Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) 2024 25(10):803-823
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2300400

Wireless closed-loop deep brain stimulation using microelectrode array probes

Qianli JIA[1,2], Yaoyao LIU[1,2], Shiya LV[1,2], Yiding WANG[1,2], Peiyao JIAO[1,2], Wei XU[1,2], Zhaojie XU[1,2], Mixia WANG[1,2]✉, Xinxia CAI[1,2]✉

[1]*State Key Laboratory of Transducer Technology, Aerospace Information Research Institute, Chinese Academy of Sciences, Beijing 100190, China*
[2]*School of Electronic, Electrical and Communication Engineering, University of Chinese Academy of Sciences, Beijing 100049, China*

Abstract: Deep brain stimulation (DBS), including optical stimulation and electrical stimulation, has been demonstrated considerable value in exploring pathological brain activity and developing treatments for neural disorders. Advances in DBS microsystems based on implantable microelectrode array (MEA) probes have opened up new opportunities for closed-loop DBS (CL-DBS) in situ. This technology can be used to detect damaged brain circuits and test the therapeutic potential for modulating the output of these circuits in a variety of diseases simultaneously. Despite the success and rapid utilization of MEA probe-based CL-DBS microsystems, key challenges, including excessive wired communication, need to be urgently resolved. In this review, we considered recent advances in MEA probe-based wireless CL-DBS microsystems and outlined the major issues and promising prospects in this field. This technology has the potential to offer novel therapeutic options for psychiatric disorders in the future.

Key words: Deep brain stimulation (DBS); Wireless closed-loop deep brain stimulation (CL-DBS) microsystem; Microelectrode array (MEA) probe; Optical stimulation; Electrical stimulation

1 Introduction

The brain is responsible for sensing and reacting to both internal and exterior stimuli. Brain diseases can lead to abnormal responses to stimuli, which result in a range of clinical symptoms including movement disorders. With advances in rehabilitation medicine, deep brain neuromodulation has provided an enhanced possibility for treating various disorders, especially when targeting specific brain nuclei. Optical stimulation, as a potentially powerful tool to modulate neurons, can be used to investigate neural circuits in experimental subjects such as rat (Király et al., 2020), zebrafish (Fernandes et al., 2021), and non-human primates (Tremblay et al., 2020), allowing scientists to learn more about how neurons function in the presence of disease. Electrical stimulation has been used to treat several neurological diseases, including essential Parkinsonian tremor (Meng et al., 2022), Alzheimer's disease (Khan et al., 2019), major depressive disorder (Scangos et al., 2021a, 2021b), epilepsy (Ryvlin and Jehi, 2022), and obsessive-compulsive disorder (Menchón et al., 2021).

Deep brain stimulation (DBS) microsystems usually use open-loop control systems in physiological research and therapeutic applications (Krauss et al., 2021). Without real-time feedback, optical or electrical stimulation must be adjusted based on behavior scores or complex instruments (McIntyre et al., 2015; Hickey and Stacy, 2016; Kumari and Kouzani, 2023; Roca et al., 2023), and patients must seek professional help for weeks or months to evaluate the stimulation effect and make necessary adjustments (Provenza et al., 2021; Cury et al., 2022). Closed-loop DBS (CL-DBS) may increase the flexibility of experiments, reduce power consumption, improve the patient's overall life

✉ Mixia WANG, wangmixia@mail.ie.ac.cn
Xinxia CAI, xxcai@mail.ie.ac.cn
Mixia WANG, https://orcid.org/0000-0002-1310-8075
Xinxia CAI, https://orcid.org/0000-0001-5997-7252

Received June 5, 2023; Revision accepted Aug. 25, 2023; Crosschecked Jan. 23, 2024; Published online Feb. 12, 2024

© Zhejiang University Press 2024

quality, and alleviate disease symptoms (Parastarfeizabadi and Kouzani, 2017; Zanos, 2019; Chen and Pesaran, 2021; Cuschieri et al., 2022; Ramot and Martin, 2022). Although imaging technologies such as calcium imaging (Zhang ZH et al., 2018; Gottschalk et al., 2019; Sità et al., 2022), near-infrared spectroscopy (Rahman et al., 2020; Yu et al., 2021; Li RH et al., 2023), magnetic resonance imaging (Zhang et al., 2020; Ramot and Martin, 2022; Martínez et al., 2023), and positron emission tomography (PET) (Thiele et al., 2020; Jørgensen et al., 2021) have made CL-DBS possible, they are relatively inconvenient to use during follow-up visits. In situ detection and stimulation provide higher sensitivity for detecting single neural activity (Frank et al., 2019) and for more precise operations on specific neurons or brain nuclei (Aravanis et al., 2007) without additional operations. Therefore, in situ detection and stimulation in CL-DBS microsystems give researchers and surgeons more manipulative tools.

Neural probes for exploring and modulating neural circuits or brain nuclei simultaneously are of great convenience for longer investigations in CL-DBS. The various forms of neural probes that have appeared successively fall into two main categories: tungsten microwire electrodes and silicon (Si) probes (Normann and Fernandez, 2016; Hong and Lieber, 2019; Oldroyd and Malliaras, 2022). However, microwire electrodes have limitations due to their design of single-channel per wire, providing less neural information and lacking the ability to selectively target specific groups of neural populations (Ghane-Motlagh and Sawan, 2013). With advances in micro-electro-mechanical systems (MEMSs), implantable microelectrode array (MEA) probes are booming due to their design of multi-site, which allows for more neural information detection and more refined and localized stimulation (Obien et al., 2015). This technology would be especially beneficial for disorders that require precise targeting of specific brain regions or neural pathways. By integrating MEA probes with optical stimulation or electrical stimulation, an in-situ CL-DBS could have tremendous potential during follow-up visits.

MEA probes integrated with DBS are often connected to control devices via wires. However, wired connections not only limit the range of free movement of experimental subjects, but also can make it difficult for patients to be treated anytime or anywhere (Fernandez-Leon et al., 2015; Topalovic et al., 2023). Wireless CL-DBS microsystems allow free roaming of animals, thereby enabling exploration of how subjects interact with their environment. Wireless CL-DBS microsystems based on MEA probes would advance neuroscience in a new direction (Zanos, 2019; Horváth et al., 2022). Generally, these microsystems require MEAs with neuromodulation and wireless closed-loop control circuits (Fig. 1).

Researchers are using wireless CL-DBS microsystems more frequently in neuroscience and disease treatments. In this review, we first introduce general schemes of wireless CL-DBS microsystems using MEA probes. Then, recent developments in optical and electrical stimulation using MEA probes are summarized and discussed. Next, data processing, wireless data transmission, and free-battery driving sources of wireless CL-DBS microsystems are discussed in turn. Finally, applied scenarios, important challenges, and research opportunities for these microsystems to address societal changes are described.

2 Overview of wireless CL-DBS microsystems based on MEA probes

Wireless closed-loop microsystems record the brain activities of experimental subjects to adjust the placement of CL-DBS probes and stimuli in real time. The microsystems drive electronics that control digitalization, process data, deliver stimuli, and record electrophysiological signals wirelessly through capturing current rectified and regulated by a regulator using wireless energy transfer. The microsystems consist of four main components: MEA probes with integrated DBS, neural recording and data processing, wireless data communication, and driving sources (Fig. 2). In this section, we introduced an overview of wireless CL-DBS microsystems design. Further details about each part were given in Sections 3–6.

A wireless optical stimulation device implanted in a bird's head designed by Ausra et al. (2021) provides a typical design scheme. Their device has two versions enabling optical stimulation. One is capable of bilateral optogenetic stimulation, while the other can realize both thermography and one-sided optogenetic stimulation. In both versions, the current is captured by a resonant magnetic coupling at the front,

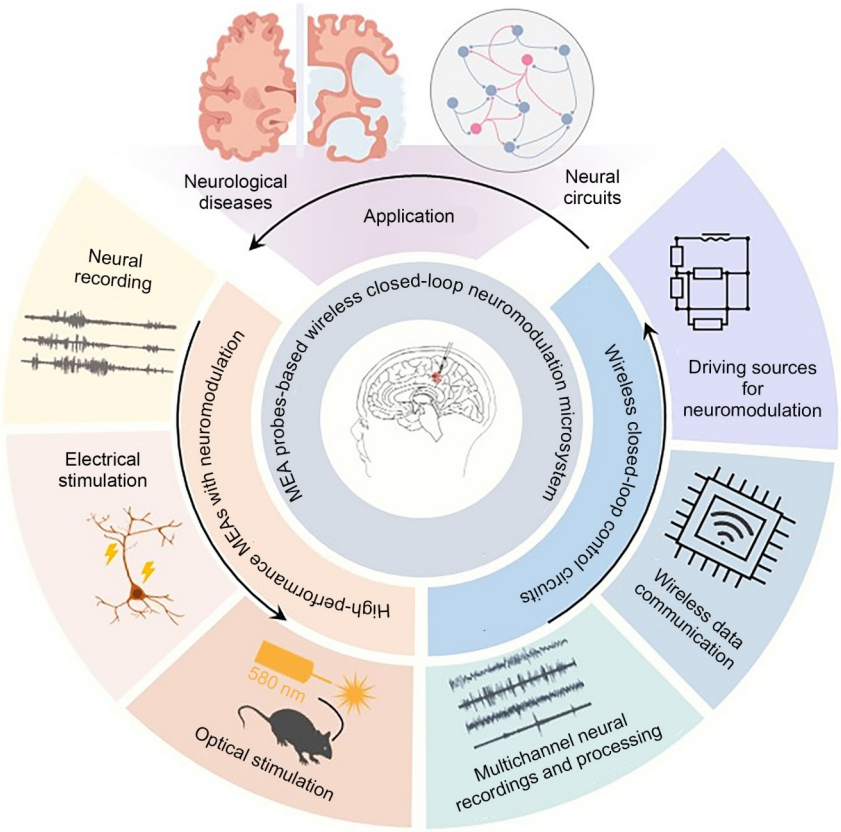

Fig. 1 Elements and applications of wireless closed-loop deep brain stimulation (CL-DBS) microsystems using microelectrode array (MEA) probes.

rectified and regulated by a low dropout regulator (LDO) to harvest the energy stored by capacitors, offering MEA probes to implement optical stimulation. The difference is that the latter version not only uses micro-inorganic light emitting diodes (LEDs) to execute optical stimulation through a microcontroller, but also modulates the thermography using an operational amplifier. This modulation scheme, with slight modifications, can be applied to nearly any scenarios using optogenetic methods (Lee S et al., 2018; Jia et al., 2019; Liu et al., 2020; Kim et al., 2021). For electrical neuromodulation microsystems, stimulation is often triggered after analyzing electrophysiological signals. Topalovic et al. (2023) developed a bidirectional neuromodulation platform (Neurostack), which records spike and local field potential (LFP) from 256 contacts and delivers stimulation through 32 contacts. The theta (3–8 Hz) power is detected as feedback, and then, neuro-stack triggers stimulation at a predefined phase of theta activity (Topalovic et al., 2023). Another typical scheme obtains the electrophysiological signals from electrodes through a signal processing module called wireless integrated neural recording and stimulation (WINeRS-8) application-specific integrated circuit (ASIC), which controls recording and biphasic stimulation via Bluetooth (Lee et al., 2019). During this process, the power is supplied through inductive coupling. A similar architecture was used by Lee B et al. (2018), Su et al. (2016), and Zaer et al. (2021). Based on these frameworks, the stimulating circuit can be adjusted according to various stimulating forms (Abdi and Cha, 2019; Mohanty et al., 2020). Furthermore, Lanzio et al. (2021) used a ring resonance circuit to achieve light precision, overcoming the nano-photon circuit's space restriction. Some noninvasive closed-loop control microsystems, such as ultrasonic neuromodulation, have emerged as promising new directions (Seo et al., 2016; Pang et al., 2022). These systems present a synergistic approach to understanding neural modulation combined with MEA probe-based CL-DBS microsystems.

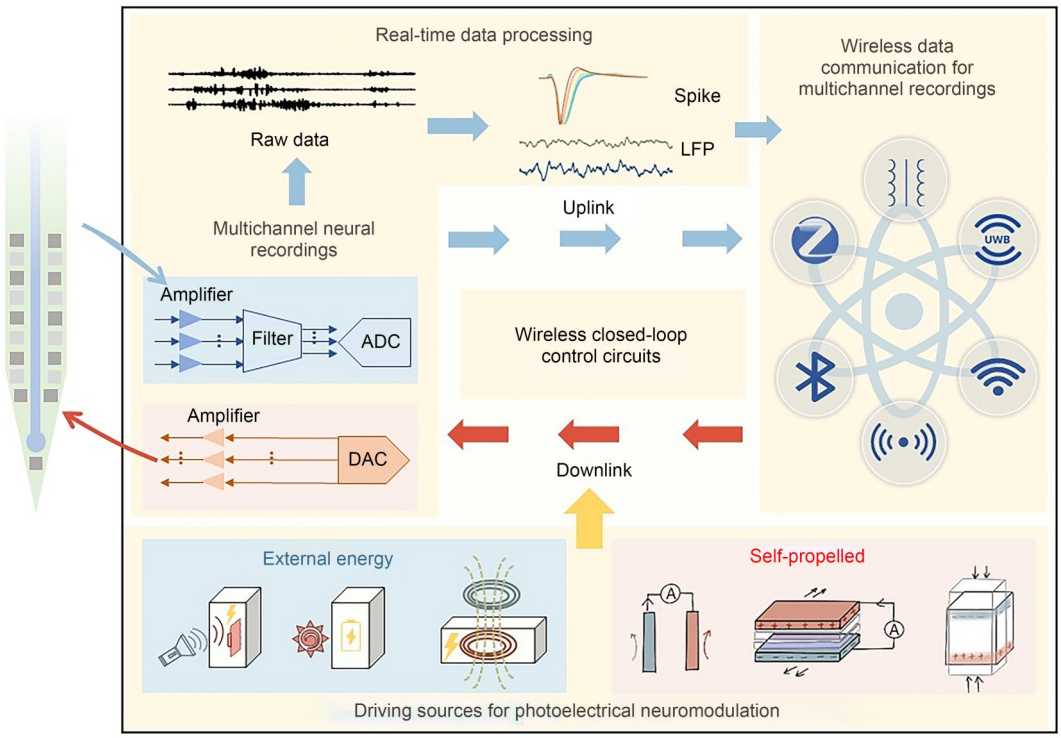

Fig. 2 Main components of wireless closed-loop deep brain stimulation (CL-DBS) microsystems. LFP: local field potential; ADC: analog-to-digital converter; DAC: digital-to-analog converter; UWB: ultra-wideband.

3 MEA probes with integrated DBS

3.1 MEA probes with integrated optical stimulation

Optogenetic techniques introduce photosensitive ion transport channels or photosensitive molecules into the plasma membrane of specific neural populations (Hart et al., 2019). Optical sources then transmit particular wavelengths of light to activate or inhibit neuronal activity (Deisseroth, 2015). Optical neural interfaces have provided most of the essential tools for optogenetic techniques in the last five years. In deep brain structures; however, it is difficult to effectively deliver light due to scattering and absorption by intervening tissue layers (Bansal et al., 2023). Many forms of optical neural interfaces are used to deliver DBS. Optical neural probes are classified into two kinds according to whether the microsystem has a light source: waveguide-based MEA probes and microLED (μLED)-integrated MEA probes. In this section, we discussed MEA probes with integrated optical stimulation that can be used in CL-DBS microsystems.

Waveguide-based optrodes require external light sources. Previous studies have typically used optical fiber to transmit the light to the fiber tip, which involves applying a tethering force to the head of the animal. Some design improvements have been made, including replacement of thick and bulky optical fiber with tapered optical fiber (Pisanello et al., 2014) (Fig. 3a) and the use of photolithographically-formed dielectric waveguides with a rectangular cross-section (Shim et al., 2016) (Fig. 3c). However, these devices are far less effective than light sources directly integrated into the outer tip of the waveguide that eliminate the need for a stiff fiber. For example, a compact injection laser diode combined with waveguide-based optrodes has been designed (Kampasi et al., 2018; Lanzio et al., 2021) (Figs. 3b and 3e). This method needs a relatively complex optical alignment process, which may limit the range of application of these devices.

The other method, using μLED-integrated optrodes, has gained popularity in numerous neuroscience labs because of its convenience and flexibility. Compared with waveguide-based optrodes, direct integration of the probe shank's light source does not require coupling between the waveguide and the light source. Therefore, it allows the wireless system to

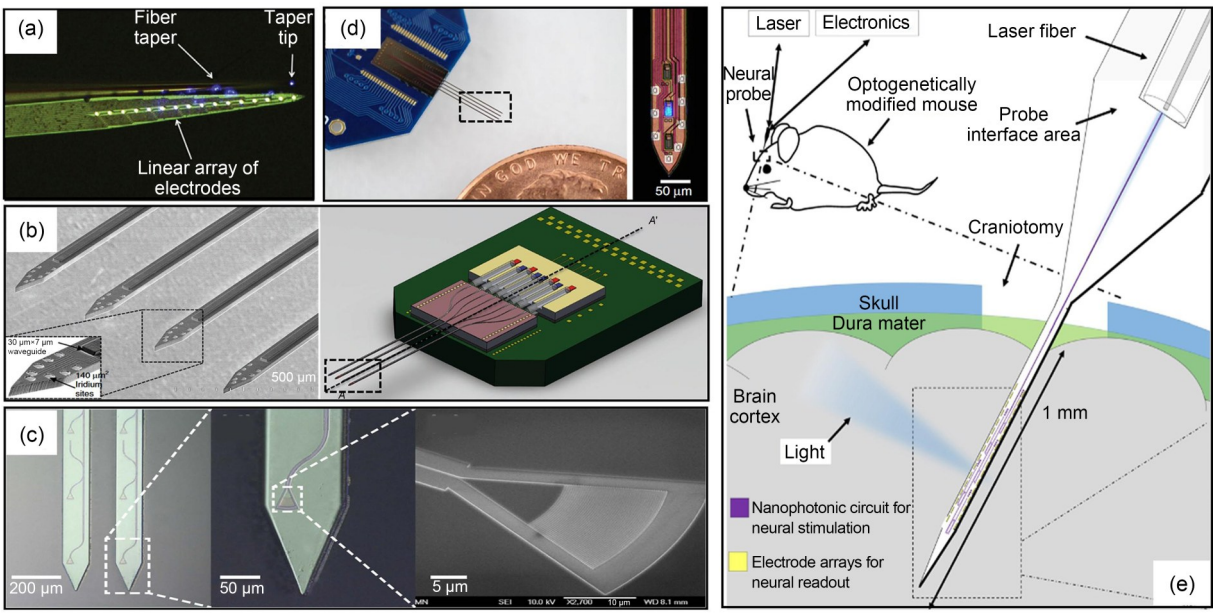

Fig. 3 Examples of microelectrode array (MEA) probes with integrated optical stimulation. (a) Optogenetics with tapered optical fiber. Reprinted from Pisanello et al. (2014), Copyright 2014, with permission from the Elsevier. (b) Multi-shank electrodes with recording sites and waveguides (Kampasi et al., 2018) (device fabrication details along *A–A'* showing final assembly of fabricated components on printed circuit board). (c) Photolithographically formed dielectric waveguide with a rectangular cross-section (Shim et al., 2016). (d) A neural probe with 32 recording sites and 12 micro light emitting diodes (μLEDs) (Kim et al., 2020). (e) A scalable neural probe combining laser fiber and recording (Lanzio et al., 2021). SEI: solid electrolyte interphase; WD: distance; MN: microstructure.

be miniaturized and makes neural modulation more precise (Kim TI et al., 2013; Kim K et al., 2020) (Fig. 3d). The surface areas of μLEDs are smaller than those of a waveguide, so the stimulated positions are more precise (Ohta et al., 2021). Although precise light stimulation brings significant effect enhancement in optogenetics, the μLED generates Joule heat during optical stimulation, which may affect cell biochemical processes (Kim et al., 2022). However, μLEDs consume less power than laser diodes while satisfying the need for power to stimulate neurons (Mendrela et al., 2018; Zhao et al., 2019). Therefore, they are more easily powered wirelessly.

Overall, both of these MEA probes with integrated optical stimulation have significantly enhanced the convenience of neuroscience studies. However, there are some potential concerns about the safety and effectiveness of optogenetics, which limit its use in terms of the intensity and wavelength of optical sources. A certain threshold of light intensity is needed to trigger the response of optogenetics, but a much higher light intensity beyond the threshold may not result in an increase in neural activities (Bansal et al., 2023), and may even lead to cell damage caused by the heat generated (Jeong et al., 2015; Maimon et al., 2018). Researchers can mitigate tissue damage by using lower light intensities and optimizing the duration of illumination. Additionally, the wavelength of optical sources affects tissue penetration and opsin activation. Common wavelengths used for optical stimulation include 280–750 nm light (Mager et al., 2018). To improve effectiveness and minimize cell damage, researchers need to carefully consider the characteristics of the target tissue and optimize the opsins used in optogenetics and the light frequency (Bansal et al., 2023). These measurements will help optogenetics fulfill its great potential in neuroscience.

3.2 MEA probes with integrated electrical stimulation

Electrical stimulation has been proved its efficacy since the first electrode was inserted subcortically in 1948 (Pool, 1954). Nowadays, there are an increasing number of commercial electrodes that can be applied to therapeutic chronic stimulation (Topalovic et al., 2020; Jarosiewicz and Morrell, 2021), including those made by Medrotonic (Minneapolis, Minnesota, USA), Boston Scientific (Natick, Massachusetts,

USA), Abbott (Chicago, Illinois, USA), and SceneRay (Suzhou, China). Although the electrical neural probes are mature enough for clinical therapy, we continue to search for safer and more efficient electrical probes to modulate the brain. Integrated recording and stimulating probes will bring benefits for investigating the neurons under electrical stimulation and adjusting the parameters of stimulation in response to the neuronal changes.

Since safety is paramount, all materials used in MEAs should be non-toxic. MEAs with electrical stimulation are usually fabricated with carbon, stainless steel, Si, and organic and other materials. Unfortunately, carbon fiber-based (Guo et al., 2017; Ashok Kumar et al., 2020), microwires-based (Du et al., 2017), and stainless steel-based MEAs (Baek et al., 2020) usually serve only as stimulators without the ability to provide high-throughput recording channels. Most MEAs with electrical stimulation are made from multilayer thin-film and other materials. Typically, the multilayers comprise an insulation and encapsulation layer, metallization layer, and substrate layer, as shown in Fig. 4a (Wang et al., 2022). To prevent undesired current from spreading to the surrounding area, the substrate and encapsulation layers usually consist of the same insulating material such as Si (Kim et al., 2018), SiO_2 (Fang et al., 2016), Al_2O_3 polyimide (PI) (Burton et al., 2021), parylene C, polydimethylsiloxane (PDMS) (Poojari, 2017), or liquid crystal polymer (LCP) (Yun et al., 2019). Different insulation materials have different biocompatibility and mechanical characteristics, which will be discussed in detail in Section 3.3.1. Most metallization uses platinum (Pt) (Pfau et al., 2019; Burton et al., 2021), Pt-iridium (Pt-Ir) (Ashok Kumar et al., 2020; Pol et al., 2021; Tala et al., 2021), or gold (Au) (Pranti et al., 2017) because of their high conductivity and resistance, but they have low charge injection capacity (CIC). The CIC is defined as the amount of injected charge density across the electrode-electrolyte interface (Becker, 2021), and is the most crucial measure for assessing the effectiveness of electrical stimulation (Araki et al., 2020). The coating material can be modified to expand the effective surface area of MEA to improve the ability to transfer charge, and thereby raise the CIC. Common coating materials include porous Pt (Boehler et al., 2020) (Fig. 4b), poly(3,4-ethylene dioxthiophene):polystryrene sulfonate (PEDOT:PSS) (Fig. 4c) (Pranti et al., 2017; Wang et al., 2022), polyaniline (Li et al., 2008), carbon nanotubes (CNTs) (Fig. 4e) (Alvarez et al., 2020; Lee D et al., 2021; Liu et al., 2022; Li JN et al., 2023), graphene, Ir oxide (IrOx) (Zeng et al., 2022) (Fig. 4d), and titanium nitride (TiN_4). The CICs of Au and Pt are usually less than 1 mC/cm^2, while the CICs of metallization modified with the coating materials are 1–15 mC/cm^2 (Alvarez et al., 2020; Zhao et al., 2020; Oldroyd and Malliaras, 2022). Therefore, modifying the surface metallization with these materials can enhance the efficiency of stimulation.

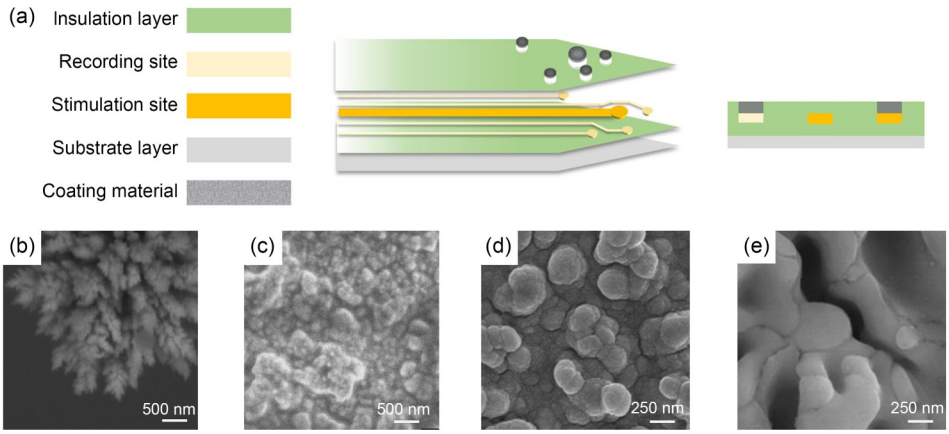

Fig. 4 Multilayers of microelectrode array (MEA) probes with integrated electrical stimulation and coating materials. (a) Multilayers of electrical stimulation electrodes. (b–e) Scanning electron microscope (SEM) images of nano platinum (nanoPt) (reprinted from Boehler et al. (2020), Copyright 2020, with permission from the American Chemical Society) (b), poly(3,4-ethylene dioxthiophene:polystryrene sulfonate (PEDOT:PSS) (Wang et al., 2022) (c), iridium oxide (IrOx) (Zeng et al., 2022) (d), and carbon nanotubes (CNTs) deposition (reprinted from Liu et al. (2022), Copyright 2022, with permission from the American Chemical Society) (e).

3.3 Improvements in neural signal detection and DBS

3.3.1 Advances in tissue fitting for improving biocompatibility

Long-term implantation of MEA probes in in vivo experiments can damage peripheral nerve tissue, increase the risk of foreign body rejection, and cause the electrode's performance to degrade over time. For long-time recording of bio-signals, the neural probes must have better biocompatibility to reduce damage to the brain and achieve a longer lifetime. Advances in improving biocompatibility are discussed below.

The neural tissue surrounding the brain has a Young's modulus of about 1 MPa, whereas a rigid Si-based photoelectrode has a Young's modulus of roughly 1 GPa. Therefore, recent developments in flexible MEAs with neuromodulation have advanced quickly to increase compatibility and lessen the mechanical and chemical mismatches between the MEAs and organic tissues. Altering the electrode material and material composition can improve the adaptability of microelectrodes implanted in the brain. A double-layered polyimide flexible neural probe was created (Pimenta et al., 2021) (Fig. 5a), whose rigidity is much lower than that of Si-based MEA probes of the same size (Lecomte et al., 2018). Kim et al. (2018) designed a foldable probe with one stimulator and three recording channels based on the same material. It lasts for at least one month. Yun et al. (2019) designed a fully implantable electrical probe with an LCP packaging and a lifetime of at least 21 d. An SU-8 packaging multifunctional probe with electrical and optical stimulation was designed, which has a lifetime of at least 7 d (Ling et al., 2020). Thiol-ene/acrylate shape memory polymer compositions on Si MEA probes have been shown to reduce stiffness and have achieved long-time recording signals in rat hippocampus and mice (Zátonyi et al., 2019; Fedor et al., 2022). In addition, more transient electronics are being applied to DBS. A resorbable silk neural probe enables simultaneous neural activity modulation while recording after dissolution of the silk substrate (Shi et al., 2019). Transient electronics may lead to new trends in DBS.

Furthermore, biocompatibility can be promoted by altering the geometry of the electrode. Some shapes such as the serpentine shape, three-dimensional (3D) grid, packed filaments, and neuron-like shapes, have shown good biocompatibility. Although the shape of a serpentine electrode allows the electrode to be highly stretched to match the physical properties of organic tissue, its use is limited by its soft structure. Therefore, this shape is usually applied to the cerebral cortex for electrocorticograms (Ji et al., 2020; Yu et al., 2021). A 3D optoelectronic grid is based on SU-8 polymer with curvature in the *Y*-axis and *Z*-axis. The stiffness of the two directions differs, which is beneficial for reducing the immune response (Lee JM et al., 2021) (Fig. 5b). In addition, Guan et al. (2019) created an elastic neurotassel coupled with an optical fiber. The assembled microelectrode filaments, like microwires, are packed using elastocapillary interactions, which can increase the number of channels in each filament without expanding the insertion footprint. The advancement of bionic design has given the design of electrode geometry a foundation. A neuron-like electronics (NeuE) design provides insights into the future development of biocompatible electrode geometries. NeuE probes have demonstrated stable cell recording without any loss for at least three months (Yang et al., 2019).

Wireless-controlled MEA probes could benefit performance by reducing inflammation and minimizing infection risks. The incorporation of wired implantable MEA probes comes with a potential drawback of inflammation and tissue damage at the insertion site due to the physical connection between the implant and external devices. However, the use of wireless control avoids the need for wires, reducing the movement of MEA probes and resulting in a reduction of tissue trauma and inflammation during the implantation process. Many wireless controlled MEA probes have demonstrated their stability in freely moving animals. Fernandez-Leon et al. (2015) tested a wireless transmission neural interface for a year in non-human primates, and Schwarz et al. (2014) successfully recorded neural information from primates for five years.

3.3.2 Minimizing artifacts during stimulation for achieving more reliable recordings

Novel optical- and electrical-stimulation MEAs have been developed to increase recording sites while implementing stimulation. However, electrical stimulation generally induces large and long-lasting artifacts that affect signal recording. On the other hand,

optical stimulation usually induces more localized and less invasive perturbations to the neural tissue, leading to artifacts with smaller amplitude and shorter duration (Dale et al., 2022). These differences may be traced back to the generation of the artifacts. Artifacts arising during optical stimulation are induced by photoelectrochemical effects, electromagnetic inference, and photovoltaic effects, and influence recordings indirectly (Kim et al., 2020). Artifacts arising during electrical stimulation are characterized by inevitably larger initial transients, which are related to the resistive and capacitive properties of the MEA probes, and act directly on recordings (Drebitz et al., 2020). Here, we introduced changes made to electrodes to minimize stimulation artifacts.

Artifacts from both optical stimulation and electrical stimulation can be reduced by increasing the external shielding layer or changing the characteristics of the material. Wang et al. (2020) developed Si-based low-noise optoelectronic electrodes that have an internal ground shield to lower noise interference and reduce the pseudo-path during stimulation. Kim et al. (2020) used a heavy boron-doped Si substrate to partially eliminate the artifacts caused by photoelectric interference (Fig. 5c). Various materials such as graphene (Liu et al., 2018; Thunemann et al., 2018), carbon nanotubes, hydrogels, transparent conductive oxides (Lee et al., 2015; Cho et al., 2022a), and PEDOT:PSS treated with ethylene glycol (Cho et al., 2022b) (Fig. 5d), have shown promise as transparent implants, especially for optrodes. These measures will help minimize stimulation artifacts and improve the recording ability of multifunctional MEA probes.

3.3.3 Progress in optional stimulation for greater flexibility

Currently, the main disadvantage of most multifunctional neural probes is that they lack sufficient

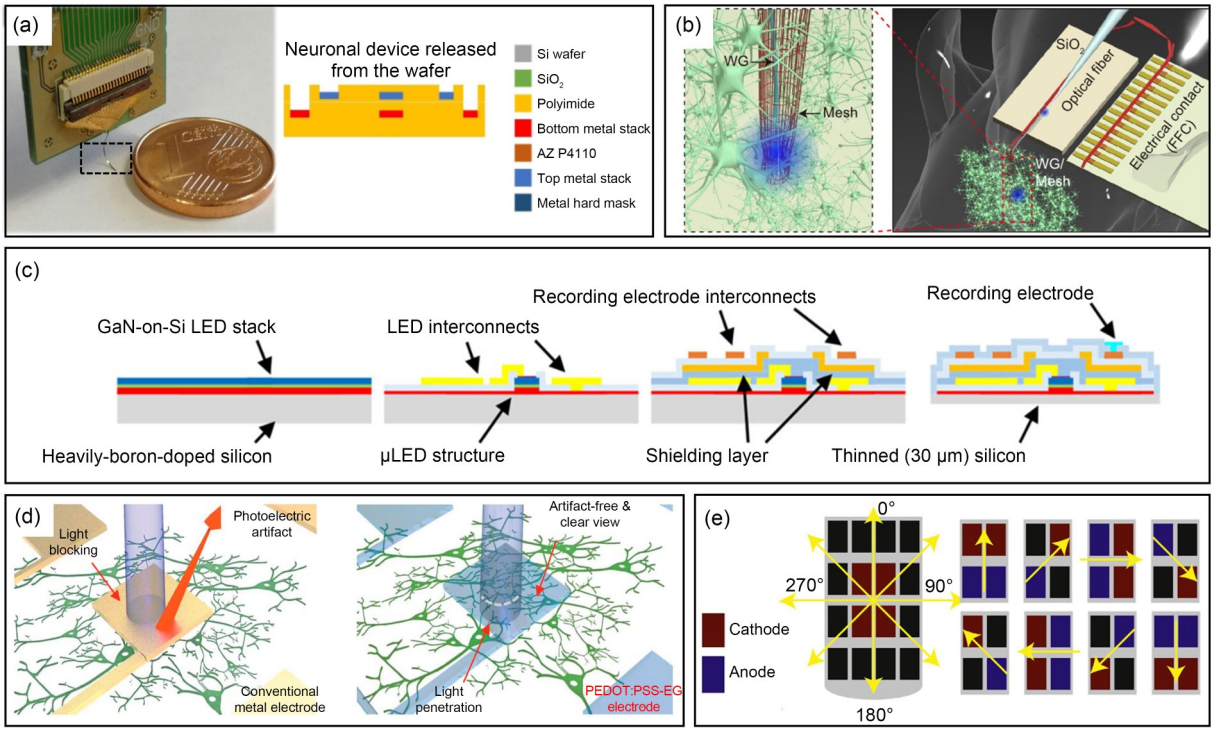

Fig. 5 Improvements in modulation and detection. (a) Lowering the Young's modulus to lessen the mechanical and chemical mismatches between the microelectrode arrays (MEAs) and organic tissues, such as in a double-layered polyimide flexible neural probe (Pimenta et al., 2021). (b) Altering the geometry of the electrode to improve biocompatibility of MEAs, such as in a three-dimensional (3D) optoelectronic grid. Reprinted from Lee et al. (2021), Copyright 2021, with permission from the American Chemical Society. (c) A flow chart of the construction of a heavily-boron-doped silicon substrate to eliminate artifacts (Kim et al., 2020). (d) The use of transparent materials such as poly(3,4-ethylene dioxthiophene):polystryrene sulfonate (PEDOT:PSS) in transparent implants to minimize stimulation artifacts (Cho et al., 2022b). (e) Achieving precise and flexible orientation-selective stimulation (Slopsema et al., 2021). Si: silicon; SiO_2: silicon dioxide; WG: waveguide; FFC: flexible flat cable; GaN: gallium nitride; LED: light emitting diode; μLED: microLED; EG: ethylene glycol.

flexibility. They can be used only to stimulate specific neurons with a few fixed sites, and they output continuous light or electricity. However, surgical variance is almost inevitable, which may affect the position of the stimulation region so much that an experiment is compromised. Therefore, when targeting brain regions, the design of the electrodes has to enable a flexible interface that can compensate for operational mistakes. In this section we discussed how to increase the flexibility of the output stimulus through the design of neural probes.

Above all, changing the structure of neural probes makes the form and range of outputs more flexible. For achieving intermittent output light, Mohanty et al. (2020) designed a switching network for precisely reconfigurable nanophotonic Si-based probes that allows beam switching, steering and focusing, and the independent stimulation of individual neurons. Furthermore, altering the structure of probes will selectively activate target regions. This is of great importance because the successful use of optical stimulation or electrical stimulation in the treatment of brain disorders depends on precise spatial targeting. Selectively and accurately activating a neural path will reduce stimulation-induced side effects and boost therapeutic effectiveness, especially during clinical stimulation. To improve the accuracy of the stimulated location, segmented leads have provided researchers with insights on orienting and selectively outputting stimuli from electrodes. Taller and shorter cylindrical electrodes provide different directions of activation (Howell et al., 2015). Therefore, varying the shapes of segments can produce orientation-selective stimulation. Slopsema et al. (2021) connected a directional DBS lead in adult swine that can induce variable degrees of directional correction (Fig. 5e).

Moreover, increasing the number of output points can enhance the output options to improve the selectivity of a stimulus. Libbrecht et al. (2018) designed an integrated high-density optoelectrode that can adjust the proximal modulation and distal modulation. More commercial electrodes increase the number of programmable contacts to enhance options for stimulation directions. For instance, three segmented electrodes can be used to replace the two central cylindrical contacts of quadripolar electrodes, allowing three radial stimulation directions that are 120° apart (Cagnan et al., 2019). These measures can improve the spatial specificity of stimulation so that the outputs will be reconfigurable.

Finally, during electrical stimulation, we can choose a more flexible stimulated field by shifting the strategies of anodes and cathodes. Advanced current field steering strategies have provided insights for researchers to orient and selectively output a stimulus. Lehto et al. (2020) have designed a selective strategy in which the spatial gradient of the electric field can be established along various orientations using several contacts with different current sources. Patel et al. (2021) have reviewed programming strategies such as interleaving programming, lighthouse strategy, and multiple monopolar programming.

4 Multichannel neural recordings and real-time data processing on chips

Wireless closed-loop microsystems are responsible for not only receiving signals from electrodes, transmitting them to a wireless communication module as an uplink (Zhang et al., 2012), and inputting the stimulus parameter data to electrodes as a downlink (Kim et al., 2021), but also fulfilling data processing in real time (Chen and Pesaran, 2021; Topalovic et al., 2023). The electronics for implementing these functions usually include amplifiers, filters, analog-to-digital converters (ADCs), and digital-to-analog converters (DACs). Because the electrical signals recorded by the electrode are usually so weak that they may be easily drowned in noise, these electronics are usually equipped with low-noise and high-gain amplifiers (Rhew et al., 2014; Ng et al., 2016; Banu and Gupta, 2022; Nordi et al., 2022), high signal-to-noise ratio filters (Qian et al., 2017; Petrucci et al., 2020), and low-power and high-speed ADCs and DACs (Banu and Gupta, 2022). Additionally, researchers have designed some custom-built integrated circuits for signal processing according to electrical stimulation demands. For instance, Lee et al. (2019) designed a WINeRS-8 chip including a 32-channel recording and 4-channel current stimulator. Zhou et al. (2019) produced a custom-designed neuromodulation-integrated circuit that can deliver different-sized pulses.

In clinical diagnosis, LFP and spikes are used as feedbacks for judging the target brain regions and adjusting stimulus parameters. Analyzing neuron types

and various firing patterns gives insights for different brain regions. Online-spike-sorting is usually processed with spike detection, feature extraction (Leibig et al., 2016), and cluster analysis (Huang et al., 2021), while online LFP analysis can be dealt with by sampling reduction, noise elimination, and filtering to select specific frequency oscillations apart from spike detection (Fig. 6). These neural signals can be processed with rasters, interspike interval histograms, spectrogram analysis, phase analysis, and other conjoint analyses. For example, in the superior region of the subthalamic nucleus (STN), the power of the slow high-frequency oscillations and the coupling of their amplitude with the beta-band phase are stronger among tremor-dominant patients than in healthy people, while in the inferior region of the STN, the cross-frequency coupling between fast high-frequency oscillations and the beta-band is stronger among gait-difficulty patients than in healthy people (Telkes et al., 2018). In addition, learning-based methods are gradually replacing manual spike sorting because automated strategies save time and human interactions. Typical learning-based methods include convolutional neural network (CNN) (Li et al., 2020), recurrent neural network (RNN) (Rácz et al., 2020), autoencoder (AE) (Eom et al., 2021), generative adversarial network (GAN), and reinforcement learning (RL) agent (Moghaddasi et al., 2020). The analyzed feedbacks not only update stimulation parameters (Zhao et al., 2018; Topalovic et al., 2023), but also optimize subsampling and resampling of CL-DBS microsystems through selecting signal channels that maximize the yield of recorded neurons (Walker et al., 2019; Choi et al., 2020). These decoded feedbacks can further reveal subjects' behaviors, such as running positions of a rat, to deliver a specific stimulation in real time (Hu et al., 2018).

5 Wireless data communication for high-throughput recordings

The common types of wireless data transmission used in neuroscience technology are near field inductive coupling (NIC), radio frequency (RF), Bluetooth, wireless fidelity (Wi-Fi), ZigBee, and ultra-wideband (UWB). NIC and RF are more suitable for shallow implants because of their relatively large coil size (Luan et al., 2020). For example, Shin et al. (2017) used NIC for wireless light delivery in optogenetic experiments, and Jia et al. (2020) designed a wireless trimodal neural interface system on a chip (SoC). Bluetooth is most commonly used in deep brain neuromodulation microsystems (Table 1). Zhou et al. (2019) used 2.4 GHz Bluetooth low energy (BLE) to

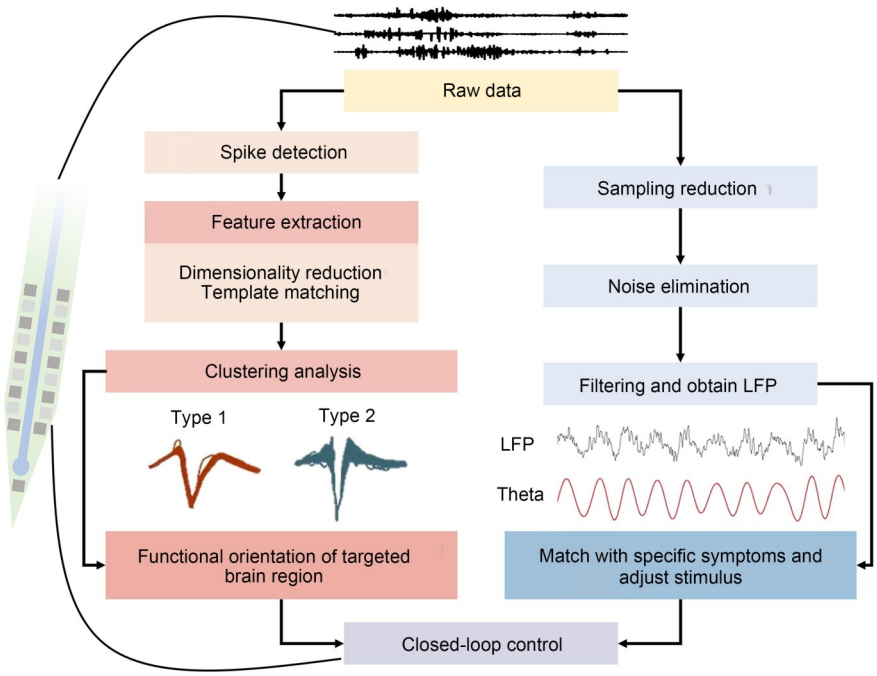

Fig. 6 Flow chart of neural signal processing. LFP: local field potential.

Table 1 Different wireless types of data communication

Wireless type	Test model	Power (mW)	Number of recordings and stimulation channels	Transmission distance (m)	Transmission speed (bit/s)	Frequency band (Hz)	Sampling frequency (SPS)	System dimension	References
NIC	Mouse	8	1		12×10^3	8.456×10^5	1×10^3	1 cm×1 cm	Shin et al., 2017
	Mouse	62	12		2×10^6	6.78×10^6	2×10^4	19.9 mm× 18.1 mm× 6.6 mm	Wright et al., 2022
RF	Rat	20.7	40	1.5	6.78×10^6	4.34×10^8	1×10^3–5×10^4	3 mm×5 mm	Jia et al., 2020
Bluetooth	Primate	172	128	2	1.96×10^6	2.4×10^9	1×10^3	36 mm×33 mm× 15 mm	Zhou et al., 2019
	Mouse	28.6	1	5		2.4×10^9	1×10^4	15 mm×15 mm× 12 mm	Idogawa et al., 2021
	Rabbit	378	32	1	15.36×10^6	2.4×10^9	3×10^4	18 mm×15 mm× 10 mm	Lee et al., 2023
Wi-Fi	Non-human primate	4000	96	2–4	24×10^6	5.7×10^9–5.8×10^9	2×10^4	56 mm×42 mm× 44 mm	Fernandez-Leon et al., 2015
		200	128		1.6×10^6	2.4×10^9	1×10^3	55 mm×55 mm	Matsushita et al., 2018
ZigBee	Rat/pigeon	15.2	16	About 10	2.5×10^5	2.4×10^9		29 mm×26 mm× 8 mm	Yun et al., 2019; Jang et al., 2021
UWB	Rhesus macaque	6.4	20	0.4	10×10^6	3×10^9–8×10^9	1×10^6	1.1 mm×0.4 mm	Zhang Z et al., 2018

NIC: near field inductive coupling; RF: radio frequency; SPS: sample per second; UWB: ultra-wideband; Wi-Fi: wireless fidelity.

detect 128 recording channels in a primate from 2 m away. Wi-Fi can be applied in remote telemedicine (Zhang CC et al., 2018) due to its faster and safer transmission, and its transmission range is greater. Unfortunately, its high-power consumption is a problem. Fernandez-Leon et al. (2015) proposed a brain–computer interface for non-human primates using Wi-Fi. The transmission speed can reach 24 Mbit/s on 96 recording channels. Compared with Bluetooth and Wi-Fi, ZigBee consumes less power to transmit a longer distance, which is highly desirable for electrophysiological signal research (Yun et al., 2019; Shim et al., 2020; Kwarteng and Cebe, 2022). Yun et al. (2019) used ZigBee in pigeons and rats to conduct electrical stimulation experiments. The power consumption was only 15.2 mW while the transmission distance was about 10 m, and the transmission speed was 250 kbit/s. Furthermore, UWB has higher working frequency bands, which is suitable for high-speed electrophysiological recording and data safety during near field communication (Abdi and Aliakbarian, 2019). Liu et al. (2021) and Zhang Z et al. (2018) designed a wireless short-range sensor based on UWB. The working frequency band ranges between 3 and 8 GHz, and the power consumption is the lowest among the above methods (Table 1). Overall, wireless data transmission is advancing towards lower power dissipation, higher data rates, and longer transmission distances (Kuan et al., 2015).

6 Driving sources for CL-DBS

The freedom of movement of experimental subjects is significantly hampered by large and cumbersome photoelectric regulation apparatus. The devices for neuromodulation experiments need to be smaller and lighter, which is a serious problem that has to be fixed urgently. The size of CL-DBS microsystems is currently constrained mainly by size of the battery

used to deliver stimulation (Obaid and Lu, 2019). Free-battery technologies are flourishing in CL-DBS microsystems due to their reproducible energy sources, thus extending their lifetime. Without electricity storage, the method of capturing electricity has become increasingly important. Nowadays, electricity sources can be categorized into two groups: external power sources, which include optical drives (Ding et al., 2018; Park et al., 2018; Hu et al., 2019; Obaid and Lu, 2019; Silverå Ejneby et al., 2022), electromagnetic energy (Shin et al., 2017; Bloch et al., 2019; Jia et al., 2019; Kim et al., 2021; Jiang et al., 2022), and ultrasonic energy devices (Zhang S et al., 2022); and internal power sources, such as nanogenerators, which represent self-driven energy (Hinchet et al., 2019; Ouyang et al., 2019; Elsanadidy et al., 2022; Shabbir et al., 2022; Solanki et al., 2023; Wang et al., 2023) (Table 2). These types of energy are converted from alternating current to direct current by rectifiers in a wireless power supply module to prolong the lifespan of the batteries inside the body by increasing the efficiency of electrical conversion (Lyu et al., 2018; Gong, 2022). Although many free-battery technologies have been miniaturized, there are still problems such as fitting a compact form in the limited space available for implantation, especially around the brain. These problems may be solved with advances in nanotechnology engineering or new energy.

7 Broad applications for CL-DBS microsystems using MEA probes

The applications of closed-loop electrical stimulation and closed-loop optogenetics have brought remarkable advances in the field of neuroscience, curing psychiatric and movement disorders and revealing the individual neural circuits. Since any therapy using optogenetics requires the use of gene therapy techniques, there is a slight difference that electrical stimulation is used more in disease treatments while optogenetics has entered clinical trials only recently (White et al., 2020). However, closed-loop optogenetics has suggested novel therapeutic methods for neurological disease in non-human animals and promising tools to reveal neural circuits.

Treatments of psychiatric disorders such as major depressive disorder, chronic pain, and movement disorders such as Parkinson's disease, epilepsy, and essential tremor, have been examined successfully using CL-DBS microsystems, particularly with the use of electrical stimulation (Table 3). For instance, in Parkinson's disease, the motor performance of closed-loop treatments has improved more than that of open-loop treatments and speech intelligibility is preserved in studies using beta power (13−35 Hz) as feedback (Tinkhauser et al., 2017; Habets et al., 2018). In patients with major depressive disorder, the patient's

Table 2 Summary of driving energy

Energy type	Factors of output power	Power density (mW/cm^2)	Battery dimension	Duration	References
External energy					
Optics	Optical power and time duration	10–100	Micron scale to millimeter scale	Months	Ding et al., 2018; Park et al., 2018; Hu et al., 2019; Obaid and Lu, 2019; Silverå Ejneby et al., 2022
Electromagnetic energy	Input power and load resistance value	2–10	Millimeter scale	Years	Shin et al., 2017; Bloch et al., 2019; Jia et al., 2019; Kim et al., 2021; Jiang et al., 2022
Ultrasonic energy	Input power	About 10	Millimeter scale to centimeter scale	Months	Xu et al., 2022; Zhang S et al., 2022
Self-propelled					
Piezoelectric nanogenerator	Amplitude and frequency of external stress	2–10	Millimeter scale	Days	Hinchet et al., 2019; Wang et al., 2023
Triboelectric nanogenerator	Contact and charge density	2–10	Millimeter scale	Months	Yao et al., 2018; Ouyang et al., 2019; Elsanadidy et al., 2022; Shabbir et al., 2022; Solanki et al., 2023

Table 3 Summary of targets and feedbacks in disease therapy

Disease	Possible feedback	Target	References
Parkinson's disease	Beta activity	STN, GPi, GPe, PPN	Tinkhauser et al., 2017; Habets et al., 2018; Su et al., 2019, 2021; Bronte-Stewart et al., 2020; Molina et al., 2021; Bahadori-Jahromi et al., 2023
Depression	Beta-low-gamma activity/sharp wave ripple	SCC, NAcc, LHb, MFB, VC/VS	Riva-Posse et al., 2018; Davidson et al., 2020; Thiele et al., 2020; van der Wal et al., 2020; Fan et al., 2023; Sierra et al., 2023
Epilepsy	Gamma activity	ANT	Elder et al., 2019
Chronic pain	Spike rate	ACC	Zhang et al., 2023
Alzheimer's disease	Theta activity	Fornix, hippocampus	Wang et al., 2023

STN: subthalamic nucleus; GPi: globus pallidus internus; GPe: globus pallidus externus; PPN: pedunculopontine nucleus; SCC: subgenual cingulate cortex; NAcc: nucleus accumbens; LHb: lateral habenula; MFB: medial forebrain bundle; VC/VS: ventral capsule/ventral striatum; ANT: anterior nucleus of thalamus; ACC: anterior cingulate cortex.

depression acutely improved and the effect was maintained when an amygdala gamma biomarker was applied in closed-loop therapy (Scangos et al., 2021b). In epilepsy, a trial demonstrated that closed-loop therapy reduces seizures by more than 40% compared to a baseline based on high-frequency oscillations, microseizures, and interictal spikes (Lo and Widge, 2017; Price et al., 2020). In chronic pain, spiking rates in the anterior cingulate cortex (ACC) can be used as feedback in closed-loop therapy to effectively inhibit sensory responses caused by thermal pain (Zhang et al., 2023).

CL-DBS is not only a successful clinical treatment for disorders, but also supports research on the circuit-level mechanisms underlying functional connections in the brain, especially using closed-loop optogenetics. Closed-loop optogenetics could provide insights about different frequency oscillations during the encoding and decoding of neuronal information and define cell types that engage in various diseases through observing local field potential changes or behaviors. For example, in epilepsy, a recent trial replicated the modulation of local field potential related to seizure oscillations through closed-loop optogenetic stimulation using excitatory opsins (Zaaimi et al., 2023). In spatial navigation tasks, theta oscillations in enhancing encoding and retrieval depending on the phase at which stimulation was administered, have been proved to be effective by using closed-loop treatments (Khodagholy et al., 2022). In memory consolidation, hippocampal sharp wave ripples play crucial roles during maze learning (Fernández-Ruiz et al., 2019). Another trial provided crucial evidence for the theory that thalamocortical neuronal activity is required for poststroke epilepsy online detection (Paz et al., 2013).

8 Summary and perspectives

CL-DBS is an exciting technique that brightens up neuroscience's prospects. Advances in MEA probes and wireless technologies have provided powerful methods for CL-DBS. The capability of wireless CL-DBS microsystems using MEA probes has been confirmed via in vivo experiments, suggesting potential for clinical applications. There are important opportunities and unmet needs in clinical therapies as followed. (1) Existing MEA probes for deep brain recording and stimulation are designed with multilayered thin-film. The detected region is limited to the same plane. A 3D design could provide a larger recording contact area than that of conventional MEA probes. (2) During the insertion of MEA probes into a deep brain region, the brain can be damaged. Although flexible materials can reduce damage to the brain tissue compared to rigid MEAs, it is difficult to implant flexible MEA probes in the target region. Future work can focus on various types of implantations and biodegradable materials for MEA probes. (3) Wireless transmission is limited either by distance or speed. Although Wi-Fi can meet the demands for behavioral experiments, its power consumption and Joule heat production are much higher than those of other methods. Therefore, it is highly desirable to solve this problem by reducing standby power loss and adopting multiplexing. (4) Most batteries are implanted in the ventral cavity because of their bulky

size and are connected to electrodes by wire. This is not safe for subjects and could cause more serious injury. The minimum portable power placed around the brain can solve this problem and has little impact on subjects. (5) Given quick development of multi-channel electrodes, there are various deep learning data processing methods that can allow the system to detect electrophysiological signals in real time. However, there are still challenges in large-scale data processing that requires methods focused on data compression and the accuracy of classification results. (6) Single characteristic neural signals provide limited information about the brain's status, whereas multimodal signals, such as electrochemical signals and wide field calcium imaging, can offer more precise neural information in clinical therapies, enabling a clearer investigation of the brain's condition. Therefore, more attention should be paid to dual-mode signals that can make neuromodulation more precise. To solve above problems, neuroscience, computer science, clinical medicine, mechanical engineering, and other disciplines should be brought together to enhance progress.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. T2293730, T2293731, 62121003, 61960206012, 61973292, 62171434, 61975206, and 61971400), the National Key Research and Development Program of China (Nos. 2022YFC2402501 and 2022YFB3205602), the Major Program of Scientific and Technical Innovation 2030 (No. 2021ZD02016030), and the Scientific Instrument Developing Project of the Chinese Academy of Sciences (No. GJJSTD20210004). We thank Dr. Yilin SONG (State Key Laboratory of Transducer Technology, Aerospace Information Research Institute, Chinese Academy of Sciences, Beijing, China) for her advice on grammar revisions.

Author contributions

Qianli JIA, Xinxia CAI, and Mixia WANG investigated the literature, and conceived and wrote the manuscript and drew figures. Xinxia CAI, Mixia WANG, Yaoyao LIU, Shiya LV, Yiding WANG, Peiyao JIAO, Wei XU, and Zhaojie XU checked the paper and revised the manuscript. All authors have read and approved to the final manuscript.

Compliance with ethics guidelines

Qianli JIA, Yaoyao LIU, Shiya LV, Yiding WANG, Peiyao JIAO, Wei XU, Zhaojie XU, Mixia WANG, and Xinxia CAI declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

References

Abdi A, Aliakbarian H, 2019. A miniaturized UHF-band rectenna for power transmission to deep-body implantable devices. *IEEE J Transl Eng Health Med*, 7:1900311. https://doi.org/10.1109/JTEHM.2019.2910102

Abdi A, Cha HK, 2019. A regulated multiple-output high-voltage charge pump IC for implantable neural stimulators. *Microelectron J*, 92:104617. https://doi.org/10.1016/j.mejo.2019.104617

Alvarez NT, Buschbeck E, Miller S, et al., 2020. Carbon nanotube fibers for neural recording and stimulation. *ACS Appl Bio Mater*, 3(9):6478-6487. https://doi.org/10.1021/acsabm.0c00861

Araki T, Bongartz LM, Kaiju T, et al., 2020. Flexible neural interfaces for brain implants—the pursuit of thinness and high density. *Flex Print Electron*, 5(4):043002. https://doi.org/10.1088/2058-8585/abc3ca

Aravanis AM, Wang LP, Zhang F, et al., 2007. An optical neural interface: *in vivo* control of rodent motor cortex with integrated fiberoptic and optogenetic technology. *J Neural Eng*, 4(3):S143-S156. https://doi.org/10.1088/1741-2560/4/3/S02

Ashok Kumar N, Chauhan M, Kandala SK, et al., 2020. Development and testing of implanted carbon electrodes for electromagnetic field mapping during neuromodulation. *Magn Reson Med*, 84(4):2103-2116. https://doi.org/10.1002/mrm.28273

Ausra J, Munger SJ, Azami A, et al., 2021. Wireless battery free fully implantable multimodal recording and neuromodulation tools for songbirds. *Nat Commun*, 12:1968. https://doi.org/10.1038/s41467-021-22138-8

Baek C, Kim S, Jang JW, et al., 2020. Investigation of stereotactic surgery for avian brain stimulation by a fully implanted wireless system. *Neurosurg Focus*, 49(1):E10. https://doi.org/10.3171/2020.4.FOCUS2025

Bahadori-Jahromi F, Salehi S, Madadi Asl M, et al., 2023. Efficient suppression of parkinsonian beta oscillations in a closed-loop model of deep brain stimulation with amplitude modulation. *Front Hum Neurosci*, 16:1013155. https://doi.org/10.3389/fnhum.2022.1013155

Bansal A, Shikha S, Zhang Y, 2023. Towards translational optogenetics. *Nat Biomed Eng*, 7(4):349-369. https://doi.org/10.1038/s41551-021-00829-3

Banu S, Gupta S, 2022. Power optimization of low noise amplifier (LNA) and DAC used in closed loop deep brain neuro-stimulator (CDBS) at 45nm using cadence virtuoso. *Int J Health Sci*, 6(S3):5491-5502. https://doi.org/10.53730/ijhs.v6nS3.7153

Becker MT, 2021. Charge injection capacity of ferroelectric microelectrodes for bioelectronic applications. *AIP Adv*, 11(6):065106. https://doi.org/10.1063/5.0049202

Bloch E, Luo Y, da Cruz L, 2019. Advances in retinal prosthesis systems. *Ther Adv Ophthalmol*, 11:2515841418817501. https://doi.org/10.1177/2515841418817501

Boehler C, Vieira DM, Egert U, et al., 2020. NanoPt—a nanostructured electrode coating for neural recording and

microstimulation. *ACS Appl Mater Interfaces*, 12(13): 14855-14865.
https://doi.org/10.1021/acsami.9b22798

Bronte-Stewart HM, Petrucci MN, O'Day JJ, et al., 2020. Perspective: evolution of control variables and policies for closed-loop deep brain stimulation for Parkinson's disease using bidirectional deep-brain-computer interfaces. *Front Hum Neurosci*, 14:353.
https://doi.org/10.3389/fnhum.2020.00353

Burton A, Won SM, Sohrabi AK, et al., 2021. Wireless, battery-free, and fully implantable electrical neurostimulation in freely moving rodents. *Microsyst Nanoeng*, 7:62.
https://doi.org/10.1038/s41378-021-00294-7

Cagnan H, Denison T, McIntyre C, et al., 2019. Emerging technologies for improved deep brain stimulation. *Nat Biotechnol*, 37(9):1024-1033.
https://doi.org/10.1038/s41587-019-0244-6

Chen ZS, Pesaran B, 2021. Improving scalability in systems neuroscience. *Neuron*, 109(11):1776-1790.
https://doi.org/10.1016/j.neuron.2021.03.025

Cho YU, Lim SL, Hong JH, et al., 2022a. Transparent neural implantable devices: a comprehensive review of challenges and progress. *npj Flex Electron*, 6:53.
https://doi.org/10.1038/s41528-022-00178-4

Cho YU, Lee JY, Jeong UJ, et al., 2022b. Ultra-low cost, facile fabrication of transparent neural electrode array for electrocorticography with photoelectric artifact-free optogenetics. *Adv Funct Mater*, 32(10):2105568.
https://doi.org/10.1002/adfm.202105568

Choi J, Kumar K, Khazali M, et al., 2020. Optimal adaptive electrode selection to maximize simultaneously recorded neuron yield. Proceedings of the 34th International Conference on Neural Information Processing Systems (NeurIPS 2020). Cold Spring Harbor Laboratory, Vancouver, Canada, p.6160-6171.

Cury RG, Pavese N, Aziz TZ, et al., 2022. Gaps and roadmap of novel neuromodulation targets for treatment of gait in Parkinson's disease. *npj Parkinsons Dis*, 8:8.
https://doi.org/10.1038/s41531-021-00276-6

Cuschieri A, Borg N, Zammit C, 2022. Closed loop deep brain stimulation: a systematic scoping review. *Clin Neurol Neurosurg*, 223:107516.
https://doi.org/10.1016/j.clineuro.2022.107516

Dale J, Schmidt SL, Mitchell K, et al., 2022. Evoked potentials generated by deep brain stimulation for Parkinson's disease. *Brain Stimul*, 15(5):1040-1047.
https://doi.org/10.1016/j.brs.2022.07.048

Davidson B, Giacobbe P, Mithani K, et al., 2020. Lack of clinical response to deep brain stimulation of the medial forebrain bundle in depression. *Brain Stimul*, 13(5):1268-1270.
https://doi.org/10.1016/j.brs.2020.06.010

Deisseroth K, 2015. Optogenetics: 10 years of microbial opsins in neuroscience. *Nat Neurosci*, 18(9):1213-1225.
https://doi.org/10.1038/nn.4091

Ding H, Lu LH, Shi Z, et al., 2018. Microscale optoelectronic infrared-to-visible upconversion devices and their use as injectable light sources. *Proc Natl Acad Sci USA*, 115(26): 6632-6637.
https://doi.org/10.1073/pnas.1802064115

Drebitz E, Rausch LP, Kreiter AK, 2020. A novel approach for removing micro-stimulation artifacts and reconstruction of broad-band neuronal signals. *J Neurosci Methods*, 332:108549.
https://doi.org/10.1016/j.jneumeth.2019.108549

Du ZJ, Kolarcik CL, Kozai TDY, et al., 2017. Ultrasoft microwire neural electrodes improve chronic tissue integration. *Acta Biomater*, 53:46-58.
https://doi.org/10.1016/j.actbio.2017.02.010

Elder C, Friedman D, Devinsky O, et al., 2019. Responsive neurostimulation targeting the anterior nucleus of the thalamus in 3 patients with treatment-resistant multifocal epilepsy. *Epilepsia Open*, 4(1):187-192.
https://doi.org/10.1002/epi4.12300

Elsanadidy E, Mosa IM, Hou BW, et al., 2022. Self-sustainable intermittent deep brain stimulator. *Cell Rep Phys Sci*, 3(10): 101099.
https://doi.org/10.1016/j.xcrp.2022.101099

Eom J, Park IY, Kim S, et al., 2021. Deep-learned spike representations and sorting via an ensemble of auto-encoders. *Neural Netw*, 134:131-142.
https://doi.org/10.1016/j.neunet.2020.11.009

Fan JM, Khambhati AN, Sellers KK, et al., 2023. Epileptiform discharges triggered with direct electrical stimulation for treatment-resistant depression: factors that modulate risk and treatment considerations. *Brain Stimul*, 16(2): 462-465.
https://doi.org/10.1016/j.brs.2023.02.006

Fang H, Zhao JN, Yu KJ, et al., 2016. Ultrathin, transferred layers of thermally grown silicon dioxide as biofluid barriers for biointegrated flexible electronic systems. *Proc Natl Acad Sci USA*, 113(42):11682-11687.
https://doi.org/10.1073/pnas.1605269113

Fedor FZ, Madarász M, Zátonyi A, et al., 2022. Soft, thiol-ene/acrylate-based electrode array for long-term recording of intracranial EEG signals with improved biocompatibility in mice. *Adv Mater Technol*, 7(5):2100942.
https://doi.org/10.1002/admt.202100942

Fernandes AM, Mearns DS, Donovan JC, et al., 2021. Neural circuitry for stimulus selection in the zebrafish visual system. *Neuron*, 109(5):805-822.e6.
https://doi.org/10.1016/j.neuron.2020.12.002

Fernandez-Leon JA, Parajuli A, Franklin R, et al., 2015. A wireless transmission neural interface system for unconstrained non-human primates. *J Neural Eng*, 12(5):056005.
https://doi.org/10.1088/1741-2560/12/5/056005

Fernández-Ruiz A, Oliva A, de Oliveira EF, et al., 2019. Long-duration hippocampal sharp wave ripples improve memory. *Science*, 364(6445):1082-1086.
https://doi.org/10.1126/science.aax0758

Frank JA, Antonini MJ, Anikeeva P, 2019. Next-generation interfaces for studying neural function. *Nat Biotechnol*, 37(9):1013-1023.
https://doi.org/10.1038/s41587-019-0198-8

Ghane-Motlagh B, Sawan M, 2013. Design and implementation challenges of microelectrode arrays: a review. *Mater Sci Appl*, 4(8):483-495.

https://doi.org/10.4236/msa.2013.48059
Gong CSA, 2022. IC-based rectification circuit techniques for biomedical energy-harvesting applications. *Micromachines (Basel)*, 13(3):411. https://doi.org/10.3390/mi13030411
Gottschalk S, Degtyaruk O, Mc Larney B, et al., 2019. Rapid volumetric optoacoustic imaging of neural dynamics across the mouse brain. *Nat Biomed Eng*, 3(5):392-401. https://doi.org/10.1038/s41551-019-0372-9
Guan S, Wang J, Gu X, et al., 2019. Elastocapillary self-assembled neurotassels for stable neural activity recordings. *Sci Adv*, 5(3):eaav2842. https://doi.org/10.1126/sciadv.aav2842
Guo YY, Jiang S, Grena BJB, et al., 2017. Polymer composite with carbon nanofibers aligned during thermal drawing as a microelectrode for chronic neural interfaces. *ACS Nano*, 11(7):6574-6585. https://doi.org/10.1021/acsnano.6b07550
Habets JGV, Heijmans M, Kuijf ML, et al., 2018. An update on adaptive deep brain stimulation in Parkinson's disease. *Mov Disord*, 33(12):1834-1843. https://doi.org/10.1002/mds.115
Hart WL, Kameneva T, Wise AK, et al., 2019. Biological considerations of optical interfaces for neuromodulation. *Adv Opt Mater*, 7(19):1900385. https://doi.org/10.1002/adom.201900385
Hickey P, Stacy M, 2016. Deep brain stimulation: a paradigm shifting approach to treat Parkinson's disease. *Front Neurosci*, 10:173. https://doi.org/10.3389/fnins.2016.00173
Hinchet R, Yoon HJ, Ryu H, et al., 2019. Transcutaneous ultrasound energy harvesting using capacitive triboelectric technology. *Science*, 365(6452):491-494. https://doi.org/10.1126/science.aan3997
Hong GS, Lieber CM, 2019. Novel electrode technologies for neural recordings. *Nat Rev Neurosci*, 20(6):330-345. https://doi.org/10.1038/s41583-019-0140-6
Horváth ÁC, Borbély S, Mihók F, et al., 2022. Histological and electrophysiological evidence on the safe operation of a sharp-tip multimodal optrode during infrared neuromodulation of the rat cortex. *Sci Rep*, 12:11434. https://doi.org/10.1038/s41598-022-15367-4
Howell B, Huynh B, Grill WM, 2015. Design and *in vivo* evaluation of more efficient and selective deep brain stimulation electrodes. *J Neural Eng*, 12(4):046030. https://doi.org/10.1088/1741-2560/12/4/046030
Hu DW, Yao MG, Fan Y, et al., 2019. Strategies to achieve high performance piezoelectric nanogenerators. *Nano Energy*, 55:288-304. https://doi.org/10.1016/j.nanoen.2018.10.053
Hu SL, Ciliberti D, Grosmark AD, et al., 2018. Real-time readout of large-scale unsorted neural ensemble place codes. *Cell Rep*, 25(10):2635-2642.e5. https://doi.org/10.1016/j.celrep.2018.11.033
Huang LB, Gan L, Ling BWK, 2021. A unified optimization model of feature extraction and clustering for spike sorting. *IEEE Trans Neural Syst Rehabil Eng*, 29:750-759. https://doi.org/10.1109/TNSRE.2021.3074162
Idogawa S, Yamashita K, Sanda R, et al., 2021. A lightweight, wireless Bluetooth-low-energy neuronal recording system for mice. *Sens Actuators B Chem*, 331:129423. https://doi.org/10.1016/j.snb.2020.129423
Jang J, Baek C, Kim S, et al., 2021. Current stimulation of the midbrain nucleus in pigeons for avian flight control. *Micromachines (Basel)*, 12(7):788. https://doi.org/10.3390/mi12070788
Jarosiewicz B, Morrell M, 2021. The RNS system: brain-responsive neurostimulation for the treatment of epilepsy. *Expert Rev Med Devices*, 18(2):129-138. https://doi.org/10.1080/17434440.2019.1683445
Jeong JW, McCall JG, Shin G, et al., 2015. Wireless optofluidic systems for programmable in vivo pharmacology and optogenetics. *Cell*, 162(3):662-674. https://doi.org/10.1016/j.cell.2015.06.058
Ji BW, Ge CF, Guo ZJ, et al., 2020. Flexible and stretchable opto-electric neural interface for low-noise electrocorticogram recordings and neuromodulation in vivo. *Biosens Bioelectron*, 153:112009. https://doi.org/10.1016/j.bios.2020.112009
Jia YY, Mirbozorgi SA, Lee B, et al., 2019. A mm-sized free-floating wirelessly powered implantable optical stimulation device. *IEEE Trans Biomed Circuits Syst*, 13(4):608-618. https://doi.org/10.1109/TBCAS.2019.2918761
Jia YY, Guler U, Lai YP, et al., 2020. A trimodal wireless implantable neural interface system-on-chip. *IEEE Trans Biomed Circuits Syst*, 14(6):1207-1217. https://doi.org/10.1109/TBCAS.2020.3037452
Jiang LM, Lu GX, Zeng YS, et al., 2022. Flexible ultrasound-induced retinal stimulating piezo-arrays for biomimetic visual prostheses. *Nat Commun*, 13:3853. https://doi.org/10.1038/s41467-022-31599-4
Jørgensen LM, Henriksen T, Mardosiene S, et al., 2021. Parkinson patients have a presynaptic serotonergic deficit: a dynamic deep brain stimulation pet study. *J Cereb Blood Flow Metab*, 41(8):1954-1963. https://doi.org/10.1177/0271678X20982389
Kampasi K, English DF, Seymour J, et al., 2018. Dual color optogenetic control of neural populations using low-noise, multishank optoelectrodes. *Microsyst Nanoeng*, 4:10. https://doi.org/10.1038/s41378-018-0009-2
Khan IS, D'Agostino EN, Calnan DR, et al., 2019. Deep brain stimulation for memory modulation: a new frontier. *World Neurosurg*, 126:638-646. https://doi.org/10.1016/j.wneu.2018.12.184
Khodagholy D, Ferrero JJ, Park J, et al., 2022. Large-scale, closed-loop interrogation of neural circuits underlying cognition. *Trends Neurosci*, 45(12):968-983. https://doi.org/10.1016/j.tins.2022.10.003
Kim CY, Ku MJ, Qazi R, et al., 2021. Soft subdermal implant capable of wireless battery charging and programmable controls for applications in optogenetics. *Nat Commun*, 12:535. https://doi.org/10.1038/s41467-020-20803-y
Kim JH, Lee GH, Kim S, et al., 2018. Flexible deep brain neural probe for localized stimulation and detection with

metal guide. *Biosens Bioelectron*, 117:436-443.
https://doi.org/10.1016/j.bios.2018.06.035

Kim K, Vöröslakos M, Seymour JP, et al., 2020. Artifact-free and high-temporal-resolution in vivo opto-electrophysiology with microLED optoelectrodes. *Nat Commun*, 11:2063.
https://doi.org/10.1038/s41467-020-15769-w

Kim T, Kadji H, Whalen AJ, et al., 2022. Thermal effects on neurons during stimulation of the brain. *J Neural Eng*, 19(5):056029.
https://doi.org/10.1088/1741-2552/ac9339

Kim TI, McCall JG, Jung YH, et al., 2013. Injectable, cellular-scale optoelectronics with applications for wireless optogenetics. *Science*, 340(6129):211-216.
https://doi.org/10.1126/science.1232437

Király B, Balázsfi D, Horváth I, et al., 2020. In vivo localization of chronically implanted electrodes and optic fibers in mice. *Nat Commun*, 11:4686.
https://doi.org/10.1038/s41467-020-18472-y

Krauss JK, Lipsman N, Aziz T, et al., 2021. Technology of deep brain stimulation: current status and future directions. *Nat Rev Neurol*, 17(2):75-87.
https://doi.org/10.1038/s41582-020-00426-z

Kuan YC, Lo YK, Kim Y, et al., 2015. Wireless gigabit data telemetry for large-scale neural recording. *IEEE J Biomed Health Inform*, 19(3):949-957.
https://doi.org/10.1109/jbhi.2015.2416202

Kumari LS, Kouzani AZ, 2023. Electrophysiology-based closed loop optogenetic brain stimulation devices: recent developments and future prospects. *IEEE Rev Biomed Eng*, 16:91-108.
https://doi.org/10.1109/RBME.2022.3141369

Kwarteng E, Cebe M, 2022. A survey on security issues in modern Implantable Devices: solutions and future issues. *Smart Health*, 25:100295.
https://doi.org/10.1016/j.smhl.2022.100295

Lanzio V, Telian G, Koshelev A, et al., 2021. Small footprint optoelectrodes using ring resonators for passive light localization. *Microsyst Nanoeng*, 7:40.
https://doi.org/10.1038/s41378-021-00263-0

Lecomte A, Descamps E, Bergaud C, 2018. A review on mechanical considerations for chronically-implanted neural probes. *J Neural Eng*, 15(3):031001.
https://doi.org/10.1088/1741-2552/aa8b4f

Lee B, Koripalli MK, Jia YY, et al., 2018. An implantable peripheral nerve recording and stimulation system for experiments on freely moving animal subjects. *Sci Rep*, 8:6115.
https://doi.org/10.1038/s41598-018-24465-1

Lee B, Jia YY, Mirbozorgi SA, et al., 2019. An inductively-powered wireless neural recording and stimulation system for freely-behaving animals. *IEEE Trans Biomed Circuits Syst*, 13(2):413-424.
https://doi.org/10.1109/TBCAS.2019.2891303

Lee D, Jeong SH, Yun S, et al., 2021. Totally implantable enzymatic biofuel cell and brain stimulator operating in bird through wireless communication. *Biosens Bioelectron*, 171:112746.
https://doi.org/10.1016/j.bios.2020.112746

Lee J, Ozden I, Song YK, et al., 2015. Transparent intracortical microprobe array for simultaneous spatiotemporal optical stimulation and multichannel electrical recording. *Nat Methods*, 12(12):1157-1162.
https://doi.org/10.1038/nmeth.3620

Lee JM, Lin DC, Kim HR, et al., 2021. All-tissue-like multifunctional optoelectronic mesh for deep-brain modulation and mapping. *Nano Lett*, 21(7):3184-3190.
https://doi.org/10.1021/acs.nanolett.1c00425

Lee KJ, Hong D, Jang JW, et al., 2023. A wireless ECoG recording system to detect brain responses to tactile stimulation. *IEEE Sens J*, 23(12):13692-13701.
https://doi.org/10.1109/JSEN.2023.3272630

Lee S, Cortese AJ, Gandhi AP, et al., 2018. A 250 μm×57 μm microscale opto-electronically transduced electrodes (MOTEs) for neural recording. *IEEE Trans Biomed Circuits Syst*, 12(6):1256-1266.
https://doi.org/10.1109/TBCAS.2018.2876069

Lehto LJ, Canna A, Wu L, et al., 2020. Orientation selective deep brain stimulation of the subthalamic nucleus in rats. *Neuroimage*, 213:116750.
https://doi.org/10.1016/j.neuroimage.2020.116750

Leibig C, Wachtler T, Zeck G, 2016. Unsupervised neural spike sorting for high-density microelectrode arrays with convolutive independent component analysis. *J Neurosci Methods*, 271:1-13.
https://doi.org/10.1016/j.jneumeth.2016.06.006

Li DF, Wang W, Wang HJ, et al., 2008. Polyaniline films with nanostructure used as neural probe coating surfaces. *Appl Surf Sci*, 255(2):581-584.
https://doi.org/10.1016/j.apsusc.2008.06.150

Li JN, Cheng YH, Gu ML, et al., 2023. Sensing and stimulation applications of carbon nanomaterials in implantable brain-computer interface. *Int J Mol Sci*, 24(6):5182.
https://doi.org/10.3390/ijms24065182

Li RH, Hosseini H, Saggar M, et al., 2023. Current opinions on the present and future use of functional near-infrared spectroscopy in psychiatry. *Neurophotonics*, 10(1):013505.
https://doi.org/10.1117/1.NPh.10.1.013505

Li ZH, Wang YT, Zhang N, et al., 2020. An accurate and robust method for spike sorting based on convolutional neural networks. *Brain Sci*, 10(11):835.
https://doi.org/10.3390/brainsci10110835

Libbrecht S, Hoffman L, Welkenhuysen M, et al., 2018. Proximal and distal modulation of neural activity by spatially confined optogenetic activation with an integrated high-density optoelectrode. *J Neurophysiol*, 120(1):149-161.
https://doi.org/10.1152/jn.00888.2017

Ling W, Yu JX, Ma N, et al., 2020. Flexible electronics and materials for synchronized stimulation and monitoring in multi-encephalic regions. *Adv Funct Mater*, 30(32):2002644.
https://doi.org/10.1002/adfm.202002644

Liu CB, Zhao Y, Cai X, et al., 2020. A wireless, implantable optoelectrochemical probe for optogenetic stimulation and dopamine detection. *Microsyst Nanoeng*, 6:64.
https://doi.org/10.1038/s41378-020-0176-9

Liu SJ, Liu L, Zhao Y, et al., 2022. A high-performance electrode based on van der Waals heterostructure for neural recording. *Nano Lett*, 22(11):4400-4409. https://doi.org/10.1021/acs.nanolett.2c00848

Liu X, Lu YC, Iseri E, et al., 2018. A compact closed-loop optogenetics system based on artifact-free transparent graphene electrodes. *Front Neurosci*, 12:132. https://doi.org/10.3389/fnins.2018.00132

Liu XL, Zhu HJ, Qiu T, et al., 2021. A fully integrated sensor-brain–machine interface system for restoring somatosensation. *IEEE Sens J*, 21(4):4764-4775. https://doi.org/10.1109/JSEN.2020.3030899

Lo MC, Widge AS, 2017. Closed-loop neuromodulation systems: next-generation treatments for psychiatric illness. *Int Rev Psychiatry*, 29(2):191-204. https://doi.org/10.1080/09540261.2017.1282438

Luan L, Robinson JT, Aazhang B, et al., 2020. Recent advances in electrical neural interface engineering: minimal invasiveness, longevity, and scalability. *Neuron*, 108(2):302-321. https://doi.org/10.1016/j.neuron.2020.10.011

Lyu HM, Wang JG, La JH, et al., 2018. An energy-efficient wirelessly powered millimeter-scale neurostimulator implant based on systematic codesign of an inductive loop antenna and a custom rectifier. *IEEE Trans Biomed Circuits Syst*, 12(5):1131-1143. https://doi.org/10.1109/TBCAS.2018.2852680

Mager T, de la Morena DL, Senn V, et al., 2018. High frequency neural spiking and auditory signaling by ultrafast red-shifted optogenetics. *Nat Commun*, 9:1750. https://doi.org/10.1038/s41467-018-04146-3

Maimon BE, Sparks K, Srinivasan S, et al., 2018. Spectrally distinct channelrhodopsins for two-colour optogenetic peripheral nerve stimulation. *Nat Biomed Eng*, 2(7):485-496. https://doi.org/10.1038/s41551-018-0255-5

Martínez S, Garcia-Violini D, Belluscio M, et al., 2023. Dynamical models in neuroscience from a closed-loop control perspective. *IEEE Rev Biomed Eng*, 16:706-721. https://doi.org/10.1109/RBME.2022.3180559

Matsushita K, Hirata M, Suzuki T, et al., 2018. A fully implantable wireless ECoG 128-channel recording device for human brain–machine interfaces: W-HERBS. *Front Neurosci*, 12:511. https://doi.org/10.3389/fnins.2018.00511

McIntyre CC, Chaturvedi A, Shamir RR, et al., 2015. Engineering the next generation of clinical deep brain stimulation technology. *Brain Stimul*, 8(1):21-26. https://doi.org/10.1016/j.brs.2014.07.039

Menchón JM, Real E, Alonso P, et al., 2021. A prospective international multi-center study on safety and efficacy of deep brain stimulation for resistant obsessive-compulsive disorder. *Mol Psychiatry*, 26(4):1234-1247. https://doi.org/10.1038/s41380-019-0562-6

Mendrela AE, Kim K, English D, et al., 2018. A high-resolution opto-electrophysiology system with a miniature integrated headstage. *IEEE Trans Biomed Circuits Syst*, 12(5):1065-1075. https://doi.org/10.1109/TBCAS.2018.2852267

Meng L, Jin MY, Zhu XD, et al., 2022. Peripherical electrical stimulation for Parkinsonian tremor: a systematic review. *Front Aging Neurosci*, 14:795454. https://doi.org/10.3389/fnagi.2022.795454

Moghaddasi M, Shoorehdeli MA, Fatahi Z, et al., 2020. Unsupervised automatic online spike sorting using reward-based online clustering. *Biomed Signal Process Control*, 56:101701. https://doi.org/10.1016/j.bspc.2019.101701

Mohanty A, Li Q, Tadayon MA, et al., 2020. Reconfigurable nanophotonic silicon probes for sub-millisecond deep-brain optical stimulation. *Nat Biomed Eng*, 4(2):223-231. https://doi.org/10.1038/s41551-020-0516-y

Molina R, Hass CJ, Cernera S, et al., 2021. Closed-loop deep brain stimulation to treat medication-refractory freezing of gait in Parkinson's disease. *Front Hum Neurosci*, 15:633655. https://doi.org/10.3389/fnhum.2021.633655

Ng KA, Greenwald E, Xu YP, et al., 2016. Implantable neurotechnologies: a review of integrated circuit neural amplifiers. *Med Biol Eng Comput*, 54:45-62. https://doi.org/10.1007/s11517-015-1431-3

Nordi TM, Gounella RH, Luppe M, et al., 2022. Low-noise amplifier for deep-brain stimulation (DBS). *Electronics*, 11(6):939. https://doi.org/10.3390/electronics11060939

Normann RA, Fernandez E, 2016. Clinical applications of penetrating neural interfaces and Utah Electrode Array technologies. *J Neural Eng*, 13(6):061003. https://doi.org/10.1088/1741-2560/13/6/061003

Obaid S, Lu LY, 2019. Highly efficient microscale gallium arsenide solar cell arrays as optogenetic power options. *IEEE Photonics J*, 11(1):8400108. https://doi.org/10.1109/JPHOT.2019.2896005

Obien MEJ, Deligkaris K, Bullmann T, et al., 2015. Revealing neuronal function through microelectrode array recordings. *Front Neurosci*, 8:423. https://doi.org/10.3389/fnins.2014.00423

Ohta Y, Guinto MC, Tokuda T, et al., 2021. Micro-LED array-based photo-stimulation devices for optogenetics in rat and macaque monkey brains. *IEEE Access*, 9:127937-127949. https://doi.org/10.1109/ACCESS.2021.3111666

Oldroyd P, Malliaras GG, 2022. Achieving long-term stability of thin-film electrodes for neurostimulation. *Acta Biomater*, 139:65-81. https://doi.org/10.1016/j.actbio.2021.05.004

Ouyang H, Liu Z, Li N, et al., 2019. Symbiotic cardiac pacemaker. *Nat Commun*, 10:1821. https://doi.org/10.1038/s41467-019-09851-1

Pang N, Meng W, Zhong YS, et al., 2022. Ultrasound deep brain stimulation modulates body temperature in mice. *IEEE Trans Neural Syst Rehabil Eng*, 30:1851-1857. https://doi.org/10.1109/TNSRE.2022.3188516

Parastarfeizabadi M, Kouzani AZ, 2017. Advances in closed-loop deep brain stimulation devices. *J Neuroeng Rehabil*, 14:79.

https://doi.org/10.1186/s12984-017-0295-1

Park S, Heo SW, Lee W, et al., 2018. Self-powered ultra-flexible electronics via nano-grating-patterned organic photovoltaics. *Nature*, 561(7724):516-521. https://doi.org/10.1038/s41586-018-0536-x

Patel B, Chiu S, Wong JK, et al., 2021. Deep brain stimulation programming strategies: segmented leads, independent current sources, and future technology. *Expert Rev Med Devices*, 18(9):875-891. https://doi.org/10.1080/17434440.2021.1962286

Paz JT, Davidson TJ, Frechette ES, et al., 2013. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. *Nat Neurosci*, 16(1):64-70. https://doi.org/10.1038/nn.3269

Petrucci MN, Anderson RW, O'Day JJ, et al., 2020. A closed-loop deep brain stimulation approach for mitigating burst durations in people with Parkinson's disease. Proceedings of the 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society. IEEE, Montreal, QC, Canada, p.3617-3620. https://doi.org/10.1109/EMBC44109.2020.9176196

Pfau J, Ganatra D, Weltin A, et al., 2019. Electrochemical stability of thin-film platinum as suitable material for neural stimulation electrodes. 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). Berlin, Germany, p.3762-3765. https://doi.org/10.1109/EMBC.2019.8856621.

Pimenta S, Rodrigues JA, Machado F, et al., 2021. Double-layer flexible neural probe with closely spaced electrodes for high-density *in vivo* brain recordings. *Front Neurosci*, 15:663174. https://doi.org/10.3389/fnins.2021.663174

Pisanello F, Sileo L, Oldenburg IA, et al., 2014. Multipoint-emitting optical fibers for spatially addressable in vivo optogenetics. *Neuron*, 82(6):1245-1254. https://doi.org/10.1016/j.neuron.2014.04.041

Pol S, Temel Y, Jahanshahi A, 2021. A custom made electrode construct and reliable implantation method that allows for long-term bilateral deep brain stimulation in mice. *Neuromodulation*, 24(2):212-219. https://doi.org/10.1111/ner.13165

Poojari Y, 2017. Silicones for encapsulation of medical device implants. *Silicon*, 9(5):645-649. https://doi.org/10.1007/s12633-017-9603-4

Pool JL, 1954. Psychosurgery in older people. *J Am Geriatr Soc*, 2(7):456-466. https://doi.org/10.1111/j.1532-5415.1954.tb02138.x

Pranti AS, Schander A, Bödecker A, et al., 2017. Highly stable PEDOT: PSS coating on gold microelectrodes with improved charge injection capacity for chronic neural stimulation. *Proceedings*, 1(4):492. https://doi.org/10.3390/proceedings1040492

Price JB, Rusheen AE, Barath AS, et al., 2020. Clinical applications of neurochemical and electrophysiological measurements for closed-loop neurostimulation. *Neurosurg Focus*, 49(1):E6. https://doi.org/10.3171/2020.4.FOCUS20167

Provenza NR, Sheth SA, Dastin-van Rijn EM, et al., 2021. Long-term ecological assessment of intracranial electrophysiology synchronized to behavioral markers in obsessive-compulsive disorder. *Nat Med*, 27(12):2154-2164. https://doi.org/10.1038/s41591-021-01550-z

Qian X, Chen Y, Feng Y, et al., 2017. A method for removal of deep brain stimulation artifact from local field potentials. *IEEE Trans Neural Syst Rehabil Eng*, 25(12):2217-2226. https://doi.org/10.1109/TNSRE.2016.2613412

Rácz M, Liber C, Németh E, et al., 2020. Spike detection and sorting with deep learning. *J Neural Eng*, 17(1):016038. https://doi.org/10.1088/1741-2552/ab4896

Rahman A, Siddik AB, Ghosh TK, et al., 2020. A narrative review on clinical applications of fNIRS. *J Digit Imaging*, 33(5):1167-1184. https://doi.org/10.1007/s10278-020-00387-1

Ramot M, Martin A, 2022. Closed-loop neuromodulation for studying spontaneous activity and causality. *Trends Cogn Sci*, 26(4):290-299. https://doi.org/10.1016/j.tics.2022.01.008

Rhew HG, Jeong J, Fredenburg JA, et al., 2014. A fully self-contained logarithmic closed-loop deep brain stimulation SoC with wireless telemetry and wireless power management. *IEEE J Solid-State Circuits*, 49(10):2213-2227. https://doi.org/10.1109/JSSC.2014.2346779

Riva-Posse P, Choi KS, Holtzheimer PE, et al., 2018. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. *Mol Psychiatry*, 23(4):843-849. https://doi.org/10.1038/mp.2017.59

Roca E, Gobetti A, Cornacchia G, et al., 2023. An expandable chamber for safe brain retraction: new technologies in the field of transcranial endoscopic surgery. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 24(4):326-335. https://doi.org/10.1631/jzus.B2200557

Ryvlin P, Jehi LE, 2022. Neuromodulation for refractory epilepsy. *Epilepsy Curr*, 22(1):11-17. https://doi.org/10.1177/15357597211065587

Scangos KW, Makhoul GS, Sugrue LP, et al., 2021a. State-dependent responses to intracranial brain stimulation in a patient with depression. *Nat Med*, 27(2):229-231. https://doi.org/10.1038/s41591-020-01175-8

Scangos KW, Khambhati AN, Daly PM, et al., 2021b. Closed-loop neuromodulation in an individual with treatment-resistant depression. *Nat Med*, 27(10):1696-1700. https://doi.org/10.1038/s41591-021-01480-w

Schwarz DA, Lebedev MA, Hanson TL, et al., 2014. Chronic, wireless recordings of large-scale brain activity in freely moving rhesus monkeys. *Nat Methods*, 11(6):670-676. https://doi.org/10.1038/nmeth.2936

Seo D, Neely RM, Shen K, et al., 2016. Wireless recording in the peripheral nervous system with ultrasonic neural dust. *Neuron*, 91(3):529-539. https://doi.org/10.1016/j.neuron.2016.06.034

Shabbir I, Lee DM, Choo DC, et al., 2022. A graphene nanoplatelets-based high-performance, durable triboelectric

nanogenerator for harvesting the energy of human motion. *Energy Rep*, 8:1026-1033.
https://doi.org/10.1016/j.egyr.2021.12.020

Shi ZF, Zheng FM, Zhou ZT, et al., 2019. Silk-enabled conformal multifunctional bioelectronics for investigation of spatiotemporal epileptiform activities and multimodal neural encoding/decoding. *Adv Sci*, 6(9):1801617.
https://doi.org/10.1002/advs.201801617

Shim E, Chen Y, Masmanidis S, et al., 2016. Multisite silicon neural probes with integrated silicon nitride waveguides and gratings for optogenetic applications. *Sci Rep*, 6:22693.
https://doi.org/10.1038/srep22693

Shim S, Yun S, Kim S, et al., 2020. A handheld neural stimulation controller for avian navigation guided by remote control. *Biomed Mater Eng*, 30(5-6):497-507.
https://doi.org/10.3233/BME-191070

Shin G, Gomez AM, Al-Hasani R, et al., 2017. Flexible near-field wireless optoelectronics as subdermal implants for broad applications in optogenetics. *Neuron*, 93(3):509-521.e3.
https://doi.org/10.1016/j.neuron.2016.12.031

Sierra RO, Pedraza LK, Barcsai L, et al., 2023. Closed-loop brain stimulation augments fear extinction in male rats. *Nat Commun*, 14:3972.
https://doi.org/10.1038/s41467-023-39546-7

Silverå Ejneby M, Jakešová M, Ferrero JJ, et al., 2022. Chronic electrical stimulation of peripheral nerves via deep-red light transduced by an implanted organic photocapacitor. *Nat Biomed Eng*, 6(6):741-753.
https://doi.org/10.1038/s41551-021-00817-7

Sità L, Brondi M, de Leon Roig PL, et al., 2022. A deep-learning approach for online cell identification and trace extraction in functional two-photon calcium imaging. *Nat Commun*, 13:1529.
https://doi.org/10.1038/s41467-022-29180-0

Slopsema JP, Canna A, Uchenik M, et al., 2021. Orientation-selective and directional deep brain stimulation in swine assessed by functional MRI at 3T. *NeuroImage*, 224:117357.
https://doi.org/10.1016/j.neuroimage.2020.117357

Solanki S, Gupta AK, Saha U, et al., 2023. Triboelectric Nanogenerator-based smart biomedical sensors for healthcare. *Sustain Energy Technol Assess*, 57:103233.
https://doi.org/10.1016/j.seta.2023.103233

Su F, Kumaravelu K, Wang J, et al., 2019. Model-based evaluation of closed-loop deep brain stimulation controller to adapt to dynamic changes in reference signal. *Front Neurosci*, 13:956.
https://doi.org/10.3389/fnins.2019.00956

Su F, Chen M, Zu LL, et al., 2021. Model-based closed-loop suppression of parkinsonian beta band oscillations through origin analysis. *IEEE Trans Neural Syst Rehabil Eng*, 29:450-457.
https://doi.org/10.1109/TNSRE.2021.3056544

Su Y, Routhu S, Moon KS, et al., 2016. A wireless 32-channel implantable bidirectional brain machine interface. *Sensors*, 16(10):1582.
https://doi.org/10.3390/s16101582

Tala F, Leiber J, Fisher H, et al., 2021. A low-cost, wireless, multi-channel deep brain stimulation system for rodents. Proceedings of the 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC). IEEE, Mexico, p.7526-7529.
https://doi.org/10.1109/EMBC46164.2021.9629826

Telkes I, Viswanathan A, Jimenez-Shahed J, et al., 2018. Local field potentials of subthalamic nucleus contain electrophysiological footprints of motor subtypes of Parkinson's disease. *Proc Natl Acad Sci USA*, 115(36):E8567-E8576.
https://doi.org/10.1073/pnas.1810589115

Thiele S, Sörensen A, Weis J, et al., 2020. Deep brain stimulation of the medial forebrain bundle in a rodent model of depression: exploring dopaminergic mechanisms with raclopride and micro-PET. *Stereotact Funct Neurosurg*, 98(1):8-20.
https://doi.org/10.1159/000504860

Thunemann M, Lu YC, Liu X, et al., 2018. Deep 2-photon imaging and artifact-free optogenetics through transparent graphene microelectrode arrays. *Nat Commun*, 9:2035.
https://doi.org/10.1038/s41467-018-04457-5

Tinkhauser G, Pogosyan A, Little S, et al., 2017. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. *Brain*, 140(4):1053-1067.
https://doi.org/10.1093/brain/awx010

Topalovic U, Aghajan ZM, Villaroman D, et al., 2020. Wireless programmable recording and stimulation of deep brain activity in freely moving humans. *Neuron*, 108(2):322-334.e9.
https://doi.org/10.1016/j.neuron.2020.08.021

Topalovic U, Barclay S, Ling CK, et al., 2023. A wearable platform for closed-loop stimulation and recording of single-neuron and local field potential activity in freely moving humans. *Nat Neurosci*, 26(3):517-527.
https://doi.org/10.1038/s41593-023-01260-4

Tremblay S, Acker L, Afraz A, et al., 2020. An open resource for non-human primate optogenetics. *Neuron*, 108(6):1075-1090.e6.
https://doi.org/10.1016/j.neuron.2020.09.027

van der Wal JM, Bergfeld IO, Lok A, et al., 2020. Long-term deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression. *J Neurol Neurosurg Psychiatry*, 91(2):189-195.
https://doi.org/10.1136/jnnp-2019-321758

Walker EY, Sinz FH, Cobos E, et al., 2019. Inception loops discover what excites neurons most using deep predictive models. *Nat Neurosci*, 22(12):2060-2065.
https://doi.org/10.1038/s41593-019-0517-x

Wang L, Fei ZX, Wu ZT, et al., 2023. Wearable bending wireless sensing with autonomous wake-up by piezoelectric and triboelectric hybrid nanogenerator. *Nano Energy*, 112:108504.
https://doi.org/10.1016/j.nanoen.2023.108504

Wang LC, Ge CF, Wang MH, et al., 2020. An artefact-resist optrode with internal shielding structure for low-noise neural modulation. *J Neural Eng*, 17(4):046024.
https://doi.org/10.1088/1741-2552/aba41f

Wang YD, Song YL, Dai YC, et al., 2022. The burst of electrophysiological signals in the suprachiasmatic nucleus of mouse during the arousal detected by microelectrode arrays. *Front Bioeng Biotechnol*, 10:970726. https://doi.org/10.3389/fbioe.2022.970726

White M, Mackay M, Whittaker RG, 2020. Taking optogenetics into the human brain: opportunities and challenges in clinical trial design. *Open Access J Clin Trials*, 2020:33-41. https://doi.org/10.2147/OAJCT.S259702

Wright JP, Mughrabi IT, Wong J, et al., 2022. A fully implantable wireless bidirectional neuromodulation system for mice. *Biosens Bioelectron*, 200:113886. https://doi.org/10.1016/j.bios.2021.113886

Xu HJ, Scholten K, Jiang WX, et al., 2022. Acute in vivo recording with a generic parylene microelectrode array implanted with dip-coating method into the rat brain. Proceedings of the 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC). Glasgow, Scotland, United Kingdom, p.214-217. https://doi.org/10.1109/EMBC48229.2022.9870987

Yang X, Zhou T, Zwang TJ, et al., 2019. Bioinspired neuron-like electronics. *Nat Mater*, 18(5):510-517. https://doi.org/10.1038/s41563-019-0292-9

Yao G, Kang L, Li J, et al., 2018. Effective weight control via an implanted self-powered vagus nerve stimulation device. *Nat Commun*, 9:5349. https://doi.org/10.1038/s41467-018-07764-z

Yu NB, Liang SQ, Lu JW, et al., 2021. Quantified assessment of deep brain stimulation on Parkinson's patients with task fNIRS measurements and functional connectivity analysis: a pilot study. *Chin Neurosurg J*, 7:34. https://doi.org/10.1186/s41016-021-00251-3

Yun S, Koh CS, Jeong J, et al., 2019. Remote-controlled fully implantable neural stimulator for freely moving small animal. *Electronics*, 8(6):706. https://doi.org/10.3390/electronics8060706

Zaaimi B, Turnbull M, Hazra A, et al., 2023. Closed-loop optogenetic control of the dynamics of neural activity in non-human primates. *Nat Biomed Eng*, 7(4):559-575. https://doi.org/10.1038/s41551-022-00945-8

Zaer H, Deshmukh A, Orlowski D, et al., 2021. An intracortical implantable brain-computer interface for telemetric real-time recording and manipulation of neuronal circuits for closed-loop intervention. *Front Hum Neurosci*, 15:618626. https://doi.org/10.3389/fnhum.2021.618626

Zanos S, 2019. Closed-loop neuromodulation in physiological and translational research. *Cold Spring Harb Perspect Med*, 9(11):a034314. https://doi.org/10.1101/cshperspect.a034314

Zátonyi A, Orbán G, Modi R, et al., 2019. A softening laminar electrode for recording single unit activity from the rat hippocampus. *Sci Rep*, 9:2321. https://doi.org/10.1038/s41598-019-39835-6

Zeng Q, Yu SJ, Fan ZH, et al., 2022. Nanocone-array-based platinum-iridium oxide neural microelectrodes: structure, electrochemistry, durability and biocompatibility study. *Nanomaterials*, 12(19):3445. https://doi.org/10.3390/nano12193445

Zhang CC, Zhang YY, Zhan SK, et al., 2018. Telemedical deep brain stimulation: merits and limitations. *Stereotact Funct Neurosurg*, 96(4):272-273. https://doi.org/10.1159/000491603

Zhang F, Aghagolzadeh M, Oweiss K, 2012. A fully implantable, programmable and multimodal neuroprocessor for wireless, cortically controlled brain-machine interface applications. *J Signal Process Syst*, 69(3):351-361. https://doi.org/10.1007/s11265-012-0670-x

Zhang QS, Hu SL, Talay R, et al., 2023. A prototype closed-loop brain–machine interface for the study and treatment of pain. *Nat Biomed Eng*, 7(4):533-545. https://doi.org/10.1038/s41551-021-00736-7

Zhang S, Zhang XP, Zhong HL, et al., 2022. Hypothermia evoked by stimulation of medial preoptic nucleus protects the brain in a mouse model of ischaemia. *Nat Commun*, 13:6890. https://doi.org/10.1038/s41467-022-34735-2

Zhang SY, Yoshida W, Mano H, et al., 2020. Pain control by co-adaptive learning in a brain–machine interface. *Curr Biol*, 30(20):3935-3944.e7. https://doi.org/10.1016/j.cub.2020.07.066

Zhang Z, Li YF, Mouthaan K, et al., 2018. A miniature mode reconfigurable inductorless IR-UWB transmitter–receiver for wireless short-range communication and vital-sign sensing. *IEEE J Emerg Sel Top Circuits Syst*, 8(2):294-305. https://doi.org/10.1109/JETCAS.2018.2799930

Zhang ZH, Russell LE, Packer AM, et al., 2018. Closed-loop all-optical interrogation of neural circuits in vivo. *Nat Methods*, 15(12):1037-1040. https://doi.org/10.1038/s41592-018-0183-z

Zhao D, Sun Q, Cheng S, et al., 2018. Extraction of Parkinson's disease-related features from local field potentials for adaptive deep brain stimulation. *Neurophysiology*, 50(1):57-67. https://doi.org/10.1007/s11062-018-9717-3

Zhao SY, Li G, Tong CJ, et al., 2020. Full activation pattern mapping by simultaneous deep brain stimulation and fMRI with graphene fiber electrodes. *Nat Commun*, 11:1788. https://doi.org/10.1038/s41467-020-15570-9

Zhao Y, Liu CB, Liu ZX, et al., 2019. Wirelessly operated, implantable optoelectronic probes for optogenetics in freely moving animals. *IEEE Trans Electron Devices*, 66(1):785-792. https://doi.org/10.1109/TED.2018.2882397

Zhou A, Santacruz SR, Johnson BC, et al., 2019. A wireless and artefact-free 128-channel neuromodulation device for closed-loop stimulation and recording in non-human primates. *Nat Biomed Eng*, 3(1):15-26. https://doi.org/10.1038/s41551-018-0323-x