results have motivated research towards the transition from *in vitro* to *in vivo* optogenetics, in an effort to

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reach the outmost frontier in optogenetics. This is supported by recent advances in the instrumentation of optogenetics (Das et al., 2020). Still, efficient *in vivo* light delivery poses a great challenge for practical *in vivo* optogenetic realizations. Indeed, it is not a straightforward task to deliver the necessary power for photostimulation deep into the brain, and at the same time comply with the *in vivo* requirements of minimal tissue invasiveness, low light induced tissue heating and biocompatibility (Goncalves et al., 2017). Optical fibers are the most researched light delivery solution for *in vivo* optogenetic photostimulation, and rightfully so as it offers a fair trade-off between these often competitive requirements.

There are now sufficient optical fiber *in vivo* optogenetic demonstrations to justify a review activity. This constitutes the scope of the paper at hand. More specifically, we review the variants of optical fibers that have been used in *in vivo* optogenetic experiments in terms of *in vivo* requirements. The rest of this paper is organized as follows: in Section 2, we briefly present the various *in vivo* optogenetic implementations found in the literature, setting the context for the subsequent sections. In Section 3, the set of requirements is defined for a fiber-based optogenetic system for efficient *in vivo* optogenetic stimulation. Section 4 categorizes the different optical fiber solutions used for *in vivo* neural photostimulation, addressing also biocompatibility issues. In Section 5, we discuss emerging optical fiber technologies that can be deployed for *in vivo* light delivery.

2. *In vivo* optogenetic implementations

Over the last few years, several *in vivo* optogenetic approaches have been developed through the exploitation of emerging and mature technologies across a range of fields, such as genetic engineering (Vlasov et al., 2018) and photonics (Ronzitti et al., 2017). In general, the implementations of *in vivo* optogenetics can be categorized based on the type of the optogenetic device used as *wired* and *wireless*.

In wired optogenetic systems (Packer et al., 2013; Fenno et al., 2011; Siuda et al., 2015), a light source is coupled to an optical fiber, as shown in Fig. 1(a). The optical fiber is inserted into the brain of the animal subject for light delivery into specific brain areas for neural photostimulation. Wired optical fiber-based systems, where the light source is in a distance from the subject, enable deep brain optogenetic stimulation by reaching its innermost parts, like the hippocampus (Liu et al., 2012). Movement of the animal subject may incur twisting of the optical fiber which can potentially lead to breakage. This can be avoided with the use of a fiber-optic commutator (Klorig and Godwin, 2014). The fiber-optic commutator is a rotary joint that enables free movement of the test animal while minimizing torque and maintaining excellent light transmission. However, this type of system is limiting for the scope of *in vivo* optogenetic experiments since the animal is tethered to the optical fiber and subsequently to the external light source, as can be seen in Fig. 1(b).

On the other hand, wireless optogenetic systems like the one depicted in Fig. 2(a), consist of a device that is fully implantable (Han and Shin, 2020) or head-mounted (Kim et al., 2013; Emara et al., 2018) on the test subject as seen in Fig. 2(b), and is wirelessly controlled by using different communication protocols found in data exchange between mobile devices (Han and Shin, 2020; Mickle et al., 2019). The wireless optogenetic device integrates a light source and an implanted probe (Mickle et al., 2019; Park et al., 2015), typically a waveguide in the form of an optical fiber (Han and Shin, 2020; Emara et al., 2018), facilitating *in vivo* light delivery. Nevertheless, a remaining challenge for wireless optogenetic systems is the heating induced by the optoelectronic device causing tissue damage.

In both systems, the light sources are LEDs (Yang et al., 2020) or lasers (Park et al., 2019). Optogenetics benefit from the maturity and low cost of the LED technology. LED modulation is easily achieved at a millisecond scale with no need of complex driving electronics (Grossman et al., 2010) and at the same time LEDs are easily integratable.

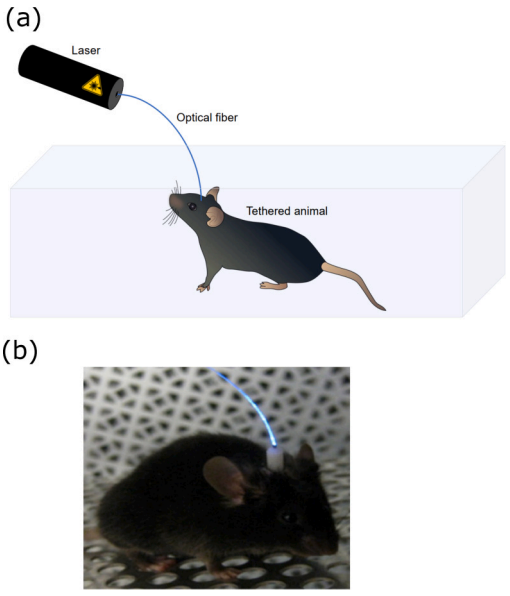

Fig. 1. (a) Schematic illustration of wired optogenetic systems. (b) Fiber-based wired system attached on the head of a rodent.

Source: Reproduced with permission (Gutierrez et al., 2011).

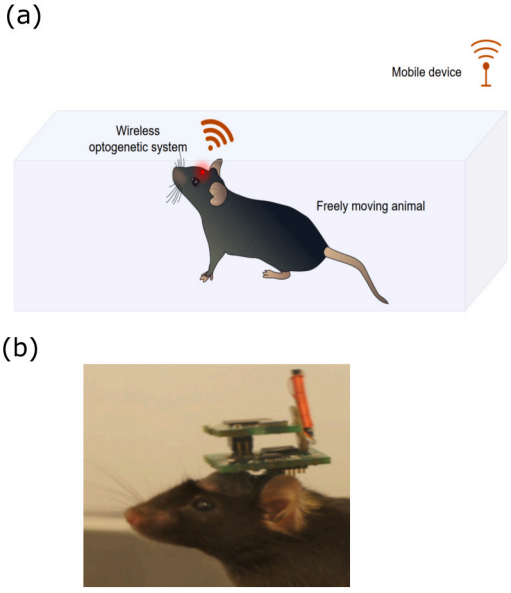

Fig. 2. (a) Schematic illustration of wireless optogenetic systems. (b) Wireless optogenetic system on a free-moving animal.
Source: Reproduced with permission (Wentz et al., 2011).

However, the somehow low output power as well as the low coupling efficiency with optical fibers compromise the overall system performance. The prospects are brighter for lasers as the optogenetic light source due to the higher output power and coupling compatibility with optical fibers. On the downside, laser technology is more expensive and also for the case of edge emitters integration is a more demanding task.

Regardless of the type of the connectivity of *in vivo* optogenetic systems, there seems to be a consensus in the adoption of the optical fiber as the bus for light delivery to the neuronal level. *In vivo* stimulation imposes a set of requirements as illustrated in Fig. 3, that must be addressed for efficient *in vivo* optogenetic stimulation through the use of optical fibers. We discuss these in the next section.

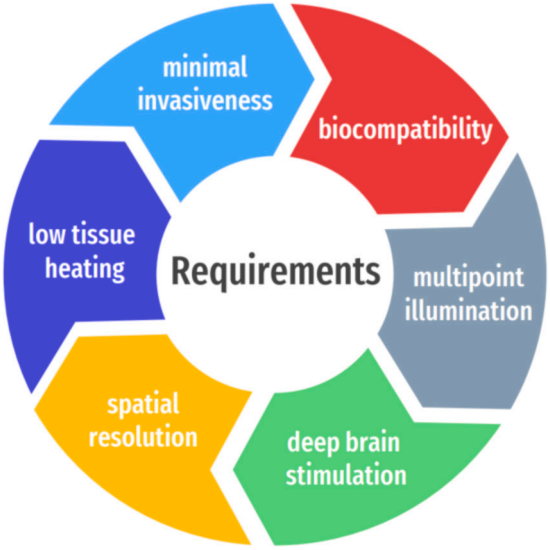

Fig. 3. Requirements for a fiber-based *in vivo* optogenetic system.

3. Requirements for *in vivo* fiber-based optogenetic stimulation

Light scattering and absorption in the brain hinder *in vivo* light delivery, reaching only superficial areas of the brain. Deep brain stimulation has been realized using two photon absorption (Packer et al., 2013) yet this solution is bulky instrumentation wise, and thus does not lend itself, as yet, for *in vivo* implementations. Instead, by inserting optical fibers into the brain, optogenetic stimulation is feasible.

The implanted optical fiber must be biocompatible in order to avoid inflammation reactions, especially in cases of chronic optogenetic stimulation. The optical fiber must be biocompatible with the brain both in terms of material and mechanical properties.

Diameter size of optical fibers is also a key parameter for minimizing tissue damage during their insertion and implantation in the brain since it was shown (Seymour and Kipke, 2007) that implants of a cross-section of a few hundred micrometers can cause excessive neuronal loss. However, simulation studies (Stujenske et al., 2015) have reported that optical fibers of smaller diameter have increased thermal effects near fiber tip, as can be observed in Fig. 4. Thus, there seems to be a trade-off between the diameter of the optical fiber and the induced thermal effects.

In vivo optogenetics must enable the investigation of neural circuit function with high spatial resolution. Single-cell stimulation, typically in the size range of a neuron soma, ~ 10 μm, can be achieved using a thinner core fiber. Stimulation of multiple neurons is also possible using an array grid of fibers (Xu et al., 2008), where a light beam is emitted in each core, resulting in optogenetic excitation of several brain regions. Arbitrary illumination patterns can be obtained by amplitude or phase modulation of an incident light beam onto a DMD or SLM device that is coupled to a fiber array (Farah et al., 2015). Indeed, these optoelectronic devices offer high refresh rate, enabling the study of fast neural circuit dynamics.

Optical fiber-based *in vivo* optogenetic stimulation must induce minimal tissue heating in order to avoid thermal damage of the neural tissue and consequent adverse changes in the overall brain function (Stujenske et al., 2015). Shin et al. (2016), have determined the required light power for neuronal activation and the maximum achievable depth that ensures minimal thermal effects. Lossless light coupling between the optical fiber and the light source is crucial for the effective photostimulation of neurons, since opsins require a minimum light irradiance level for their activation. Coupling losses lead to inefficient activation of opsins thus necessitating increased light power (Fan and Li, 2015) resulting in undesirable heating of the brain tissue.

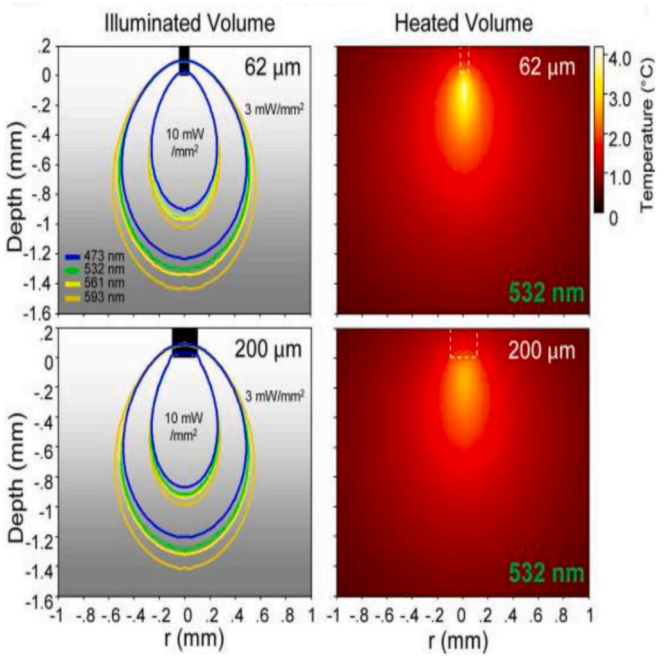

Fig. 4. Monte Carlo simulation of optical fibers with different diameters. It is clearly shown that the fiber of 200 μm in diameter has reduced thermal effects near its tip in comparison with the optical fiber of 62 μm.

Source: Reproduced with permission (Stujenske et al., 2015).

4. Fiber technologies

Optical fibers have been used extensively in multiple areas ranging from telecommunications (Willner, 2019) to biomedical engineering (Sarabi et al., 2021). The technological maturity of the optical fibers in these fields can be easily transitioned in other disciplines, such as optogenetics. Conventional optical fibers have been used in the past for neural photostimulation (Grosenick et al., 2015), but various optical fiber configurations, such as tapered fibers (Pisanello et al., 2017), fiber bundles and multicore fibers, have attracted attention. In view of the *in vivo* requirements outlined in the previous section, here we focus on the various geometries of optical fibers that are usually employed in *in vivo* optogenetic experiments.

4.1. Materials for optogenetic fibers

Often material biocompatibility is overlooked in favor of functionality in *in vivo* optogenetic experiments. It is obvious that for long term implantation, biocompatibility must be prioritized. Here we will address some basic materials aspects of optogenetic optical fibers. The interested reader may refer to Gierej et al. (2021) for an extensive review of biocompatible materials used for fabrication of optogenetic optical fibers.

One of the most common challenges for the fabrication of optogenetic fiber-based devices is material selection (Gierej et al., 2021; Shukla et al., 2019; Wu and Guo, 2021). Silica-based optical fibers have been widely used for *in vivo* optogenetic manipulation of neurons, since they are chemically inert and offer low optical losses. However the suitability of this kind of fibers is questionable for long-term implantation in the brain. Silica is a stiff material compared to brain tissue that can cause neuronal damage (Wang et al., 2018).

Optical fibers based on natural materials, such as cellulose thin films using raw natural cotton targets (Karoutsos et al., 2019), and synthetic materials (Gierej et al., 2021), e.g. hydrogels show improved biocompatibility. Wang et al. (2018) demonstrated a flexible and

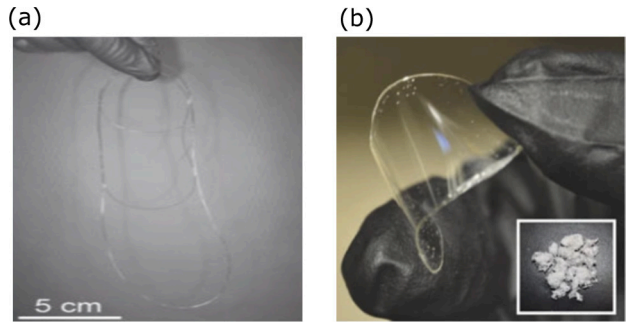

Fig. 5. Hydrogel optical fiber. Reproduced with permission (Choi et al., 2015), Copyright ©2015, John Wiley & sons. (b) PLLA flexible substrate used for the fabrication of optical fibers. Reproduced with permission (Nizamoglu et al., 2016), Copyright ©2016, Nature Publishing Group.

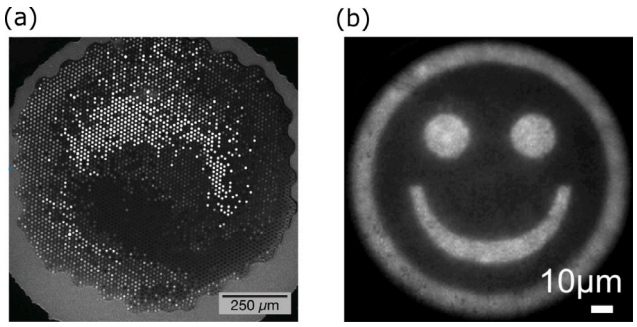

Fig. 7. (a) Cross-section SEM image of a fiber bundle. Reproduced with permission (Perkins et al., 2018) under CC by 4.0, Copyright ©2018, SPIE. (b) Arbitrary holographic illumination pattern transmitted through a fiber bundle. Reproduced with permission (Szabo et al., 2014), Copyright ©2014, Elsevier.

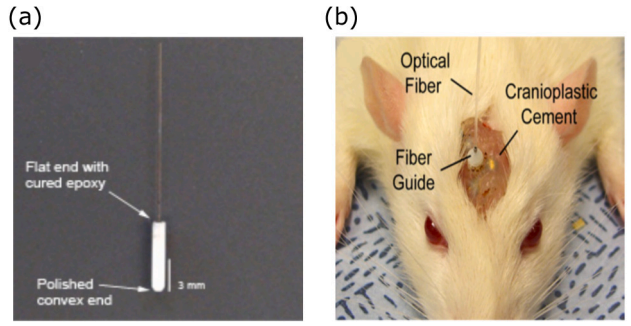

Fig. 6. (a) Implantable standard optical fiber for *in vivo* light delivery. Reproduced with permission (Sparta et al., 2012), Copyright ©2011, Nature Publishing Group. (b) Optical fiber implanted into the brain of a living animal. Reproduced with permission (Aravanis et al., 2007), Copyright ©2007, IOP Publishing Ltd.

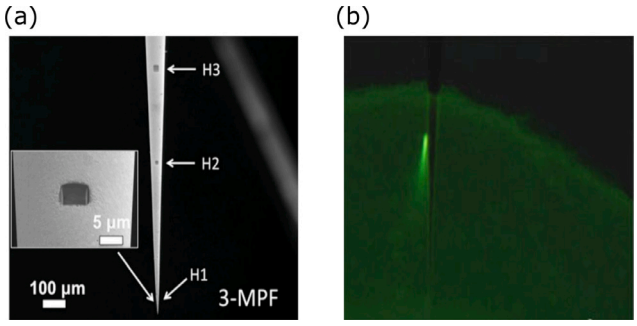

Fig. 8. (a) SEM image of a tapered fiber with three optical windows of a few micrometers in size. (b) Tapered fiber implanted into the brain emitting light by a specific optical window. Copyright ©2014, Elsevier.
Source: Reproduced with permission (Pisanello et al., 2014).

stretchable hydrogel optical fiber and reported optogenetic stimulation of neurons successfully in freely-behaving animals. Hydrogel optical fibers, shown in Fig. 5(a), are an appropriate biocompatible choice but their overall size should be decreased in order to minimize tissue damage. Fiber-based optogenetic devices can also take advantage of the flexibility and compactness of poly(L-lactic acid) (PLLA), shown in Fig. 5(b), for simultaneous light delivery and recording of brain activity (Fu et al., 2018).

4.2. Standard optical fibers

Several research groups (Aravanis et al., 2007; Sparta et al., 2012) have adopted standard optical fibers into their *in vivo* optogenetic experiments, with a typical diameter size of 50 μm to 200 μm and a step-index fiber geometry (Fig. 6(a)). The first demonstration of optical fiber technology for *in vivo* optogenetic stimulation was performed by Aravanis et al. (2007), where they utilized a multimode optical fiber of ∼ 200 μm in size, attached to the skull of an intact animal (Fig. 6(b)).

Illumination and readout of an *in vivo* optogenetic experiment can be carried out by using a single fiber probe. Pashaie and Falk (2012) used a single optical fiber for optical excitation and at the same time detection of neuronal activity via fluorescence signals.

However, Monte Carlo simulations (Dubois et al., 2018) have reported that single fibers are not able to stimulate a large volume of brain tissue, since increased light power is required in order to activate opsins which are located far away from the fiber tip. As a consequence, thermal effects are induced which may alter brain function.

4.3. Fiber bundles

Fiber bundles have been used successfully in the past for *in vivo* optogenetic stimulation in freely moving animals (Hayashi et al., 2012). A fiber bundle consists of several thousand fibers (Szabo et al., 2014) as can be seen in Fig. 7(a), based on silica (Orth et al., 2019; Murayama and Larkum, 2009) or polymer (Chang Liao et al., 2015) bundled together. This group of fibers forms a fiber bundle with a common end of a few millimeters in diameter (Farah et al., 2015). Fiber bundles enable deep brain optogenetic stimulation with high spatial specificity, since they are long enough to access brain areas at various depths (Kim et al., 2017).

The main advantage of this fiber-based technology is simultaneous illumination of multiple brain areas. Szabo et al. (2014) achieved targeted photostimulation of multiple neurons with high spatial resolution in freely-behaving animals by transmitting the reconstructed image of a holographic pattern (Fig. 7(b)), using a fiber bundle. Hence, fiber bundles can employ computer generated holography for the generation of arbitrary illumination patterns (Farah et al., 2015; Szabo et al., 2014). The obvious drawback of fiber bundles is their large diameter (Farah et al., 2015), that makes them unsuitable for chronical optogenetic implantation.

Apart from neural photostimulation, fiber bundles can be employed for fluorescence imaging of neuronal activity as demonstated by Szabo et al. (2014) who obtained fluorescence images of near-cellular resolution in rodents.

4.4. Tapered fibers

Extending the toolbox of fiber-based optogenetic devices, tapered fibers have recently gained a lot of interest for targeted neural photostimulation (Pisanello et al., 2014). By chemically or thermo-mechanically etching the tip of a standard optical fiber, the resulting fiber end has a size of a few hundred nanometers (Pisanello et al., 2017). Therefore, the tapered fiber is minimally invasive when it is

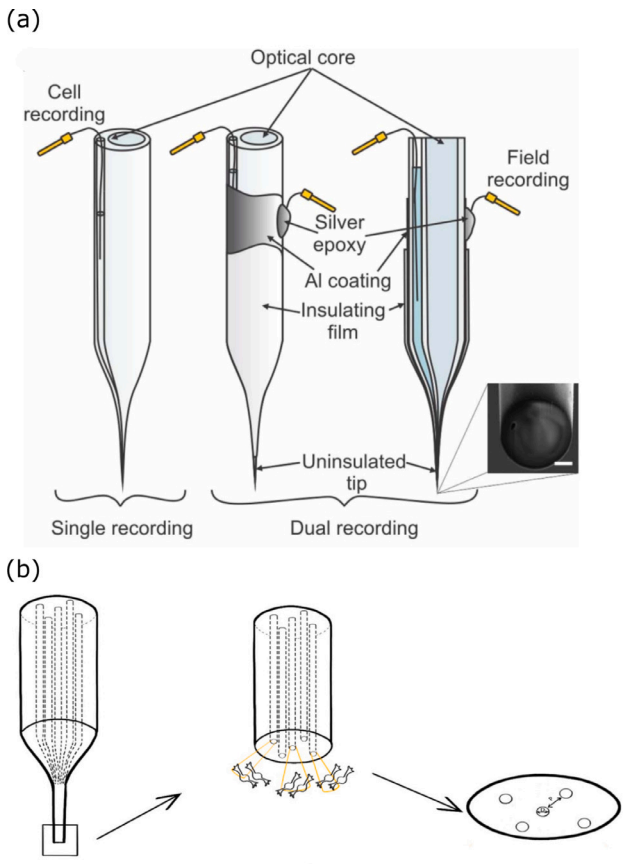

Fig. 9. (a) A hollow core for optogenetic stimulation and recording. Reproduced with permission (Dufour et al., 2013), Copyright ©2013, Public Library of Science. (b) A tapered multicore fiber for *in vivo* light delivery. Reproduced with permission (Mohit et al., 2021), Copyright ©2021, Elsevier.

implanted into the brain. Silica is often used for the fabrication of tapered fibers. A thin metal film covers the tapered area to prevent undesirable light emission (Pisanello et al., 2015). Optical windows where light escapes the fiber and stimulates targeted brain regions can be fabricated. The optical windows are a few micrometers in size and they are fabricated using Focused Ion Beam (FIB) milling (Pisanello et al., 2014) or direct laser writing (Rizzo et al., 2018). Multi-point illumination using tapered fibers is feasible by fabricating multiple optical windows along the fiber as shown in Fig. 8(a).

Tapered fibers enable dynamic and selective stimulation of light-sensitive neurons by simply changing the angle of the incident light coupled into the fiber. The input angle of light launched into the taper fiber enables different propagation modes and thus light is emitted at a particular optical window, as seen in Fig. 8(b), stimulating a specific brain area (Pisanello et al., 2018). By changing the numerical aperture of the tapered fiber, larger or smaller volumes of brain tissue are illuminated (Pisanello et al., 2017). The illuminated volume can be a few hundreds of micrometers extended up to a few millimeters corresponding to various depths in the brain.

Tapered fibers are multi-mode fibers and the propagation modes are easily affected by fiber impurities causing modal mixing (Pisanello et al., 2017). As such, light power is rearranged to other propagation modes and the spatial specificity is decreased to a large extent (Pisanello et al., 2018). Despite the functional versatility of silica based tapered fibers, their mechanical properties do not match brain tissue properties thus hindering long-term implantation.

5. Future prospects

More exotic types of optical fibers like hollow core fibers have been explored for *in vivo* optogenetic applications. In (LeChasseur et al., 2011), a dual-core fiber probe that consists of a graded-index core and a hollow core is used for parallel stimulation and recording of brain activity respectively. Dufour et al. (2013) employed a hollow core fiber for recording brain activity that was coated with aluminum, as shown in Fig. 9(a), to prevent optical losses. The tapered part of the probe was uncoated, so that it could be used for electrical recording.

It is anticipated that in the future apart from recording LeChasseur et al. (2011) the hollow core fibers will be used for *in vivo* optogenetic stimulation. It was previously demonstrated (Adamu et al., 2019) that hollow core fibers filled with gas can generate pulses ranging from deep-UV up to mid-IR. The versatility of wavelengths offered by the hollow core technology can potentially impact optogenetics with respect to the required opsins (Deisseroth, 2015).

Multicore fibers consist of some tens of cores with core diameter of the order of a few micrometers. Compared to fiber bundles they have small overall diameter and therefore are less invasive. Mohit et al. (2021), demonstrated a tapered multicore fiber of 20 μm in diameter, as shown in Fig. 9(b). They could steer the output beam by controlling the phase and the wavelength of the input signals coupled to the tapered multicore fiber. In particular, each core of the fiber is treated as an optical antenna and as a result an antenna array is formed at the fiber tip. By changing the phase of each optical antenna, the direction of the light beam changes based on the interfering and superpositioning phenomena. The tapered multicore fiber can generate spots of 5 μm and thus it is able to stimulate single neurons.

6. Conclusion

The use of optical fibers for *in vivo* optogenetics, regardless of the implementation type i.e. wired or wireless, is the most efficient way to deliver light deep into the brain. In this paper we reviewed the light delivery strategies for *in vivo* deep brain optogenetic stimulation that employ optical fiber-based devices. The most commonly-used optical fibers (single core fibers, fiber bundles and tapered fibers) have been discussed with regard to the set of requirements defined for an *in vivo* optogenetic system. It is anticipated that the optical fiber optogenetics literature will be soon enriched with accounts of hollow core and multicore fibers.

CRediT authorship contribution statement

Anastasios Tsakas: Writing – original draft. **Christos Tselios:** Writing – original draft. **Dimitris Ampeliotis:** Writing – original draft. **Christina (Tanya) Politi:** Writing – original draft. **Dimitris Alexandropoulos:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Adamu, A.I., Habib, M.S., Petersen, C.R., Lopez, J.E.A., Zhou, B., Schülzgen, A., Bache, M., Amezcua-Correa, R., Bang, O., Markos, C., 2019. Deep-UV to mid-IR supercontinuum generation driven by mid-IR ultrashort pulses in a gas-filled hollow-core fiber. Sci. Rep. 9 (1), 1–9.

Amunts, K., Knoll, A.C., Lippert, T., Pennartz, C.M., Ryvlin, P., Destexhe, A., Jirsa, V.K., D'Angelo, E., Bjaalie, J.G., 2019. The human brain project—Synergy between neuroscience, computing, informatics, and brain-inspired technologies. PLoS Biol. 17 (7), e3000344.

Aravanis, A.M., Wang, L.-P., Zhang, F., Meltzer, L.A., Mogri, M.Z., Schneider, M.B., Deisseroth, K., 2007. An optical neural interface: in vivo control of rodent motor cortex with integrated fiberoptic and optogenetic technology. J. Neural Eng. 4 (3), S143.

Berger, A., 2003. How does it work?: Positron emission tomography. Br. Med. J. 326 (7404), 1449.

Berndt, A., Deisseroth, K., 2015. Expanding the optogenetics toolkit. Science 349 (6248), 590–591.

Biasiucci, A., Franceschiello, B., Murray, M.M., 2019. Electroencephalography. Curr. Biol. 29 (3), R80–R85.

Carter, M.E., de Lecea, L., 2011. Optogenetic investigation of neural circuits in vivo. Trends Mol. Med. 17 (4), 197–206.

Chang Liao, M.-L., De Boer, T.P., Mutoh, H., Raad, N., Richter, C., Wagner, E., Downie, B.R., Unsöld, B., Arooj, I., Streckfuss-Bömeke, K., et al., 2015. Sensing cardiac electrical activity with a cardiac myocyte–targeted optogenetic voltage indicator. Circ. Res. 117 (5), 401–412.

Choi, M., Humar, M., Kim, S., Yun, S.-H., 2015. Step-index optical fiber made of biocompatible hydrogels. Adv. Mater. 27 (27), 4081–4086.

Das, R., Moradi, F., Heidari, H., 2020. Biointegrated and wirelessly powered implantable brain devices: A review. IEEE Trans. Biomed. Circuits Syst. 14 (2), 343–358.

Deisseroth, K., 2015. Optogenetics: 10 years of microbial opsins in neuroscience. Nature neuroscience 18 (9), 1213–1225.

Deisseroth, K., Feng, G., Majewska, A.K., Miesenböck, G., Ting, A., Schnitzer, M.J., 2006. Next-generation optical technologies for illuminating genetically targeted brain circuits. J. Neurosci. 26 (41), 10380–10386.

Dubois, A., Chiang, C.-C., Smekens, F., Jan, S., Cuplov, V., Palfi, S., Chuang, K.-S., Senova, S., Pain, F., 2018. Optical and thermal simulations for the design of optodes for minimally invasive optogenetics stimulation or photomodulation of deep and large cortical areas in non-human primate brain. J. Neural Eng. 15 (6), 065004.

Dufour, S., Lavertu, G., Dufour-Beauséjour, S., Juneau-Fecteau, A., Calakos, N., Deschênes, M., Vallée, R., De Koninck, Y., 2013. A multimodal micro-optrode combining field and single unit recording, multispectral detection and photolabeling capabilities. PLoS One 8 (2), e57703.

Emara, M.S., Pisanello, M., Sileo, L., De Vittorio, M., Pisanello, F., 2018. A wireless head-mountable device with tapered optical fiber-coupled laser diode for light delivery in deep brain regions. IEEE Trans. Biomed. Eng. 66 (7), 1996–2009.

Fan, B., Li, W., 2015. Miniaturized optogenetic neural implants: a review. Lab Chip 15 (19), 3838–3855.

Farah, N., Levinsky, A., Brosh, I., Kahn, I., Shoham, S., 2015. Holographic fiber bundle system for patterned optogenetic activation of large-scale neuronal networks. Neurophotonics 2 (4), 045002.

Fenno, L., Yizhar, O., Deisseroth, K., 2011. The development and application of optogenetics. Annu. Rev. Neurosci. 34, 389–412.

Fu, R., Luo, W., Nazempour, R., Tan, D., Ding, H., Zhang, K., Yin, L., Guan, J., Sheng, X., 2018. Implantable and biodegradable poly (l-lactic acid) fibers for optical neural interfaces. Adv. Opt. Mater. 6 (3), 1700941.

Gierej, A., Geernaert, T., Van Vlierberghe, S., Dubruel, P., Thienpont, H., Berghmans, F., 2021. Challenges in the fabrication of biodegradable and implantable optical fibers for biomedical applications. Materials 14 (8), 1972.

Goncalves, S., Ribeiro, J., Silva, A., Costa, R., Correia, J., 2017. Design and manufacturing challenges of optogenetic neural interfaces: a review. J. Neural Eng. 14 (4), 041001.

Grosenick, L., Marshel, J.H., Deisseroth, K., 2015. Closed-loop and activity-guided optogenetic control. Neuron 86 (1), 106–139.

Grossman, N., Poher, V., Grubb, M.S., Kennedy, G.T., Nikolic, K., McGovern, B., Palmini, R.B., Gong, Z., Drakakis, E.M., Neil, M.A., et al., 2010. Multi-site optical excitation using ChR2 and micro-LED array. J. Neural Eng. 7 (1), 016004.

Gutierrez, D.V., Mark, M.D., Masseck, O., Maejima, T., Kuckelsberg, D., Hyde, R.A., Krause, M., Kruse, W., Herlitze, S., 2011. Optogenetic control of motor coordination by Gi/o protein-coupled vertebrate rhodopsin in cerebellar Purkinje cells. J. Biol. Chem. 286 (29), 25848–25858.

Han, S., Shin, G., 2020. Biodegradable optical fiber in a soft optoelectronic device for wireless optogenetic applications. Coatings 10 (12), 1153.

Hayashi, Y., Tagawa, Y., Yawata, S., Nakanishi, S., Funabiki, K., 2012. Spatio-temporal control of neural activity in vivo using fluorescence microendoscopy. Eur. J. Neurosci. 36 (6), 2722–2732.

Insel, T.R., Landis, S.C., Collins, F.S., 2013. The NIH brain initiative. Science 340 (6133), 687–688.

Ji, N., Freeman, J., Smith, S.L., 2016. Technologies for imaging neural activity in large volumes. Nature Neurosci. 19 (9), 1154–1164.

Karoutsos, V., Raptis, P., Bagiokis, E., Lorusso, A., Perrone, A., Vainos, N.A., 2019. High optical quality cellulose thin films grown from raw natural cotton by pulsed laser deposition. Appl. Phys. A 125 (4), 1–11.

Kim, M., Hong, J., Kim, J., Shin, H.-j., 2017. Fiber bundle-based integrated platform for wide-field fluorescence imaging and patterned optical stimulation for modulation of vasoconstriction in the deep brain of a living animal. Biomed. Opt. Express 8 (6), 2781–2795.

Kim, T.-i., McCall, J.G., Jung, Y.H., Huang, X., Siuda, E.R., Li, Y., Song, J., Song, Y.M., Pao, H.A., Kim, R.-H., et al., 2013. Injectable, cellular-scale optoelectronics with applications for wireless optogenetics. Science 340 (6129), 211–216.

Klorig, D.C., Godwin, D.W., 2014. A magnetic rotary optical fiber connector for optogenetic experiments in freely moving animals. J. Neurosci. Methods 227, 132–139.

Kravitz, A.V., Kreitzer, A.C., 2011. Optogenetic manipulation of neural circuitry in vivo. Curr. Opin. Neurobiol. 21 (3), 433–439.

Kriegeskorte, N., Mur, M., Bandettini, P.A., 2008. Representational similarity analysis-connecting the branches of systems neuroscience. Front. Syst. Neurosci. 2, 4.

LeChasseur, Y., Dufour, S., Lavertu, G., Bories, C., Deschênes, M., Vallée, R., De Koninck, Y., 2011. A microprobe for parallel optical and electrical recordings from single neurons in vivo. Nature Methods 8 (4), 319–325.

Liu, X., Ramirez, S., Pang, P.T., Puryear, C.B., Govindarajan, A., Deisseroth, K., Tonegawa, S., 2012. Optogenetic stimulation of a hippocampal engram activates fear memory recall. Nature 484 (7394), 381–385.

Matthews, P.M., Jezzard, P., 2004. Functional magnetic resonance imaging. J. Neurol. Neurosurg. Psychiatry 75 (1), 6–12.

Mickle, A.D., Won, S.M., Noh, K.N., Yoon, J., Meacham, K.W., Xue, Y., McIlvried, L.A., Copits, B.A., Samineni, V.K., Crawford, K.E., et al., 2019. A wireless closed-loop system for optogenetic peripheral neuromodulation. Nature 565 (7739), 361–365.

Mohit, F., Ricciardi, A., Cusano, A., Cutolo, A., 2021. Tapered multicore optical fiber probe for optogenetics. Results Opt. 100109.

Murayama, M., Larkum, M.E., 2009. In vivo dendritic calcium imaging with a fiberoptic periscope system. Nat. Protoc. 4 (10), 1551–1559.

Nizamoglu, S., Gather, M.C., Humar, M., Choi, M., Kim, S., Kim, K.S., Hahn, S.K., Scarcelli, G., Randolph, M., Redmond, R.W., et al., 2016. Bioabsorbable polymer optical waveguides for deep-tissue photomedicine. Nature Commun. 7 (1), 1–7.

Orth, A., Ploschner, M., Wilson, E., Maksymov, I., Gibson, B., 2019. Optical fiber bundles: Ultra-slim light field imaging probes. Sci. Adv. 5 (4), eaav1555.

Packer, A.M., Roska, B., Häusser, M., 2013. Targeting neurons and photons for optogenetics. Nature Neurosci. 16 (7), 805–815.

Papagiakoumou, E., 2013. Optical developments for optogenetics. Biol. Cell 105 (10), 443–464.

Park, S.I., Brenner, D.S., Shin, G., Morgan, C.D., Copits, B.A., Chung, H.U., Pullen, M.Y., Noh, K.N., Davidson, S., Oh, S.J., et al., 2015. Soft, stretchable, fully implantable miniaturized optoelectronic systems for wireless optogenetics. Nature Biotechnol. 33 (12), 1280–1286.

Park, S., Loke, G., Fink, Y., Anikeeva, P., 2019. Flexible fiber-based optoelectronics for neural interfaces. Chem. Soc. Rev. 48 (6), 1826–1852.

Pashaie, R., Falk, R., 2012. Single optical fiber probe for fluorescence detection and optogenetic stimulation. IEEE Trans. Biomed. Eng. 60 (2), 268–280.

Perkins, L.N., Devor, A., Gardner, T.J., Boas, D.A., 2018. Extracting individual neural activity recorded through splayed optical microfibers. Neurophotonics 5 (4), 045009.

Pisanello, F., Mandelbaum, G., Pisanello, M., Oldenburg, I.A., Sileo, L., Markowitz, J.E., Peterson, R.E., Della Patria, A., Haynes, T.M., Emara, M.S., Spagnolo, B., Datta, S.R., De Vittorio, M., Sabatini, B.L., 2017. Dynamic illumination of spatially restricted or large brain volumes via a single tapered optical fiber. Nature Neurosci. 20 (8), 1180–1188. http://dx.doi.org/10.1038/nn.4591.

Pisanello, M., Pisano, F., Sileo, L., Maglie, E., Bellistri, E., Spagnolo, B., Mandelbaum, G., Sabatini, B.L., De Vittorio, M., Pisanello, F., 2018. Tailoring light delivery for optogenetics by modal demultiplexing in tapered optical fibers. Sci. Rep. 8 (1), 4467. http://dx.doi.org/10.1038/s41598-018-22790-z.

Pisanello, F., Sileo, L., Oldenburg, I.A., Pisanello, M., Martiradonna, L., Assad, J.A., Sabatini, B.L., De Vittorio, M., 2014. Multipoint-emitting optical fibers for spatially addressable in vivo optogenetics. Neuron 82 (6), 1245–1254.

Pisanello, F., Sileo, L., Pisanello, M., Della Patria, A., De Vittorio, M., Oldenburg, I.A., Sabatini, B.L., Assad, J.A., 2015. Nanomachined tapered optical fibers for in vivo optogenetics. In: 2015 IEEE 15th International Conference on Nanotechnology. IEEE-NANO, IEEE, pp. 1528–1531.

Rizzo, A., Lemma, E.D., Pisano, F., Pisanello, M., Sileo, L., De Vittorio, M., Pisanello, F., 2018. Laser micromachining of tapered optical fibers for spatially selective control of neural activity. Microelectron. Eng. 192, 88–95. http://dx.doi.org/10.1016/j.mee.2018.02.010.

Ronzitti, E., Ventalon, C., Canepari, M., Forget, B.C., Papagiakoumou, E., Emiliani, V., 2017. Recent advances in patterned photostimulation for optogenetics. J. Opt. 19 (11), 113001.

Sarabi, M.R., Jiang, N., Ozturk, E., Yetisen, A.K., Tasoglu, S., 2021. Biomed. opt. fibers. Lab Chip 21 (4), 627–640.

Seymour, J.P., Kipke, D.R., 2007. Neural probe design for reduced tissue encapsulation in CNS. Biomaterials 28 (25), 3594–3607.

Shin, Y., Yoo, M., Kim, H.-S., Nam, S.-K., Kim, H.-I., Lee, S.-K., Kim, S., Kwon, H.-S., 2016. Characterization of fiber-optic light delivery and light-induced temperature changes in a rodent brain for precise optogenetic neuromodulation. Biomed. Opt. Express 7 (11), 4450–4471.

Shukla, S., Kushwaha, C.S., Guner, T., Demir, M.M., 2019. Chemically modified optical fibers in advanced technology: An overview. Opt. Laser Technol. 115, 404–432.

Siuda, E.R., Copits, B.A., Schmidt, M.J., Baird, M.A., Al-Hasani, R., Planer, W.J., Funderburk, S.C., McCall, J.G., Gereau IV, R.W., Bruchas, M.R., 2015. Spatiotemporal control of opioid signaling and behavior. Neuron 86 (4), 923–935.

Sparta, D.R., Stamatakis, A.M., Phillips, J.L., Hovelsø, N., Van Zessen, R., Stuber, G.D., 2012. Construction of implantable optical fibers for long-term optogenetic manipulation of neural circuits. Nat. Protoc. 7 (1), 12–23.

Stujenske, J.M., Spellman, T., Gordon, J.A., 2015. Modeling the spatiotemporal dynamics of light and heat propagation for in vivo optogenetics. Cell Rep. 12 (3), 525–534.

Szabo, V., Ventalon, C., De Sars, V., Bradley, J., Emiliani, V., 2014. Spatially selective holographic photoactivation and functional fluorescence imaging in freely behaving mice with a fiberscope. Neuron 84 (6), 1157–1169.

Vázquez-Guardado, A., Yang, Y., Bandodkar, A.J., Rogers, J.A., 2020. Recent advances in neurotechnologies with broad potential for neuroscience research. Nature Neurosci. 23 (12), 1522–1536.

Vlasov, K., Van Dort, C.J., Solt, K., 2018. Optogenetics and chemogenetics. Methods Enzymol. 603, 181–196.

Wang, L., Zhong, C., Ke, D., Ye, F., Tu, J., Wang, L., Lu, Y., 2018. Ultrasoft and highly stretchable hydrogel optical fibers for in vivo optogenetic modulations. Adv. Opt. Mater. 6 (16), 1800427.

Wentz, C.T., Bernstein, J.G., Monahan, P., Guerra, A., Rodriguez, A., Boyden, E.S., 2011. A wirelessly powered and controlled device for optical neural control of freely-behaving animals. J. Neural Eng. 8 (4), 046021.

Willner, A., 2019. Optical Fiber Telecommunications, Vol. 11. Academic Press.

Wu, X., Guo, Q., 2021. Bioresorbable photonics: Materials, devices and applications. In: Photonics, Vol. 8. (7), Multidisciplinary Digital Publishing Institute, p. 235.

Xu, H., Davitt, K.M., Dong, W., Song, Y.-K., Patterson III, W.R., Aizenman, C.D., Nurmikko, A.V., 2008. Combining multicore imaging fiber with matrix addressable blue/green LED arrays for spatiotemporal photonic excitation at cellular level. IEEE J. Sel. Top. Quantum Electron. 14 (1), 167–170.

Yang, L., Lee, K., Villagracia, J., Masmanidis, S.C., 2020. Open source silicon microprobes for high throughput neural recording. J. Neural Eng. 17 (1), 016036.

Yizhar, O., Fenno, L.E., Davidson, T.J., Mogri, M., Deisseroth, K., 2011. Optogenetics in neural systems. Neuron 71 (1), 9–34.