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Structural and Functional Designs of Advanced Neural Electrodes

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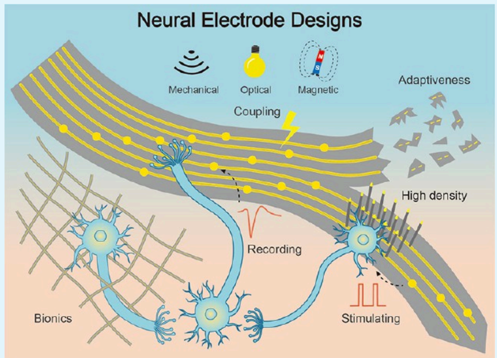
ABSTRACT: Neural electrodes are essential tools for recording and modulating neural activity, particularly in scenarios that require long-term monitoring or complex clinical interventions. This Review highlights recent advances in the structural and functional design of next-generation neural interfaces. We explore the core design principles and emerging trends, focusing on four key strategies: high density, bionic design, adaptive design, and multimodal signal coupling. These innovations are propelling neural electrodes toward more biologically compatible, responsive, and integrated systems, thereby enhancing their potential in clinical therapy and neuroscience investigation.



KEYWORDS: *neural electrodes, high density, bionic design, adaptive design, multimodal signal coupling*

1. INTRODUCTION

The nervous system is a complex network composed of a vast number of neurons and glial cells. It is one of the most complex systems in the human body.[1] This intricate neural network regulates various physiological processes in the human body, including autonomic functions, cognitive abilities, sensory perception, and motor skills.[2,3] Neurons are the basic signaling units of the nervous system, and they communicate with each other by generating and transmitting action potentials.[4,5] The orderly firing of action potentials realizes the encoding, processing, and transmission of information in the brain and peripheral nervous system.

As early as the 18th century, Galvani explored the mechanism of nerve signal transmission by electrically stimulating nerves, marking the inception of modern neurophysiology. Over the past two centuries, the research on the electrical activity of the nervous system has given rise to the birth of neural electrode technology (Figure 1).[6] In the early studies, researchers mainly processed metal wires for neural recording due to the limited technology (Figure 1a). With the advancement of semiconductor technology, Utah electrodes and Michigan electrodes have greatly facilitated research in neuroscience (Figure 1b). As the application of neural electrode technology progresses from the laboratory bench to the bedside, flexible (Figure 1c and d) and advanced neural electrodes offer greater tissue compatibility and recording accuracy. In the future, as more emerging materials and designs (Figure 1e and f) are incorporated, neural electrode technology will further improve medical services and enhance clinical efficacy. Neural electrodes have become an indispensable technology for enabling the transmission of energy and information between the human nervous system and external electronic systems. Advanced neural electrodes can both precisely record the information transmission in complex neural networks and regulate the electrical activity of the nervous system.[7] The interaction between neural electrodes and biological tissues is a dynamic process. Biological systems mainly transmit information through the flow of ions, which is different from the current in neural electrodes. The information exchange between neural electrodes and nerves mainly involves the faradaic charge injection mechanism, which relies on the limited electrochemical reactions at the electrode surface, and the capacitive charge injection mechanism, which depends on the charging/discharging process of the electric double layer (EDL) on the electrode surface without electrochemical reactions. After implantation, the nerve electrodes will trigger an immune response, resulting

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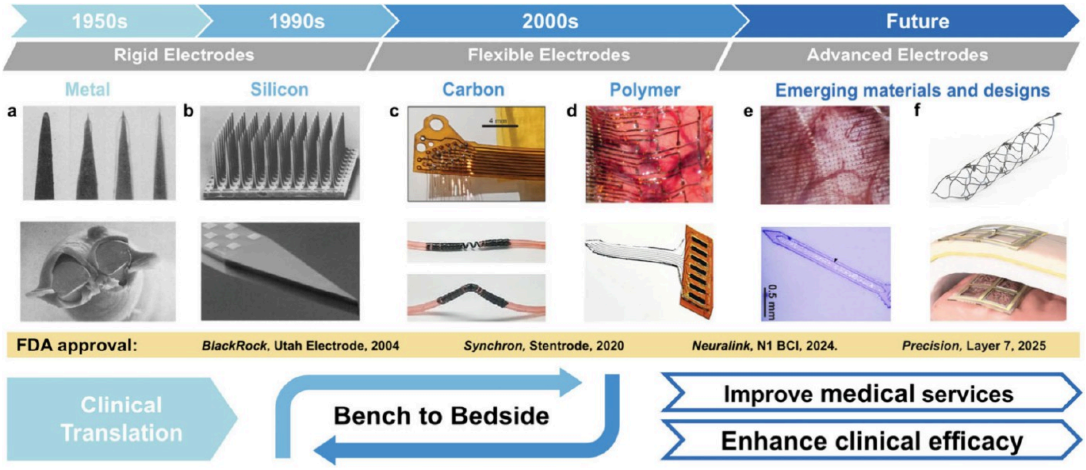

Figure 1. Timeline of neural electrode technology and the clinical transformation roadmap. (a) The tungsten microwire electrode (top)[8] and the tetrode electrode (bottom).[9] Reproduced with permission from ref 8. Copyright 1957 The Authors, AAAS. Reproduced with permission from ref 9. Copyright 1983 Elsevier. (b) Utah electrode array (top)[10] and the Neuropixels probe (bottom).[11] Reproduced with permission from ref 10. Copyright 1997 Elsevier. Reproduced with permission from ref 11. Copyright 2017 The Authors, Springer Nature. (c) Parylene-coated carbon fiber electrode (top)[12] and carbonene fiber neural electrode (bottom).[13] Reproduced with permission from ref 12. Copyright 1990 Elsevier. Reproduced with permission from ref 13. Copyright 2001 Wiley-VCH. (d) The silk fibroin film neural electrode (top)[14] and hydrogel scaffold microelectrode array.[15] Reproduced with permission from ref 14. Copyright 2018 The Authors, Springer Nature. Reproduced with permission from ref 15. Copyright 2001 Wiley-VCH. (e) The multichannel platinum nanorods grid neural electrode (top).[16] Neural stem cell-seeded probe (Hoechst staining nuclei; blue).[17] Reproduced with permission from ref 16. Copyright 2022 The Authors, AAAS. Reproduced from ref 17 under the terms of the CC-BY 4.0 license.[17] (f) The self-expanding nitinol scaffold on which platinum electrodes are mounted (top).[18] Concept of a transcutaneous RF power and data link for a neurograin array.[19] Reproduced with permission from ref 18. Copyright 2018 The Authors, Springer Nature. Reproduced with permission from ref 19. Copyright 1998 Wiley-VCH.

in glial scar formation. At the same time, the mechanical mismatch between the rigid neural electrodes and soft brain tissue can also cause chronic damage. Advanced neural electrode technology has promoted the high-level interaction between the human nervous system and external electronic systems, becoming an important tool for diagnosing and treating neurological diseases and also helping to deeply study the functions and mechanisms of the brain.

One of the most revolutionary applications of neural electrode technology is establishing direct communication pathways between the brain and external devices in the field of brain−computer interfaces (BCIs) (Figure 2). Through neural electrodes, external computer systems receive instructions from the brain, enabling individuals with severe motor disorders to control prosthetic limbs or wheelchairs.[20,21] Similarly, external systems can also issue instructions to the brain, allowing the visually impaired to receive visual signals and the disabled to perceive virtual tactile sensations.[20,22,23] In clinical applications, neural electrodes are also widely utilized for deep brain stimulation (DBS) in the treatment of Parkinson's disease,[24] epilepsy,[25−27] as well as mental disorders such as depression and obsessive-compulsive disorder. Furthermore, neural electrodes play a crucial role in the rehabilitation therapy. They can help individuals with spinal cord injuries regain their motor functions, and can also achieve precise limb movements by stimulating the peripheral nervous system.[28,29] In neuroscience research, neural electrodes can realize real-time, high-quality monitoring of neural signals and closed-loop feedback stimulation.[30−33] This provides powerful technical support for studying the mechanism of brain function, cognition, and learning.

Despite these advancements, neural electrodes exhibit significant limitations, particularly when considered for long-term implantation or for use in complex clinical scenarios. One

Figure 2. A schematic diagram illustrating the applications of neural electrode interfaces, including brain−computer interfaces, nerve stimulation, and neuroscience research. The insets show: brain−computer interfaces for perceiving tactile sensations[23] and controlling prosthetic limbs or wheelchairs,[34] deep brain stimulation for depressive disorder,[35] spinal cord stimulation for the paralyzed,[36] and neural modulation and recording devices for rats[37] and primates.[38] Reproduced with permission from ref 23. Copyright 2025 The Authors, AAAS. Reproduced with permission from ref 34. Copyright 1974 Elsevier. Reproduced with permission from ref 35. Copyright 2014 Canadian Medical Association. Reproduced from ref 36 under the terms of the CC-BY 4.0 license. Reproduced with permission from ref 37. Copyright 2023 The Authors, Springer Nature. Reproduced from ref 38 under the terms of the CC-BY 4.0 license.

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major shortcoming of neural electrodes is their limited spatial resolution. The nervous system contains a dense population of neurons. To achieve effective signal transmission and intervention, high-resolution recording and precise stimulation are essential.[39−43] However, due to the constraints of electrode manufacturing technology and materials, it is difficult to attain a density comparable to that of neurons in the nervous system, making it challenging to capture complex neural activities. In high-resolution recordings, missing or mischaracterizing even a small subset of neural signals can result in the incomplete decoding of brain states or poor therapeutic outcomes. Second, the human nervous system is not only structurally intricate but also functionally diverse.[44] The disparity between the traditional neural electrodes and the live neural tissue can lead to various issues, including signal degradation, inflammation,[45,46] glial scarring,[47−50] and eventual loss of function. These challenges are further exacerbated when electrodes are implanted in different regions of the nervous system, which possess distinct anatomical, structural, and electrophysiological characteristics. The third limitation is the dynamic adaptability of traditional neural electrodes. The brain and surrounding nerves move during physiological activities and also grow with the human body.[51,52] Once a fixed neural electrode is implanted in this environment, it is unable to adapt to the movements of neural tissues. This results in prolonged mechanical stimulation, leading to the formation of a glial sheath around the implant, which insulates it from the neurons and, consequently, diminishes its performance over time. Furthermore, the immutable design of the traditional neural electrodes renders them unsuitable for various surgical conditions and anatomical constraints.[37,53−55] Additionally, implanted neural electrodes require an external energy source to operate effectively. However, the confined space and immune response restrict the permissible size, shape, and material composition of the neural electrodes, thereby introducing additional challenges to maintaining stable and efficient signal exchange. To address these complex challenges, the structural and functional design of neural electrodes has become a central focus of research in the field of neural engineering.

In this Review, we summarize four primary directions in the design of neural electrode structures and their functions: high density, bionic design, adaptive design, and multimodal signal coupling (Figure 3). Advances in microfabrication technology have made it possible to have hundreds or even thousands of recording check points on a single nerve electrode. These high-density nerve electrodes can record the spatial distribution of nerve activity with high resolution and enable effective neural intervention. The structural design of neural electrodes is focused on replicating the characteristics of natural nerve tissue through the utilization of various materials, including polymers, hydrogels, biomolecules, and even living cells. This approach seeks to reduce foreign body responses and enhance the long-term stability of the recording process.

Electrodes that can actively adapt to changes in the nervous system are also crucial for long-term implantation. Recent advancements in adaptive designs include shape-adapted materials, self-healing, biodegradable nerve electrodes, etc. It is imperative that neural electrodes effectively receive and transmit electrical signals while operating within the limitations imposed by the internal physiological environment. Multimodal signal coupled transmission significantly enhances the versatility of neural interfaces, making neural electrodes suitable for a wider range of research and clinical scenarios.

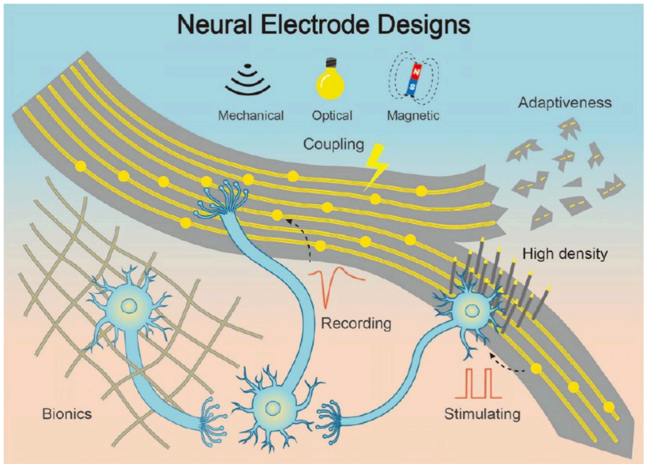

Figure 3. A schematic diagram illustrating the structural and functional designs of advanced neural electrode interfaces, which include high density, bionic design, adaptive design, and multimodal signal coupling.

The design strategy of these four neural electrodes marks a new chapter in the evolution of neural interfaces. It represents the transition from traditional single-function neural electrodes to advanced neural electrodes that can intelligently interact with complex nervous systems. With the wider clinical application of neural electrodes, the design of neural electrodes with specific structures and functions for different clinical scenarios will be the main research direction in the future.

2. HIGH-DENSITY NEURAL ELECTRODES

Advanced neural electrode interfaces must effectively communicate with the complex nervous system. The human brain contains nearly 100 billion neurons, and each forms synaptic connections with approximately 1,000 others, resulting in an immensely dense and interconnected network.[51] During the exchange of electrical signals between electrodes and neurons, voltage-gated ion channels cause depolarization of the cell membrane, generating action potentials that can be recorded by the neural electrodes. To accurately target specific neurons and capture detailed signals, the probe must be sufficiently small and positioned close to the depolarized membrane region.[56,57] Additionally, electrodes can stimulate neighboring neurons by inducing a localized electric field that activates voltage-gated ion channels,[58,59] without influencing distant neurons.[50] These pose a challenge to the density of the neural electrodes. The high-density neural electrode is critical for achieving precise neural stimulation and reliable single-neuron recording.[60]

The progression of electrode density within neural interface technology mirrors the advancements outlined by Moore's Law in semiconductor electronics. In neurotechnology, a comparable trend has been observed: the number of neurons that can be recorded simultaneously has approximately doubled every seven years.[61] Although recent advancements have increased the number of recording channels up to thousands, the current recording capacity still falls significantly short of the theoretical requirements for comprehensive brain monitoring.[62] Traditional high-resolution neural electrodes are typically fabricated from metal or silicon. These rigid materials

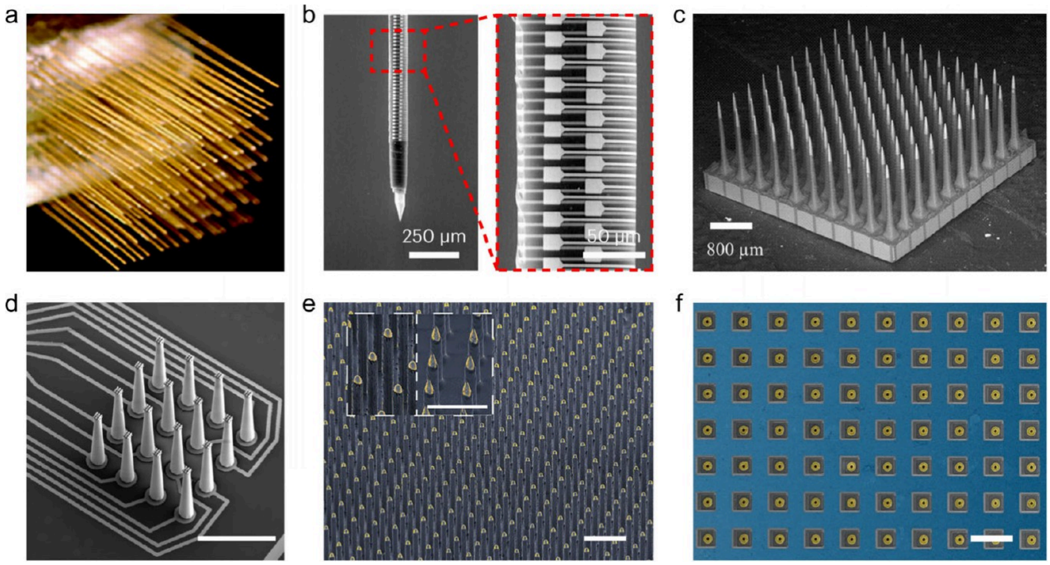

Figure 4. (a) 128-channel, 50 μm Teflon-coated stainless steel microwire electrode array.[33] Reproduced with permission from ref 33. Copyright 2003 National Academy of Sciences, U.S.A. (b) The Cr/Au array is encapsulated between two thin layers of polyimide and wound around a tungsten microwire to create a cylindrical high-density probe array.[64] Reproduced with permission from ref 64. Copyright 2024 The Authors, Springer Nature. (c) The Utah Electrode Array consists of 100 silicon electrodes arranged in a 10 × 10 grid.[69] Reproduced with permission from ref 69. Copyright 1996 IOP Publishing. (d) A 16-channel, 3D-printed electrode array was fabricated using direct laser writing.[70] Scale bar: 400 μm. Reproduced from ref 70 under the terms of the CC-BY 4.0 license. (e) A highly uniform 6600-microelectrode array is presented. The inset illustrates the conical and the hemispherical tips.[71] Scale bar: 50 μm. Reproduced from ref 71 under the terms of the CC-BY 4.0 license. (f) A platinum/platinum-black microhole electrode array was fabricated on a complementary metal-oxide semiconductor chip.[72] Scale bar: 20 μm. Reproduced with permission from ref 72. Copyright 2025 The Authors, Springer Nature.

support high-precision microfabrication, allowing for well-defined electrode geometries and a high channel count. However, rigid neural electrodes have considerable drawbacks. Due to their mechanical mismatch with soft brain tissue, they can induce chronic damage, inflammation, and glial scarring, all of which compromise long-term recording performance and biocompatibility. Moreover, the rigid structure of traditional electrodes limits their ability to adapt to the curved surfaces of neural tissue, thereby limiting their spatial coverage and effectiveness.

To address these limitations, researchers have focused on developing high-density electrodes made from flexible and stretchable materials, such as polymers, hydrogels, and elastomers. These soft electrode arrays can conform to the mechanical properties of neural tissues, thereby enhancing the stability of long-term recordings. Soft electrodes with a high channel count and fine spatial resolution present the potential for both long-term and high-resolution signal acquisition. In summary, research on complex nervous systems is driving the demand for high-density neural electrodes.

2.1. High-Density Rigid Neural Electrodes. Traditional high-density rigid neural electrodes are primarily fabricated from metal- and silicon-based materials. Metals, recognized for their excellent electrical conductivity and ease of processing, were among the earliest materials utilized in the manufacture of high-density neural electrodes. Commonly employed metals in neural interfaces include gold, tungsten, platinum, platinum−iridium alloys, and nickel−chromium alloy. A representative example is the microwire electrode, which consists of fine metal wires insulated with materials, such as rubber or polyimide. These microwires can be individually assembled onto custom-designed printed circuit boards (PCBs), facilitating efficient electrical connections to external systems. By stacking multiple PCBs populated with microwires, researchers can construct high-resolution microwire electrode arrays capable of recording action potentials from up to 247 individual cortical neurons simultaneously (Figure 4a).[33] To further enhance electrode density, complementary metal-oxide-semiconductor (CMOS) technology has been integrated with metal electrodes. By combination of platinum−iridium microwire arrays with CMOS voltage amplifier arrays, a high-resolution in vivo neural recording system has been developed. This system can record spiking activity from 791 neurons in rats and surface local field potential (LFP) signals from over 30,000 channels in sheep.[63] Metal microelectrode arrays can also be produced by using standard photolithography, metal deposition, and dry etching processes. One example involves chromium/gold (Cr/Au) electrode arrays encapsulated between two thin layers of polyimide, which are subsequently rolled onto tungsten microwires to create cylindrical high-density probe arrays (Figure 4b).[64] This configuration has facilitated the simultaneous recording of hundreds of well-isolated single units in the brains of rhesus macaques.

In addition to metal electrodes, there has been a notable emphasis on the advancement of silicon-based high-resolution neural electrodes. These include planar neural microelectrodes and out-of-plane neural probe arrays. Silicon-based planar neural microelectrodes, often referred to as Michigan probes,[65] are fabricated using integrated circuit (IC) processing techniques. By employing advanced microfabrication techniques, such as ultraviolet (UV) lithography[66] and electron beam lithography,[67] a high density of fine conductive traces can be patterned onto silicon substrates with widths as narrow as 100 μm. One of the most notable silicon-based electrodes is the Neuropixels probe developed by the Interuniversity Microelectronics Centre (IMEC). These probes feature 384 recording channels that can address 960 CMOS-compatible, low-impedance titanium nitride (TiN_6) sites.[68] Neuropixels

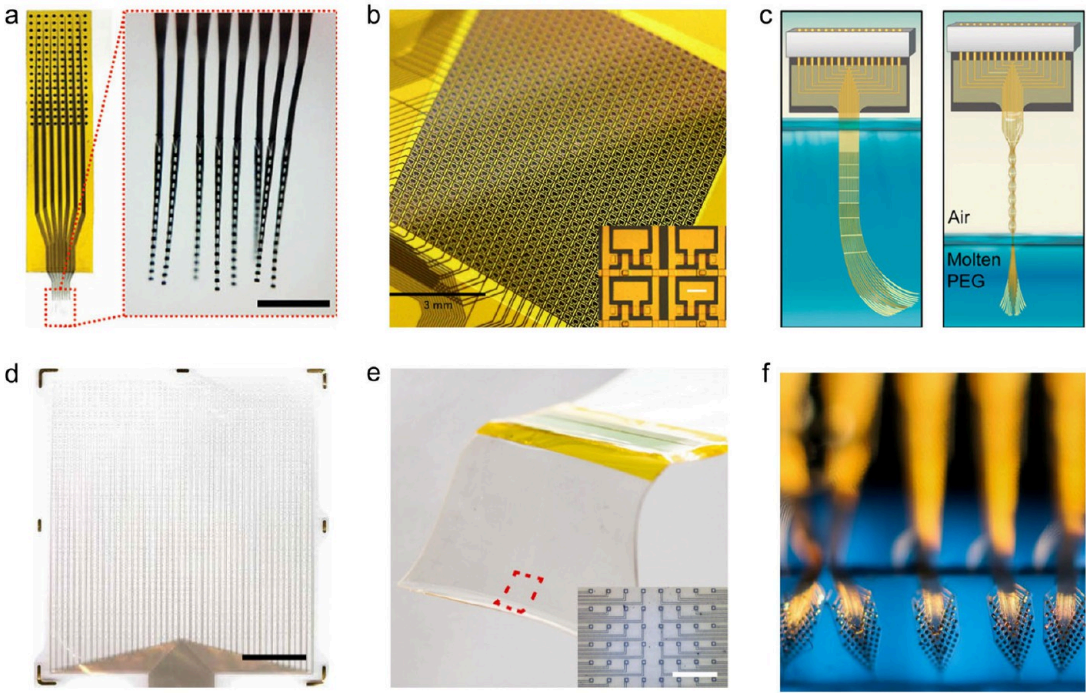

Figure 5. (a) A 128-channel electrode array module featuring a polyimide substrate. The red dotted box highlights the released front end.[86] Scale bars: 500 μm. Reproduced with permission from ref 86. Copyright 2017 The Authors, Springer Nature. (b) 1008-channel Neural Matrix array.[30] The inset illustrates that each electrode is connected to a unit cell composed of two flexible silicon transistors. Scale bar: 100 μm. Reproduced with permission from ref 30. Copyright 2020 The Authors, AAAS. (c) The thin, implantable fibers spontaneously assembled through elastocapillary interactions.[87] Reproduced with permission from ref 87. Copyright 2019 The Authors, AAAS. (d) A 2048-channel platinum nanorod grid neural electrode array.[16] Scale bars: 2 cm. Reproduced with permission from ref 16. Copyright 2022 The Authors, AAAS. (e) The flexible and stretchable electrode features a 100 mm electrode site.[107] The inset illustrates the active site with a 100 mm electrode width. Scale bars: 1 mm. Reproduced with permission from ref 107. Copyright 2022 The Authors, AAAS. (f) PFPE-DMA elastomer-encapsulated neural probes featuring four layers of electrode arrays that self-wrap around a glass capillary.[109] Reproduced with permission from ref 109. Copyright 2006 The Authors, Springer Nature.

probes facilitate large-scale neural recordings from freely moving animals and have become a widely adopted tool in systems neuroscience. Another prominent example is the Utah Electrode Array (UEA), developed at the University of Utah. The microneedles utilized in the UEA are usually short and can be tailored to different lengths according to the experimental requirements, making them highly suitable for cortical recordings. To enhance longevity, the UEA interface is typically encapsulated. After deinsulation, the electrode tips are exposed for high-resolution signal acquisition (Figure 4c).[69] By integrating traditional silicon thin-film processes with direct laser writing, complex three-dimensional electrode structures can now be fabricated at micron-scale resolution (Figure 4d).[70] The combination of two-photon polymerization and scalable micronano fabrication techniques enables high-resolution 3D printing, allowing for the direct creation of dense, tissue-penetrating electrode arrays. For instance, a neural probe comprised of 6,600 microelectrodes spaced at 35 μm intervals has been fabricated directly on a planar microelectronic substrate (Figure 4e).[71] The application of two-photon lithography in neural engineering represents a significant step toward high-resolution and minimally invasive brain-machine interfaces. In addition to the microneedle design, neural probes can also be fabricated in a microhole form. For instance, 4,096 platinum/platinum-black microhole electrodes can be integrated onto a CMOS chip, enabling parallel and high-resolution measurement of synaptic signals within neural networks. This microhole configuration provides an effective method for capturing intracellular activity across numerous sites simultaneously, thereby enhancing our ability to study complex neural dynamics at both cellular and subcellular levels (Figure 2f).[72]

Although rigid electrodes made from metals and silicon provide high fabrication precision, their mechanical stiffness can result in considerable tissue damage following implantation, thereby limiting their suitability for long-term applications. The discrepancy in the Young's modulus between the electrode and the soft neural tissue frequently results in inflammation and signal degradation over time. To address these challenges, researchers have increasingly focused on developing flexible, high-resolution neural electrodes that provide enhanced mechanical compatibility with biological tissue and improved long-term performance in neural recording and stimulation.

2.2. High-Density Flexible Neural Electrodes. To address the mechanical rigidity difference between the neural electrodes and the brain tissue, researchers have proposed advanced strategies and developed flexible neural electrodes: structural designs such as ultrathin mesh designs,[41,73−75] and flexible materials like flexible polymers[76−79] and hydrogels.[80−82] Constructing high-density flexible neural electrodes is essential for minimizing mechanical mismatch at the electrode−tissue interface, thereby facilitating high spatial resolution and long-term stability when recording from soft, structurally complex neural tissues. Flexible polymers are commonly employed utilized the development of these electrodes due to their excellent mechanical compliance and electrochemical stability.[83,84] Among these materials, poly-

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imide is widely favored for its outstanding electrical insulation and flexibility.[85] Flexible high-density neural electrode arrays fabricated with polyimide substrates have demonstrated the ability to stably record electrophysiological signals across multiple cortical regions in rats for extended periods. These arrays can achieve a recording density of up to 1000 neural units per cubic millimeter (Figure 5a).[86]

However, a significant limitation of high-density neural electrodes lies in the lead wire routing. The number of electrodes that can be simultaneously sampled is often constrained by the capacity of the connection interface. To address this issue, multiplexed electrode arrays have been developed, allowing for a large number of electrodes to be connected to a limited number of external leads. This approach has facilitated intracerebral neural recordings with over 1,000 channels distributed across centimeter-scale brain regions (Figure 5b).[30] Additionally, polyimide can be processed into microelectrode wires to create compact and dense linear electrode arrays. Notably, ultrathin implantable fibers that self-assemble through elastic capillary action have demonstrated the ability to enable stable, long-term monitoring of individual neurons (Figure 5c).[87]

Despite these advances, the mechanical properties of polyimides still fall short of those of certain applications. Although they are flexible, their stiffness exceeds that of soft neural tissues, especially in regions with considerable curvature such as the cerebral cortex. This discrepancy can impede the high-resolution recordings in anatomically complex regions. To address this issue, researchers are exploring softer polymer substrates. For example, a platinum nanorod electrode array fabricated on a thin, highly conformal parylene C substrate has facilitated detailed spatial mapping of epileptic discharge dynamics with a resolution of 1 mm in human patients undergoing epilepsy surgery (Figure 5d).[16]

While polyimide and Parylene C are classic choices for flexible neural probes, the SU-8 epoxy photoresist offers distinct advantages. Possessing a lower Young's modulus (∼2–3 GPa) yet high strength and excellent pattern fidelity, SU-8 enables lithography of high-aspect-ratio features. When used as thin films or mesh patterns, these properties provide sufficient flexibility while maintaining mechanical robustness, making it widely employed as a structural and passivation layer in advanced flexible/mesh neural probes.[88−90] Moreover, this capability extends to multifunctional designs, enabling seamless and simultaneous optogenetic stimulation and electrophysiological recording via integrated SU-8 waveguides.[91]

The research on new materials aims to improve the performance of neural recording and stimulation. Conductive polymers,[92−94] liquid metals, MXene, and carbon-based materials[95] have been explored as alternative material choices for designing neural electrodes.[96] Graphene-related materials have become an attractive candidate material for electrode manufacturing due to their unique properties. Graphene electrodes provide capacitive interactions through a wide potential window in aqueous media and have a mechanical flexibility. To further enhance performance, multilayer porous graphene electrodes have been explored, which reduce the impedance of graphene-based electrodes and increase the charge injection limit (CIL) while maintaining the stability of biological-related current pulse stimulation.[97] MXenes are a class of layered two-dimensional transition metal carbides, nitrides and carbon nitrides with high electrical conductivity.[98] When used to modify electrode arrays, MXenes exhibit electrical properties that surpass those of most 2D materials,[99] and they also show excellent compatibility for magnetic resonance imaging (MRI).[100] The formation of a dense-packed micronano structure can further enhance the performance of MXene electrodes. Liquid metal (LM) is an emerging functional material with high conductivity, fluidity and biocompatibility.[101] The transformation of neural electrodes from rigid to flexible is an inevitable trend.[102] Room-temperature liquid metals usually refer to gallium (Ga) metal and Ga-based low-melting-point alloys, which are suitable candidates for the preparation of flexible stretchable neural electrodes.[103] Flexible neural microelectrode arrays of EGaIn can be fabricated based on spray printing technology.[104] Neural electrode arrays based on LM channels are also prepared by the injection method.[105] Patterning of LM on elastic substrates can be achieved through selective wetting.[106] The incorporation of emerging functional materials has greatly enriched the morphology of neural electrodes, marking an important step toward achieving high-performance neural recording and stimulation technologies.

Although polymer-based interfaces enhance flexibility and biocompatibility, they also introduce fabrication challenges, particularly in maintaining the structural fidelity and high electrode density. Recent studies has demonstrated that by engineering topologically organized supramolecular polymer networks and utilizing direct photopatterning techniques, researchers can create highly stretchable neural electrode arrays with subcellular spatial resolution (Figure 5e).[107] These devices provide both mechanical resilience and precision in signal acquisition, effectively bridging the gap between device flexibility and recording resolution.

Scaling neural recordings requires not only high spatial resolution but also the capability to monitor large volumes of neural tissue. One promising approach involves the 3D stacking of elastomer-based electrode layers. By utilizing perfluoropolyether (PFPE) elastomers, which retain mechanical softness and structural integrity at the tissue level, researchers have developed electrode arrays with enhanced density and spatial scalability, while maintaining flexibility (Figure 5f).[108]

As neural electrodes become increasingly integrated into both research and clinical applications, the demand for high density continues to grow. While rigid high-density neural electrodes have made significant advancements in increasing channel counts and integration levels, their inherent stiffness poses a challenge for long-term in vivo applications. In contrast, flexible neural electrodes demonstrate superior mechanical compatibility with soft neural tissues, making them ideal for long-term implantation. Their ability to fit soft nerve tissue facilitates a high-resolution recording and precise stimulation according to the topology of the nerve tissue. This structural adaptability enables a more accurate representation of the neural activity. As research continues to investigate complex neural activities, the ability to interact with complex nervous systems at high density will become a key direction in the structural and functional design of neural electrodes.

High-density neural electrodes are crucial, but their reliability faces severe challenges. Miniaturized electrodes are prone to impedance changes, fractures, or functional failures due to tissue strain, biofilm formation, or electrochemical corrosion, which significantly affect the stability of long-term recordings and the controllability of stimulation.[110−113] The greater challenge lies in crosstalk between channels: when the distance between adjacent electrodes is extremely small through capacitive or ohmic coupling (especially in humid environments or with poor insulation), the neural activity in one channel can significantly contaminate the weak signals of adjacent channels, even simulating false neuronal activity ("ghost" units). This severely confuses signal source localization, decoding of neuronal cluster activities, and evaluation of stimulation effects. Corresponding suppression strategies must be coordinated at multiple levels. The first strategy is physical isolation optimization: by adding a high-performance biologically inert insulating layer to increase the dielectric constant or by optimizing the electrode geometrical configuration to enhance physical separation. The second strategy is the front-end circuit design strategy: it can integrate a low-impedance grounding layer or shield electrodes, or select a dedicated low-noise amplifier with ultrahigh input impedance and low input capacitance. Finally, the back-end algorithm processing strategy involves adopting noise-adaptive local references instead of remote common references, and identifying and separating the crosstalk sources at the software level.[114]

To faithfully capture the emergent network-level dynamics unfolding across spatially distributed neural circuits, simultaneous multiregion recording is imperative. Concurrent sampling is essential for resolving precise causal interactions and phase relationships inherently obscured by sequential measurements, while crucially avoiding artifacts from posthoc synchronization attempts and cross-setup variability. This necessity is powerfully exemplified by multiprobe Neuropixels studies, which have yielded unprecedented neural data sets—recording from tens of thousands of neurons across dozens of brain regions in behaving mice.[11] However, the surgical burden and headstage complexity associated with multiple independent implants can be prohibitive for long-term studies tracking identified units across regions. Conversely, emerging single-interface, multisite approaches utilize highly integrated, flexible designs to access distributed targets via a minimized number of implants and interconnects, significantly reducing invasiveness and complexity.[115,116]

3. BIONIC NEURAL ELECTRODES

The internal neural environment consists of a diverse array of neurons, glial cells, and an extracellular matrix, intricately interwoven into a complex three-dimensional architecture. To effectively record and regulate the electrical activity of the nervous system, neural electrodes must achieve seamless and long-term integration with the surrounding neural tissue.[85,117−120] This integration remains one of the primary challenges in the development of neural electrodes. Surface neural electrodes positioned on the surface of neural tissue are characterized by their minimally invasive nature and relative ease of implementation.[60,121,122] However, when surface neural electrodes are applied to the highly curved and soft surfaces of the brain or spinal cord, their Young's modulus is still relatively high compared to neural tissues. These electrodes lack sufficient flexibility and conformability, compromising their ability to maintain stable, high-quality recordings over extended periods. In contrast, penetrating nerve electrodes can enter deeper nerve structures and achieve high-resolution recording.[123,124,66,28,125] However, artificial electrode materials are generally hard and do not match soft nerve tissue mechanically. This can lead to tissue damage and foreign body reactions. Over time, the formation of glial scars will isolate the electrodes and gradually weaken the signal.

To address these challenges, recent research has concentrated on the bionic design of neural electrodes.[126−130] In this context, bionic design encompasses two primary strategies: (1) developing electrode structures that physically resemble and conform to the geometry of neural tissue,[73−75,129] and (2) engineering neural electrodes that chemically and biologically mimic the natural neural environment to minimize immune responses.[17,131−135] By mimicking the mechanical and biochemical properties of natural tissues, neural electrodes can effectively improve tissue compatibility and reduce chronic inflammation. This design concept is expected to significantly improve the biocompatibility of neural electrodes and improve the long-term stability of signal recording and nerve stimulation in the future.

3.1. Bionic Structure Neural Electrodes.

To align with the structural characteristics of neural tissue, researchers have developed mesh neural electrodes that replicate the natural organization of neurons in vivo.[75,136−138] These bionic electrodes are soft, porous, and highly conformable, allowing for intimate interactions with neurons and glial cells while preserving the local tissue architecture. This design promotes stable, long-term implantation by minimizing the disruption to the surrounding tissue.

An ultrathin, minimally invasive neural electrode composed of hexagonal boron nitride and graphene features an open-grid design that provides excellent flexibility and strong tissue adhesion (Figure 6a).[122] This configuration enables the probe to form a conformal, tight interface with the irregular surface of the mouse brain. The mesh-like electrodes are capable of detecting individual neuronal activity with a high signal-to-noise ratio. Beyond surface applications, fully expandable, tissue-like mesh electrodes can also be implanted within brain regions (Figure 6b).[139] The open mesh structure interweaves with the native neural network, creating a stable and integrated interface that prevents micromotion and drift of the recording electrodes during long-term implantation. This stability allows for continuous tracking of neural activity from the same cell throughout the adult life of a mouse. A biomimetic neural probe features a neurite-like connecting structure composed of a polymer/metal/polymer composite (Figure 6c).[126] Its diameter and bending stiffness closely match those of neuronal axons, ensuring mechanical compatibility at the subcellular level. This design allows the probe to flexibly conform to neural tissue and interpenetrate neuronal structures, establishing a structurally and functionally stable interface. The mesh architecture facilitates seamless integration with neural tissue, significantly reducing immune responses, enhancing signal fidelity, and supporting the development of next-generation neural interfaces capable of long-term, high-resolution neural recording and modulation.

Neural tissue is a highly hydrated polymer network, and hydrogels are often employed to replicate its microscopic structure due to their similar composition and mechanical properties.[118,140−149] During fabrication, hydrogel-based electrodes provide excellent biocompatibility and an effective functional integration. Additionally, hydrogels exhibit mechanical properties that closely match those of neural tissue, significantly reducing the risk of damage during insertion. This mechanical compatibility also helps alleviate chronic inflammatory responses over time. Consequently, hydrogel-based bionic neural electrodes represent a promising approach for

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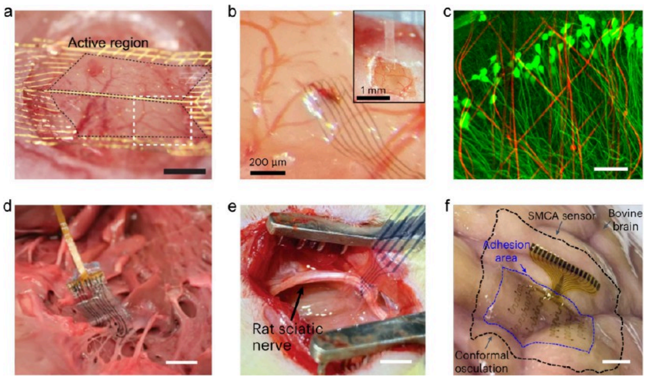

Figure 6. (a) A neural electrode with an open lattice structure (indicated by black dashed lines) is securely attached to the brain surface.[122] Scale bar: 1 mm. Reproduced from ref 122 under the terms of the CC-BY 4.0 license. (b) The tetrode-like microelectrode arrays implanted with minimal tissue damage. Inset shows ultrathin polymer shuttle-enabled implantation.[139] Reproduced with permission from ref 139. Copyright 2023 The Authors, Springer Nature. (c) 3D interfaces between bioinspired neuron-like electrodes (red) and neurons (green) at 2 days.[126] Scale bars: 50 μm. Reproduced with permission from ref 126. Copyright 2019 The Authors, Springer Nature. (d) The assembled viscoelastic surface neural electrode array was wrapped around the nerves of a bovine heart.[150] Scale bars: 3 mm. Reproduced with permission from ref 150. Copyright 2021 The Authors, Springer Nature. (e) The robust adhesive integration of the all-hydrogel electrode interface on a rat sciatic nerve.[151] Scale bars: 5 mm. Reproduced with permission from ref 151. Copyright 2023 The Authors, Springer Nature. (f) The conformal and robust performance of shape-morphing, cortex-adhesive neural electrodes on an ex vivo bovine cortex with a curvilinear surface.[152] Scale bars: 3 mm. Reproduced with permission from ref 152. Copyright 2024 The Authors, Springer Nature.

achieving long-term neural recording and stimulation with minimal biological disruption.

An electrode array employs a hydrogel as its outer layer, with the hydrogel conductor consisting of an ionically conductive alginate matrix reinforced with carbon nanomaterials (Figure 6d).[150] This design effectively addresses previous challenges in matching the stiffness and elastic properties of soft biological tissues. Due to its exceptional flexibility and biocompatibility, the hydrogel can closely conform to complex anatomical surfaces, such as those of the heart and cerebral cortex. A fully hydrogel-based bioelectronic interface has been fabricated using 3D printing techniques, utilizing a bicontinuous conducting polymer hydrogel (Figure 6e).[151] This structure achieves a high electrical conductivity while maintaining mechanical stability in physiological environments. Furthermore, the adhesive neural electrode made from catechol-conjugated alginate hydrogel demonstrated superior tissue integration (Figure 6f).[152] Upon implantation, the hydrogel expands to fill interfacial micropores, ensuring conformal contact and secure attachment to the curved cortical surface. This stable interface facilitates reliable neural signal acquisition even during transcranial focused ultrasound stimulation. These bionic neural electrodes, which are based on hydrogels, significantly enhance the performance, durability, and biocompatibility of neural electrodes, positioning them as promising candidates for future neural electrode and bioelectronic applications.

3.2. Biologically Integrated Neural Electrodes.

In addition to achieving mechanical compatibility between neural electrodes and the surrounding neural tissue, recent research has increasingly emphasized the importance of mitigating the immune responses triggered by electrode implantation. A key challenge in ensuring the long-term stability and performance of neural interfaces is the body's innate inflammatory reaction to foreign materials. This immune response often results in the formation of glial scars, signal degradation, and eventual failure of the implanted electrode. To address this limitation, researchers have progressed beyond merely replicating the physical properties of neural tissue. Instead, they have begun to emulate their physiological environment as well, leading to the development of a new generation of biomimetic neural electrodes.

These neural electrode interfaces are designed to mimic physiological conditions. Strategies include biochemical surface modifications that resist protein adsorption and cell adhesion, the integration of cell-based biological interfaces that promote tissue compatibility, and even the incorporation of living cells as active components of the electrodes themselves. By replicating both the structural and biochemical features of native neural tissue, these biomimetic designs aim to reduce chronic immune responses, enhance biocompatibility, and maintain signal fidelity over extended periods.

A significant advancement in the biomimetic surface modification of neural electrodes involves the development of a coating that is both immune-invisible and lubricating (Figure 7a).[153] Inspired by the frictionless surface of the Nepenthes pitcher plant, this coating exhibits ultralow friction and strong resistance to biofouling. When applied to neural electrodes, it significantly reduces mechanical damage and cellular adhesion during insertion. Consequently, it minimizes the recruitment of inflammatory cells and suppresses the formation of glial scars, thereby enhancing the biocompatibility and long-term functional stability of the implanted device. Another innovative biomimetic strategy involves integrating bioinspired, atomically precise clusters onto the electrode surface (Figure 7b).[154] The nanozyme facilitates rapid electron and ion transport at the electrode-tissue interface, effectively reducing the interfacial impedance and enhancing signal transmission. In addition to their electrical advantages, the nanozyme also demonstrates antioxidant properties and multienzyme-like catalytic activities. These biochemical characteristics help inhibit the activation and proliferation of reactive glial cells, thereby maintaining stable neural recordings over extended periods.

In addition to surface coatings, researchers have investigated cellular strategies to improve the integration of neural electrodes into biological tissue. One innovative approach involves inoculating induced pluripotent stem cell (iPSC)-derived muscle cells onto flexible electrode arrays (Figure 7, c and d).[133] These muscle cells serve as biological targets for input from the surrounding nerves, facilitating long-term functional integration. In freely moving rats, this biohybrid system successfully maintained stable electrophysiological recordings for up to 4 weeks. This method brings neural electrodes closer to mimicking the natural physiological functions of the human body.

Building on this concept, some cutting-edge strategies propose utilizing neurons themselves as "living electrodes" (Figure 7e and f).[155] By employing tissue engineering techniques, researchers have developed neural constructs in which neuronal populations extend long axonal bundles through hydrogel scaffolds, forming columnar microstructures.

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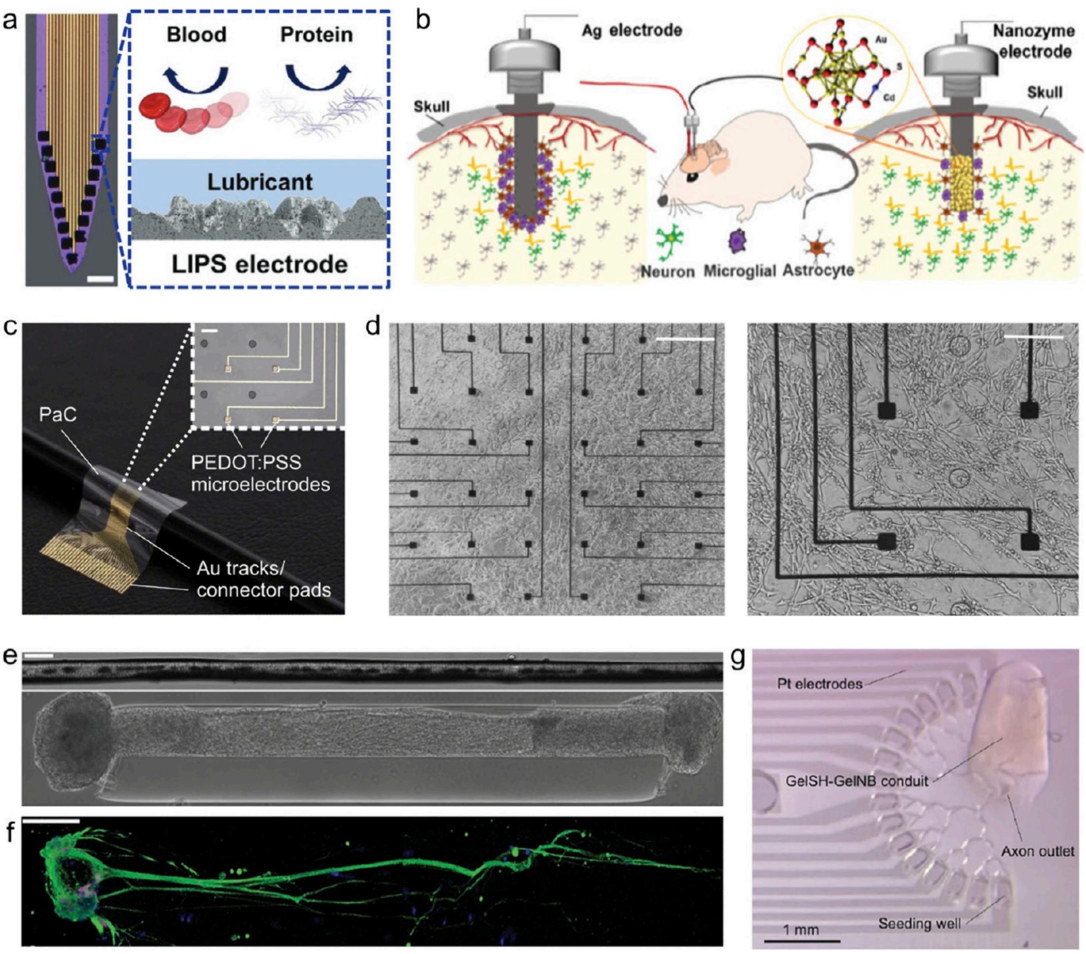

Figure 7. (a) The lubricated immune-stealth probe surface (LIPS) was submerged in blood for 30 min and retrieved.[153] Scale bars: 50 μm. The dashed box illustrates the mechanism for minimizing the immune response of the LIPS-coated probe. Reproduced from ref 153 under the terms of the CC-BY 4.0 license. (b) The nanozyme electrodes implanted in the hippocampal CA3 region exhibited minimal neuroinflammation and consistently recorded electrical signals.[154] Reproduced with permission from ref 154. Copyright 1998 Wiley-VCH. (c) An in vivo biohybrid device consisting of two parylene-C (PaC) layers, which contain gold (Au) tracks and PEDOT:PSS microelectrodes designed for peripheral neural electrode.[133] Scale bar: 60 μm. Reproduced from ref 133 under the terms of the CC-BY 4.0 license. (d) Human iPSC-derived myocytes at day 8 of culture on the peripheral neural electrode.[133] Scale bars: 465 (left) and 230 μm (right). Reproduced from ref 133 under the terms of the CC-BY 4.0 license. (e) The directional (below) "living electrodes" built using cerebral cortical neurons, next to a single human hair (above).[155] Scale bars: 100 μm. Reproduced with permission from ref 155. Copyright 2001 Wiley-VCH. (f) The living electrode constructed from dorsal root ganglia neurons exhibits unidirectional axonal tracts, which are immunolabeled to indicate neuronal somata (MAP-2; purple) and axons (tau; green), along with a nuclear counterstain (blue).[155] Scale bars: 100 μm. Reproduced with permission from ref 155. Copyright 2001 Wiley-VCH. (g) A biohybrid neural interface combines stretchable electrode arrays with neural spheroids in a GelSH-GelNB hydrogel conduit.[132] Reproduced with permission from ref 132. Copyright 2001 Wiley-VCH.

These axons penetrate specific depths in the brain and establish synaptic connections with host neurons, facilitating direct signal transmission. Notably, only biological neural components are implanted, significantly minimizing the chronic immune response typically associated with synthetic materials.

In a related development, another biohybrid neural interface integrates neural spheroids with stretchable electrode arrays (Figure 7g).[132] Axons from these spheroids extend through hydrogel conduits, gradually organizing into nerve-like bundles that can be guided into deep brain regions. Once implanted, these bundles integrate with local neural circuits, facilitating both electrical stimulation and high-fidelity signal recording. Additionally, this design preserves tissue integrity and minimizes the risk of immune rejection.

Collectively, these advances indicate an increasing trend toward designing neural electrodes that can closely resemble the mechanical and physiological properties of neural tissue. Bionic neural electrodes are constructed by using materials or even living cells that can mimic the structure and function of neural tissue. Their bionic designs are able to reduce tissue damage, immune responses, and foreign body reactions, helping to achieve long-term stable neural recording and stimulation. Bionic design of structure and function is an important direction for the future development of neural electrodes.

4. ADAPTIVE NEURAL ELECTRODES

Although substantial progress has been made in developing neural electrodes that match the mechanical and biochemical properties of native neural tissue, achieving long-term fusion with dynamic neural tissue remains a huge challenge. Most neural electrodes are static in nature and lack the necessary adaptations to cope with the highly dynamic properties of the

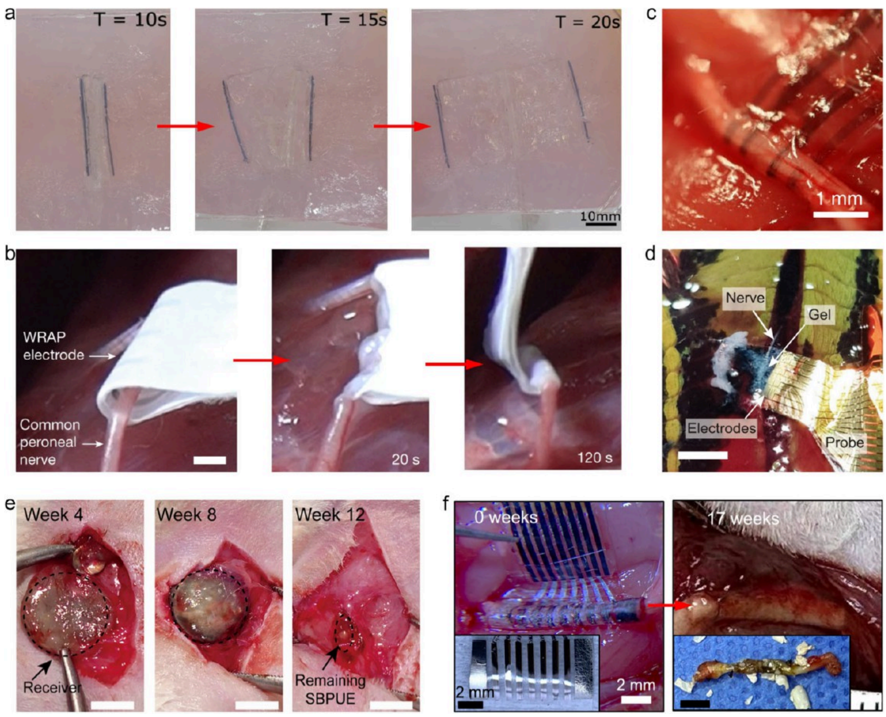

Figure 8. (a) The expansion of a minimally invasive, large-area subdural ECoG implant in the brain phantom model.[160] Reproduced from ref 160 under the terms of the CC-BY 4.0 license. (b) The water-responsive, shape-adaptive polymer electrode, which is looped around the common peroneal nerve, contracted and conformed wrapped when wetted.[161] Scale bars: 1 mm. Reproduced with permission from ref 161. Copyright 2023 The Authors, Springer Nature. (c) The morphing electrode created a stable, closed structure around the sciatic nerve.[162] Reproduced with permission from ref 162. Copyright 2020 The Authors, Springer Nature. (d) In vivo polymerization surrounding the nervous system of medicinal leeches.[163] Scale bars: 2.5 mm. Reproduced with permission from ref 163. Copyright 2020 The Authors, AAAS. (e) The biodegradation of the implanted biodegradable capacitive-coupling neural electrode occurred within 12 weeks.[175] Scale bars: 5 mm. Reproduced from ref 175 under the terms of the CC-BY 4.0 license. (f) The biodegradable and restorative neural interface was implanted at the injured sites of the sciatic nerves at various stages of biodegradation.[173] The inset shows the retrieved device isolated from the regenerated nerve tissues. Reproduced from ref 173 under the terms of the CC-BY 4.0 license.

nervous system in long-term application scenarios. The nervous system will continue to undergo growth, remodeling, and physiological changes.[51] Traditional neural electrodes not only cause tissue damage during surgical implantation but also fail to adapt to physiological changes in neural tissue after implantation, triggering inflammatory reactions and glial scar formation. In order to solve these limitations, it is necessary to develop adaptive neural electrodes for long-term matching of changing neural tissues. Recent research has increasingly focused on the development of adaptive neural electrodes.[156−159] These electrodes are designed to effectively conform to the natural changes of neural tissues and provide long-term dynamic fusion through the adaptive design of materials and structures.

4.1. Structurally Responsive Neural Electrodes. Structurally responsive neural electrodes can respond to external stimuli and changes in the physiological environment, demonstrating an appropriate structural design. One key application of adaptive electrodes is in minimizing surgical trauma during implantation. Traditional electrode arrays often necessitate relatively large incisions or invasive procedures to cover extensive cortical areas. In contrast, a recent study demonstrated a shape-adaptive neural implant that can be compressed and inserted through a small burr hole (Figure 8a).[160] After insertion, the implant unfolds to cover a large surface area of the brain, facilitating a broad cortical recording and stimulation. This approach reduces invasiveness while enhancing spatial coverage, representing a major advancement in minimally invasive neural interface technology. Another notable innovation involves the use of adaptive materials to create conformal electrode-tissue interfaces. A supercontractile polymer film, composed of poly(ethylene oxide) and poly(ethylene glycol)-α-cyclodextrin inclusion complexes, has been engineered to respond dynamically to moisture (Figure 8b).[161] In its dry state, the film is flexible and stable; however, upon exposure to body fluids, it contracts and wraps around neural tissues of various sizes, ensuring a tight conformal fit. This water-activated shape transformation facilitates stable in vivo neural stimulation and recording while minimizing stress on the surrounding tissues. Adaptive neural electrodes are particularly valuable in long-term implantation scenarios where the neural tissue may grow, shift, or remodel over time. One study addressed this challenge by designing a neural electrode composed of a viscoelastic conductive polymer combined with a self-healing viscoelastic matrix (Figure 8c).[162] This composite material allows the electrode to gradually change shape in response to the natural enlargement of the rat sciatic nerve during maturation while maintaining minimal mechanical stress at the tissue interface. An even more innovative approach involves the in situ fabrication of neural electrodes utilizing the body's own biochemistry (Figure 8d).[163] Researchers have developed injectable gels that contain organic precursors and enzymes. Once injected, the enzymatic polymerization of these organic precursors is triggered by endogenous metabolites, resulting in the formation of conductive polymer networks precisely within the target tissue.

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This technique enables the neural electrode to "grow" in situ, fabricating conductive hydrogel electrodes that are tailored to the specific geometry of the host environment. Neural tissue in vertebrate changes from a two-dimensional structure to a three-dimensional structure during development. Recent studies have shown that soft mesh microelectrode arrays can be integrated into embryonic neural plate. As organogenesis progresses, mesh electrodes deform, stretch, and distribute throughout the brain, achieving seamless integration with neural tissue.[164]

The development of structurally responsive neural electrodes mainly relies on emerging stimulus-responsive materials. These materials can respond to external stimuli (such as temperature,[165] water,[166] magnetic fields,[167] etc.) through the design of device structure or material. Stimuli-responsive materials are revolutionizing the optimization of the neural electrode-tissue interface.

4.2. Bioabsorbable Neural Electrodes. In specific clinical scenarios, neural electrodes are needed sorely for temporary monitoring or stimulation. The permanent implantation of these devices can disrupt tissue regeneration or provoke chronic inflammation, while surgical removal poses risks such as tearing caused by fibrotic encapsulation.[168−170] To tackle these challenges, there is an increasing demand for neural electrodes that can fulfill their intended function for a specific duration and then degrade adaptively to be absorbed by the body.[171−174] Consequently, adaptive, bioresorbable neural electrodes are garnering significant attention in both research and clinical practice. One notable example is the development of a wireless, biodegradable stimulation electrode designed for short-term vagus nerve stimulation in the treatment of postinfection bowel disease (Figure 8e).[175] This electrode delivers therapeutic stimulation for a preprogrammed duration and subsequently degrades within the body, thereby eliminating the need for surgical removal. By minimizing secondary operations, this strategy decreases the risk of infection, nerve injury, and other complications. Similarly, a biodegradable neural interface was developed for the real-time monitoring and repair of long-gap peripheral nerve injuries (Figure 8f).[173] This implant not only provided electrical stimulation to enhance nerve regeneration but also degraded in a controlled manner, thereby eliminating the need for further surgical intervention. Its biodegradable properties significantly reduced the risk of infection, inflammation, and secondary tissue damage, which are critical factors in nerve repair and rehabilitation.

The degradation products of long-term implant materials are of crucial importance for the toxicological assessment of neural tissues, mainly focusing on the potential hazards caused by chronic and low-dose exposure.[171,176] Due to the high sensitivity of neural tissues and their limited regenerative capacity, the trace degradation products (such as metal ions, polymer fragments, oligomers, and catalyst residues) generated by long-term implanted biological materials (such as neural interface electrodes and vascular stents) in the in vivo environment (such as oxidation, hydrolysis, and enzymatic degradation) need to be strictly evaluated. These degradation substances may enter the neural tissues through direct contact or systemic circulation, crossing or damaging the integrity of the blood−brain barrier (BBB), and interfering with the normal functions of neurons and glial cells. The core concerns of the assessment include: neurotoxicity (neuronal apoptosis/necrosis), glial response (activation of microglia/astrocytes leading to neuroinflammation, gliosis/scarring formation), axonal demyelination or progressive degeneration, neurotransmitter system disorders, metabolic dysfunction (such as mitochondrial damage), mutagenicity, or carcinogenic potential. It is worth noting that the relatively "immune privilege" environment of neural tissues may alter the clearance rate and local accumulation concentration of degradation substances,[177−179] exacerbating their chronic toxicity risks, which also becomes a core challenge and safety assessment focus in the biocompatibility design and safety evaluation of long-term implant materials.

The innovative work presented above highlights the importance of structural and functional adaptability in the development of neural electrodes. Adaptive neural electrodes have the ability to adapt to physiological changes in neural tissue, reduce surgical damage and adverse reactions, promote the stability of long-term recording, and prevent secondary tissue damage. Adaptive neural electrodes are a major breakthrough in the field of neural interface engineering. By dynamic adaptation to the changing structure and biochemical environment of neural tissue, these electrodes can achieve better integration with neural tissue, thereby improving the functionality and biocompatibility of neural electrodes in long-term application scenarios.

Advanced adaptive designs such as shape memory materials, self-healing polymers, in situ polymerization, or biodegradability have broken through many of the limitations of traditional electrodes. With the continuous advancement of research, adaptive electrodes are expected to play an increasingly important role in fields such as brain-computer interfaces and neurostimulation. The design of next-generation neural electrodes is likely to emphasize their ability to dynamically adapt to biological systems. This means that adaptability is not only an ideal characteristic but also a basic principle for the structural and functional design of neural electrodes.

5. MULTIMODAL SIGNAL COUPLING NEURAL ELECTRODES

After the nerve electrode and peripheral nerve tissue establish a stable long-term information and energy exchange interface, the electrode must also be effectively connected to external devices. However, due to the limitations of the internal physiological environment and the need for long-term implantation, the signal transmission between the nerve electrode and bioelectronic devices is limited. The limited battery capacity of bioelectronic devices brings harm to patients undergoing secondary surgery.[54,170,180] At the same time, the implanted wires also bring hidden dangers of inflammation. Researchers are beginning to consider the design of nerve electrodes to overcome these limitations. Recent advances in neural electrodes have focused on the exchange of information and energy between neural electrodes and bioelectronic devices through multimodal signal coupling.[181−185] This multimodal coupling signal transmission method significantly improves the flexibility and clinical applicability of neural electrodes. Among them, the most widely explored coupling signals include mechanical force,[152,186−189] light[190−196] and magnetic field.[183,197−199]

5.1. Mechanical Signal Coupling. Ultrasound waves are extensively utilized to transmit mechanical signals into the human body owing to their exceptional tissue penetration capabilities. Beyond diagnostic imaging, ultrasound also

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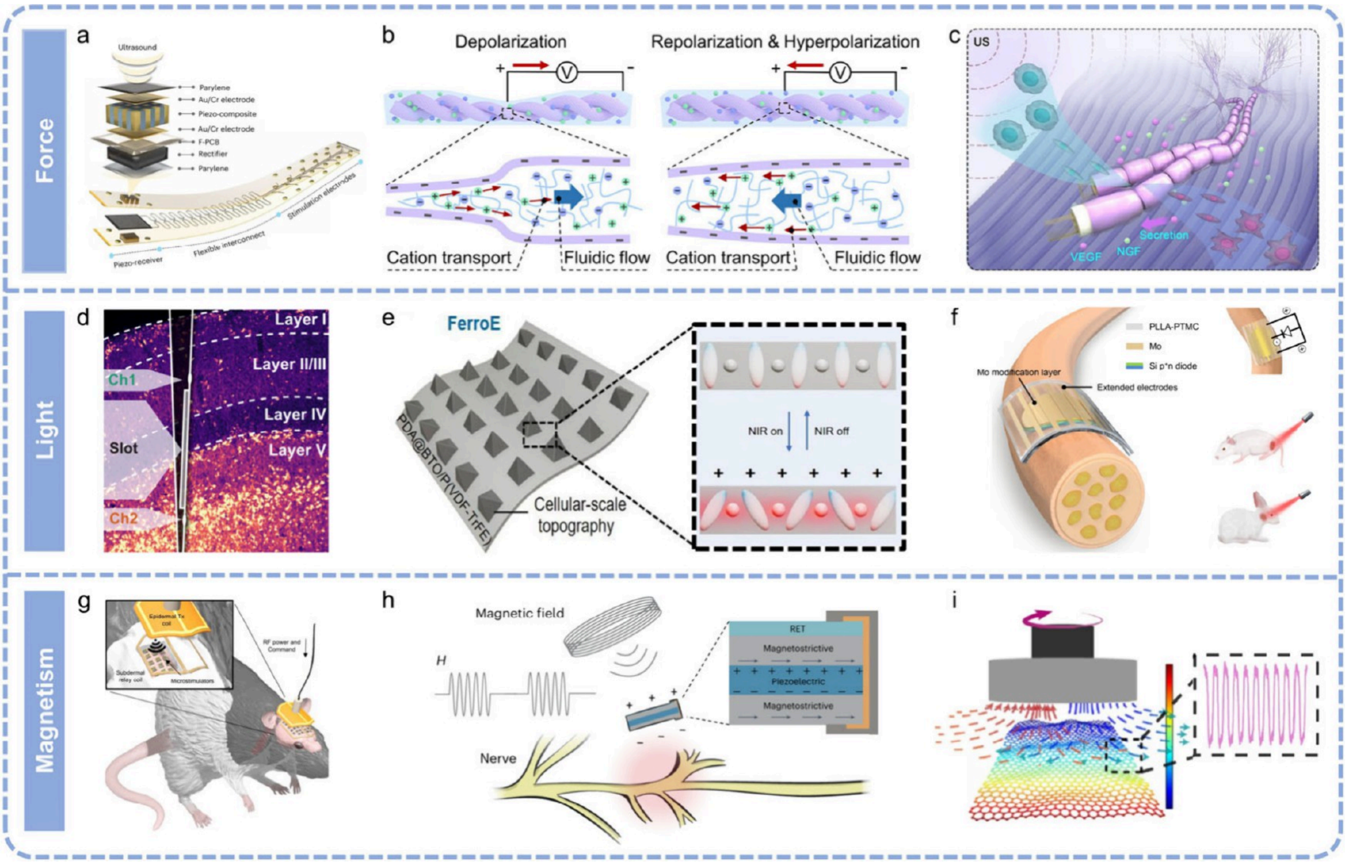

Figure 9. (a) The schematics of the ultrasound-induced wireless implantable stimulator.[189] Reproduced with permission from ref 189. Copyright 2025 The Authors, Springer Nature. (b) The ultrasonic-responsive piezoelectric film applies electrical stimulation to nerve cells.[200] Reproduced with permission from ref 200. Copyright 2023 Elsevier. (c) Different stages of the piezoionic process and ion distribution between the interval of fibers.[201] Reproduced under the terms of the CC-BY 4.0 license.201 (d) The two-photon image illustrates the implant depth and the extent of the slot of the fibertrode in the cortex.[208] Reproduced with permission from ref 208. Copyright 2022 The Authors, Springer Nature. (e) The ferroelectric neural electrode is constructed from polydopamine-modified barium titanate nanoparticles and a ferroelectric copolymer of poly(vinylidene fluoride-*co*-trifluoroethylene).[157] Reproduced with permission from ref 157. Copyright 1998 Wiley-VCH. (f) Schematic illustration of the biodegradable and flexible neural interface for optoelectronic stimulation of peripheral nerves.[209] Reproduced from ref 209 under the terms of the CC-BY 4.0 license. (g) The schematic diagram illustrates that a group of microchips was implanted into the cerebral cortex of rats, accompanied by surface and subcutaneous coils. These coils were utilized to facilitate the resonant transmission of near-field radio frequency energy and to convey stimulation instructions.[210] Reproduced from ref 210 under the terms of the CC-BY 4.0 license. (h) A schematic illustrating remote neural stimulation utilizing a magnetoelectric nonlinear metamaterial and the laminate structure of the magnetoelectric nonlinear metamaterial.[211] Reproduced with permission from ref 211. Copyright 2023 The Authors, Springer Nature. (i) Schematic illustrating the generation of induced electrical signal on a graphene nanosheet under the periodic magnetic field.[212] Reproduced from ref 212 under the terms of the CC-BY 4.0 license.

enables energy delivery and signal transmission, rendering it a valuable tool for neural modulation. Ultrasound-responsive neural electrodes represent a promising approach to wireless neural stimulation. A notable example is a flexible, ultrasound-induced wireless implantable stimulator that incorporates composite piezoelectric materials (Figure 9a).[189] These materials can capture programmable acoustic energy and convert it to precise electrical stimulation for targeted pain management at varying intensities. By eliminating the need for wired connections, this ultrasound-based platform facilitates the minimally invasive, programmable control of neural activity. Piezoelectric thin films further enhance the design of ultrasound-responsive neural electrodes. For instance, a neural scaffold composed of a piezoelectric polylactic acid (PLLA) film with ordered micro/nanostructures has been developed (Figure 9b).[200] When stimulated by ultrasound, the PLLA film generates piezoelectric potentials that mimic the endogenous electrical signals present during embryonic development, thereby promoting neuronal repair and regeneration. In addition to ultrasound, low-frequency mechanical pressure can also be harnessed for neuromodulation. One innovative design incorporates an ion hydrogel with a directional microfiber structure to construct pressure-responsive neural electrodes (Figure 9c).[201] When mechanical pressure is applied, the differing migration rates of anions and cations within the hydrogel convert pressure stimuli into piezoionic signals,[202] which can effectively stimulate the sciatic nerve for neural regulation. These innovations highlight the increasing potential of mechanical signal coupling as a powerful, wireless, and minimally invasive method for neural regulation. With advantages such as deep tissue penetration, adjustable stimulation, and compatibility with soft biological structures, mechanical signal coupling neural electrodes present new opportunities for both clinical therapy and fundamental neuroscience research.

5.2. Optical Signal Coupling. Optical signals can be utilized to regulate neural activities, particularly through optogenetics, which has transformed the study of neural

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circuits by enabling precise spatial and temporal control of neuronal activation.[191,203−207] By integration of optoelectronic components into neural electrodes, researchers can achieve simultaneous optical stimulation and electrical recording. For instance, a specialized opto-electrical neural electrode with a conical design positions the light-emitting and recording components in close proximity (Figure 9d).[208] This spatial configuration facilitates highly localized optogenetic stimulation while concurrently recording artifact-free local field potentials (LFPs) and action potentials. The conical structure enhances targeting precision and minimizes signal interference.

Beyond optogenetics, light itself can be utilized to generate electrical signals for neural stimulation. A ferroelectric neural electrode constructed from polydopamine-modified barium titanate nanoparticles and ferroelectric poly(vinylidene fluoride-*co*-trifluoroethylene) copolymer demonstrates reversible polarization in response to light exposure (Figure 9e).[157] This process generates real-time electrical signals that modulate the neural activity. When implanted on the vagus nerve or motor cortex of mice, this electrode successfully enabled wireless, nongenetic control of heart rate and motor behavior. Another significant advancement involves biodegradable neural electrodes constructed from thin-film silicon diodes (Figure 9f).[209] These devices react to tissue-penetrating red light, generating an adequate photoelectric stimulation to facilitate both neuromodulation and tissue regeneration. Optical-coupled neural electrodes for wireless control of neural activity represent a promising avenue for broadening the clinical applications of neural interface technologies.

5.3. Magnetic Signal Coupling. Magnetic fields also serve as an effective medium for wireless energy transfer and signal modulation in neural electrodes. Electromagnetic coupling allows for deep tissue penetration and noninvasive control. One example is an implantable network of epidermal silicon microchips designed for multipoint cortical stimulation. These microchips harvest energy from external radiofrequency (RF) sources and convert it into biphasic currents, which are delivered to specific cortical regions through integrated microwires (Figure 9g).[210] Beyond electromagnetic induction, magnetoelectric materials provide a more direct approach for converting magnetic fields into electrical signals. A novel magnetoelectric neural electrode utilizes semiconductor layer rectification to generate a stable bias voltage in the presence of alternating magnetic fields (Figure 9h).[211] This voltage facilitates precise wireless stimulation of the peripheral nerves. Magnetoelectric materials present dual advantages of wireless control and device miniaturization, rendering them ideal for chronic implantation. Magnetic signal coupling facilitates further miniaturization of neural electrodes. One study demonstrated that conductive graphene nanosheets can deliver in situ electrical stimulation to stem cells through electromagnetic induction (Figure 9i).[212] These nanosheets were functionalized with adhesion proteins, enabling them to encapsulate closely the cell membrane. When stem cells coated with the nanosheets were implanted into mice with brain injuries, magnetic-field-induced electrical stimulation significantly enhanced brain tissue repair. This approach highlights the potential of magnetically coupled neural electrodes based on nanomaterials for minimally invasive neural modulation and regenerative therapies.

Information and energy exchange between neural electrodes and bioelectronic devices through multimodal signal coupling is a major breakthrough in the field of neural engineering. Neural electrodes can achieve more accurate, flexible, and less invasive neuromodulation by responding to external mechanical, optical, and magnetic signals. Multimodal signal coupling marks a shift in the structural and functional design of neural electrodes to a flexibility and practicability.

6. CHALLENGES AND PROSPECTS

Over the past few decades, neural electrode technology has made remarkable advancements, driven by a growing demand for precise and stable communication between the nervous system and external electronic systems. While traditional neural electrodes have played a fundamental role in neuroscience research and clinical neuromodulation, they also encounter significant limitations, particularly regarding resolution, adaptability, and long-term functionality.

This Review comprehensively summarizes four key design strategies for advanced neural electrodes: high density, bionic design, adaptive design, and multimodal signal coupling (Figure 10). These approaches signify a paradigm shift toward more biocompatible, dynamic, and integrated neural interfacing systems that can meet the diverse demands of both research and clinical applications.

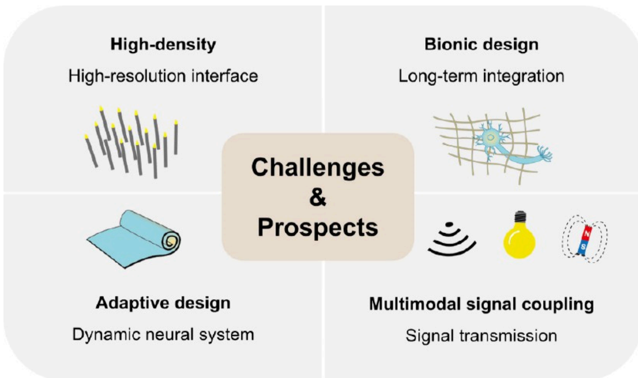

Figure 10. Challenges and prospects in the structural and functional design of advanced neural electrodes.

First, high-density neural electrodes are crucial for achieving high-resolution interfacing with complex neural systems. Rigid neural electrodes, such as Neuropixels and Utah arrays, provide high spatial resolution and stability but suffer from mechanical mismatch with soft tissue. In contrast, flexible polymer-based interfaces enhance biocompatibility and conformability, facilitating long-term, stable recordings with minimal immune responses. These high-density systems are particularly valuable for brain-computer interfaces and neuroprosthetics, where the precise decoding of neural signals is essential.

Second, the bionic design greatly improves the long-term compatibility of the neural electrodes after implantation. Structurally, mesh-like architectures or hydrogel-based structures replicate the mechanical properties of neural tissues, thereby minimizing tissue damage caused by mechanical mismatch and reducing glial scarring. Biologically, surface modifications and biohybrid strategies that integrate living cells or promote endogenous tissue integration create immunologically "invisible" interfaces. These advances ensure more stable signal acquisition and mitigate the risks associated with chronic implantation.

Third, adaptive neural electrodes can adapt to changing neural tissues. Shape-memory polymers, self-healing materials,

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Table 1. Summary of Materials, Characteristics, And Applications of Representative Neural Electrodes

Form of electrode	Materials	Channels	Impedance	SNR	Signal transmission	Single electrode size	Applications	Reference
Microwire	Stainless steel	704	1.5 MΩ (1 kHz)	5:1	Wired	50 μm	Recording single cortical neurons	33
MEA	PI/Cr/Au	1024	6.4 kΩ	4.9–10.6	Wired	101.3 μm	Recording large neural populations	64
3D electrode	CMOS	1024	3.8 MΩ ± 1.5 Ω (1 kHz)	<10 μV	Wired	10 μm	Large-scale retinal recording	71
Tassel electrode	PI/Au/PEG	1024	54 ± 15 kΩ (1 kHz)	6	Wired	3/1.5 μm^2	Population of neurons	87
Surface electrode	SU-8/h-BN/Pt/Au/Graphene	32	∼540 kΩ (1 kHz)	9.3 ∼ 10.7	Wired	20 μm	Cortex and cerebellum	122
Hydrogel electrode	PU/PEDOT:PSS	6	5 kΩ (1 kHz)	100–150	Wired		Various organs	151
MEA	PaC/Au/PEDOT:PSS/myocyte	32	159.00 ± 35.8 kΩ (1 kHz)	32 dB	Wired		Forearm nerve bundle	133
Film electrode	PEO/PEG/α-CD/SEBS/Au	3	600 Ω (1 kHz)	1.2	Wired		Nerves, muscles and hearts	161
Ferroelectric electrode	PDA@BTO/P(VDF-TrFE)	1			Optical signal coupling	2 mm × 2 mm	Peripheral and central neural networks	157
Ultrasonic electrode	Au/Cr/Piezo-composite	12	452 kΩ (10 kHz)		Mechanical signal coupling	1.5 mm	Spinal cord	189
Magnetoelectric electrode	$PZT/ZnO/HfO_2$	1			Magnetic signal coupling	5 mm × 2 mm	Peripheral nerves	198
Electromagneticelectrode	CMOS	48	300 kΩ (1 kHz)	5–12 dB	Electromagnetic link	650 × 650 × 250 μm	Rat cortical surface	183

and in situ polymerization techniques have enabled the creation of electrodes that respond to tissue movement, growth, or remodeling. Furthermore, bioresorbable neural electrodes offer a transient functionality for temporary therapeutic applications, such as short-term stimulation during rehabilitation or postoperative recovery. These temporary electrodes undergo natural degradation without the need for removal, thereby reducing the risk of secondary surgical complications. As a complementary approach to achieving the same goal, minimally invasive endovascular stent-electrode arrays leverage neurointerventional delivery techniques to achieve chronic cortical electrocorticography (ECoG) and stimulation without requiring craniotomy, typically eliminating the need for surgical explantation.[213,214]

Finally, multimodal signal coupling is used for the transmission of energy and information, significantly enhancing the flexibility and clinical practicability of neural electrodes. Mechanical coupling, optical coupling, and magnetic coupling enable more accurate, flexible, and less invasive neuromodulation. These methods open new avenues for signal modulation and targeted therapy, particularly in deep tissue regions, where wired interfaces are difficult to use.

For the sake of clarity and ease of comparison, Table 1 summarizes the standardized indicators (materials, characteristics, and applications) of the representative neural devices mentioned previously in this Review. Although neural electrodes have made significant progress, several challenges persist. One of the most pressing issues is the integration of multiple functionalities without compromising device miniaturization or biocompatibility. Many of the most promising approaches require complex fabrication processes or depend on materials that are challenging to scale or integrate with standard microelectronic systems. Additionally, ensuring long-term stability in vivo remains problematic due to persistent immune responses and the biological remodeling of neural tissue.

To address these challenges, future research on neural electrodes should prioritize interdisciplinary collaboration among neuroscientists, materials scientists, engineers, and clinicians. This is essential to advance the development of standardized and scalable neural electrode manufacturing platforms.

7. CONCLUSION

The emergence of advanced neural electrodes marks a crucial transformation in the field of neurotechnology. High-density, bionic, adaptive, and multimodal signal coupling designs in next-generation electrodes are expected to surpass the limitations of conventional neural electrodes, offering significant potential for clinical therapy and scientific investigations. High-density neural electrodes can record complex neural electrical activity and stimulate neurons precisely, but future design needs to conform to the physiological structure of neural tissue. Biomimetic neural electrodes replicate tissue mechanics and enable seamless integration in vivo through biochemical and biohybrid approaches. Adaptive neural electrodes can conform to dynamic neural tissues, enabling a long-term stable integration. Coupling signal patterns enable neural electrodes to surpass structural limitations with flexibility and efficient energy conversion driving their clinical applications. With the evolution of neural electrode technology, advanced neural electrodes are expected to broaden their clinical application scenarios and may facilitate a seamless integration with the nervous system. In the future, neural electrode technology will not only restore the function of impaired nerve tissue but also enhance the capabilities of the human nervous system in an unprecedented way.

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Notes

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