Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) in press
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, PR China*

Abstract: Deep brain stimulation (DBS), including optical and electrical stimulation, has 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 consider recent advances in MEA probe-based wireless CL-DBS microsystems and outline 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: Wireless closed-loop deep brain stimulation (CL-DBS) microsystem; Deep brain stimulation (DBS); Microelectrode array (MEA) probes; 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 rats (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.*,

✉ 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/0000-0002-2705-6827

Received June 5, 2023; Revision accepted Aug. 25, 2023;
Crosschecked xxx. xx, 20xx; Published online xxx. xx, 20xx

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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 (Hickey and Stacy, 2016; Kumari and Kouzani, 2023; McIntyre *et al.*, 2015), and patients must seek professional help for weeks or months to evaluate the stimulation effect and make necessary adjustments (Cury *et al.*, 2022; Provenza *et al.*, 2021). Closed-loop deep brain stimulation (CL-DBS) may increase the flexibility of experiments, reduce power consumption, improve the patient's overall life quality, and alleviate disease symptoms (Cuschieri *et al.*, 2022; Chen and Pesaran, 2021; Parastarfeizabadi and Kouzani 2017; Ramot and Martin 2022; Zanos, 2019). Although imaging technologies such as calcium imaging (Sità *et al.*, 2022; Gottschalk *et al.* 2019; Zhang *et al.* 2018), near-infrared spectroscopy (Li *et al.*, 2023b; Rahman *et al.*, 2020; Yu *et al.*, 2021), magnetic resonance imaging (Martinez *et al.*, 2023; Ramot and Martin, 2022; Zhang *et al.*, 2020), and positron emission tomography (PET) (Jørgensen *et al.*, 2021; Thiele *et al.*, 2020) 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 probes (Hong and Lieber, 2019; Normann and Fernandez, 2016; Oldroyd and Malliaras, 2022). However, microwire electrodes have limitations due to their single-channel per wire design, 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 (MEMS), implantable microelectrode array (MEA) probes are booming due to their multi-site design, which allows for more neural information detection and more refined, 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 could make it difficult for patients to be treated anytime or anywhere (Topalovic *et al.*, 2023; Fernandez-Leon *et al.*, 2015). 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 (Horváth *et al.*, 2022; Zanos, 2019). 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.

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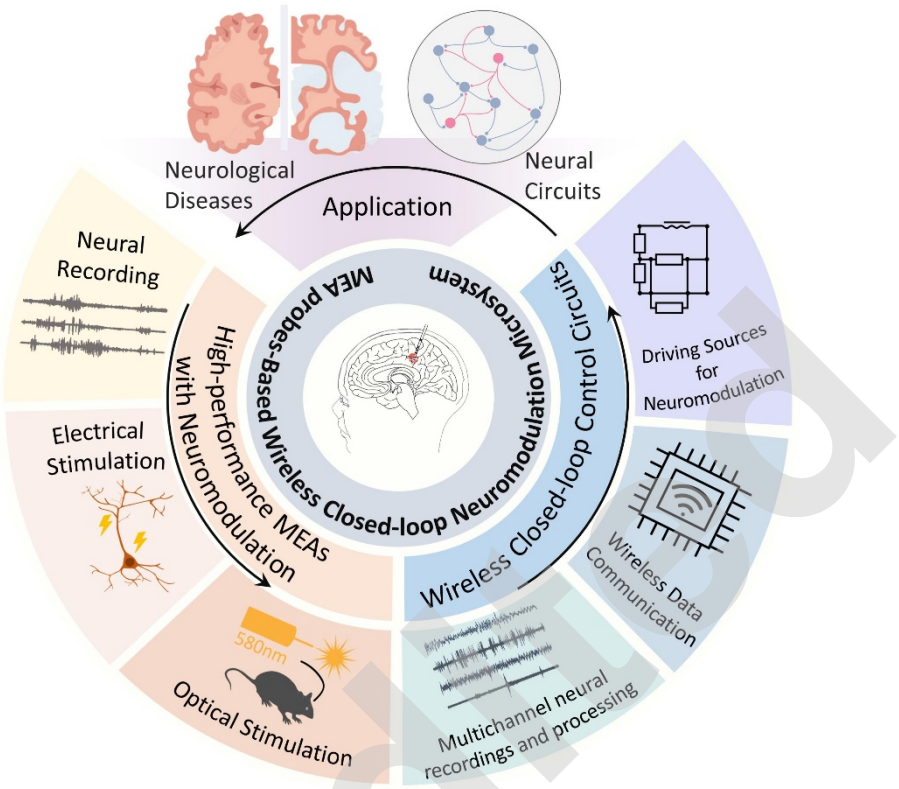

Fig. 1 Elements and applications of wireless CL-DBS microsystems using MEA probes

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 integrated recording and modulating devices 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 introduce an overview of wireless CL-DBS microsystems design. Further details about each part are given in sections 3, 4, 5, and 6.

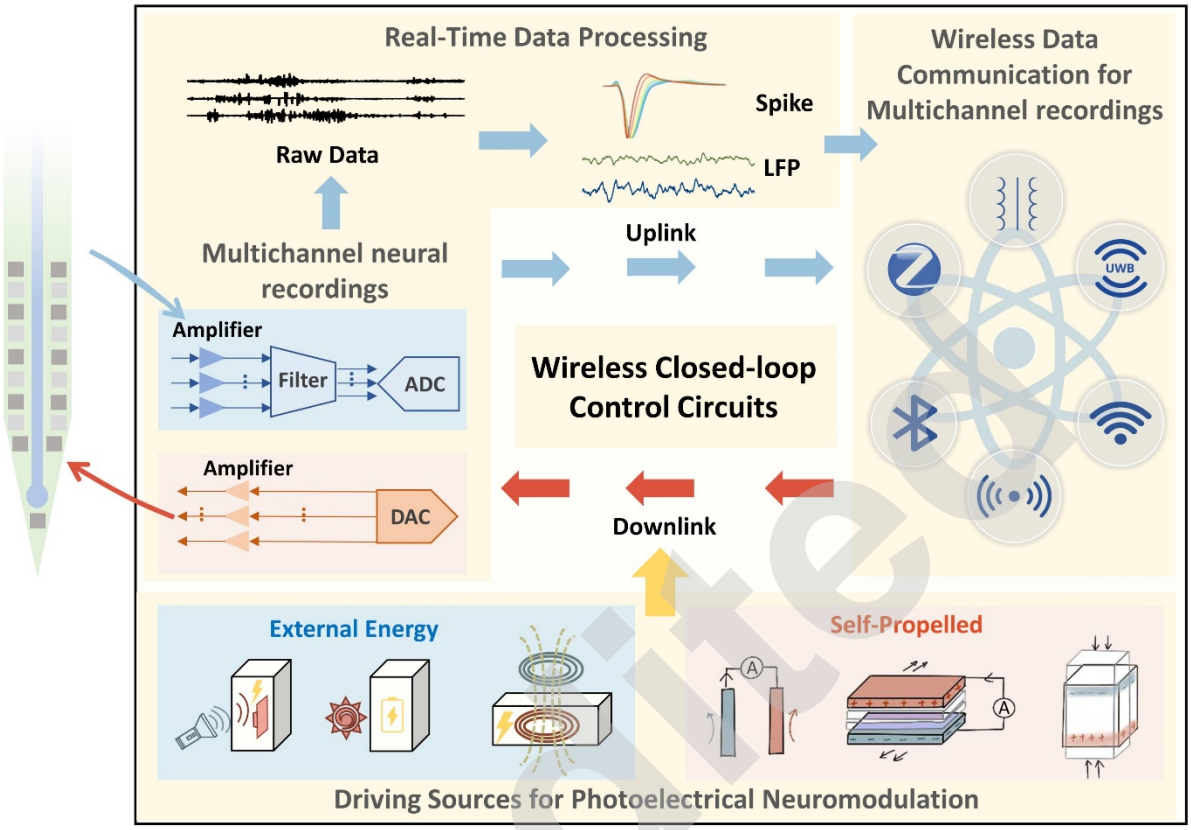

Fig. 2 Main components of wireless CL-DBS microsystems.

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, 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 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 (Liu 2020; Lee *et al.*, 2018; Kim *et al.*, 2021; Jia *et al.*, 2019). For electrical neuromodulation microsystems, stimulation is often triggered after analyzing electrophysiological signals. *Neuro-stack* provides a bidirectional neuromodulation platform. It 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 *WINeRS-8 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 (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 while 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

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systems present a synergistic approach to understanding neural modulation combined with MEA probe-based CL-DBS microsystems.

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.*, 2022). 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 discuss 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) (Fig. 3b,e). This method needs a relatively complex optical alignment process, which may limit the range of application of these devices.

The other method, using microLED 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 be miniaturized and makes neural modulation more precise (Kim *et al.*, 2013; Kim *et al.*, 2020) (Fig 3d). The surface areas of μLEDs are smaller than that 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.*, 2018b). Therefore, they are more easily powered wirelessly.

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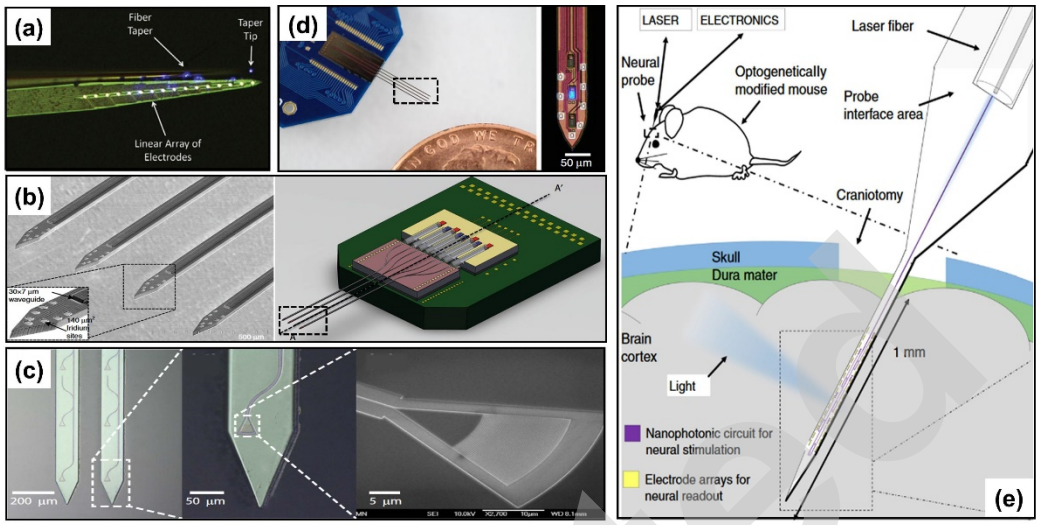

Fig. 3 Examples of MEA probes with integrated optical stimulation

(a) Optogenetics with tapered optical fiber (Pisanello *et al.*, 2014). (b) Multi-shank electrodes with recording sites and waveguides (Kampasi *et al.*, 2018). (c) Photolithographically-formed dielectric waveguide with a rectangular cross-section (Shim *et al.*, 2016). (d) A neural probe with 32 recording sites and 12 μLEDs (Kim *et al.*, 2020). (e) A scalable neural probe combining laser fiber and recording (Lanzio *et al.*, 2021).

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.*, 2022), 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.*, 2022). 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, Boston Scientific, Abbott, and SceneRay. 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

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stimulation are usually fabricated with carbon, stainless steel, silicon (Si), organic and other materials. Unfortunately, carbon fiber (Kumar *et al.*, 2020; Guo *et al.*, 2017), microwires (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, and substrate, 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), SiO2 (Fang *et al.*, 2016), Al2O3 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 2.3.1. Most metallization uses platinum (Pt) (Burton *et al.*, 2021; Pfau *et al.*, 2019), platinum-iridium (Pt-Ir) (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 a low charge injection capacity. The charge injection capacity (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 MEAs to improve the ability to transfer charge and thereby raise the CIC. Common coating materials include porous Pt (Boehler *et al.*, 2020) (Fig. 4b), CP 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 nantotubes (CNTs) (Fig. 4e) (Alvarez *et al.*, 2020; Lee *et al.*, 2021; Li *et al.*, 2023a; Liu *et al.*, 2022), graphene, IrOx (Zeng *et al.*, 2022) (Fig. 4d), and TiN4. 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; Oldroyd and Malliaras, 2022; Zhao *et al.*, 2020). Therefore, modifying the surface metallization with these materials can enhance the efficiency of stimulation.

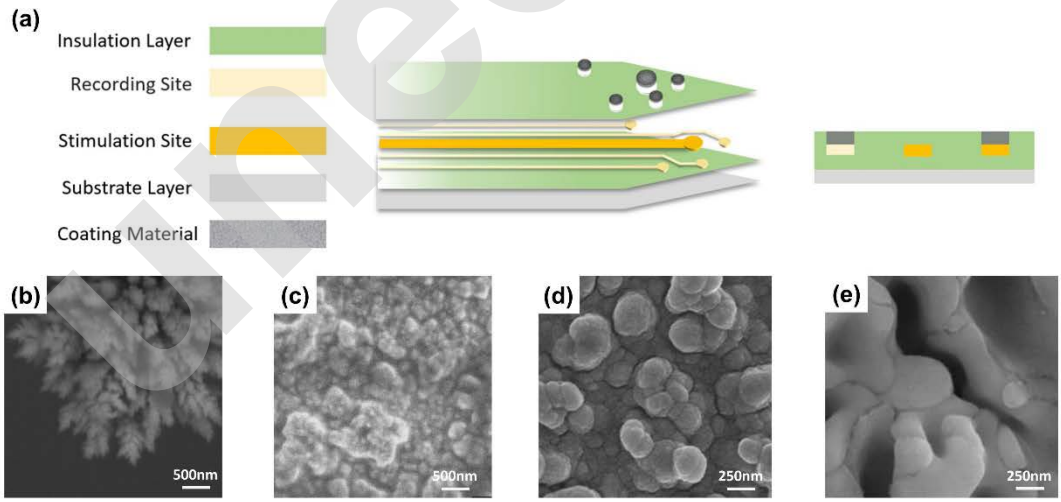

Fig. 4 Multilayers of MEA probes with integrated electrical stimulation and coating materials.
(a) Multilayers of electrical stimulation electrodes. (b-e) SEM images of nanoPt, PEDOT: PSS, IrOx, and graphene deposition. (Boehler *et al.*, 2020; Wang *et al.*, 2022; Zeng *et al.*, 2022; Liu *et al.*, 2022)

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3.3 Improvements in neural signal detection and DBS

3.3.1 Advances in tissue fitting for better 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 silicon-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. On the one hand, 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 silicon-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 liquid crystal polymer packaging and a lifetime of at least 21 days. An SU-8 packaging-multifunctional probe with electrical and optical stimulation was designed, which has a lifetime of at least 7 days (Ling *et al.*, 2020). Thiol-ene/ acrylate shape memory polymer compositions on silicon 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 deep brain stimulation. 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.

On the other hand, biocompatibility can be promoted by altering the geometry of the electrode. Some shapes such as the serpentine shape, 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.*, 2020). 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 *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 electronic design provides insights into the future development of biocompatible electrode geometries. Neuron-like electronic (NeuE) probes have demonstrated stable cell recording without any loss for at least 3 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 5 years.

3.3.2 Minimizing artifacts during stimulation to achieve more reliable recordings

Novel optical and electrical-stimulation MEAs have been developed to increase recording sites while

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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 a 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 introduce 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 silicon-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 silicon substrate to partially eliminate the artifacts caused by photoelectric interference (Fig. 5c). Various materials such as graphene (Thunemann *et al.*, 2018; Xin Liu *et al.*, 2018), carbon nanotubes, hydrogels, transparent conductive oxides (Cho *et al.*, 2022; Lee *et al.*, 2015), and PEDOT: PSS treated with ethylene glycol (Cho *et al.*, 2022) (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 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 discuss 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, Motanty *et al.* (2020) designed a switching network for precisely reconfigurable nanophotonic silicon-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 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 shape 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 and distal modulation. More commercial electrodes increase the number of programmable contacts to enhance options for stimulation direction. 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 degrees 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

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strategies of anodes and cathodes. Advanced current field steering strategies have provided insights for researchers to orient and selectively output a stimulus. Letho *et al.* (2020) have designed a selective strategy in which the spatial gradient of the electric field can be established along various orientations by 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.

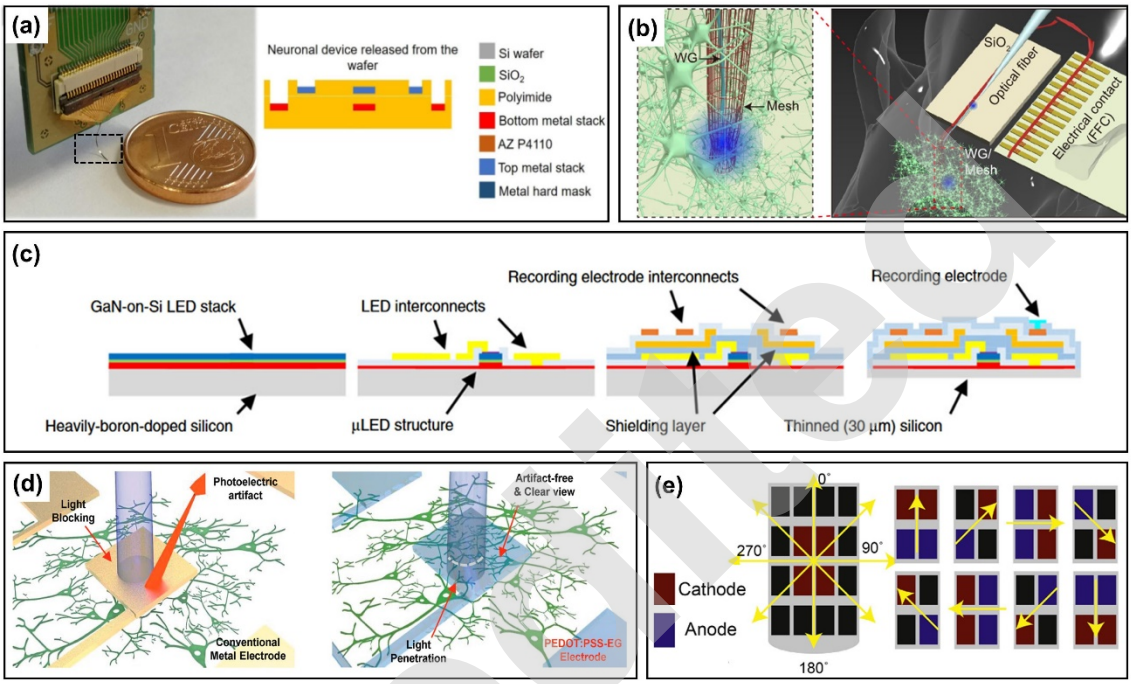

Fig. 5 Improvements in modulation and detection

(a) Lowering the Young's modulus to lessen the mechanical and chemical mismatches between the 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 3D optoelectronic grid (Lee *et al.*, 2021). (c) A flow chart of the construction of a heavy boron doped silicon substrate to eliminate artifacts (Kim *et al.*, 2020). (d) The use of transparent materials such as PEDOT: PSS in transparent implants to minimize stimulation artifacts (Cho *et al.*, 2022). (e) Achieving precise and flexible orientation-selective stimulation (Slopsema *et al.*, 2021).

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

Wireless closed-loop microsystems are responsible for not only receiving signals from electrodes and 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 (Topalovic *et al.*, 2023; Chen and Pesaran, 2021). The electronics for implementing these functions usually includes amplifiers, filters and analog-digital converters (ADC), and digital-analog converters (DAC). 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 (Banu and Gupta, 2022; Rhew *et al.*, 2014; Ng *et al.*, 2016; Nordi *et al.*, 2022), high signal-to-noise ratio filters (Petrucci *et al.*, 2020; Qian *et al.*, 2016), and low-power, high-speed ADC and DAC (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-ch recording and 4-ch

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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 region 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. 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 agent (RL) (Moghaddasi *et al.*, 2020). The analyzed feedbacks not only update stimulation parameters (Zhao *et al.*, 2018a; 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 a rat's running position, to deliver a specific stimulation in real time (Hu *et al.* 2018).

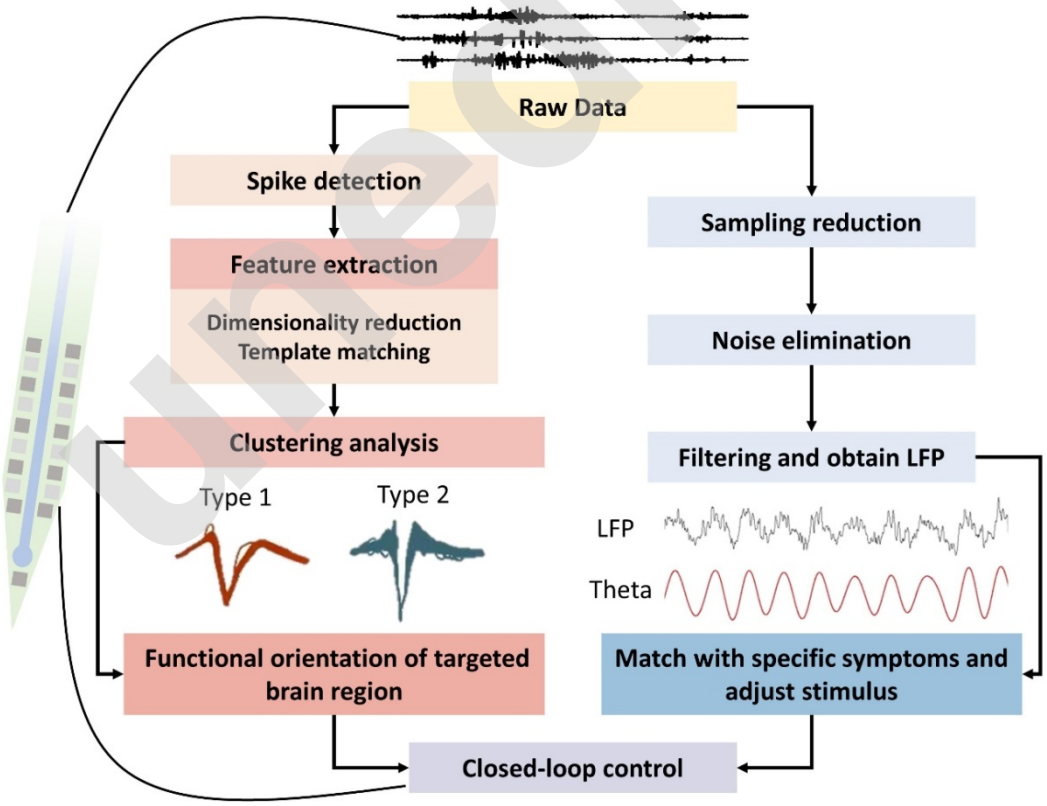

Fig. 6 Flow chart of neural signal processing

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, Wi-fi, Zig-Bee 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-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 detect 128 recording channels in a primate from 2 m away. Wi-Fi can be applied in remote telemedicine (Zhang *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 Mbps 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 (Kwarteng and Cebe, 2022; Shim *et al.*, 2020; Yun *et al.*, 2019). Yun *et al.* (2019) and Zhang *et al.* (2021) 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 250 kpbs. 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 *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).

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Table 1 Different wireless types of data communication

Wireless Type	Model Tested	Power (mW)	Recording and Stimulation Channels	Transmission Distance (m)	Transmission Speed (bps)	Frequency Band (Hz)	Sampling frequency (sps)	Size	References
NIC	-	8	1	-	12 k	845.6 k	1k	1 cm × 1 cm	Shin *et al.*, 2017
RF	Mouse	62	12	-	2 M	6.78 M	20 k	19.9 × 18.1 × 6.6 mm^3	Wright *et al.*, 2022
	Rat	20.7	40	1.5	6.78 M	434	1 – 50 k	3 × 5 mm^2	Jia *et al.*, 2020
	Primate	172	128	2	1.96 M	2.4 G	1 k	36 × 33 ×15 mm^3	Zhou *et al.*, 2019
Bluetooth	Mouse	28.6	1	5	-	2.4 G	10 k	15 × 15 × 12 mm^3	Idogawa *et al.*, 2021
	Rabbit	378	32	1	15.36 M	2.4 G	30 k	18 × 15 × 10 mm^3	Lee *et al.*, 2023
Wi-fi	Non-human Primate	4000	96	2 ~ 4	24 M	5700 - 5800 M	20 k	56 × 42 × 44 mm^3	Fernandez-Leon *et al.*, 2015
	-	200	128	-	1.6 M	2.4 G	1 k	55 × 55 mm^2	Matsushita *et al.*, 2018
Zig-Bee	Rat / Pigeons	15.2	16	~10	250 k	2.4 G	-	29 × 26 × 8 mm^3	Jang *et al.*, 2021; Yun *et al.*, 2019
UWB	Rhesus macaque	6.4	20	0.4	10 M	3 - 8G	1 M	1.1 × 0.4 mm^2	Zhang *et al.*, 2018

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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; Obaid and Lu, 2019; Ejneby *et al.*, 2021; Park *et al.*, 2018; Hu *et al.*, 2019), electromagnetic (Kim *et al.*, 2021; Jia *et al.*, 2019; Shin *et al.*, 2017; Jiang *et al.*, 2022; Bloch *et al.*, 2019), and ultrasonic energy conversion technology (Zhang *et al.*, 2022); and internal power sources, such as nanogenerators, which represent self-driven energy (Shabbir *et al.*, 2022; Ouyang *et al.*, 2019; Elsanadidy *et al.*, 2022; Solanki *et al.*, 2023; Hinchet *et al.*, 2019; 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.

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Table 2 A summary of driving energy

Energy Types		Factors of Output Power	Power Density (mW/cm^2)	Size	Duration	References
External Energy	Optics	Optical power and time duration	10~100	μm^3~mm^3	Months	Ding *et al.*, 2018; Obaid and Lu, 2019; Ejneby *et al.*, 2021; Park *et al.*, 2018; Hu *et al.*, 2019
	Electromagnetic	Input power and load resistance value	2~10	mm^3	Years	Kim *et al.*, 2021; Jia *et al.*, 2019; Shin *et al.*, 2017; Jiang *et al.*, 2022; Bloch *et al.*, 2019
	Ultrasonic	Input power	~10	mm^3~cm^3	Months	Zhang *et al.*, 2022; Xu *et al.*, 2022
Self-Propelled	Piezoelectric nanogenerator	Amplitude and frequency of external stress	2~10	mm^3	Days	Hinchet *et al.*, 2019; Wang *et al.*, 2023
	Triboelectric nanogenerator	Contact and charge density	2~10	mm^3	Months	Shabbir *et al.*, 2022; Yao *et al.*, 2018; Ouyang *et al.*, 2019; Elsanadidy *et al.*, 2022; Solanki *et al.*, 2023

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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 in 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 and 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 (Habets *et al.*, 2018; Tinkhauser *et al.*, 2017). In major depressive disorder, the patient's depression acutely improved and the effect was maintained when an amygdala gamma biomarker was applied in closed-loop therapy (Scangos *et al.*, 2021a). 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.*, 2021).

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.*, 2022). 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 recent trial provided crucial evidence for the theory that thalamocortical neuronal activity is required for poststroke epilepsy online detection. (Paz *et al.*, 2013).

Table 3 Summary of targets and feedbacks in disease therapy

Disease	Possible feedback	Targets	References
Parkinson's disease	Beta activity	STN, GPi, GPe, PPN	Bahadori-Jahromi *et al.* 2023; Bronte-Stewart *et al.* 2020; Molina *et al.* 2021; Su *et al.* 2021; 2019; Habets *et al.* 2018; Tinkhauser *et al.* 2017
Depression	Beta-low-gamma activity / Sharp wave-ripples	SCC, NAcc, LHb, MFB, VC/VS	Fan *et al.* 2023; Riva-Posse *et al.* 2018; Sierra *et al.* 2023; Van Der Wal *et al.* 2020; Davidson *et al.* 2020; Thiele *et al.* 2020
Epilepsy	Gamma activity	ANT	Elder *et al.* 2019
Chronic pain	Spike rates	ACC	Zhang *et al.* 2020
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 the thalamus; ACC, cingulate cortex.

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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 including (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 three-dimensional 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 be focused 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 have 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 to large-scale data processing that require 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.

Data availability statement

Not applicable.

Acknowledgments

This work was sponsored by the National Natural Science Foundation of China (No. T2293731, 62121003, 61960206012, 61973292, 62171434, 61975206 and 61971400), the National Key Research and Development Program of China (No. 2022YFC2402501, 2022YFB3205602), Major Program of Scientific and Technical Innovation 2030 (No. 2021ZD02016030), the Scientific Instrument Developing Project of the Chinese Academy of Sciences (No. GJJSTD20210004). We thank Dr. Yilin Song for her advice on grammar revisions.

Author contributions

Q. Jia, X. Cai, and M. Wang investigated the literature, conceived and wrote the manuscript and figures. X. Cai, M. Wang, S. Lv, Y. Liu, Z. Xu and P. Jiao checked the paper and revised the manuscript. All authors have given approval to the final version of the manuscript.

Compliance with ethics guidelines

Qianli JIA, Yaoyao LIU, Shiya LV, Yiding WANG, Peiyao JIAO, Wei 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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