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Perspective: Implantable optical systems for neuroscience research in behaving animal models—Current approaches and future directions

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Compared to many other organ systems, the fundamental means by which the central and peripheral nervous systems connect and communicate remain poorly understood. The overall aging of populations in the developed world increases the significance of degenerative and mental health disorders, thereby motivating research into the development of effective therapies, founded on basic insights into the working principles of the brain. Progress in these endeavors can be accelerated by the development of optical tools and techniques capable of tracking and evoking changes in cell-level activity and in system-level neuronal interactions, both in the brain and in the peripherals, especially in unrestricted, freely behaving subjects. This perspective highlights the recent emergence of active optoelectronic platforms that leverage genetically targeted stimulators, inhibitors, and sensors and their vital role in brain research and therapy development. The technological advances that underpin the latest, most powerful device embodiments include miniaturized, highly efficient semiconductor light emitters and detectors that can operate chronically in a fully implantable, battery-free, wireless manner. Recent progress in this field enables a range of powerful modes of operation, with key advantages over traditional systems.
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INTRODUCTION

Genetically targeted techniques for optically stimulating or inhibiting the activity of neurons and neural circuits (e.g., optogenetics) are increasingly popular as means for manipulating cell specific signals in complex biological systems to uncover relationships to behavioral patterns. Here, light activated ion channels, or opsins, are packaged and delivered to cells using viral vectors, thereby allowing researchers to use light to control cellular activity. While most commonly used in rodent studies, this approach is rapidly expanding to other models, ranging from worms and fish to non-human primates.[1] Such capabilities now allow probing of neural circuits, from the cellular level to large networks,[2] a task vastly more difficult or impossible with nonspecific tools such as electrical stimulators or electrode arrays.[3] Genetically targeted methods to record neural activity are also prevalent in the form of fluorescent calcium[4] indicators and, more recently, voltage sensitive dyes.[5] The temporal resolution available for stimulation and detection continue to increase, suggesting future capabilities in real-time, all-optical probing of neural circuits.[6,7]

While the underlying genetic toolbox has grown exponentially over the past 10 years, the optoelectronic systems necessary to deliver optical stimuli to activate opsins or to record fluorescence

signals in behaving animals has improved more slowly. Even now, most labs surgically implant small fiber optic components, each borrowed from the telecommunications industry, directly into the brain and cement them in place, creating bulky headpieces that are time consuming to make and are prone to failure. During experimental sessions, these fibers physically couple to externally located lasers as means to introduce light into the targeted tissue, much as in the original published report on optogenetics.[8] For the powerful underlying genetic sensitization methods to realize their full experimental potential, they must be accompanied with more sophisticated capabilities for light delivery and detection. Here, advances in photonics and optics are critically important. Technologies with the proper set of properties and operational modes will not only accelerate progress in neuroscience research, but they may also provide the basis for unusual routes for treating of various diseases.[9] Specifically, studies in *ex vivo* preparations using techniques[10] such as confocal and two photon[11] methods for stimulating and recording fluorescence must evolve to those that allow investigations of awake animals during natural behaviors in realistic settings and in social groups.[12]

TECHNOLOGY CONSIDERATIONS FOR APPLICATIONS IN FREELY MOVING SUBJECTS

Common experimental environments for small animal studies range from open fields[13] (typically $1\,\text{m} \times 1\,\text{m}$) to enclosures that present food or drugs based on rewarding tasks (as small as $15 \times 15\,\text{cm}$).[14] Behavior in these arenas can be analyzed with respect to subject location, mobility, feeding behavior, and other queues.[15] Setups that test motor coordination are also common, wherein the subjects balance on small diameter, rotating rods,[16] or navigate through water mazes.[17] While these studies generate useful data on their own, combining them with optogenetics would allow researchers to probe the underlying neural activity or circuity in these contexts. Conventional approaches require physical connections between the subject and laser and/or electrical systems with fiber or cable management hardware (e.g., commutators or automated actuators) that minimize the effect of the tethers on mobility.[18] This mode of operation prohibits use of a range of relevant obstacles and useful enclosures, or they must be heavily modified to accommodate the cables. In addition, to reduce the impact of this equipment on behavioral outcomes, the animals must be habituated to the hardware for some length of time before experiments are possible,[19] and even in such cases, residual behavioral impacts may remain. Such requirements add time and cost to each experiment, and they increase the occurrence of mechanical failures in the fibers/cables and/or headpieces. Tethering animals to equipment also limits experimental design options to single animal setups to avoid tangling of wires/fiber optics from multiple subjects and to suppress aggressive behavior of cage-mates that can occur toward exposed devices and connections.[20] Cages and enclosures with complex, three dimensional obstacles also cannot be used, thereby restricting the scope of experimental designs.

Figure 1 outlines the most common categories of neuroscience approaches for delivering and recording optical signals in freely moving animals. Optical fiber-based systems are the most widely used due to their simplicity and their compatibility with a wide choice of light sources and optoelectronic components. A schematic illustration appears in Fig. 1(a). Light emitting diodes (LEDs)[21] and lasers with wavelengths specific to the excitable opsin or fluorescent indicator are popular choices for most labs. The main disadvantages are in limited control over the location of light delivery/collection and in measurement artifacts that result from motion of the fibers. In addition, micromotions and mechanical constraints associated with the fibers can lead to tissue damage and poor chronic stability.[22] These and other considerations motivate the development of systems that incorporate light sources, in some cases along with recording equipment, on stages that mount on the heads of the subjects, as in Fig. 1(b). These embodiments can support multiple optical or electrical elements, as needed when addressing multiple points with optical stimuli.[23,24]

Ultimately, approaches that eliminate the tether entirely, as illustrated in Fig. 1(c), are preferred. Such devices feature a wireless transmitter and a control system, typically powered by an electrochemical supply such as a battery or large energy harvesting head stage.[25] Advantages in freedom of motion, however, are balanced by the addition of weight and bulk to the head of the animal, both

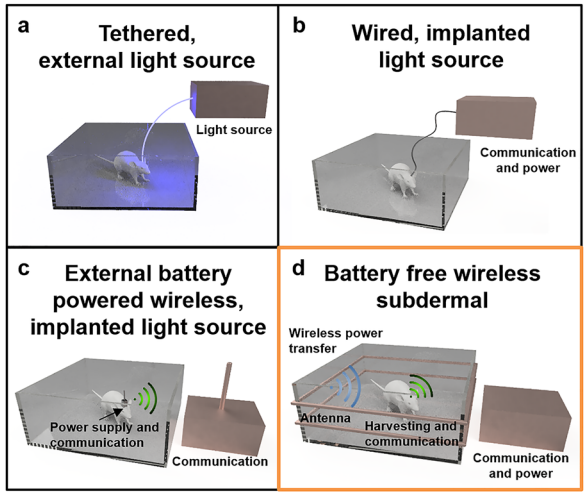

FIG. 1. Schematic illustrations of options in neuroscience tools designed for freely moving subjects. (a) Tethered, fiber optic interface to an external light source for optical stimulus and recording. (b) Tethered, wired interface to an implanted light source, with options in multichannel recording and stimulation. (c) External, battery-powered wireless system with an implanted light source. (d) Battery-free subdermal implant.

mostly associated with the power source, which can lead to other types of alterations in behavior and constraints in experimental possibilities.

The ideal is in fully wireless platforms that operate in a battery-free fashion via energy harvesting from external sources. A schematic illustration of such a setup that uses radio frequency power transfer is in Fig. 1(d). These devices can be fabricated in highly miniaturized form factors with ability for full subdermal implantation. Here, subjects with and without implants are virtually indistinguishable in terms of their appearance, behavior, and health. The result allows for a fundamentally expanded range of experimental paradigms, with completely naturalistic patterns of behavior.

TETHERED APPROACHES

As outlined in Fig. 1(a), delivery of light into various regions of the brain can be accomplished with standard optical fibers traditionally used for telecommunications. Here, illumination is mostly controlled by the material properties and geometry of the fiber (e.g., numerical aperture, NA) and by the characteristics of light coupled into the system. Control over the pattern of the optical output is, however, limited. Efforts toward light delivery designed to the requirements of optogenetics applications are shown in Figs. 2(a) and 2(b).[22,26] A technique displayed in Fig. 2(a), where the output of a tapered fiber changes depending on the angle of incidence for coupling into the fiber, represents an attempt to control the illumination volume and, therefore, the area of activation of the genetically targeted cells.[26,27] Here, various cell groups in the motor cortex can be targeted and scanned in the sagittal orientation in a fashion such that dorsal neurons can be excluded from stimulation.[26]

Multi-functionality in the fiber itself can be achieved through advanced processes in fiber drawing. One example includes a conducting polymer and open channels in a fiber to allow for electrical recording and optogenetic stimulation in conjunction with delivery of liquid chemical or biological agents such as receptor antagonists.[28] Such schemes can also yield fibers with sizes and moduli that are superior to those of standard silica-based fibers. However, trade-offs in optical capabilities such as transmission losses and nonlinear attenuation over the usable wavelength range are necessary to support multi-functionality. An example of such a system is shown in Fig. 2(b).

Other examples of fiber-based platforms include systems that stimulate and record fluorescence for genetically targeted calcium indicators[29] and, most recently, fluorescent voltage reporters.[5] In such cases, standard optical fibers with core diameters of up to 400 μm[30] and fiber bundles with multi-site stimulation and recording capabilities have been utilized.[31] The bulk and size of such probes can, however, limit deployment in dense arrays for probing multiple brain regions.

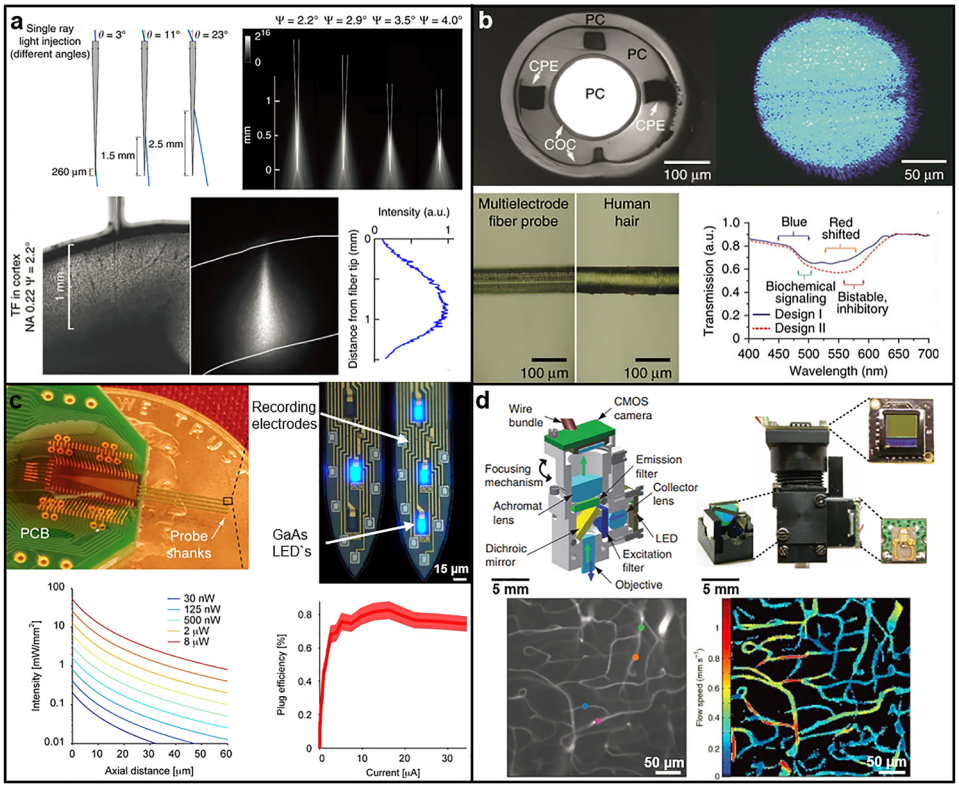

FIG. 2. Tethered stimulation and recording approaches. (a) Tapered optical fiber for delivery of spatially defined optical stimulus, controlled by the input coupling angle of incidence. Reprinted with permission from Pisanello *et al.*, Nat. Neurosci. **20**(8), 1180 (2017). Copyright 2017 Springer Nature. (b) Multimodal optical fiber for delivery of optical, fluidic, and electrical stimuli. Reprinted with permission from Canales *et al.*, Nat. Biotechnol. **33**(3), 277 (2015). Copyright 2015 Springer Nature. (c) Stiff, monolithically defined probe arrays for delivery of optical stimulus at spatially defined sites for single unit optogenetic activation and electrical recording. Reproduced with permission from Wu *et al.*, Neuron **88**(6), 1136 (2015). Copyright 2015 Elsevier. (d) Miniaturized endoscope for calcium indicator imaging in behaving animals. Reprinted with permission from Ghosh *et al.*, Nat. Methods **8**(10), 871 (2011). Copyright 2011 Springer Nature.

Embodiments that enable optogenetic stimulation and recording with near cellular resolution generally feature micro-structured needles with recording and illumination capabilities. Figure 2(c) shows an example, where injectable needles fabricated on GaAs substrates offer the ability to structure light emitting diodes (LEDs) and electrical recording sites in a small space for high spatial resolution.[32] The low efficiencies of the LEDs in these cases, however, limit the emission power levels that can be achieved without adverse effects (>1.5 μW corresponding to 1 mW/mm^{-2} and 2 °C increase in local temperature), such as damage and unintentional alteration of cellular activity associated with the thermal load. The result restricts activation distances to less than 100 μm with standard opsins, making broad illumination of larger brain areas difficult. Electrical connection to the probe also requires a large head stage along with cables to manage the high channel count (in this embodiment, 7 electrodes per probe with 4 probes combined in one implant).

High resolution recordings of dynamic changes in neural circuits are of specific interest. Optical methods that exploit genetically modified calcium indicators allow visualization of cellular level activity. Solutions that bring these capabilities, usually found only in microscope setups that require the head to be mechanically fixed, to freely moving animals are possible with miniaturized camera setups. An example is in Fig. 2(d). Here, a camera, light source, and filter system are mounted into a head stage that couples to a chronically implanted lens (0.5–2 mm) for recordings in moving animals. Insights into circuit dynamics enabled by such hardware are important, but the behavior of the animal changes due to the large weight (2.5-3 g) of the head stage, which, not including cable connections, outweighs the heads of small rodents.[33,34]

MINIATURIZED LIGHT SOURCES AND OPPORTUNITIES FOR INJECTABLE AND IMPLANTABLE DEVICES

Means to circumvent drawbacks intrinsic to tethered approaches include the use of optical upconverters that can be activated by tissue-penetrating light in the infrared[35] and of highly miniaturized, light-powered microelectronic recording devices.[36] Substantial recent research is in injectable, thin flexible filaments designed to carry microscale optoelectronic components, including highly efficient microscale inorganic LEDs (μ-ILED's) [Fig. 3(a)] that result in negligible increases in temperature (>2 °C) for optogenetic stimulation[37,38] with intensities (up to 50 mW/mm^{-2}) and modulation schemes (duty cycles ranging from 1% to 100% ON/OFF ratio) used in standard fiber-based systems. The advantages are in small dimensions, mechanical flexible designs,[39] and the ability to exploit power from external energy sources for completely tether-free operation.[40] The sizes and shapes of these technologies can also be further tailored to facilitate implantation, to minimize damage to the brain tissue, and to accommodate anatomical considerations, ultimately enhancing experimental outcomes and improving the degree of illumination control.

Examples of illumination profiles that can be achieved with such μ-ILED-based probes, with comparisons to fiber-based systems, are in Fig. 3(b). The profiles, shown herein as fluorescent solutions, include bidirectional μ-ILED setups enabled by transparent substrates and arrays of μ-ILEDs, as well as unidirectional illumination with off-the-shelf μ-ILED's components and polyimide supports.[40]

The side-oriented illumination patterns that result from μ-ILEDs, compared to the downward-oriented situation with fiber optics, are advantageous for certain brain geometries, especially small oblong shaped regions, such as the basolateral amygdala (BLA) in the deep brain.[41] Successful implantation of such devices has also been demonstrated in various other brain regions such as the ventral tegmental area (VTA)[42] or the nucleus accumbens (NAc).[43] A numerical simulation appears

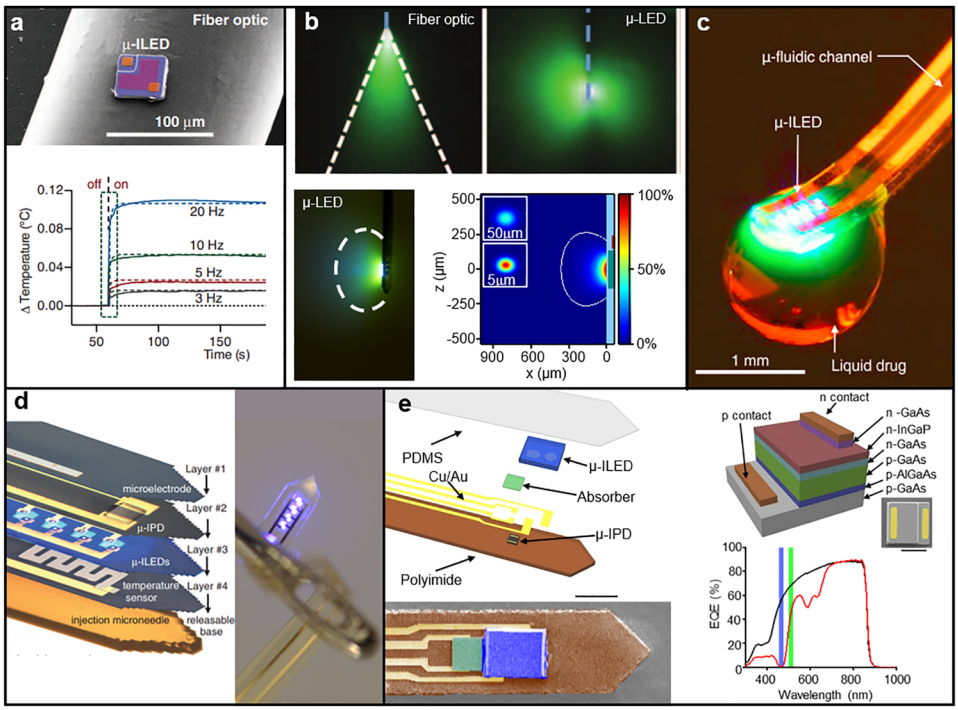

FIG. 3. Miniaturized light sources and detectors for wireless implantable neuroscience tools. (a) Thermal behavior of a μ-ILED in the brain tissue. Reprinted with permission from Kim *et al.*, Science **340**(6129), 211 (2013). Copyright 2013 AAAS. (b) Emission profiles of μ-ILED devices and fiber-based devices.[41] (c) Multimodal injectable platforms with capabilities in optogenetic stimulation and fluid delivery. Reproduced with permission from Jeong *et al.*, Cell **162**(3), 662 (2015). Copyright 2015 Elsevier. (d) Multimodal injectable platforms with capabilities in electrical recording, photometry, optogenetic stimulation, and temperature sensing. Reprinted with permission from Kim *et al.*, Science **340**(6129), 211 (2013). Copyright 2013 AAAS. (e) Photometry probe designed for genetically targeted calcium indicator recording.[41]

in Fig. 3(b) in the lower bottom panel. Here, absorption and scattering of blue light in the brain tissue (475 nm, a wavelength used to activate channelrhodopsins such as ChR2) result in an activation radius of ~300 μm. Illumination volumes can be tuned by controlling the sizes of the μ-ILEDs, their spatial distributions, and the input power, which provides significantly enhanced versatility over fiber-based alternatives.

Additional benefits of the heterogeneous construction of these platforms include the ability to integrate microfluidic channels for drug delivery. An injectable device with this type of multifunctionality is displayed in Fig. 3(c). This system allows the injection of up to four drugs from separate channels which, together with independently controlled optogenetic stimulation, affords opportunities in spatiotemporal delivery of small molecule agents, peptides, and viral vectors as well as light. The ultraminiaturized form factor also provides advantages over conventional cannula systems which have significantly larger displacement volumes, along with correspondingly higher levels of trauma to brain tissue (cannula of 500 μm diameter and optofluidic probe of 80 μm thickness and 500 μm width).[42]

This basic approach to the probe design also allows for a wide range of choices in sensors and actuators. The example with four layers of sensors in Fig. 3(d) supports investigations that require electrical, photonic, and temperature signatures.[40] The photometric setup is of particular interest because it provides the opportunity to observe fluorescent signals which has the potential to support all optical control of neural circuits. A photometry system based on integration of a μ-ILED and a photodetector with a filter to block the stimulation wavelength allows real-time recording of fluorescent signals, as shown in Fig. 3(e).[41] The system offers performance comparable to that of traditional fiber-based systems, with options in wireless operation as discussed next.

WIRELESS APPROACHES

Technologies to miniaturize light sources and detectors and to integrate them on thin, flexible supports provide the basis for highly miniaturized wireless platforms that are compatible with the physical demands of freely moving animals. Examples of such systems are shown in Fig. 4. Here, the application as well as the requirements in stimulation and recording capabilities determine the choice for wireless strategies.

Systems that require high operating powers typically rely on externalized elements such as batteries. As an example, the fluidic delivery system shown in Fig. 4(a) features pumps that are activated by heaters that demand significant power for operation (up to 200 mW) to trigger thermally expandable polymer layers. The pumps terminate in a microfluidic probe coupled with an optogenetic stimulator that uses μ-ILEDs [injectable probe shown in Fig. 3(c)]. The system allows for remote, wirelessly triggered delivery of fluids from four separate reservoirs. The system weight, including a protective housing for the electronics, batteries, and pumps, is 1.85 g. Time-locked delivery of pharmacological agents without the need to handle the animal is a distinct advantage over tethered systems, allowing researchers to generate a continuous data stream from the baseline through manipulation in the same experiment. Coupled with the ability to separately and conjunctively activate opsins, this type of tool offers advanced capabilities in creating experimental paradigms that enable a facile dissection of neural circuits.

For platforms that require less power, such as those that provide only optogenetic functionality, miniaturized energy harvesting circuits can be considered. An example of such a device is displayed in Fig. 4(b).[43] Here the entire system uses a flexible printed circuit board (polyimide substrate with top and bottom copper layers with parylene or butyl polymer encapsulation), with a size, thickness, and set of mechanical properties that allow for fully subdermal implantation. Thin film materials and conformal deposition processes yield efficient fluid barriers to enable device lifetimes comparable to those of small rodents. The resulting devices seamlessly integrate with the test subject, such that after recovery from the surgery, the animals are indistinguishable from their control counterparts and studies with multiple animals in social contexts are possible without impact on behavior. Examples of such experiments are shown in the lower panel of Fig. 4(b), where a clear place preference is developed in animals that express ChR2 in the mesolimbic dopaminergic (DA) terminals of the nucleus accumbens. Related device platforms explore variants in power supply such as those based

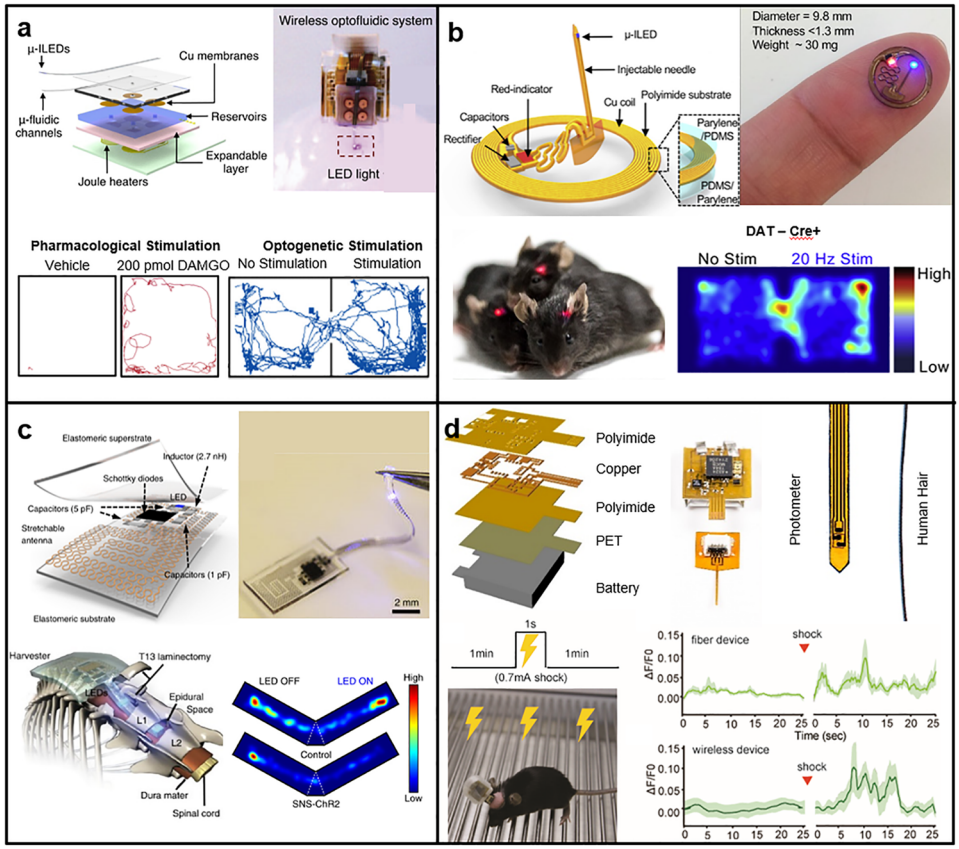

FIG. 4. Miniaturized wireless optogenetic stimulation and recording tools. (a) Battery-powered multimodal system for fluid delivery and optogenetic stimulation. Reproduced with permission from Jeong *et al.*, Cell **162**(3), 662 (2015). Copyright 2015 Elsevier. (b) Subdermal battery-free tool for chronic optogenetic stimulation in the brain. Reproduced with permission from Shin *et al.*, Neuron **93**(3), 509 (2017). Copyright 2015 Elsevier. (c) Soft, subdermal optogenetic device for use with the spinal cord. Reprinted with permission from Park *et al.*, Nat. Biotechnol. **33**(12), 1280 (2015). Copyright 2015 Springer Nature. (d) Battery-powered, two-part system for wireless recording of genetically targeted calcium indicators.[41]

on far field multichannel energy harvesting[44] and simultaneous harvesting of RF and photovoltaic power.[45] Other embodiments allow deployment in the spine, as in Fig. 4(c),[46] where a flexible tail positions μ-ILEDs to stimulate the spinal cord. When used in subjects expressing SNS-ChR2, a robust place aversion is also evident. For all passive and subdermal devices for optogenetic stimulus, the weight is considerably lower than that of active devices powered by electrochemical power sources and is typically well below 0.1 g. These results highlight the engineering design versatility of these integration approaches, as well as the utility of fully wireless and subdermal devices.[47] Deployment of conventional fiber platforms in highly mobile areas such as the spine would require stiffening with dental cement, thereby drastically limiting the mobility of the animal and affecting its behavior.

Another step toward fully wireless, all-optical interrogation of neuronal circuits is shown in Fig. 4(d), where a miniaturized, battery-powered device with a weight <0.5 g allows for the measurement of calcium transients from genetically targeted calcium indicators (GCaMP6) in a fully wireless fashion.[41] Validation experiments featuring activity monitoring in the BLA during a foot shock experiment over a cohort of animals show good correlation with traditional methods based on fiber photometry. The performance of the systems, such as the signal to noise ratio, is comparable to those of commercially available fiber-based systems. The fully implantable platform, however, has potential to be more sensitive because it omits losses in the optical path associated with the traditional approach. Development of improved filters to suppress the excitation light, optimization of the miniaturized photodiodes, and introduction of micro-optical elements are likely to yield further improvements.

ADVANTAGES OF ULTRAMINIATURIZED, WIRELESS DEVICES

Demonstrations of multiple, fully wireless stimulation and recording tools with capabilities that supersede those of traditional fiber-based approaches point toward a future with devices that are subdermally implanted with diverse capabilities in all optical interrogation of circuits in the brain and peripherals. The elimination of physical tethers not only improves the convenience in measurement but also, potentially, increases reliability in even basic behavior studies. Such advantages of wireless systems appear prominently in the context of studies using photometry, where the impact of the tether in fiber based photometry measurements leads to significant differences in animal mobility and overall activity.[41] The results in Fig. 5(a) show that animals in the context of social experiments, as well as behavior in larger arenas, are significantly affected by the tether.[41] Specifically, social interaction time and the number of social bouts decrease for fiber tethered animals and wild type subjects in a home cage environment, as compared to untethered, wireless implanted animals. Experiments to determine overall anxiety levels and mobility in larger experimental arenas, such as an open field box, show even more pronounced differences. Total activity is statistically compromised in fiber-tethered animals, and the time spent in the center zone is decreased, a metric for anxiety. Furthermore, mobility is impeded even in a task that is locally confined to a small area such as the rotarod assay. Here, tethered subjects perform worse than those with battery powered devices [Fig. 5(b)]. An additional benefit of the integrated approach is that implantable probes can be fabricated with a smaller footprint, resulting in less damage to the surrounding tissue [Fig. 5(b), right hand panel], yielding cleaner behavioral results and higher fidelity recordings.

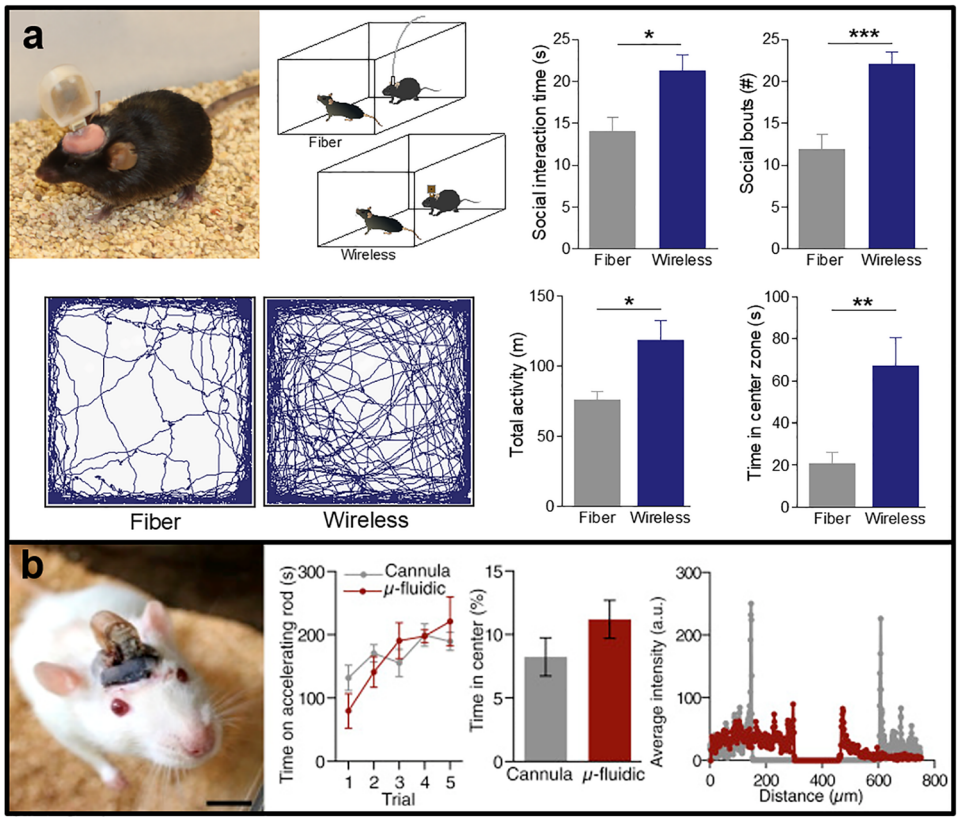

FIG. 5. Behavioral comparisons of animals implanted with wireless, implantable systems and with tethered optical fiber-based systems. (a) Direct comparison of wireless and tethered photometry systems via experimental data that define overall mobility, social interactions and anxiety in mice.[41] (b) Experimental characterization of rats implanted with wireless multimodal fluidic and optogenetic stimulation systems with analysis of tissue damage. Reproduced with permission from Jeong *et al.*, Cell **162**(3), 662 (2015). Copyright 2015 Elsevier.

Collectively, wireless solutions clearly minimize the experimental impact of the devices on behavior and therefore provide more naturalistic responses appropriate to the experimental design.[48] Trends toward fully wireless systems are also reflected in the increasing adoption of commercially available devices. Companies that offer optogenetic stimulation in a wireless system with varying system capabilities, weight, and bulk include Triangle biosystems, Inc. IS series (system weight 7.8 g, external head stage 31 × 25 × 12 mm, wireless communication and power transfer, indefinite operation), Plexon, Inc. Helios (system weight 2.8 g, infrared connection, 20 × 15 × 20 mm external head stage, battery powered hours of operation), Amuza, Inc. Teleopt series (system weight 1.4–3 g, infrared connection, 13 × 18 × 7 mm–18 × 22 × 8 cm external head stage, battery powered hours of operation), and Neurolux, Inc. (system weight 30 mg, wireless communication and power transfer, as small as 10 × 5 × 1.3 mm subdermal implants, indefinite operation). It is also likely that other animal models will similarly benefit from wireless embodiments, particularly for animals that move substantially in three dimensions,[49] such as fish[50] and bats,[51] and for those where the weights and lengths of the cables become increasingly problematic.[52]

NEAR AND DISTANT FUTURE CHALLENGES

The current rate of development for fully implanted wireless optoelectronic systems suggests ever more complex systems for multichannel stimulation in spatially separate brain regions and for high speed recording. Wireless power transfer approaches that can replace electrochemical power storage in even power demanding systems have recently been demonstrated *ex vivo*,[53] indicating the possibility to eventually remove tethers and batteries from most neuroscience tools. This progression will ultimately yield devices with all optical modes of interrogation and control and assessment of neuronal systems. The constituent materials and optical components will offer completely stable operation over timeframes that match the biological lifetimes of the organisms, where continuous energy harvesting, supply, and communication schemes will provide means to extract the gathered data in fully implantable devices. Opportunities to expand the active materials to those based on organic or nanoscale materials have potential to increase options in illumination geometries to large areas on contoured surfaces and to scale current devices used in small animal models to those suitable for non-human primates and ultimately to human applications. Here light sources such as flexible organic LEDs[54] appear interesting,[55] particularly when paired with unusual ways to deploy these platforms in minimally invasive embodiments. Insights gained from the use of these and other classes of devices summarized in this article will eventually lead to important breakthroughs in uncovering the working principles of the brain and to precise human machine interfaces, advanced insights into behavior, and ultimately therapeutic tools to solve some of the most challenging problems related to advanced healthcare.

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