



## Review

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# Wireless closed-loop deep brain stimulation using microelectrode array probes

Qianli JIA<sup>1,2</sup>, Yaoyao LIU<sup>1,2</sup>, Shiya LV<sup>1,2</sup>, Yiding WANG<sup>1,2</sup>, Peiyao JIAO<sup>1,2</sup>, Wei XU<sup>1,2</sup>, Zhaojie XU<sup>1,2</sup>, Mixia WANG<sup>1,2</sup>✉, Xinxia CAI<sup>1,2</sup>✉

<sup>1</sup>State Key Laboratory of Transducer Technology, Aerospace Information Research Institute, Chinese Academy of Sciences, Beijing 100190, China

<sup>2</sup>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>

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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

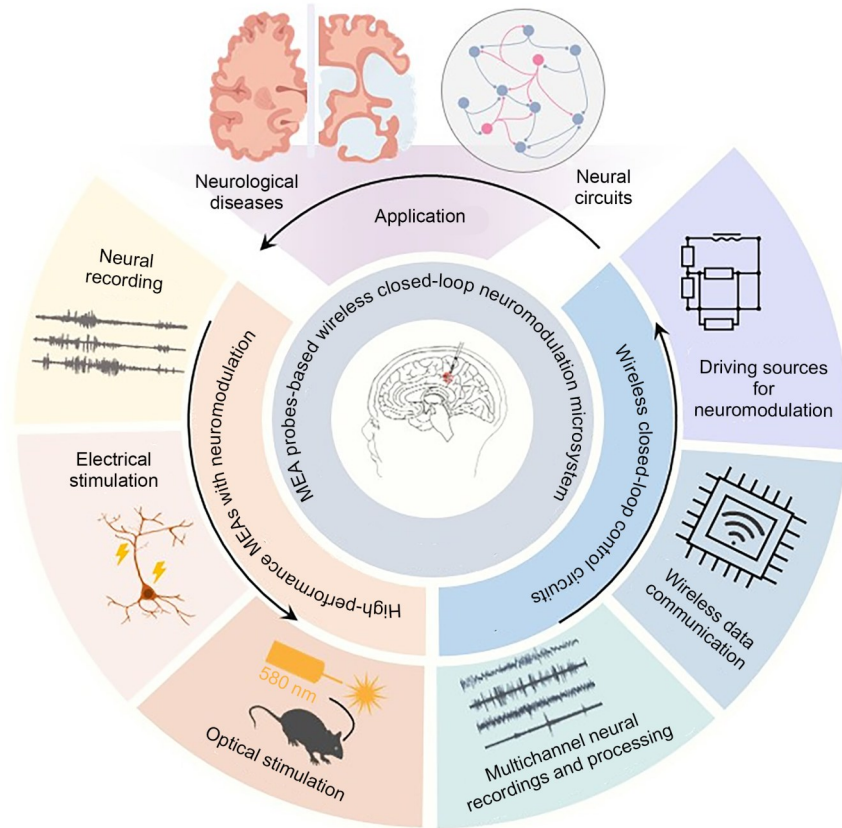
(Fernandez-Leon et al., 2015; Topalovic et al., 2023). Wireless CL-DBS microsystems allow free roaming of animals, thereby enabling exploration of how subjects interact with their environment. Wireless CL-DBS microsystems based on MEA probes would advance neuroscience in a new direction (Zanos, 2019; 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.

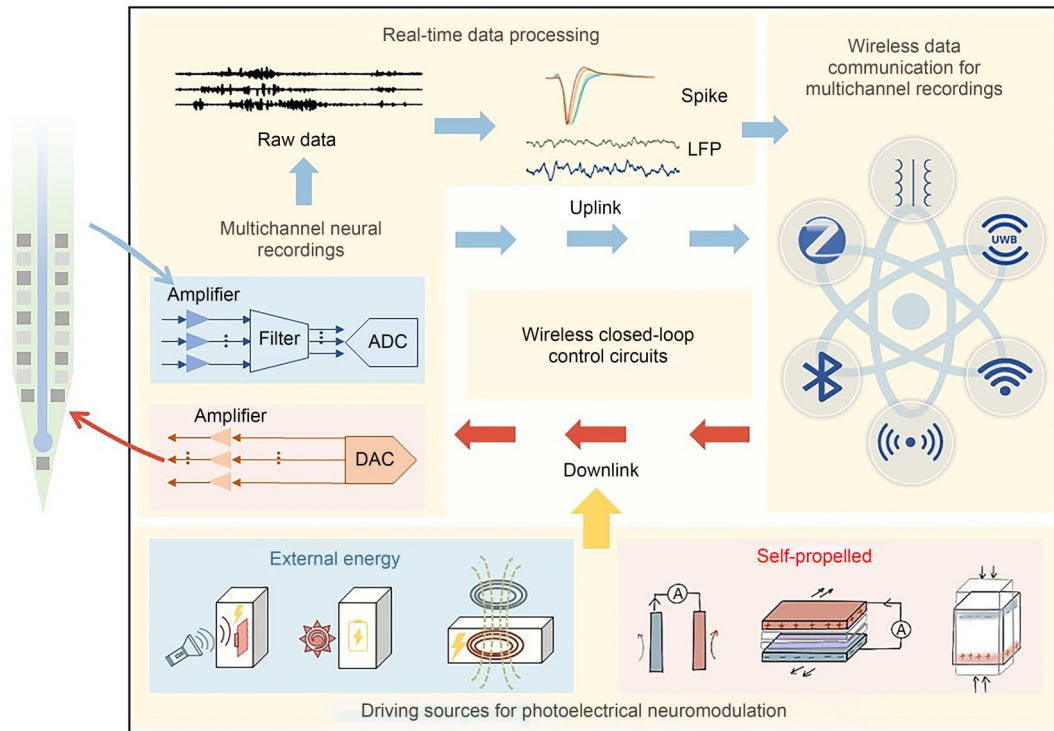
A wireless optical stimulation device implanted in a bird's head designed by Ausra et al. (2021) provides a typical design scheme. Their device has two versions enabling optical stimulation. One is capable of bilateral optogenetic stimulation, while the other can realize both thermography and one-sided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

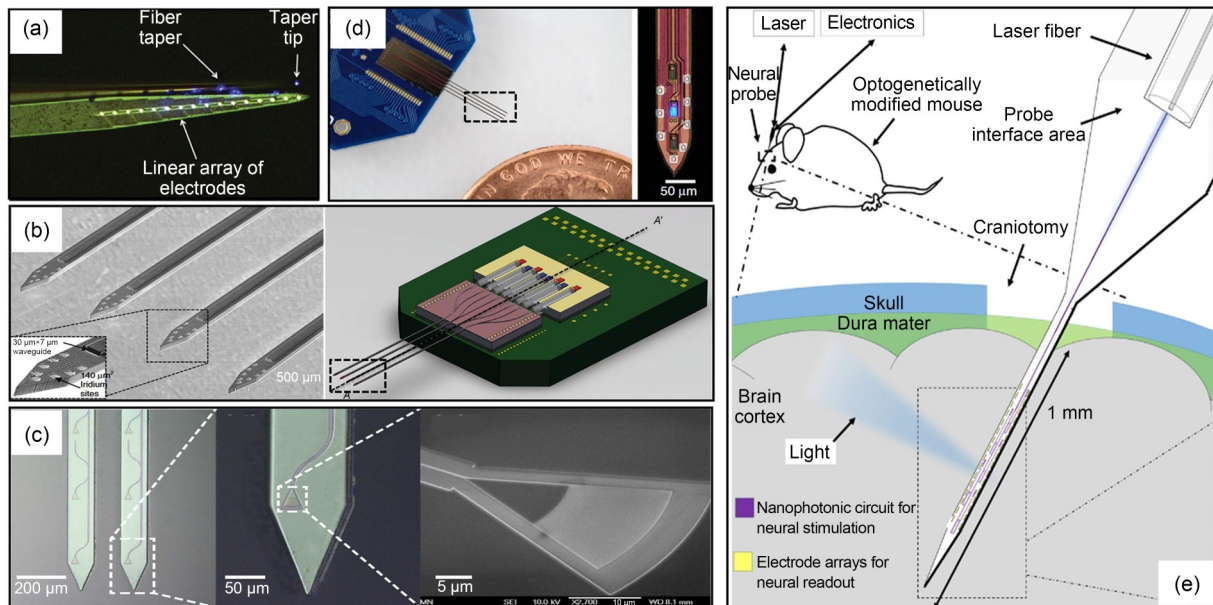
#### 3.1 MEA probes with integrated optical stimulation

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 ( $\mu$ LED)-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  $\mu$ LED-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 ( $\mu$ LEDs) (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  $\mu$ LEDs 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  $\mu$ LED generates Joule heat during optical stimulation, which may affect cell biochemical processes (Kim et al., 2022). However,  $\mu$ LEDs 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.

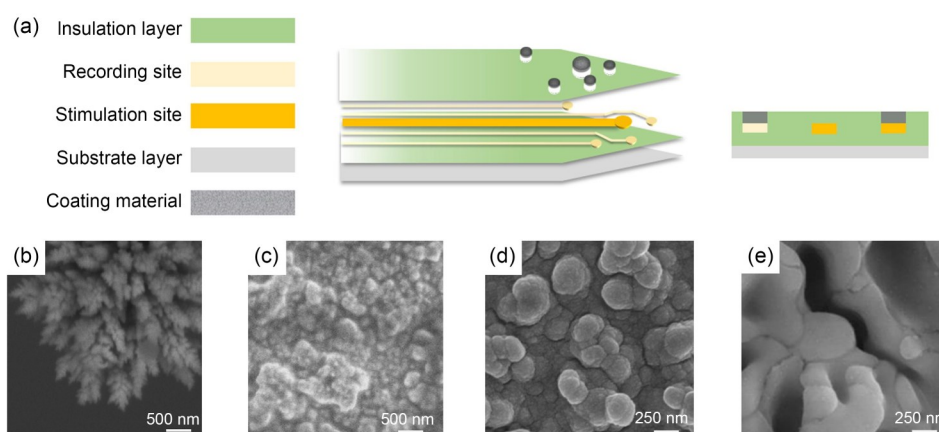
### 3.2 MEA probes with integrated electrical stimulation

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 Medtronic (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<sub>2</sub> (Fang et al., 2016), Al<sub>2</sub>O<sub>3</sub>, 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<sub>4</sub>). The CICs of Au and Pt are usually less than 1 mC/cm<sup>2</sup>, while the CICs of metallization modified with the coating materials are 1–15 mC/cm<sup>2</sup> (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,

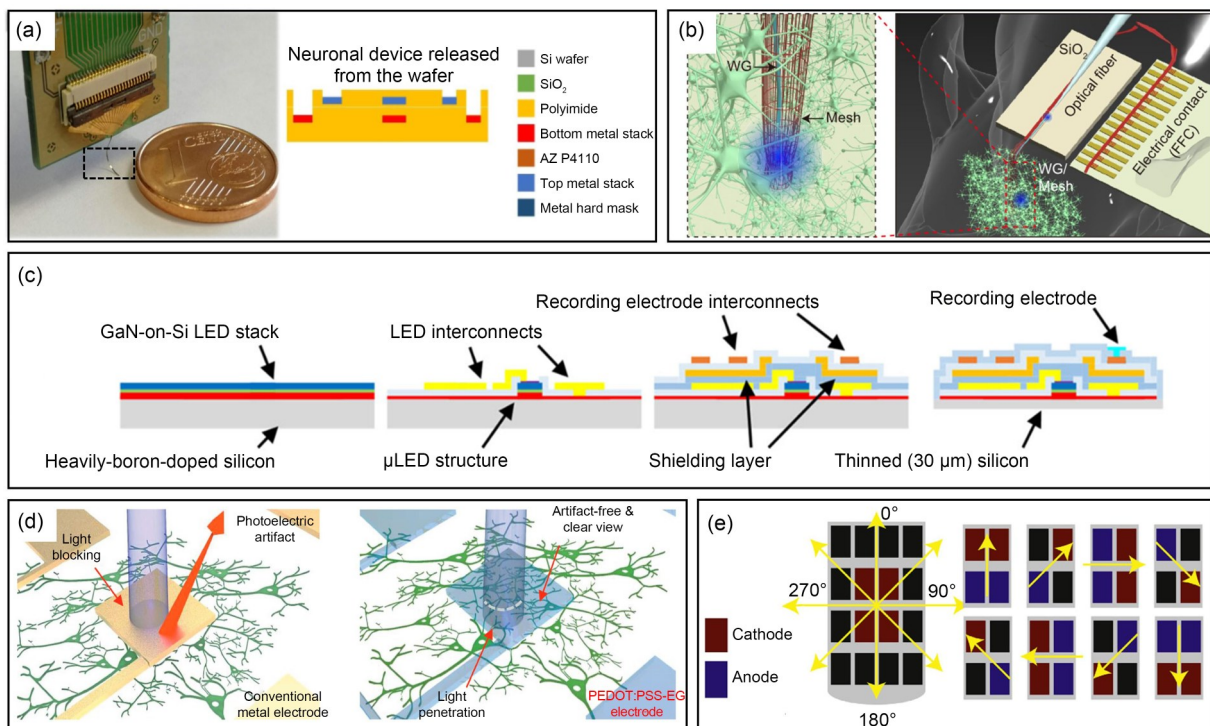
optical stimulation usually induces more localized and less invasive perturbations to the neural tissue, leading to artifacts with smaller amplitude and shorter duration (Dale et al., 2022). These differences may be traced back to the generation of the artifacts. Artifacts arising during optical stimulation 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):polystyrene 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<sub>2</sub>: silicon dioxide; WG: waveguide; FFC: flexible flat cable; GaN: gallium nitride; LED: light emitting diode;  $\mu$ LED: 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) (Rác 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 neuro-modulation microsystems (Table 1). Zhou et al. (2019) used 2.4 GHz Bluetooth low energy (BLE) to

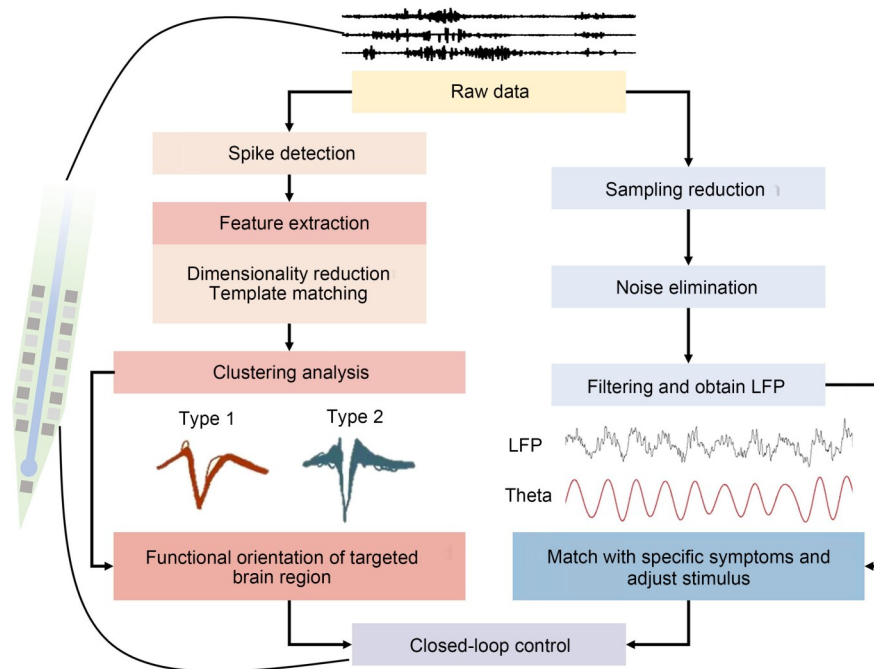


Fig. 6 Flow chart of neural signal processing. LFP: local field potential.

**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		$12 \times 10^3$	$8.456 \times 10^5$	$1 \times 10^3$	1 cm×1 cm	Shin et al., 2017
	Mouse	62	12		$2 \times 10^6$	$6.78 \times 10^6$	$2 \times 10^4$	19.9 mm×18.1 mm×6.6 mm	Wright et al., 2022
RF	Rat	20.7	40	1.5	$6.78 \times 10^6$	$4.34 \times 10^8$	$1 \times 10^3 - 5 \times 10^4$	3 mm×5 mm	Jia et al., 2020
Bluetooth	Primate	172	128	2	$1.96 \times 10^6$	$2.4 \times 10^9$	$1 \times 10^3$	36 mm×33 mm×15 mm	Zhou et al., 2019
	Mouse	28.6	1	5		$2.4 \times 10^9$	$1 \times 10^4$	15 mm×15 mm×12 mm	Idogawa et al., 2021
	Rabbit	378	32	1	$15.36 \times 10^6$	$2.4 \times 10^9$	$3 \times 10^4$	18 mm×15 mm×10 mm	Lee et al., 2023
Wi-Fi	Non-human primate	4000	96	2–4	$24 \times 10^6$	$5.7 \times 10^9 - 5.8 \times 10^9$	$2 \times 10^4$	56 mm×42 mm×44 mm	Fernandez-Leon et al., 2015
		200	128		$1.6 \times 10^6$	$2.4 \times 10^9$	$1 \times 10^3$	55 mm×55 mm	Matsushita et al., 2018
ZigBee	Rat/pigeon	15.2	16	About 10	$2.5 \times 10^3$	$2.4 \times 10^9$		29 mm×26 mm×8 mm	Yun et al., 2019; Jang et al., 2021
UWB	Rhesus macaque	6.4	20	0.4	$10 \times 10^6$	$3 \times 10^9 - 8 \times 10^9$	$1 \times 10^6$	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 <sup>2</sup> )	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.

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### 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.

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