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# Implantable, wireless device platforms for neuroscience research

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## Abstract

Recently developed classes of ultraminiaturized wireless devices provide powerful capabilities in neuroscience research, as implantable light sources for simulation/inhibition via optogenetics, as integrated microfluidic systems for programmed pharmacological delivery and as multimodal sensors for physiological measurements. These platforms leverage basic advances in biocompatible materials, semiconductor device designs and systems engineering concepts to afford modes of operation that are qualitatively distinct from those of conventional approaches that tether animals to external hardware by means of optical fibers, electrical cables and/or fluidic tubing. Neuroscience studies that exploit the unique features of these technologies enable insights into neural function through targeted stimulation, inhibition and recording, with spatially and genetically precise manipulation of neural circuit activity. Experimental possibilities include studies in naturalistic, three dimensional environments, investigations of pair-wise or group related social interactions and many other scenarios of interest that cannot be addressed using traditional hardware.

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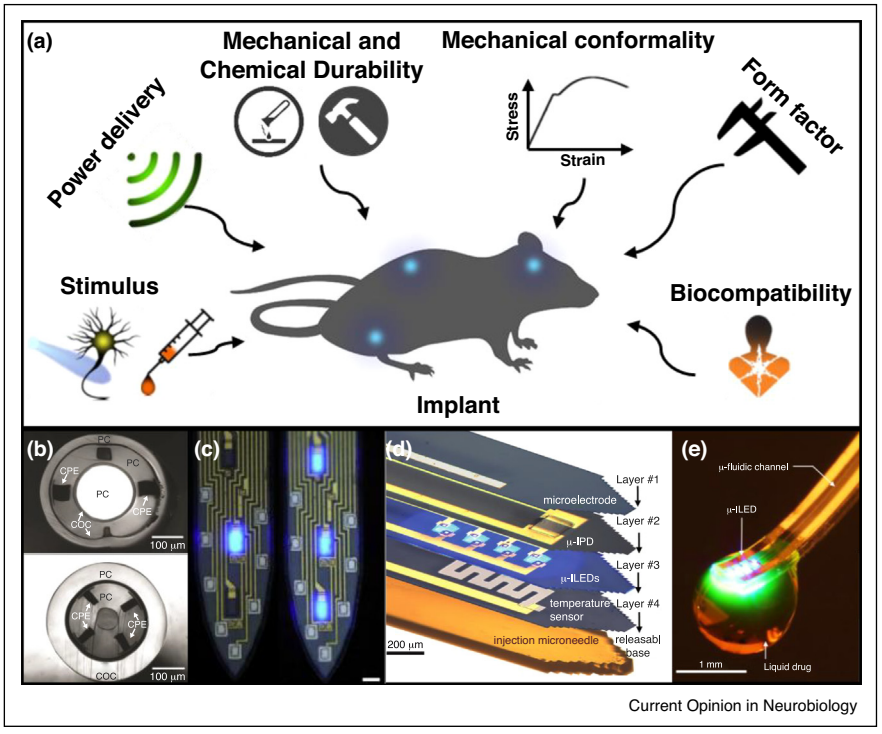
## Introduction

Uncovering the foundational working principles of the brain and the peripheral nervous system represent scientific grand challenges, with deep intellectual significance in academic research as well as profound practical value in human healthcare. Here, the advent of genetically targeted neuroscience techniques such as optogenetics via light sensitive ion channels [1,2] and photometry via fluorescent indicators of calcium [3–5] represent recent breakthrough developments of critical importance in this context. The insights already gained by implementation of these methodologies with conventional technologies are numerous; further progress will be accelerated by the development of advanced technologies for delivering optical and pharmacological stimuli and for recording relevant responses [6].

Conventional means for delivering and/or capturing light from targeted regions in behaving animals use optical fibers inserted with stereotactic apparatus and held in place via surgical glues, cements, sutures and external fixtures [7–9]. Pharmacological delivery and electrical recording occur in conceptually similar modes, but where plastic tubes and metal wires, respectively, replace the optical fibers [10]. The stiff, high moduli materials used for these systems are, however, fundamentally mismatched with the soft, compliant tissues of the brain and peripheral nerves. Micromotions induced by forces delivered through the associated hardware [11,12] together with those that arise from natural, biological movements can lead to degradation at the biotic/abiotic interface through cellular damage and glial scar formation [13]. The physical tethers as well as heavy battery powered wireless hardware also impose strict limitations on behavioral tests [14], as they prevent experiments that involve social interactions or activities in naturalistic environments with three dimensional obstacles. In addition, the tethers unavoidably affect the animals by limiting their motion and altering their behaviors in ways that can be difficult to quantify, thereby frustrating experimental reproducibility and clouding interpretation of data collected in certain classes of studies.

Emerging technologies enabled by interdisciplinary advances in materials science, optoelectronic devices, system engineering and mechanics design offer some compelling options in this context. Some key system attributes appear in Figure 1a. In all cases, an important goal is for miniaturized, fully implantable platforms with wireless capabilities and battery-free operation, to avoid the limitations that characterize conventional approaches, as outlined above [15]. Biocompatibility at the level of both the chemistry and the mechanics is essential to allow for stable, minimally invasive function within the challenging set of conditions that exist inside the animal and around its environment [16]. Of critical importance for the former is mechanical compliance with and conformal contact to the targeted tissues as the basis of a stable

**Figure 1**




**(a)** Schematic illustration of key considerations in technologies for neuroscience research. Examples of emerging tools. **(b)** Multifunctional fiber with electrical, optical and fluidic interfaces [31]. **(c)** Silicon shank with electrical and optical interfaces [32]. **(d)** Exploded-view images of a flexible probe with electrical, optical (emission and detection) thermal interfaces [34]. **(e)** Soft probe with optical and fluidic interfaces [35•].

bio-interface [17]. Highly mobile, time-dynamic tissues intrinsic to many parts of the peripheral nervous system [18] give rise to difficulties in integration that are even more daunting than those associated with the brain. In all cases, minimizing size and weight is an essential engineering consideration [19].

## Injectable, multifunctional platforms

Recent engineering developments greatly expand the scope of capabilities in neural interfaces. Platforms based on optical fibers as simple waveguides to transport light for optical stimulation [7] have evolved to multimodal probes for delivery of light, fluid and electrical current [20–23], sometimes with *in situ* recording and computing capabilities [24,25]. Other notable advances include syringe injectable electronics that unfold in target tissue to record electrical signals [26], ultra-thin organic transistor arrays for *in situ* myoelectric signal recording of optogenetically evoked spikes in muscles [27,28] and multifunctional electrodes for recordings in non-human primates [29] and wireless ultrasonic powered electrical devices for electromyogram and electroneurogram measurements [30].

Successful animal behavioral experiments have been reported using multicore fibers shown in Figure 1b in which a core waveguide is surrounded by fluidic channels and recording electrodes [31]. Another example is in Figure 1c, where optical stimulation occurs via a light emitting diode (LED) monolithically integrated on a silicon platform that also supports electrodes for electrical recordings in the style of a conventional Michigan probe [32]. Traditional wireless hardware has some utility in such cases, but major disadvantages follow from complex connections, undesirable mechanics, large sizes and weights [25,33], resulting in requirements for externally mounted head stages that can be cumbersome for small animal models. Monolithically integrated structures that combine diverse classes of materials in optimized mechanics layouts represent qualitatively differentiated types of technology. Here, entire optoelectronic systems with cellular-scale components can be configured as thin, flexible, injectable probes. Figure 1d shows such a miniaturized collection of devices, including a precision temperature sensor to monitor thermal load, microscale inorganic LEDs (μ-ILEDs) to enable optical stimulation, a micro photodiode to allow for photometry and a micro electrode to perform electrical recording. The entire system has lateral dimensions of 300 μm and uses a thin (20 μm) polyimide support. The cross sectional size and bending stiffness are significantly smaller than those of optical fibers [34]. Another example is in Figure 1e, where a collection of soft, microfluidic channels couple with μ-ILEDs to allow combined

pharmacological delivery (up to four different liquid agents) and optogenetic illumination with a single device [35•]. Such platforms follow from advanced concepts for materials growth and epitaxial liftoff [36], lithographic device processing for miniaturized, high-performance components, deterministic assembly methods for heterogeneous integration [37], and hard/soft mechanics designs for flexible/stretchable properties [38]. Efficient heat dissipation from μ-ILEDs, which follows from their large surface area to volume ratios and small thermal mass, is critically important for their safe operation in the brain or adjacent to peripheral nerves [34].

## Strategies in power supply

In nearly all cases, means for power supply are among the most challenging aspects for implementing these types of systems in small animal models. Approaches based on electrochemical energy storage, such as batteries and supercapacitors, consume significant space, they are heavy and often involve toxic materials, and they offer limited operational lifetimes [39]. Reported examples include devices that incorporate signal processing capabilities [24] as well as high data rate wireless transmission subsystems [40] and thermally initiated microfluidic pumps [35•], all supported by externally attached electronics and battery packs [41]. For prolonged operation, detachable modules (size $> 1.5\ cm^2$ and weight $> 1$ g) [42] allow the battery to be removed for recharging. Particularly for small animal models, weight becomes a primary concern, where even 1 g can be problematic for mice.

Wireless power transfer schemes implemented with miniaturized circuitry and specialized antenna designs can circumvent these limitations. Here, sufficient power can be generated to operate μ-ILEDs, microfluidic pumps and other demanding components, indefinitely throughout regions of interest in home cages (typically $20 \times 30$ cm for mice and $25 \times 40$ cm for rats) and other experimental assays [43]. Table 1 compares features of recently reported approaches. Far field energy transfer involves electromagnetic waves, typically with frequencies between 420 MHz and 2.4 GHz [44], that leave the confinement of the transmission antenna to enable power delivery across large distances, with operation that can be enhanced by use of real-time tracking systems [45•]. Disadvantages include efficiencies that depend strongly on relative orientations of the antenna pairs, interferences and standing waves that occur due to reflections from environmental obstacles and absorption associated with metal components, water or moisture. The latter effects can be detrimental to systems that are fully implanted into the body [46] and they limit practical operating ranges to 0.1–3 m. Electromagnetic absorption results in heating of the tissue, thereby limiting the total power that can be used without adverse consequences [47], representative specific absorption rate (SAR) values for far field powered devices can be found in Table 1. Resulting SAR strongly varies with system efficiency which is specifically problematic for miniaturized devices [48]. To circumvent these disadvantages, hybrid solutions that combine far field RF power transfer with solar cells and/or local energy storage can be attractive [49]. Other strategies use containment of the RF field operated at 1.5 GHz in a machined aluminum resonant cavity designed to selectively couple the field into the test subject. The result offers a self-tracking effect that reduces the field distribution fluctuations and ambient absorption of traditional far field systems, but is only efficient in close proximity with the cavity [50•].

An alternative uses magnetic resonant coupling [51,52]. Here, a loop antenna wrapped around the test area forms an oscillating magnetic field that can be harnessed by miniaturized receiver coils [53]. In this way, transfer of significant power (~5–10 mW) across cage sizes relevant for small animal models allow miniaturized device dimensions with supporting RF transmission hardware that is both compact and efficient. In comparison to far field systems, the same power can be harvested with a reduction in overall device size and SAR [54] (Table 1) and greatly reduced dependence on orientation and

**Table 1**

**Summary of options in power supply**

| | Battery powered [35•,39,41] | Battery free Far field — 1–2.7 GHz [45•,50•,55••] | Battery free mixed — Solar + Far field [49] | Battery free near field resonant magnetic coupling 13.56 MHz [56••] |
|---|---|---|---|---|
| Weight | <1.8 g | 16–33 mg | ~70 mg | ~30 mg |
| Embodiment | External | Subdermal | External | Subdermal |
| Available power | <50 mW | ~3–5 mW | ~3–5 mW | ~5–10 mW |
| Power source setup | Recharge needed for continuous operation | Complex primary antenna setup | Complex antenna and light setup | Simple, versatile primary antenna setup |
| Operational distance | Depending on wireless communication method <3 m | 0.1–3 m | 0.1–3 m | 0.1–1 m |
| Electromagnetic impact | None | High (SAR 6150 [48]-69 [55••] mW/kg) | Medium (SAR ~20 mW/kg [49]) | Low (SAR~ <20 mW/kg [54]) |

reflection. For example, a typical miniaturized single channel far field system might occupy an area of 9–10 $mm^2$ [55••], dominated by the antenna, while magnetic resonant coupling can be supported using a coil with an area of only 1–2 $mm^2$ [56••]. Additionally, the inductance of the coil defines the device geometry in a way that yields operation independent of dielectric environment to enable a wide range of design options without the need for extensive optimization of antenna configuration [57].

## Wireless systems for optogenetic studies of the brain

The most recent generation of wireless devices for optogenetics represents a significant advance over prior work in terms of form factor, weight, biocompatibility and chronic implantability. Optimized antenna designs in the RF regime allow for efficient transfer of energy to power highly miniaturized light sources [55••], in platforms that can be subdermally implanted. As illustrated in Figure 2a, a typical device can be injected into the brain of a small animal model with minimal impact on the host due to small size (5.4 × 4.3 mm with thickness of 0.7 mm) biocompatible encapsulation and stretchable implantable filament with biodegradable polymer support for mechanical support during surgery (width, length and thickness of 0.5 mm, 3.5 mm and 0.1 mm). The device dimensions of the harvester sub-system allow its complete subdermal implantation, thereby resulting in minimal effects on the animal after recovery. Advanced platforms of this type also feature multimodal operation as shown in Figure 2a [45•]. Here, two distinct RF frequencies (2.3 and 2.7 GHz) allow for independent control over blue and green light sources, were chosen to be spectrally separated to for independent optogenetic stimulation and inhibition [58].

Related embodiments provide means to illuminate spatially distinct sites for advanced interrogation of neural circuits. The miniaturized antenna uses in this case parallel capacitive coupling of adjacent serpentine wires in the overall layout, thereby reducing the antenna area by 100-fold compared to traditional designs. Experimental demonstrations show robust place aversion and preference with spatially and optically separated stimulation of the ventral and dorsal regions of the nucleus accumbens shell. Figure 2b shows a similarly miniaturized device (9.8 mm in diameter and maximum thickness of 1.3 mm, with injectable filament of maximum thickness 75 μm) [56••]. As in the previous case, complete implantation is possible, with stable operation for up to 1-year. Successful biological studies include real-time place preference in animals that express dopaminergic terminals in the nucleus accumbens. The commercial availability of μ-ILEDs for these purposes with various emission wavelengths enables use of this platform with most opsins [2] and the near field magnetic coupling based power transfer facilitates easy experimental setup with a variety of test enclosures.

A different, but related device formed using hand-wound coils exploits resonant cavity designs, as described previously, to supply high field densities as displayed in Figure 2c [50•]. The use of such devices is limited to custom-designed experimental areas that can be difficult to adapt for varied experimental paradigms. Published demonstrations include stimulation of the motor cortex via optical illumination of the right premotor cortex in mice expressing Thy1-ChR2-EYFP to yield an increase in circling locomotion compared to wild type control animals.

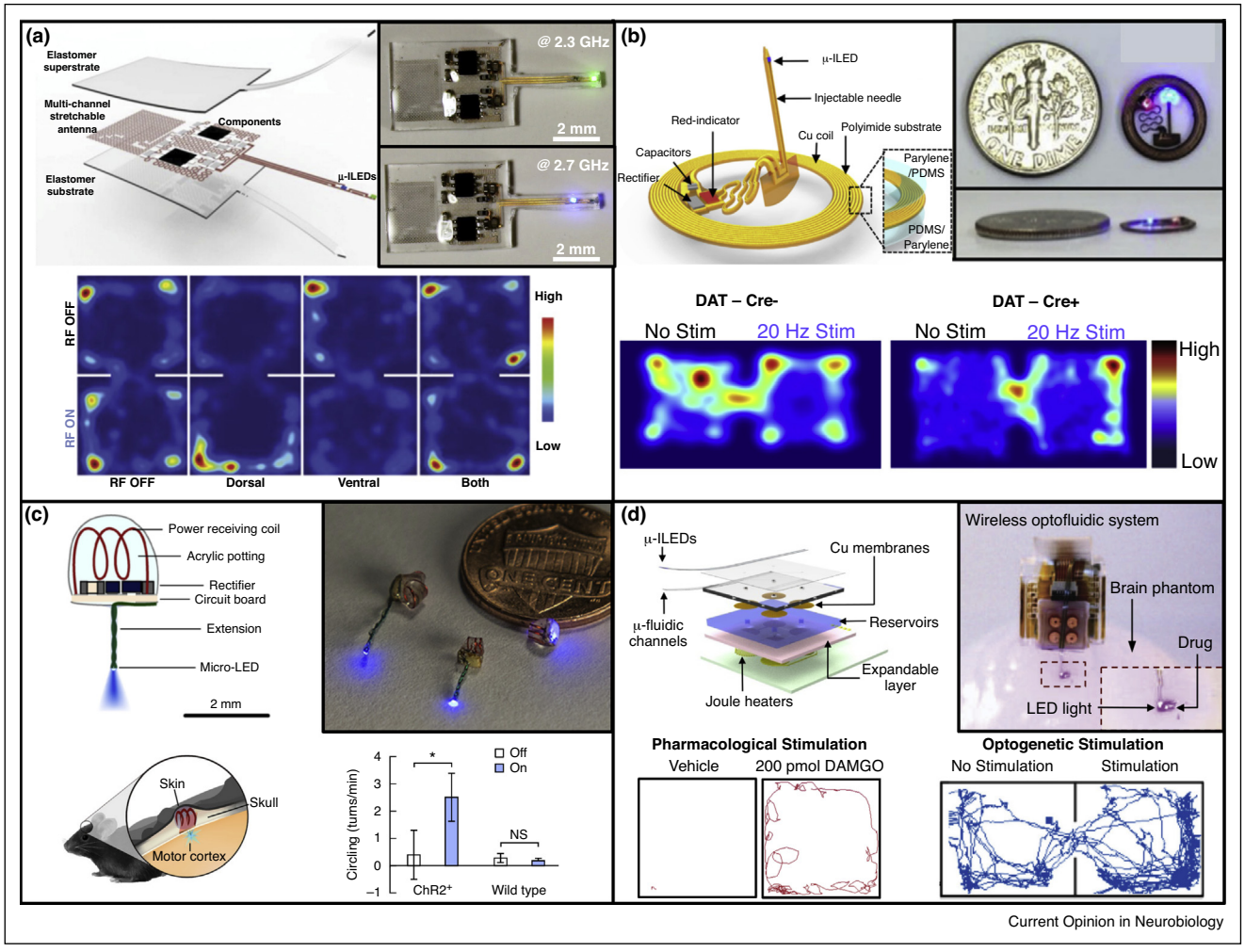
Another complementary capability in stimulation and analysis of neural circuitry involves delivery of liquid drugs [35•] in a time locked and highly localized fashion, without tethers and combined with options in optogenetic activation and viral vector delivery. Figure 2d shows a wireless device for simultaneous, and independently controlled, optical and fluidic delivery (up to four different drugs, separately) with demonstration of drug induced rotational locomotion as well as real time place preference via optical stimulation. This technology has relevance in other contexts as well as, the alteration of gene expression at multiple time points without the need for disruptive handling of animals or surgery, with straightforward control of within-subject studies.

## Wireless systems for optogenetic studies of peripheral nerves

Applications of optogenetics also offer promise for dissecting neural circuits of the spinal cord and peripheral nervous system [59,60], with additional potential relevance in the reduction of pain [61], stimulation of paralyzed muscles [62] and treatment of cardiovascular dysfunction [63]. As with the brain, technologies for chronic studies depend critically on materials biocompatibility, and non-invasive mechanical interfaces with soft and highly sensitive tissues. The adaptation of conventional optical fiber approaches is particularly problematic for these applications [64]. Here, miniaturized, wireless soft devices are highly beneficial because they provide a platform with minimal impact on soft targets [30].

Figure 3a shows a compact (~16 $mm^3$) lightweight (~16 mg) and stretchable (strains of up to 30%) device applied to the epidural space and the sciatic nerve in a mouse [55••], with ability for full subdermal implantation and stable operation for 6 months or more. The technology builds on the type of device highlighted in Figure 2a. Unconditioned place aversion studies demonstrate efficacy for optogenetic modulation of pain. The left panel in Figure 3b shows heat maps of animals expressing ChR2 in nociceptors under the TrpV1 promoter (TrpV1-ChR2) and sensory neuron — specific gene Advillin (Advillin-ChR2), activated with wireless sciatic nerve stimulators in one arm of the Y-maze. The right-hand panel shows the same experimental setup with SNS-ChR2 mice with

**Figure 2**




Battery-free optogenetic stimulators: **(a)** Soft, stretchable multichannel optogenetic stimulator. Heat maps show an experimental demonstration of place aversion and preference using selective stimulation of ventral and dorsal regions of the nucleus accumbens shell [45•]. **(b)** Monolithically defined, thin, stretchable optogenetic stimulator for application in the deep brain. Heat maps show results of place preference experiments with stimulated Cre subjects that express ChR2 in the mesolimbic dopaminergic (DA) terminals of the nucleus accumbens and non-Cre control animals [56••]. **(c)** Miniaturized subdermal implant with capabilities for optogenetic stimulation of the motor cortex as shown by increased circling rates compared to a control [50•]. Wireless multimodal devices. **(d)** Battery powered wireless implant for *in situ* pharmacology. Movement traces demonstrate Mu-Opioid induced rotational locomotion and optogenetic (ChR2 expressing animals) induced place preference [35•].

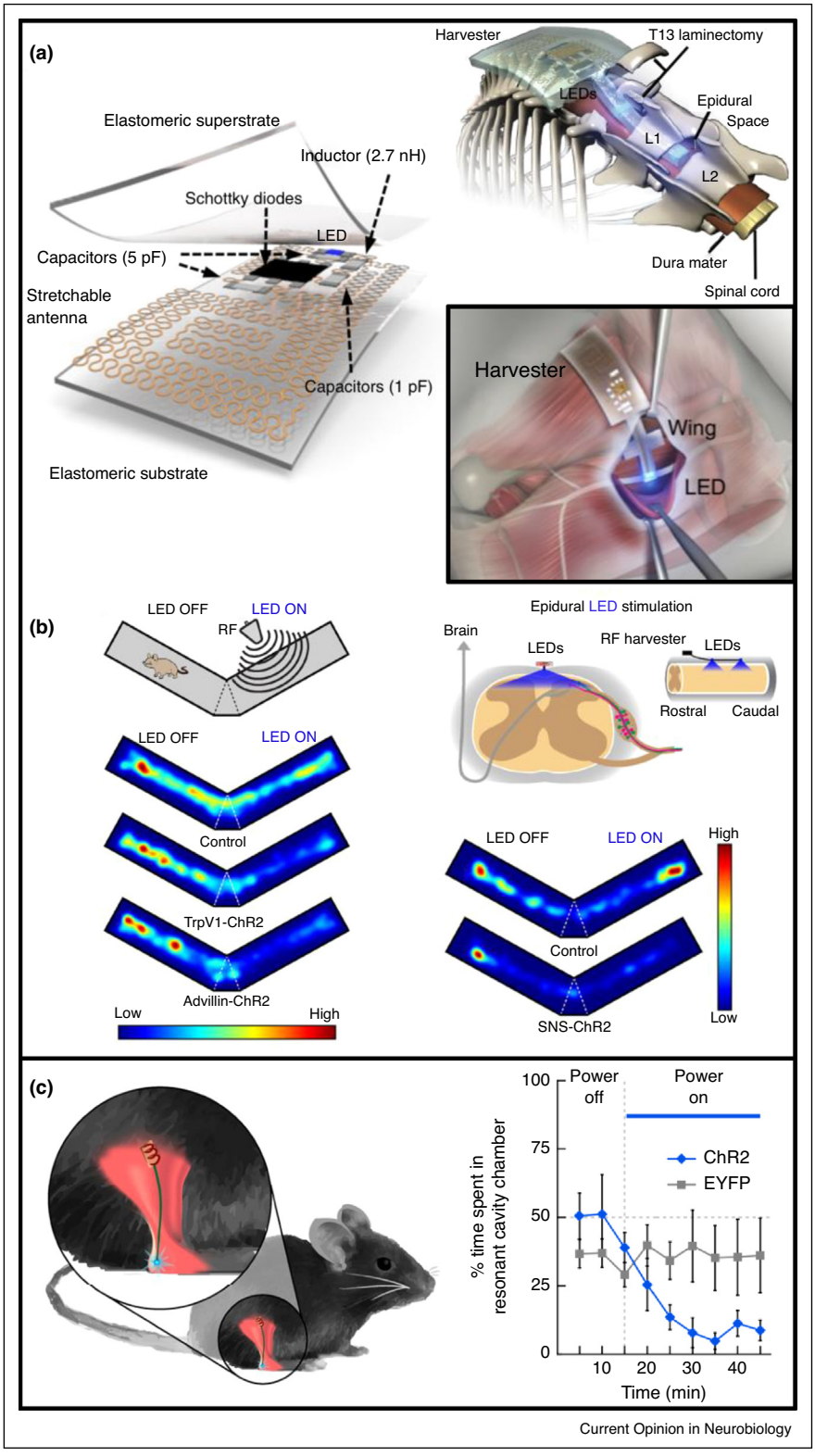
epidural implants, where a robust place aversion is also evident.

Figure 3c provides a schematic illustration of a miniaturized device that uses a slightly modified energy harvester to accommodate the vertical mounting orientation shown in Figure 2c with extension wires connecting to a μ-ILED (volume 25 $mm^3$, weight 50 mg) positioned adjacent to the triceps surae muscle group to allow for minimal disruption from joint rotation [50•]. The need for this careful positioning highlights a key drawback of mechanically hard devices of this type over stretchable platforms as shown in Figure 3a. Place aversion tests involving illumination of nerve endings in the heel of the paw of ChR2 + mice show expected results, as in the right-hand panel of Figure 3c.

## Conclusion

Advances in neuroscience often follow from the development of new tools and measurement techniques. The emerging wireless technologies summarized in this article can, through their diverse modes of operation, create significant new opportunities for research. Specifically, recent developments allow for ultraminiaturized, high-performance optoelectronic/microfluidic devices, wireless power delivery systems and soft mechanics designs

**Figure 3**




**(a)** RF powered optogenetic stimulator for application in the epidural space and the sciatic nerve. **(b)** Heat maps of place preference experiments with transgenetic mice demonstrate effective wireless optostimulation in the epidural space and the sciatic nerve [55••]. **(c)** Schematic illustration of a miniaturized implant positioned to stimulate cutaneous nociceptors and corresponding place preference experiment results [50•].

in platforms that can be fully implanted and operated continuously for long periods of time without adverse effects on even the smallest animal models. Active programs in advanced technologies that combine sensing, stimulation and high data rate information transfer have the potential to enable closed feedback loops that can be responsive, in real time, to biological processes. The prospects are significant not only for research, but also for eventual clinical translation in therapeutic devices and bioelectronic medicines.

## Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest


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