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Recent progress of hydrogels in brain-machine interface

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Abstract

The long-term stable monitoring of brain signals, including electroencephalogram (EEG), electrocorticogram (ECoG) and local field potential (LFP), is of great significance for the fundamental research in brain science, artificial intelligence and the diagnosis and treatment of brain-related disorders. Therefore, both non-invasive and invasive brain-machine interfaces based on different materials and structures have been widely studied due to their unique performance. Among these materials, hydrogels have emerged as a promising interface material for brain signal collection systems due to their similar mechanical properties to biological tissues, excellent biocompatibility, strong self-adhesive properties, and exceptional ionic conductive characteristics. This review aims to provide an overview on the recent progress of hydrogel-based brain interfaces in the recording of brain signals with non-invasive and invasive methods. It is expected that this paper will serve as a valuable summary and reference for future research in the hydrogel-based brain interface.

Keywords: Brain-machine interface, hydrogels, brain science, flexible electronics, neural signal

INTRODUCTION

The recording of high-quality neural signals, including electroencephalogram (EEG), electrocorticogram (ECoG), and local field potential (LFP), is of great importance for the exploration of working mechanism of brain activity, which is considered as the foundation for the development of the artificial intelligence and the diagnosis and treatment of brain-related disorders[1-3]. In addition, brain-machine interaction also has various applications in the fields of aerospace, surgery, and the military. Therefore, the acquisition of neural signals with non-invasive or invasive detection methods has received extensive attention[4-6].

Firstly, despite the rapid development of material science, the acquisition of high-quality EEG signals through non-invasive methods remains a challenging task[7-12]. The existing non-invasive EEG electrodes are often rigid, which leads to a mismatch in electrical and mechanical properties between human tissue and electrodes, and they can not be used in a wearable form and stably record the EEG signals. Also, the electrodes suffer from high noise due to poor resistance to environmental interference[13-19]. As a result, it is difficult to record high-quality EEG signals with the non-invasive method[20-25]. Therefore, it is urgent to develop interface materials that can adapt to the human skin to improve the performance of non-invasive EEG electrodes. Among various materials, viscoelastic materials, such as hydrogels, are able to conformally adhere to the skin and improve the interfacial quality[26-33]. In addition, hydrogels have a unique selective frequency damping effect, which can minimize environmental noise. In contrast to filtering the noise with signal processing after acquisition, electrodes with selective frequency damping effect can effectively obtain signals with a high-to-noise ratio at low cost and with a simple interface[34-38]. As a result, the hydrogel-based electrode is desired since it can record the EEG signals with a high signal-to-noise ratio (SNR) even in noisy conditions[39-45].

In the application of scientific research and exploration of the working mechanism of brain activity, an invasive neural electrode is more attractive since it is able to monitor single-neuron activity[46-52]. ECoG and LFP signals can be recorded by the invasive method, as shown in Figure 1. However, gradual encapsulation of the implanted electrodes by glial scars often occurs for long-term implantation, which will lead to the loss of recording and stimulation capabilities of the electrodes[53-59]. These phenomena result from the mechanical and biological incompatibility between the implanted electrodes and the nerve tissue, which causes chronic tissue damage. Also, the mismatch in mechanical properties, such as bending stiffness and elastic modulus between the implants and biological tissues, will also lead to imperfect conformal contact and may exert pressure on the organ. As a result, permanent deformation of the organ will be caused[60-62]. Therefore, the development of an implantable electrode based on viscoelastic materials that match the neural tissue in both biological and mechanical properties is a promising method to minimize the damage to the tissues and realize long-term implantation.

Furthermore, conventional invasive devices can only monitor unimodal neural signals, which lack spatial or temporal resolution and cannot meet the requirements of precision medicine[48]. Hydrogel, a soft material with high conductivity and transparency, is compatible with magnetic resonance imaging (MRI), computed tomography (CT) and optogenetics[63-68]. Thus, hydrogel-based electrodes can be integrated with optogenetic, CT, and MRI for multimode signal requisition, which is of great significance in brain science and neurological disease diagnosis[69-72]. As a result, it can provide a new way and method for clinical diagnosis and treatment of neurological diseases[73-75].

Although both non-invasive and invasive neural electrodes have been widely investigated, the dehydration of hydrogel when applied non-invasively and the swelling of hydrogel for invasive devices are still crucial issues, especially for long-term applications[76]. Therefore, wet, semi-dry and dry electrodes were proposed

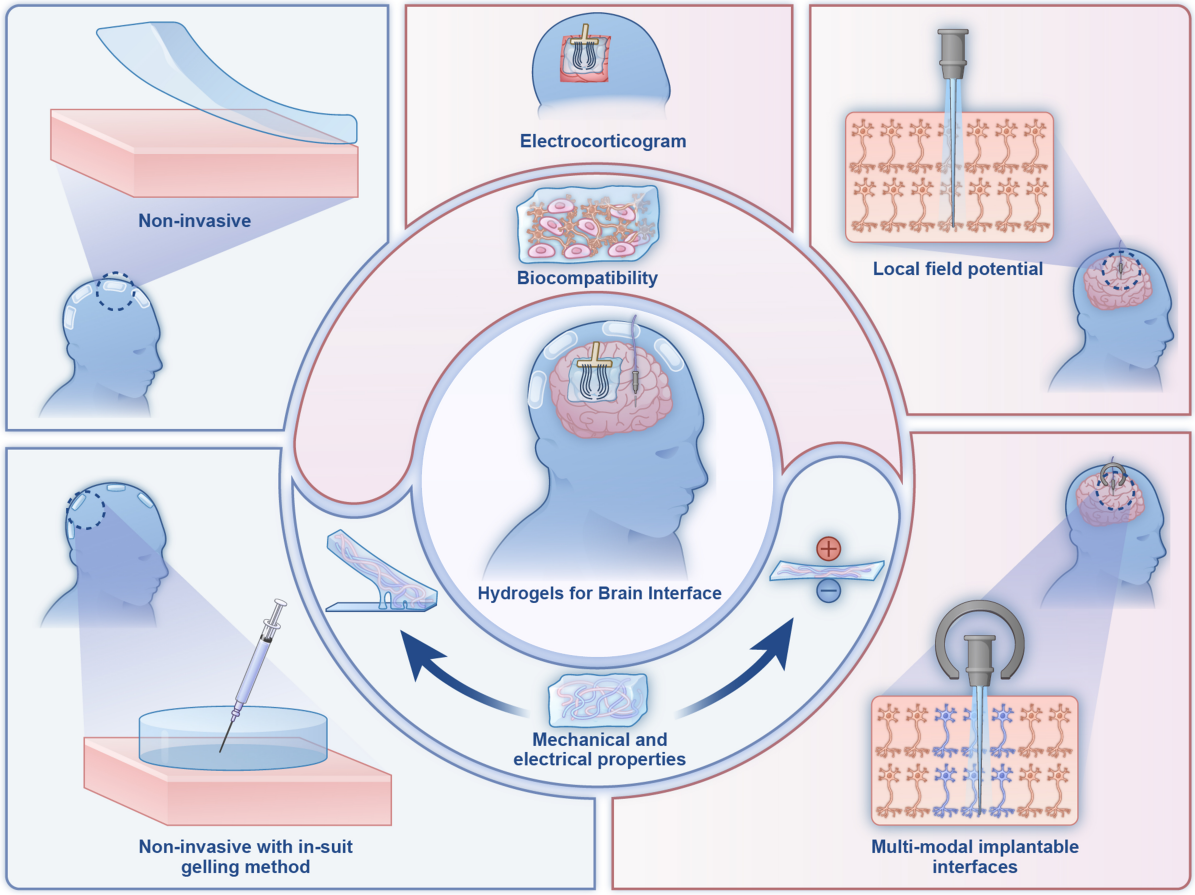

Figure 1. The application of hydrogels for brain signal monitoring.

to overcome the challenges. Wet electrodes maintain a continuous layer of electrolyte gel or liquid, which provides stable conductivity and reduces impedance at the interface. This design minimizes dehydration and ensures reliable signal acquisition over extended periods. Semi-dry electrodes strike a balance between wet and dry designs. They often incorporate a thin layer of hydrogel that retains moisture while allowing for some evaporation. This configuration helps reduce the swelling issues associated with invasive electrodes while still providing a good level of signal fidelity and comfort for the user. Therefore, wet and semi-dry electrodes are frequently used for non-invasive real-time monitoring. Dry electrodes, on the other hand, eliminate the need for a gel or liquid interface entirely. They are designed with materials that have high electrical conductivity and biocompatibility, which allows them to maintain effective signal quality without the complications of dehydration or swelling. While dry electrodes may face challenges in terms of impedance, they are suitable for invasive devices.

Based on the challenges of the existing brain interface and the advantages of hydrogel materials, this paper will provide a comprehensive review of the hydrogel materials in neural electrodes for brain signal acquisition. Firstly, this review discusses the synthesis, property optimization, and application of hydrogel materials for brain signal monitoring, as shown in Figure 1. Then, the tendency from non-invasive to invasive methods and from unimodal to multimodal signals is covered, which aims to provide insights and references for the development of brain electrodes in the field of neuroscience and brain-machine interfaces.

PROPERTY OF HYDROGELS FOR BIOELECTRONICS

Mechanical properties of hydrogels

The mechanical property of hydrogels is a crucial factor in brain-machine interfaces, as it will significantly influence the biocompatibility of the electrodes and affect performance and functionality. In the context of non-invasive devices, our group designed a unique polymer composite hydrogel, which exhibits stretchable, self-healing, and degradable properties at room temperature[77], as illustrated by Figure 2A-C. The hydrogel material can form patterned electrodes through a self-vaporization process with the optimized mass ratio of glycerol and hydroxyethyl cellulose (HEC) aqueous solution. At room temperature of 25 °C and humidity of 40% relative humidity (RH), the glycerol-doped hydroxyethyl cellulose gel-based material (GHECs) demonstrates excellent extensibility (~304%) and rapid self-healing capability (~9 min). Furthermore, GHECs exhibit controllable degradation behavior due to their solubility in water. Based on these properties, we designed and fabricated a range of flexible and stretchable hydrogel devices, including self-healing electrodes, transient electronics, and robotic tactile sensors, to show the applications of the hydrogel.

Figure 2D and E shows the combability of hydrogel material with biological tissues[78]. Therefore, hydrogels are widely applied in the fields of biomedicine and bioelectronics, including wearable hydrogel electronics, hydrogel coatings, and hydrogel soft robots. However, due to the presence of surface moisture, it is still a challenge to achieve strong adhesion between materials due to the hetero-interface. In 2015, Yuk *et al.* at the Massachusetts Institute of Technology (MIT) proposed the adhesion principle of tough hydrogel, which is attributed to the long-chain polymer network anchoring and internal energy dissipation within tough hydrogels[78]. Compared to physical interactions, chemical bond anchoring offers higher intrinsic adhesion strength and absorbs a significant amount of energy during the separation process, which results in an interface adhesion exceeding 1,000 J/m^2.

The electrophysiological signals often include artifacts, and Figure 2F-H demonstrates the requirements on the material stiffness of bioelectronics for continuous monitoring of electrophysiological signals to reduce noise[79]. These noise signals have a wide frequency range, spanning from 0.01 to nearly 15 Hz, including respiration (0.11 Hz), heartbeat (0.34 Hz), and gait movements (1-15 Hz). Due to the overlap of these low-frequency noises with the low-frequency bands of brain, muscle, and electrocardiographic signals, the conventional approach to filter the signals by bandpass filters will lead to the loss of target signals. Inspired by the selective removal of dynamic mechanical noise artifacts of the spiders, Park *et al.* proposed a novel bandpass filter based on a viscoelastic gelatin@chitosan hydrogel damper[79]. The hydrogel exhibits frequency-dependent phase transitions and acts as an adaptive bandpass filter, which enables the acquisition of high-quality signals without the need of complex signal processing. In brief, the reversible hydrogen bonds between chitosan and gelatin contribute to the viscoelastic properties of the hydrogel, and the material transitions from a rubbery state to a glassy state at an applied frequency of 30 Hz. This phase transition allows the material to selectively transmit target signals (> 30 Hz) while filtering out low-frequency noise (< 30 Hz). Also, the frequency band for noise absorption can be regulated by the relaxation time of viscoelastic materials, which is dependent on the elastic modulus and viscoelasticity of the hydrogel. In addition, the viscoelasticity can be precisely controlled by adjusting the molecular weight of gelatin, water content, and temperature to obtain high SNRs of the target signals. Therefore, the employment of hydrogel dampers in bioelectronics is a promising technique for the continuous detection of biological signals without the need of complex signal processing units.

The mechanical properties of hydrogels are essential for their application in brain-machine interfaces, since they significantly influence the biocompatibility and overall performance. The challenges of adhesion due to surface moisture highlight the need for advanced design strategies to enhance stability. The viscoelastic

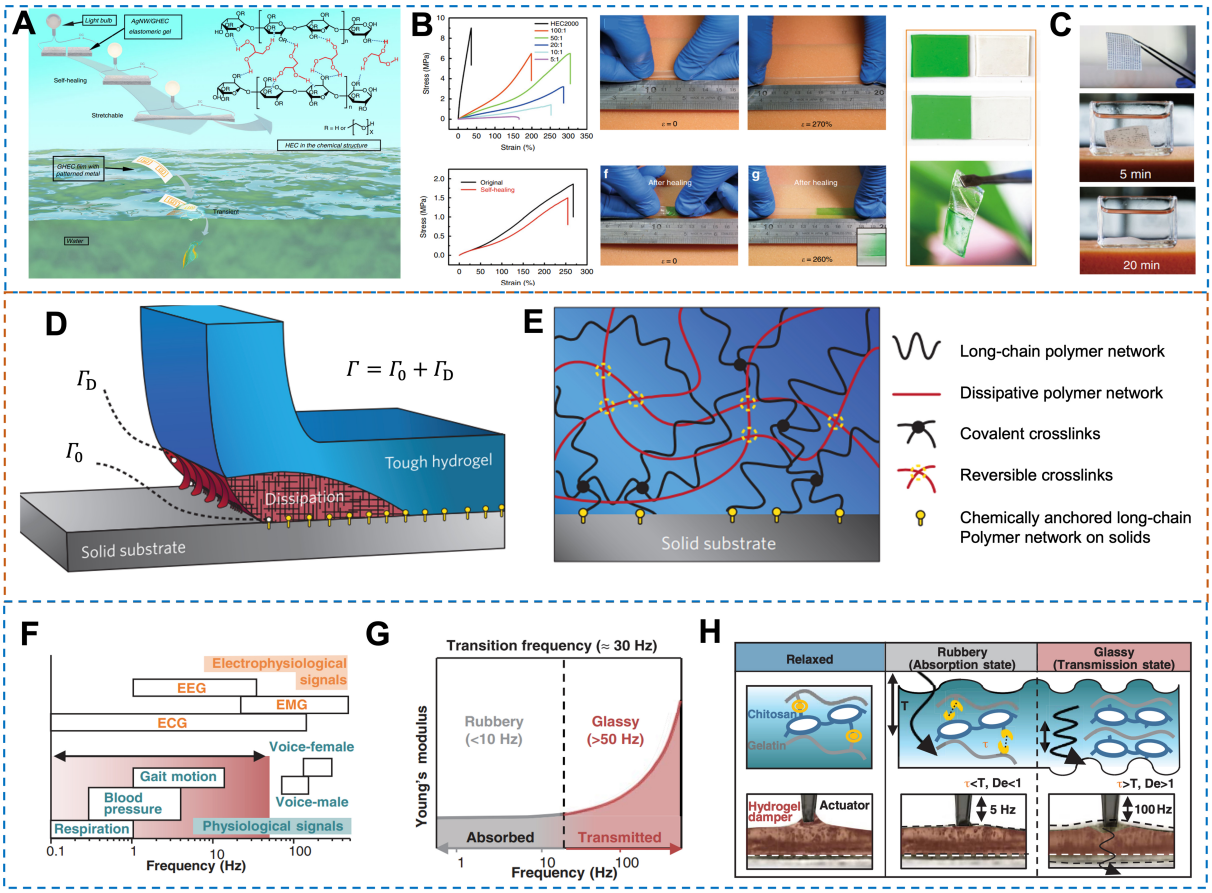

Figure 2. Mechanical properties of hydrogels in bioelectricity. (A-C) GHECs exhibit stretchable, self-healing, and degradable properties at room temperature[77]; (D and E) Tough bonding of adhesive hydrogels[78]; (F-H) Viscoelastic hydrogels with active noise reduction[79]. GHECs: Glycerol-doped hydroxyethyl cellulose gel-based material.

properties of hydrogels are capable of contributing to the versatility, enabling selective signal transmission while minimizing noise artifacts in electrophysiological recordings. This innovative approach to managing low-frequency noise through tailored phase transitions exemplifies the potential of hydrogels in creating high-fidelity bioelectronics. Overall, the mechanical characteristics of hydrogels not only enhance their functionality but also open new avenues for their use in biomedical applications, reinforcing their significance in the ongoing development of advanced neural interfaces.

Conduction mechanisms of the hydrogels

In recent years, the development of brain-computer interfaces (BCIs) has been the subject of considerable attention. However, both dry and wet electrodes present significant challenges in increased impedance, unstable signals, and user discomfort, especially for long-term monitoring of brain signals. Consequently, the development of hydrogels with high conductivity, biocompatibility, and long-term stability has become a major research focus. The conduction mechanism of the materials is the key factor for the performance of electrodes. Therefore, the conduction mechanism was widely investigated. Li *et al.* developed a temperature-triggered adhesive ionic conductive hydrogel, which is composed of polyacrylamide (PAM), gelatin, and sodium alginate (SA) as shown in Figure 3A-C[80]. The triple helix structure of the gelatin unfolds at body temperature and the contact area and adhesion strength with the skin surface will increase when the hydrogel is applied to the human skin. By increasing the content of LiCl, the conductive properties of the hydrogel can be effectively enhanced. Since the modulus of the hydrogel is comparable to

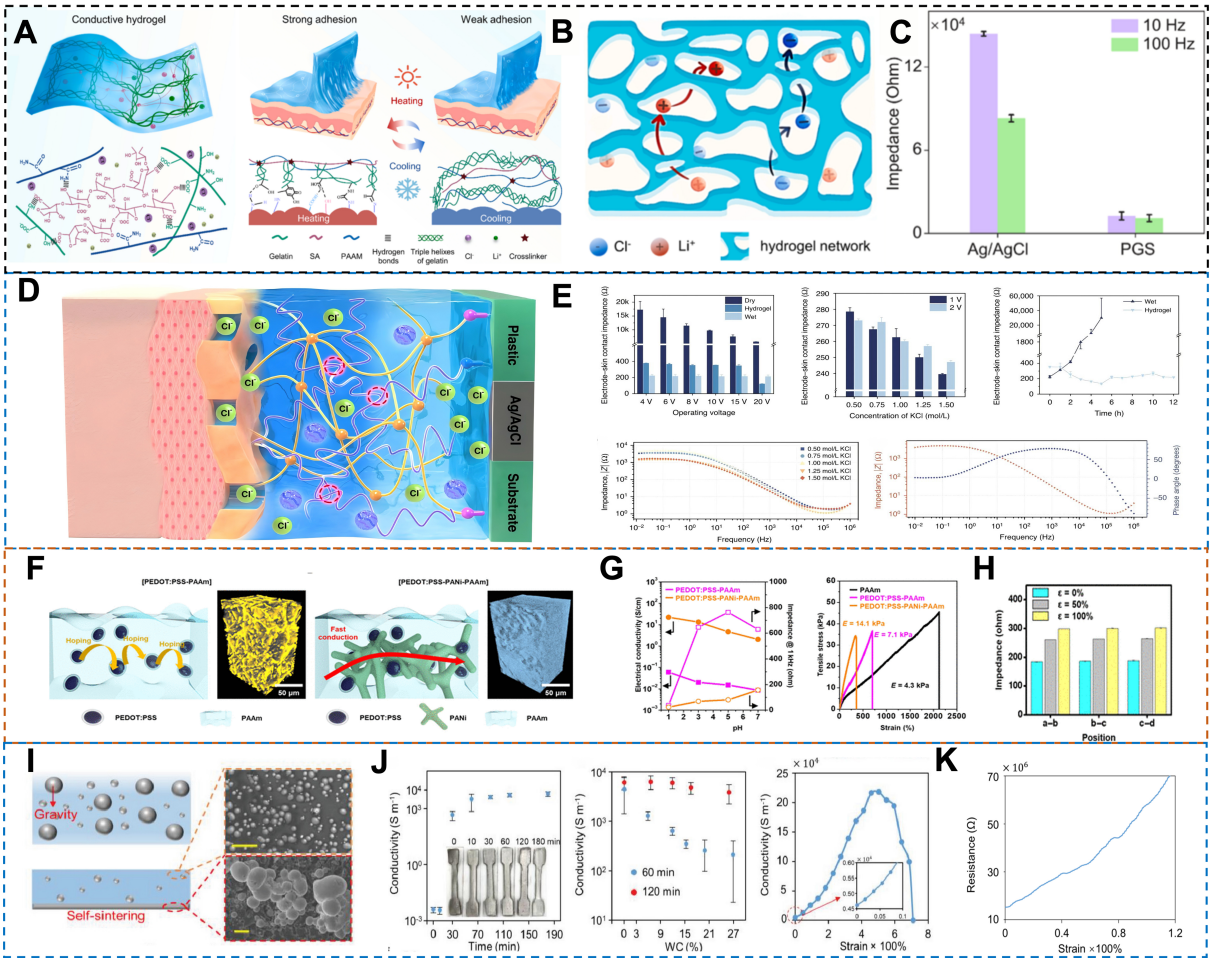

Figure 3. Conductive mechanisms in different types of hydrogels. (A-C) Ionic conductive hydrogel[80]; (D and E) Ion-conductive hydrogel electrode impedance performance under varying KCl concentrations[81]; (F-H) PEDOT:PSS hydrogels: Structural and electrical property optimization[82]; (I-K) Self-sintering mechanism and electrical stability of LM-doped hydrogels[83]. PEDOT:PSS: Poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate); LM: liquid metal.

that of the skin, conformal attachment and low electrode-epidermis impedance can be achieved.

Xue *et al.* at Dalian University of Technology have developed a bilayer electronic and ionic conductive hydrogel electrode[81]. Figure 3D and E depicts the structure of the hydrogel, which comprises a stable network constructed by PAM chains, alginate chains, and chemical anchors. Poly(3,4-ethylenedioxythiophene) (PEDOT) provides an effective electron conduction path for the hydrogel, while chloride (Cl^-) ions move through ionic cross-linked microchannels in the hydrogel to conduct electrical signals. The conductive hydrogel electrode is capable of maintaining a low impedance over an extended period of wear, thereby ensuring the long-term acquisition of high-quality EEG signals. Figure 3B depicts the electrochemical impedance spectra of the hydrogel electrode at varying concentrations of potassium chloride (KCl). As the concentration of KCl increased from 0.50 to 1.50 mol/L, the impedance of the hydrogel electrode exhibited a gradual decrease, particularly in the high-frequency range (10^2 to 10^5 Hz) and reaching a stable value of approximately 10^2 Ω. This indicates that the material demonstrates good electrical conductivity at varying KCl concentrations. This electronic and ionic conductivity-based mechanism ensures the stability of the hydrogel in a wide range of environments, which demonstrates its potential for applications in biomedical sensing and long-term EEG recording.

To enhance the conductivity and mechanical properties of hydrogels, Shin *et al.* proposed a strategy to optimize the materials by incorporating polymers and conductive fillers[82]. Figure 3F-H illustrates the conductive network structure of a conductive hydrogel based on poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) and polyaniline (PANI), wherein PEDOT:PSS serves as the conductive matrix and PANI further enhances the electron transport efficiency. The combination not only improves the electrical conductivity of the hydrogel, but also maintains its mechanical flexibility. Figure 3G illustrates the variation in homogeneity and conductivity of the hydrogels under different PEDOT:PSS doping concentrations. The experimental results demonstrate that the synergistic effect of PEDOT:PSS and PANI effectively optimizes the conductive pathways, while improving the homogeneity of the material and ensuring its stability under different application conditions.

Electronic conduction mechanism is also mainstream for the design and fabrication of conductive bioelectronics. Zhang *et al.* developed a liquid metal (LM)-doped polyvinyl alcohol (PVA)-based hydrogel, which achieved high electrical conductivity and strong toughness through a self-sintering mechanism[83]. Figure 3I illustrates the settling of LM microdroplets under the influence of gravity, which subsequently undergo self-sintering to form a conductive network. Figure 3J illustrates the morphology of the hydrogel with cyclic stretching, which demonstrates the adaptive nature of the material. Figure 3K depicts the resistance change of the hydrogel under 1,000 cycles of stretching to show stability under prolonged mechanical strain. This LM-doped hydrogel exhibits excellent electrical conductivity and mechanical strength, which indicates its potential for use in flexible brain electrodes.

The conduction mechanism of hydrogels is essential for their effectiveness in BCIs, which directly influences the performance in terms of conductivity, impedance, and user comfort during long-term monitoring. Adhesive ionic conductive hydrogel has the advantages in the enhancement of adhesion and conductivity upon skin application and low impedance can be obtained. The electronic and ionic conductive hydrogel can create a stable network and this synergy results in sustained low impedance and high-quality EEG signal acquisition. The innovative use of LM-doped hydrogels demonstrates a self-sintering mechanism that achieves high conductivity and mechanical strength. Overall, the advancements in hydrogels with different conduction mechanisms significantly enhance their functionality, which can expand their potential applications in biomedical sensing and long-term neural monitoring.

Biocompatibility of hydrogels in bioelectronics

The biocompatibility of hydrogel materials is of great significance for long-term monitoring, especially for implantable electronics. As shown in Figure 4A and B, our team conducted systematic *in vitro* cytotoxicity experiments on the hydrogel to validate its biocompatibility[84]. Mouse skeletal muscle (MSkM) cells were cultured *in vitro* on the surface of the STEHy-6 hydrogel to assess their cellular compatibility with tissue culture plates (TCP) as a control. Figure 4A shows that the growth rate of MSkM cells on both TCP and the hydrogel is consistent[84]. In detail, in the initial three days, there is no significant difference in cell proliferation between TCP and STEHy-6, indicating that STEHy-6 has no significant impact on cell growth. MSkM cells exhibited the ability to adhere to and proliferate on both the STEHy-6 and TCP surfaces, which indicates the excellent biocompatibility of the materials. Subsequently, cell proliferation was further confirmed using the CCK-8 assay. Figure 4B demonstrates that with extended culture time, both the control and experimental groups showed a significant increase in skeletal muscle cells[83]. Additionally, live/dead assays were conducted after one, two, and three days of cultivation to identify live cells (green) and dead cells (red). The results showed that the number of cells continued to increase during the cultivation, and few dead cells were observed even after three days of culture. Importantly, the number of MSkM cells was equivalent to that of the TCP control group, indicating that the STEHy-6 hydrogel is suitable for the survival and proliferation of isolated skeletal muscle cells and the material has excellent biocompatibility.

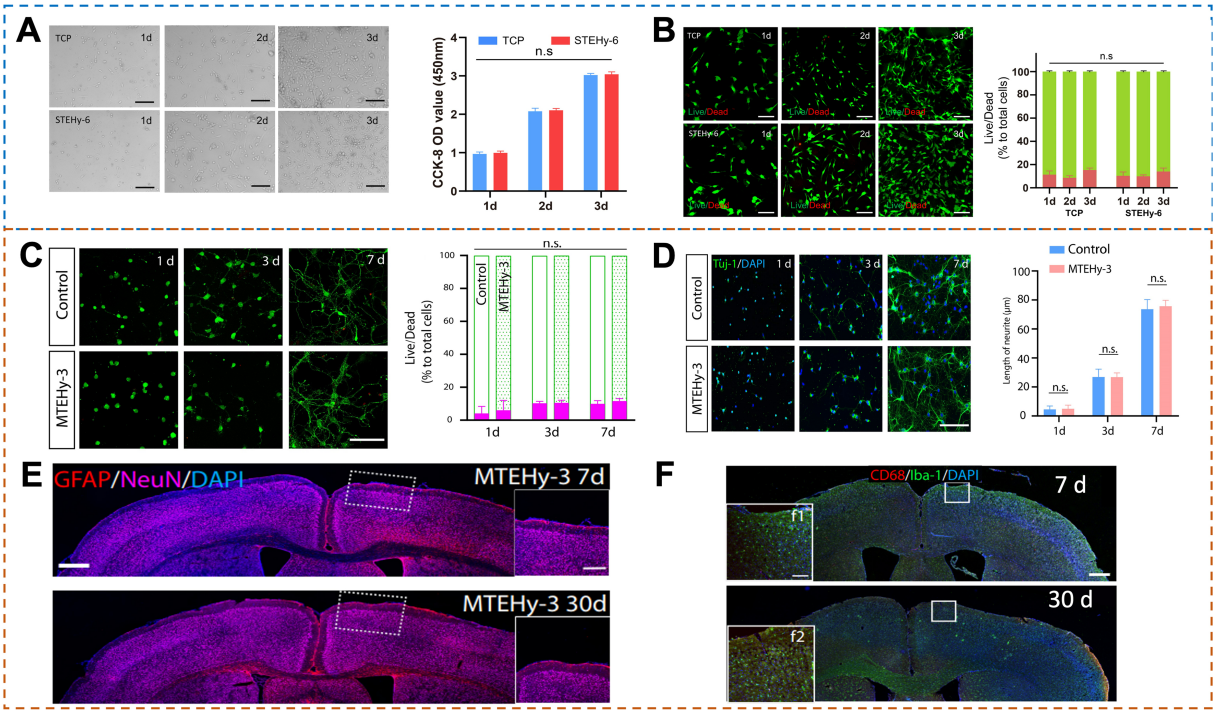

Figure 4. Biocompatibility of hydrogels in bioelectricity. (A and B) MSkM cells were cultured *in vitro* on the surface of the STEHy-6 hydrogel to assess their cellular compatibility[84]; (C-F) The biocompatibility of MTEHy-3 hydrogel as an implantable device through *in vivo* animal tissue toxicity experiments[85]. MSkM: Mouse skeletal muscle.

We further explored the biocompatibility of hydrogel as an implantable device for animal tissues, as shown in Figure 4C-F. We verified the biocompatibility of the multimodal hydrogel EEG electrode, MTEHy-3, through *in vivo* animal tissue toxicity experiments. Since the implanted hydrogel electrode adheres to the brain cortex surface, we conducted cortical neuron live/dead staining to quantitatively analyze live/dead cells. After a day of culture, the average neuronal cell viability in the MTEHy-3 experimental group was 90%, and it remained at 85% after three and seven days of culture, which shows no significant difference in the control group. In addition, we examined the influence of MTEHy-3 hydrogel on primary neurons. As shown in Figure 4C and D, after one, three, and seven days of culture, there is no difference in neuronal axons and dendritic morphology in both the control and experimental groups[85]. Furthermore, we investigated the impact of the MTEHy-3 hydrogel-based device on brain tissue *in vivo*. The mechanical combability of the hydrogel with brain tissue was assessed by using GFAP antibody and NeuN antibody to label astrocytes and neurons, respectively. After implantation of MTEHy-3 for seven and thirty days, a large number of cortical neurons were found to be alive in the implanted region of the skull window with no significant difference in the number of astrocytes compared to the control group. This result suggests that MTEHy-3 does not exert significant compression on brain tissue and is conducive to *in vivo* applications. To further investigate the impact of MTEHy-3 implantation in the mouse skull window on cortical inflammation, we used CD68 antibodies to label inflammatory cells and Iba1 antibodies to label microglial cells. After the implantation for seven and thirty days of MTEHy-3 implantation, we observed few $CD68^+$ cells in the implantation area, and microglial cells were in an inactive state. This result further indicates the biocompatibility of the materials.

The biocompatibility of hydrogels is essential for their use in bioelectronics, particularly in long-term monitoring and implantable devices. Recent studies have shown that hydrogels can effectively support cell

growth and proliferation, which demonstrates minimal cytotoxicity when cultured with various cell types. *In vivo* assessments further confirm their compatibility, as they typically exhibit low inflammation and maintain normal cellular morphology in implanted sites. Also, benefiting from the mechanical properties of hydrogels, they can make conformal contact with tissues without causing significant compression or damage, which also contributes to their biocompatibility. Overall, the favorable interactions between hydrogels and biological tissues highlight their potential for applications in advanced neuroelectronic interfaces and other biomedical areas.

Moisturizing and swelling properties of hydrogels in bioelectronics

Hydrogels possess excellent flexibility and biocompatibility, which provides the fundamental properties for applications in flexible electronics. However, due to the high water content, almost all hydrogels inevitably lose water when exposed to an environment with low humidity, which leads to reduced flexibility or even loss of function. To address the dehydration of hydrogels, highly water-soluble inorganic salts, organic solvents, surface modification or encapsulation were proposed.

Zhu *et al.* developed a hydrogel with excellent water retention using a dual hydrophobic coating, which was referred to as PAAm-ASO[86], as shown in Figure 5A and B. Firstly, the hydrogel underwent plasma treatment to create a rich hydroxyl surface. It was sequentially immersed in a solution of (3-aminopropyl) triethoxysilane (APTES) in ethyl acetate (EtOAc), a stearic acid (STA) solution, and silicone oil. The robust coating, which consists of a hydrophobic polymer layer and a hydrophobic oil layer, provides dual shielding against water evaporation. Since the coating is much thinner than the hydrogel, it does not significantly affect the mechanical properties of the hydrogel while its water retention property is enhanced.

Inspired by the structure of spider silk, Wu *et al.* constructed hydrogel fibers with high mechanical performance and water retention properties by introducing ionic cross-linking and crystalline domains through the incorporation of Zr^{4+} based on ionic coordination of inorganic salts and the Hofmeister effect as shown in Figure 5C and D[87]. The S-PAZr (S-PVA/PAA/Zr^{4+}) hydrogel fibers can maintain 79.91% of the original weight at 43% RH. In addition, the material can spontaneously absorb water molecules from the environment when moving from a low-humidity to a high-humidity environment.

Lan *et al.* also proposed a hydrogel by combining gelatin with pyrrolidone carboxylic acid sodium (PCA-Na), as shown in Figure 5E and F[88]. With the protonation of the amino groups in gelatin, it can electrostatically attract the carboxyl groups of PCA-Na. Therefore, the mechanical properties of the gelatin-PCA-Na gel can be improved due to the enhanced ionic cross-linking and the tight network structure. Additionally, the hydrophilic groups of PCA-Na can form hydrogen bonds with water molecules, which further improves the water retention of the hydrogel. As a result, the hydrogel can be used as a conformal biological interface for the recording of physiological electrical signals with high fidelity.

Besides the dehydration of hydrogels, the swelling of hydrogels in aqueous environments is also an issue, especially for *in vivo* applications, such as implantable electronic devices. The swelling mechanism of hydrogels results from the balance between the polymer-water interaction forces that promote swelling and the elastic recoil forces that resist the swelling. To address this issue, researchers have developed anti-swelling hydrogels by adjusting the hydrophilic-hydrophobic property, cross-linking density and monomer content.

Dou *et al.* developed an anti-swelling hydrogel with a protective layer by adjusting non-covalent interactions as shown in Figure 6A-C[89]. In brief, the chitosan/poly(N-acryloylglycine) (CS/PACG)

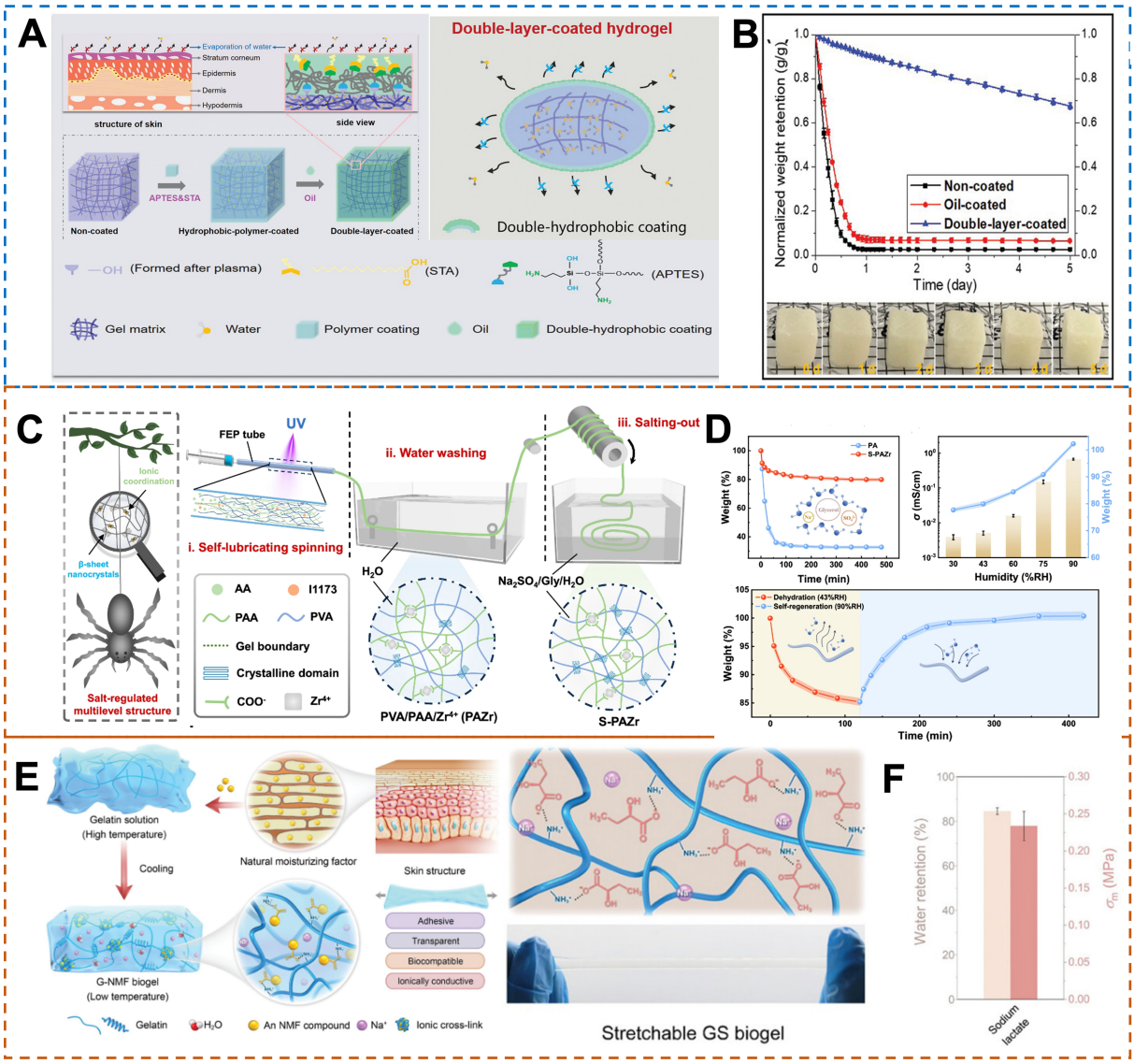

Figure 5. Bio-inspired design for the enhancement of water retention and conductivity. (A and B) Skin-inspired double-hydrophobic coating[86]; (C and D) A self-lubricating spinning method for hydrogel fibers with ionic cross-linking and crystalline structures inspired by spider silk[87]; (E and F) Skin-inspired biogel for water retention and ionic conductivity[88].

hydrogels were first immersed in $FeCl_3$. The Fe^{3+} ions diffused into the gel matrix and interact with carboxyl groups to form the cationic domains. Due to the large ionic radius of Fe^{3+}, a dense cross-linked polymer network formed through diffusion within the hydrogel. As swelling time increases, Fe^{3+} gradually restructured and optimized the network. As a result, it became a tough double-network hydrogel with a soft core and hard shell structure, which can significantly enhance its anti-swelling and mechanical properties.

As shown in Figure 6D and E, Li *et al.* reported a conductive hydrogel with excellent anti-swelling properties and biocompatibility. In the hydrogel, PVA and cellulose nanofibers (CNF) were used as biocompatible polymer matrices and nanofiber-reinforced fillers, respectively[90]. The PEDOT:PSS was used as the conductive material. With the combination of uniaxial pre-stretching and drying/rehydration processes, dense polymer chains were formed by PVA, CNF, and PEDOT. The dense hydrogen bonds and crystalline domains effectively resist water. Therefore, the hydrogel shows excellent anti-swelling properties.

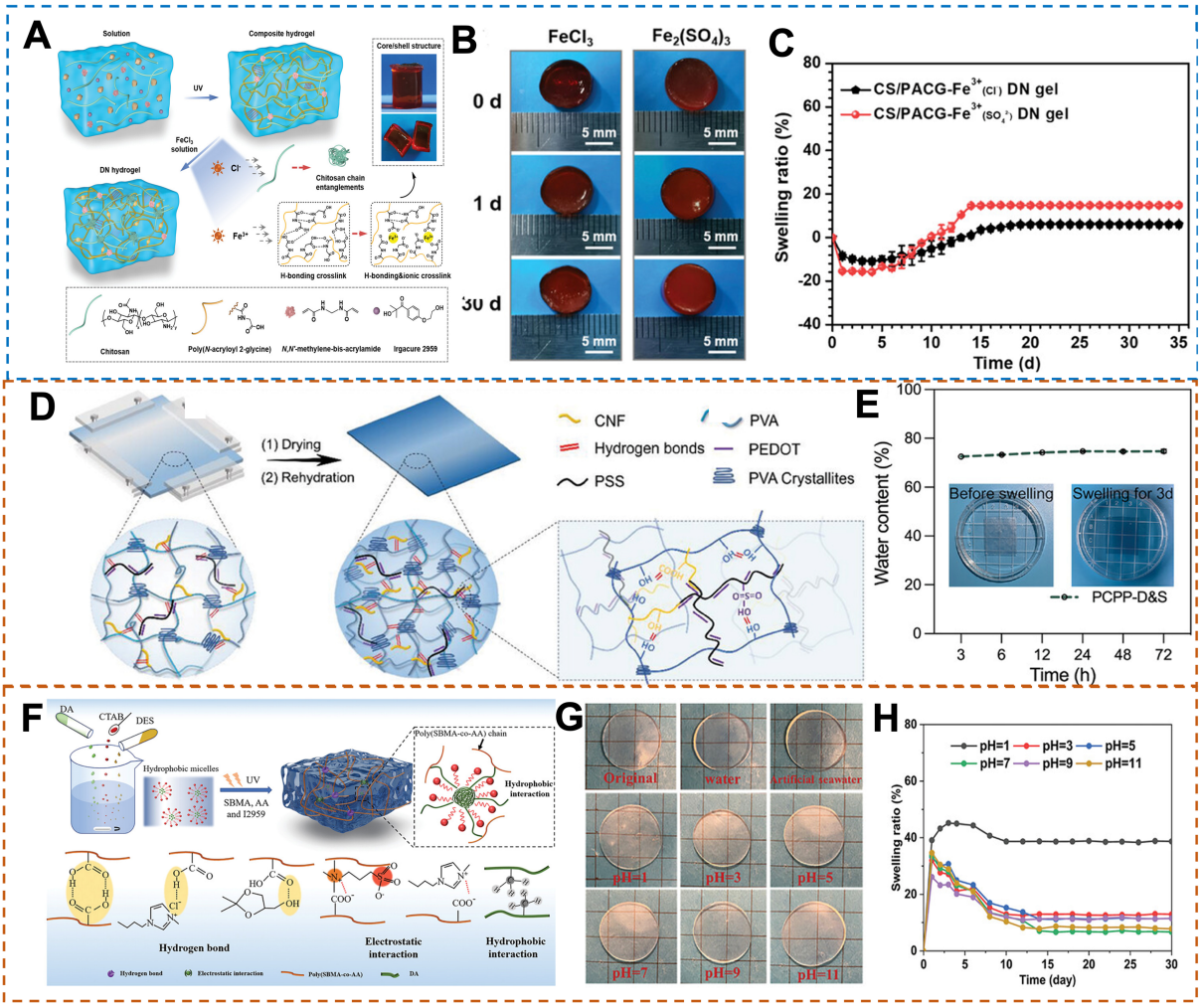

Figure 6. Anti-swelling hydrogels. (A-C) Shell-structured double-network hydrogel with enhanced anti-swelling and mechanical stability via one-step soaking[89]; (D and E) Anisotropic conductive hydrogel with high mechanical strength and anti-swelling properties achieved through pre-stretching and drying-rehydration[90]; (F-H) Deep eutectic solvent (DES)-enhanced conductive hydrogel exhibits excellent anti-swelling properties and remains stable across various solvents and pH conditions[91]. DES: Deep eutectic solvent.

Zhang *et al.* also reported a multifunctional hydrogel with high transparency, freeze-resistance, and anti-swelling[91]. As shown in Figure 6F-H, the hydrogel formed a physically cross-linked network through electrostatic interactions, hydrogen bonds, and hydrophobic interactions of monomer chains. The presence of hydrophobic segments effectively resisted water molecules, which significantly reduced the affinity for water. Therefore, it was able to maintain the original structure by preventing excessive water absorption and swelling. The material also demonstrated strong anti-swelling properties even in solutions with varying pH from 1 to 11.

Dehydration and swelling are significant challenges in the long-term application of hydrogels for bioelectronics. While hydrogels offer excellent flexibility and biocompatibility, their high water content makes them susceptible to dehydration in low-humidity environments, which leads to reduced functionality and flexibility. This can compromise their effectiveness in flexible electronic applications. To overcome the challenges, various strategies, such as surface modifications and the incorporation of water-retaining agents, have been developed to enhance water retention and prevent evaporation. Conversely, swelling in aqueous

environments can also pose risks, particularly for implantable devices, as it may affect the mechanical integrity and performance. Researchers have proposed anti-swelling hydrogels through adjustments in hydrophilic-hydrophobic balance and cross-linking density, which help maintain structural stability during prolonged exposure to bodily fluids. Together, these approaches highlight the importance of optimizing hydrogel properties to ensure their reliability and performance in bioelectronic applications, ultimately supporting their use as effective interfaces for physiological signal monitoring.

In addition, SNR is crucial in the performance of electrodes used for signal monitoring, particularly in brain-machine interfaces. Hydrogel-based electrodes offer distinct advantages and face specific challenges, especially concerning long-term monitoring. The high biocompatibility and low modulus of hydrogels give them a softness similar to that of soft tissues, allowing them to better conform to biological tissues and form close contact, which is beneficial for long-term interface stability. Hydrogels contain large amounts of water and ions, enabling charge transfer through ionic conductivity. This conductive mechanism is consistent with the ion conduction mechanism in biological tissues, which is beneficial for electrical signal transmission and reducing interface impedance caused by conductivity differences. Low impedance can also reduce energy loss during signal transmission, which will result in clearer electrophysiological signals. Compared to rigid electrodes, this soft interface does not exert additional mechanical stimulation on tissues which can be helpful to reduce noise caused by interface movement. Therefore, hydrogel electrodes can achieve good interface integration and long-term stability with biological tissues through their biocompatibility, softness, ionic conductivity, and low interface impedance. As a result, it can effectively reduce interference in electrophysiological signals and improve the SNR.

HYDROGEL-BASED BRAIN-MACHINE INTERFACES

Tables 1 and 2 show the main features of non-invasive and invasive hydrogel electrodes in different bioelectronic applications. These tables give a complete picture of how hydrogel electrodes can be used in biosignal monitoring, health management, and neural interfaces. They can be used to improve performance and find the best materials.

Non-invasive hydrogel interfaces

General non-invasive hydrogel interfaces

Hydrogel is gaining recognition as an ideal material for semi-dry EEG electrodes due to its unique ability to improve signal quality, comfort, and practicality. It provides excellent skin conformability, ensuring a stable and low-impedance contact between the electrode and the skin, which enhances the accuracy of EEG recordings. Unlike traditional wet electrodes, hydrogel electrodes are more comfortable for long-term wear, reduce skin irritation, and are easier to apply and remove without the mess of conductive pastes or gels. They also maintain consistent electrical properties, which can offer better signal integrity, even in dynamic or mobile settings. With their durability, ease of use, and reduced maintenance requirements, hydrogel-based electrodes offer a more hygienic, cost-effective, and user-friendly alternative for both clinical and home-based EEG monitoring[32]. Therefore, the monitoring of EEG signals is widely investigated by the incorporation of hydrogels with commercial electrodes or EEG caps to realize multi-channel EEG signals with non-invasive method. In these frameworks, the hydrogels are pre-prepared and are attached on the EEG caps for electrodes to use the interface.

Chen from the Institute of Materials at the Chinese Academy of Sciences reported a hydrogel[92], which is composed of a physically cross-linked interpenetrating network based on calcium ions and zwitterionic [2-(methacryloyloxy)ethyl] dimethyl-(3-sulfopropyl) ammonium hydroxide (SBMA) and 2-hydroxyethyl methacrylate (HEMA), for the recording of EEG signals as shown in Figure 7A and B. Due to the ion-dipole

Table 1. Advantages, disadvantages, applications, material composition and signal quality of different non-invasive hydrogel electrodes

Materials	Advantages	Disadvantages	Applications	Conduction type	Signal quality	Ref.
Glycerol, Hydroxyethylcellulose, HEC	Highly stretchable, adapts to dynamic surfaces	Transient nature may limit lifespan	Wearable electronic, health monitoring patch	Ionic conductive gel	Stable for dynamic monitoring	[77]
Acrylamide, N,N'-methylenebisacrylamide	Strong adhesion to non-porous surfaces	May lose adhesion under extreme stress	Wearable sensor, health patch	Ionic conductive gel	Stable signal, strong interface contact	[78]
Gelatin, chitosan	Reduces dynamic noise, enhances signal clarity	Complexity may increase manufacturing cost	Bioelectronic, wearable sensor	Ionic conductive gel	High clarity, selective frequency damping	[79]
PAM/PVA, CNTs	Strong adhesion for long-term monitoring	Adhesive may cause skin irritation over time	Non-invasive, long-term EEG monitoring	Ionic conductive gel	High signal quality, stable contact	[81]
PANI-PEDOT, PAM	Low impedance, enhances signal quality	Complexity in chemical bonding process	Stretchable bioelectronic, dynamic monitoring	Ion-electron co-conductive hydrogel	High-quality, low-noise signals	[82]
PVA, EGaIn, TA	Exceptional toughness and conductivity	Potential complexity in fabrication	Wearable electronic, high-strength sensor	Electronically conductive hydrogel	High signal quality, low impedance	[83]

HEC: Hydroxyethyl cellulose; PAM: polyacrylamide; PVA: polyvinyl alcohol; CNTs: carbon nanotubes; EEG: electroencephalogram; PANI: polyaniline; PEDOT: poly(3,4-ethylenedioxythiophene); TA: tannic acid.

Table 2. Advantages, disadvantages, applications, material composition and signal quality of different Invasive hydrogel electrodes

Materials	Advantages	Disadvantages	Applications	Conduction type	Signal quality	Ref.
PVA, HACC, HA	Transparent, enables optical imaging	Potential limitations in long-term use	Two-photon neuroimaging, ECoG monitoring	Ionic conductive gel	High-fidelity signals	[85]
PEG, channelrhodopsin-2	Conformal contact with brain tissue	Complex integration process	BMI, neural recording	Ion-electron co-conductive hydrogel	High signal fidelity	[99]
PVA, PEDOT	Forms synaptic-like connections with neuron	Complex setup, may require precise control	Synaptic BMI, neural interfacing	Ionic conductive gel	High-fidelity synaptic signals	[100]
PAM, PAA, CNTs	Strong adhesion, high conductivity, and durability	May require precise coating techniques	Neural recording and modulation	Ion-electron co-conductive hydrogel	High-quality, low-noise signals	[102]

PVA: Polyvinyl alcohol; HACC: hydroxypropyltrimethyl ammonium chloride chitosan; HA: hyaluronic acid; ECoG: electrocorticogram; PEG: polyethylene glycol; BMI: brain-machine interfaces; PEDOT: poly(3,4-ethylenedioxythiophene); PAM: polyacrylamide; PAA: polyacrylic acid; CNTs: carbon nanotubes.

or dipole-dipole interactions generated by the strong dipolar zwitterionic units within the polymer chains, the reversible physical cross-linking offers advantages in energy dissipation, superelasticity, adaptive adhesion, and ionic conduction. As a result, this flexible hydrogel electrode can be used for continuous recording of EEG signals. Also, eye movement and forehead temperature can also be monitored by integrating with other sensors, which indicates the potential application of the hydrogel in the monitoring of body movement or analysis of mental states.

Figure 7C and D demonstrates the continuous monitoring of high-quality brain signals with hydrogel and commercial EEG electrodes by Park *et al.*[79]. The hydrogel works as the interface and can filter out mechanical signals due to the low-frequency noise. In the experiment, the volunteers were asked to blink their eyes at a fixed frequency and it was demonstrated that the hydrogel can selectively filter 10 Hz noise.

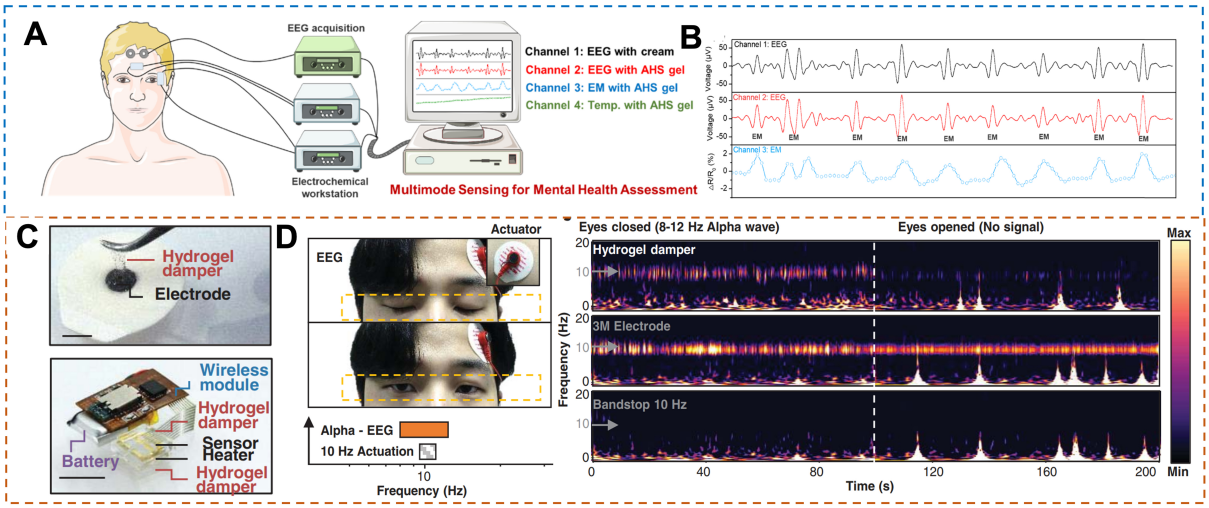

Figure 7. Non-invasive hydrogel interfaces. (A and B) Physically cross-linked interpenetrating network based on calcium ions[92]; (C and D) Viscoelastic hydrogel dampers for electrophysiological sensors[79].

Moreover, when the volunteers closed their eyes naturally, the hydrogel detected intermittent signals in the range of 9 to 12 Hz, signifying stable EEG signal acquisition regardless of the presence of the noise. Therefore, the hydrogel not only works as the conductive medium for the record of EEG signals but also as a filter for the removal of noise, which can simplify the signal processing system.

Non-invasive hydrogel interfaces offer a promising solution for the monitoring of EEG signals due to their ease of use and compatibility with biological tissues. However, challenges such as high impedance, low adhesion force, and concerns regarding long-term stability can hinder their effectiveness. These issues can lead to suboptimal performance and potential failure in clinic scenarios. To address these limitations, *in-situ* gelling methods are emerging as a promising approach, enabling the hydrogels to form and adhere directly at the site of application, potentially enhancing their mechanical properties and stability.

Non-invasive hydrogel-based semi-dry interfaces

Semi-dry hydrogel electrodes leverage the excellent water retention and conductivity of hydrogels to create a low-impedance interface on the skin for a long period, which enables efficient bioelectrical signal acquisition[32,93]. By carefully managing the water content within the hydrogel, the electrodes remain moderately moist without becoming overly wet, which can reduce skin irritation and maintain stable signal acquisition. Typically, these electrodes are designed with a dual-network structure, which can provide both high mechanical strength and flexibility. The performance can be further enhanced with a multi-layer design. In brief, an adhesive base layer is designed for conformable skin attachment, a conductive hydrogel layer for signal acquisition, and a protective layer for extended lifespan. With outstanding biocompatibility and a stable electrode-skin interface, semi-dry hydrogel electrodes can be used for prolonged, high-quality bioelectrical signal monitoring.

Figure 8A and B illustrates the silver nanowire (AgNW)/PVA hydrogel/melamine sponge (AgPHMS) semi-dry EEG electrode[94]. The water retention capacity of the PVA hydrogel enables the electrode to maintain the stability of the electrolyte. Consequently, the impedance between the skin and the electrode remains within the range of 10 to 15 kΩ. Furthermore, the flexibility of the device ensures the stability of the mechanical properties and wearing comfort. Therefore, the electrode exhibits high conductivity, excellent

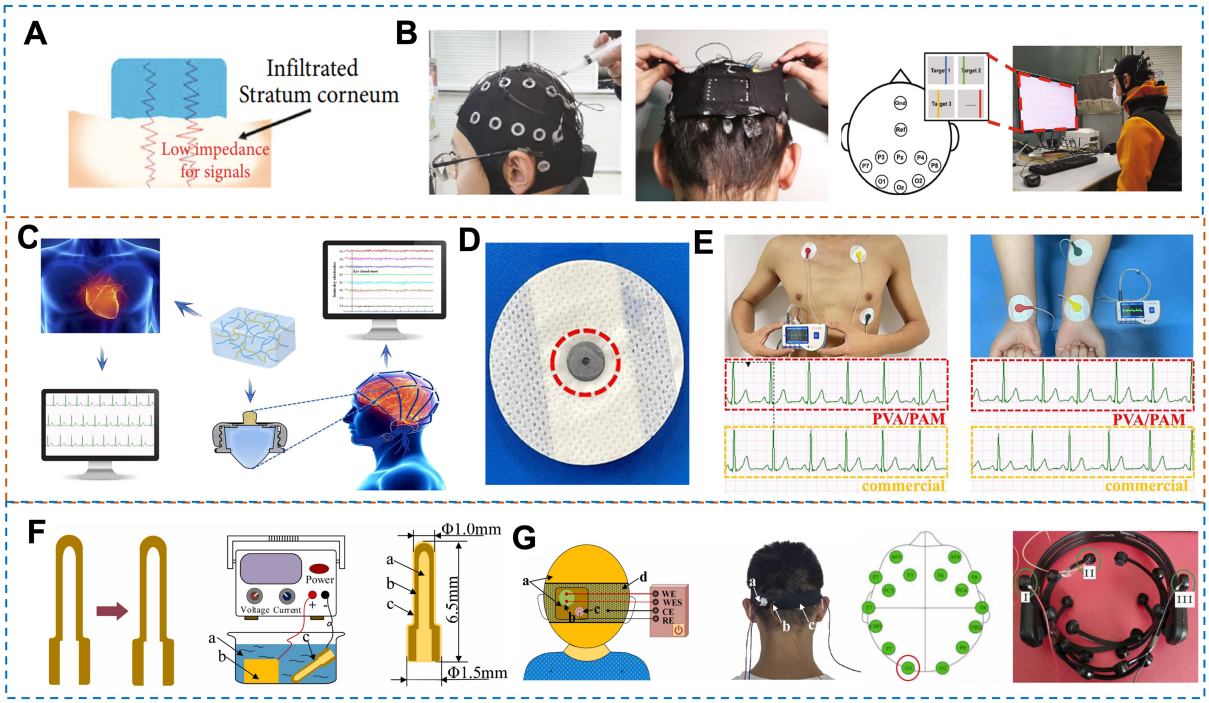

Figure 8. Semi-dry electrode interfaces. (A and B) The AgNW/AgPHMS semi-dry EEG electrode[94]; (C-E) Semi-dry electrode based on PVA/PAM double-network hydrogel, providing low-impedance contact for long-term high-quality signal bioelectric acquisition[95]; (F and G) Semi-dry electrode for EEG acquisition[96]. AgNW/AgPHMS: Silver nanowire/PVA hydrogel/melamine sponge; EEG: electroencephalogram; PVA: polyvinyl alcohol; PAM: polyacrylamide.

flexibility and stable electrochemical and mechanical properties. As a demonstration, the electrodes were used to acquire EEG signals for three hours, achieving a recognition accuracy ranging from 77% to 100%, which is comparable to commercial electrodes. The result illustrates its potential for long-term BCI applications.

A semi-dry electrode based on a PVA/PAM dual-network hydrogel was proposed by Prof. Li from Hunan University of Technology for long-term stable acquisition of EEG signals[95]. Figure 8C-E illustrates the structure and application of the electrodes. The excellent water retention capacity of the PVA/PAM hydrogel enables the electrode to release electrolytes continuously. As a result, a low-impedance contact within a stable range of 18.2 ± 8.9 kΩ was achieved. Furthermore, the flexibility and adhesion properties of the PVA/PAM hydrogel endowed the electrodes with excellent mechanical stability and wearing comfort. In BCI applications, the semi-dry electrodes demonstrated good conductivity, flexibility and stability, with a recognition accuracy of more than 91%.

In a recent publication, Prof. Wang from Northeast Electric Power University proposed a semi-dry electrode for the acquisition of EEG signals as shown in Figure 8F and G[96]. The electrodes are designed with a height of 6.5 mm, a diameter of 1.0 mm at the top and 1.5 mm at the bottom to ensure stable contact with the skin while providing moderate comfort. Inside the electrodes, there is an absorbent sponge composed of polyurethane and PVA to control the release of conductive fluid and maintain a moderate level of wetness. To enhance conductivity, the surface of the electrodes is coated with silver through an electrochemical method. As a demonstration, the authors apply the semi-dry electrode in a fatigue detection scenario. The results indicate that the electrode could recognize fatigue-related signal patterns during prolonged driving sessions with more than three hours.

Traditional dry electrodes are challenging for signal acquisition because of their high contact impedance and unstable interface, especially in the condition of dynamic movement. In contrast, wet electrodes, which utilize conductive gels to reduce impedance, can cause skin irritation with extended periods and require frequent rehydration to maintain conductivity. Semi-dry electrodes can achieve low impedance between the skin and electrodes benefiting from the water retention capabilities of hydrogel, while also offering excellent flexibility and adhesion. This design ensures stable signal quality and a comfortable wearing experience and semi-dry electrodes are considered as an ideal alternative to traditional dry and wet electrodes.

Non-invasive hydrogel interfaces with in-suit gelling method

Long-term EEG signal monitoring with high fidelity is of great significance for clinical applications and neuroscience research. However, conventional electrodes are based on conductive liquids or hydrogels and incorporation with commercial EEG caps to realize multi-channel monitoring of EEG signals, which lacks adaptability in deformation and hairy scalp conditions. As a result, long-term EEG recordings remain a challenge. Therefore, there has been extensive research in the development of self-adhesive for multi-channel EEG interfaces based on the in-suit gelling hydrogel to overcome the challenge.

As illustrated in Figure 9A and B, Han *et al.* reported a multifunctional hydrogel with high conductivity, adhesiveness, and biocompatibility[34]. The proposed hydrogel can realize in-suit gelling and bridges the mechanical mismatch between human tissues and electrodes and offers an efficient and stable method for brain signal acquisition. In brief, they proposed a strategy based on free radical oxidation to prepare mussel-inspired polydopamine (PDA) nanoparticles. The PDA nanoparticles are uniformly distributed throughout the hydrogel network, with carboxyl groups ionized into carboxylate anions, which serve as fixed ions. Simultaneously, positive ions, such as hydrogen and sodium ions, are introduced during the preparation of the hydrogel and uniformly dispersed in the hydrogel network. As a result, it provides excellent and stable conductivity. The EEG signal recording indicates that the hydrogel-based electrodes exhibit exceptional performance in impedance and resistance to noise and other interference, such as sweat and motion artifacts.

Wang *et al.* have developed a conductive bio-gel, which realizes the reversible fluid-to-gel transition characteristics at a desired temperature by adjusting the collagen content and cross-linking density as depicted in Figure 9C and D[35]. The phase transition provides unique skin adaptability and *in-situ* gelling capability for the bio-gel, which enables conformal contact between the electrodes and the scalp. The phase transition property is particularly suitable for EEG monitoring on hairy scalps for long-term stable EEG recordings with high quality.

Also, Luo *et al.* reported a highly flowable pre-polymerized sodium polyacrylate (PAAS)-based ion-conductive hydrogel that rapidly conforms to the structure of the scalp as shown in Figure 9E and F[97]. They used MXene as a cross-linking agent, which allows the PAAS-MXene to solidify on the skin within five seconds. This method significantly reduces the electrode-skin impedance and improves the quality of bioelectrical signals. In addition, PAAS-MXene demonstrates excellent electrical properties, including outstanding polarization potential stability, extremely low impedance and stable electrical performance after stretching for 1,000 cycles.

Non-invasive hydrogel interfaces utilizing in-suit gelling methods represent a transformative approach to long-term EEG signal monitoring. Traditional electrodes often struggle with adaptability and stability, but advancements in self-adhesive hydrogels have led to more effective solutions. These innovative materials not only provide high conductivity and biocompatibility but also enable real-time gelling upon application,

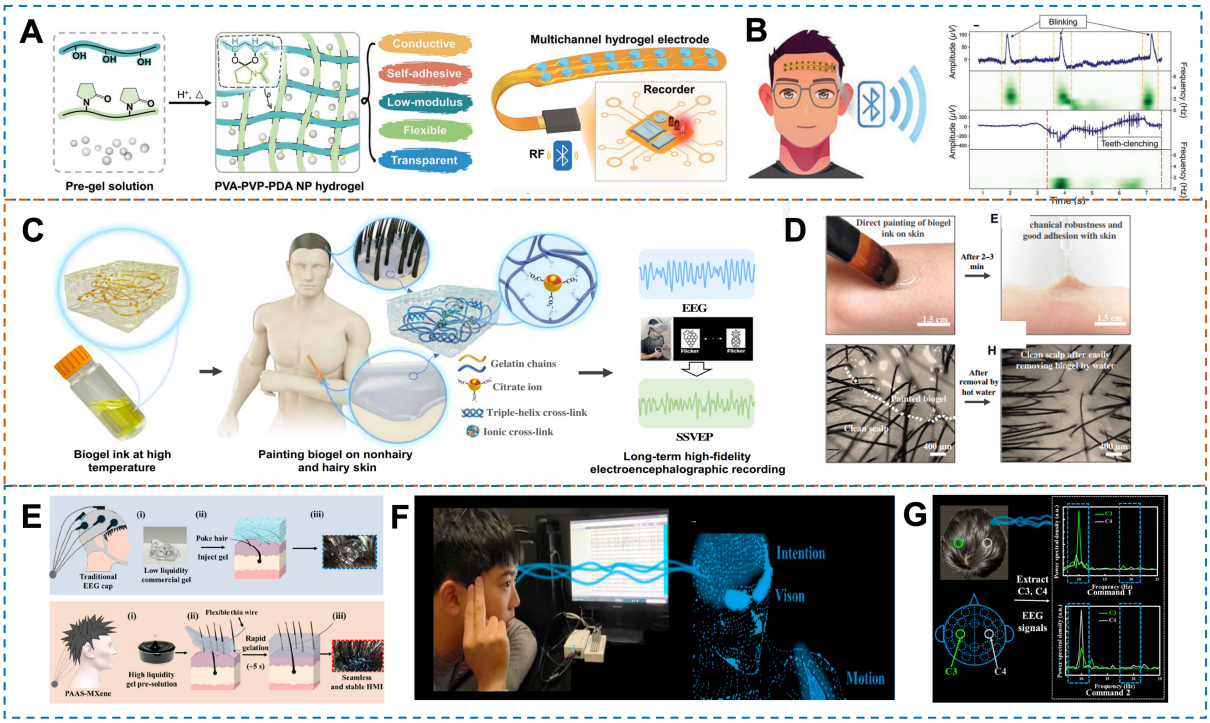

Figure 9. Non-invasive hydrogel interfaces with in-suit gelling method. (A and B) The hydrogel-based electrodes exhibit exceptional performance in impedance and resistance to noise and other interference[34]; (C and D) The phase transition property of the hydrogen can be used for EEG monitoring on hairy scalps[35]; (E-G) PAAS-MXene significantly reduces the impedance between electrode and skin and improves the quality of bioelectrical signals[97]. EEG: Electroencephalogram; PAAS: sodium polyacrylate.

ensuring a conformal fit with the scalp and mitigating issues such as motion artifacts and sweat interference. The ability to achieve a fluid-to-gel transition enhances the interface's adaptability, making it suitable for diverse anatomical variations and promoting stable signal acquisition over extended periods. Additionally, rapid solidification methods significantly reduce electrode-skin impedance, further improving the quality of recorded bioelectrical signals. Overall, these developments pave the way for more reliable and user-friendly EEG monitoring systems, facilitating advancements in both clinical diagnostics and neuroscience research.

Implantable hydrogel interfaces for ECoG

Compared with non-invasive applications, hydrogel shows unique advantages in invasive electrodes to monitor the ECoG and LFP signals benefiting from biocompatibility. Therefore, numerous studies have been carried out for the design and fabrication of implantable devices with hydrogels.

Wang reported a hydrophilic conductive hydrogel composed of poly(3,4-ethylenedioxythiophene) nanoparticles (dPEDOT NPs) synthesized through a dopamine-limited area polymerization process as shown in Figure 10A and B[98]. With the introduction of nanoparticles into a hydrogel network comprised of κ-carrageenan (CA), PDA and PAM, a highly flexible, tissue-adhesive, and biocompatible conductive hydrogel (dPEDOT-CA-PDA-PAM) was obtained. The hydrogel was used as a flexible conductive interface to seamlessly connect the rigid microcircuits with soft brain tissue. Also, due to the *in-situ* self-cure property, microcircuits can be transferred to arbitrary surfaces without sacrificing integrity. Benefiting from its biocompatibility, the hydrogel suppresses neural inflammation during implantation and enhances the stability of the BCI in long-term recording of neural signals.

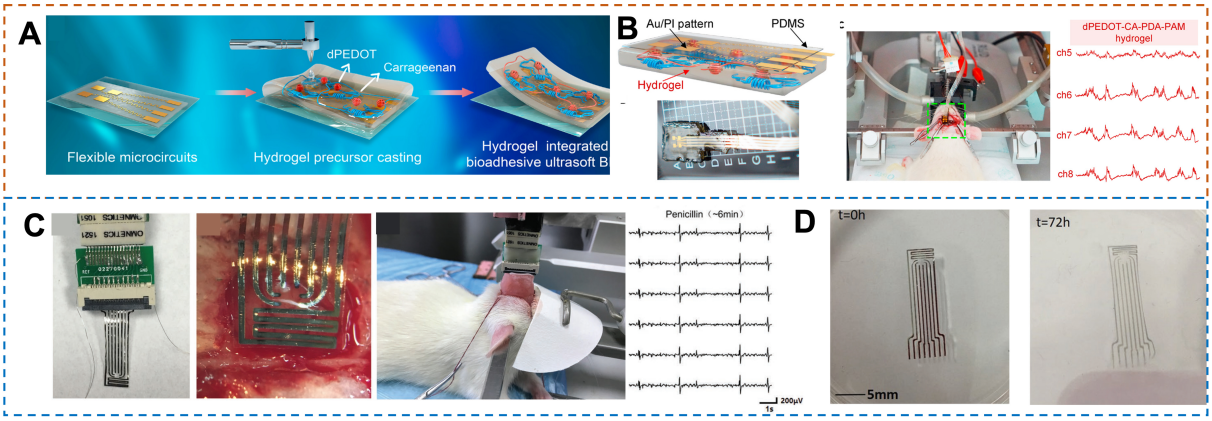

Figure 10. Implantable hydrogel interfaces. (A and B) Adhesive and conductive hydrogel-integrated brain-machine interfaces for conformal contact with brain tissue[98]; (C and D) gradable electrode array for electrophysiological and pressure recording in the brain[33].

Our team also proposed a flexible biodegradable ECoG device integrated with an intracranial pressure sensor with poly-l-lactic acid (PLLA) and polycaprolactone (PCL) film as the substrate and encapsulation layer[33], respectively, as shown in Figure 10C and D. Molybdenum (Mo) was used as the conductive electrode. The ECoG interface has excellent biocompatibility and can conform to the cortex to record brain signals for about five days, which meets the needs for most chronic implantation requirements. Furthermore, the ECoG electrode completely degrades in phosphate-buffered saline (PBS) within about 100 days, indicating that it can also be potentially used in other bioelectronic devices in medical applications.

Implantable hydrogel interfaces for ECoG are considered as a promising material in enhancing the performance and biocompatibility of neural interfaces. These hydrogels, designed to match the mechanical properties of soft biological tissues, address the critical issue of stiffness mismatch, which allows for better integration with neural environments. The use of conductive materials within a flexible hydrogel matrix not only facilitates effective bioelectric signal recording and stimulation but also enhances tissue adhesion and flexibility. Moreover, the incorporation of self-curing properties enables seamless connections between rigid microcircuits and soft brain tissue, which is crucial for maintaining signal integrity. Importantly, these hydrogels also demonstrate excellent biocompatibility, which is beneficial for reducing neural inflammation and improving the stability of BCIs during long-term recordings. The development of biodegradable ECoG devices further highlights their potential for safe, temporary applications without permanent implants. Overall, these advances in implantable hydrogel interfaces hold great promise for improving the functionality and safety of neurotechnology in both research and clinical settings.

Implantable hydrogel interfaces for LFP

While ECoG provides a broad view of cortical electrical activity, LFP offers a more refined insight by capturing the synchronized activity of neuronal populations within a localized region. This granularity is vital for deciphering the intricate patterns of neural communication and understanding how specific circuits contribute to cognitive processes and behavior. Utilizing LFPs enhances the ability to investigate the underlying mechanisms of neural oscillations and their role in various neurological disorders, ultimately paving the way for more targeted therapeutic interventions. Therefore, implantable electrodes for deep brain recording and stimulation were extensively investigated.

Adewole *et al.* at the University of Pennsylvania developed "living" electrodes for micro-tissue-engineered neural networks (μTENN)[99]. The electrodes are fabricated by forming agarose microcolumns with designed geometries in custom acrylic molds. These microcolumns solidify and form hollow structures upon cooling. The *in vivo* experiment shows that the electrodes optically modulate synaptic transmission and neural activity as illustrated in Figure 11A and B.

Park *et al.* at the MIT developed a multifunctional sensing and stimulation platform based on a soft hydrogel matrix, as shown in Figure 11C and D[100]. The elastic modulus of the device in its dry state is three orders of magnitude higher than in its swollen state, which allows the device to be implanted into deep brain structures directly. Also, benefiting from the low elastic modulus after swelling and the outstanding biocompatibility, the issue of chemical and mechanical mismatch between the synthetic device and neural tissue can be addressed. In addition, minimal stress and strain in the surrounding neural tissue was induced with micro-movements of the brain relative to the skull. As a result, minimum tissue damage associated with brain micro-motion after implantation was observed.

For implantable devices, stability is one of the most effective approaches for diagnosing and treatment of various neurological disorders and diseases. However, in the moist physiological environment, an inferior interface stability between conductive neural tissue and electrodes is a challenge and the instability becomes more severe during electrical stimulation. For example, PEDOT:PSS coating can continuously expand and lead to structural damage, such as cracks and coating delamination within the hydrogel layer at the interface. This phenomenon will result in a significant deterioration in electrochemical performance, as well as brain scarring and inflammatory reactions. These challenges limit the reliability of neural disease diagnosis and treatments. Zhang *et al.* proposed a strategy to overcome the issue by chemically grafting a functional long-chain polymer, poly (styrene sulfonic acid-co-4-vinylpyridine) [Poly(SS-4VP)], onto a metal substrate[101]. In detail, they electrochemically deposited the conductive polymer PEDOT and further chemically cross-linked PEDOT to create a PEDOT:Poly(SS-4VP) interpenetrating network hydrogel, as shown in Figure 11E and F. This method not only enables the formation of a resilient conformational interface between the conductive hydrogel and rigid electrodes but also provides mechanical flexibility, high conductivity, and long-term electrochemical stability. Furthermore, the research team implanted bioelectrodes modified with PEDOT:Poly(SS-4VP) hydrogel into the brains of living organisms. Under low-voltage stimulation, the conductive hydrogel/electrode interface remained stable, which provides a foundation for stable electrophysiological recording and electrical stimulation.

LFP is crucial and attritive in the scientific research to investigate neural dynamics. These interfaces enhance the ability to capture synchronized activity from neuronal populations, which provides insights into the intricate neural circuits that underlie cognitive processes and behaviors. The development of flexible, biocompatible hydrogel electrodes addresses challenges related to mechanical mismatch between the devices and soft neural tissues, minimizing tissue damage during brain micro-movements. Innovations such as living electrodes and multifunctional sensing platforms are paving the way for more effective neural recordings and stimulation, while addressing stability issues inherent in moist physiological environments. By enhancing interface stability through advanced polymer grafting techniques, researchers are creating resilient, conductive networks that maintain their electrochemical performance over time. This stability is essential for reliable diagnostics and therapeutic interventions in various neurological disorders. Overall, implantable hydrogel interfaces for LFPs represent a promising frontier in neurotechnology, with the potential to revolutionize our understanding of brain function and the treatment of neurological conditions.

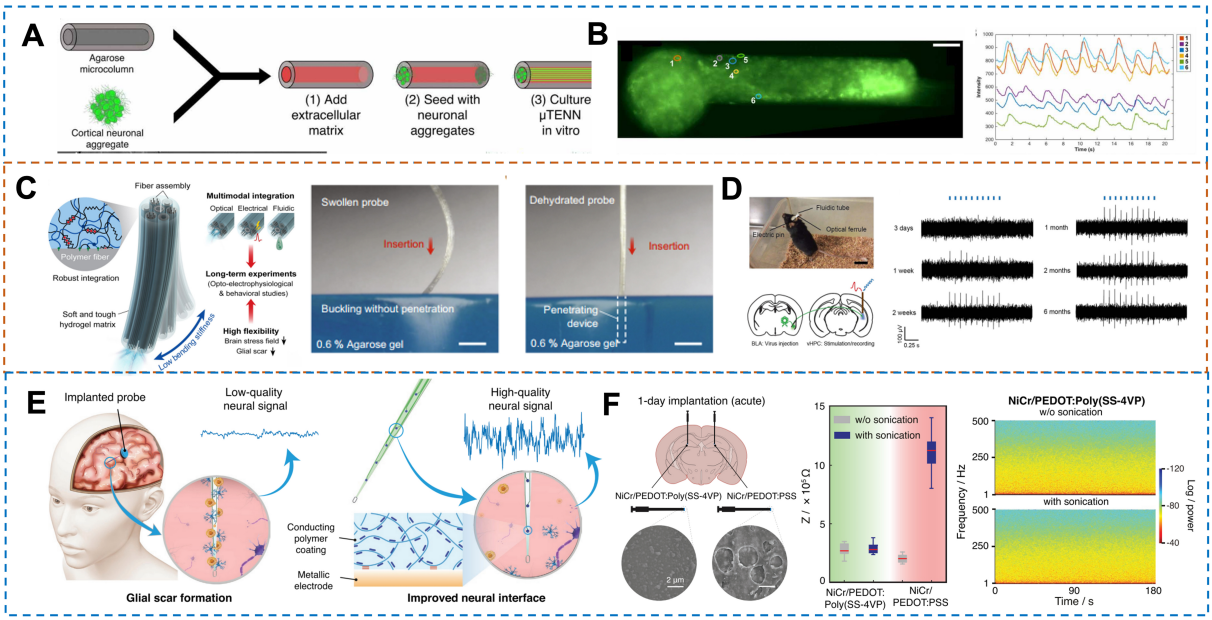

Figure 11. Implantable hydrogel interfaces. (A and B) Development of optically controlled "living electrodes" with long-projecting axon tracts for a synaptic brain-machine interface[99]; (C and D) Adaptive and multifunctional hydrogel hybrid probes for long-term sensing and modulation of neural activity[100]; (E-F) Electrodes with robust conducting hydrogel coating for neural recording and modulation[101].

Multimodal implantable hydrogel interfaces

As mentioned above, ECoG and LFP electrodes are essential neural signal recording and widely used in various applications, especially for neuroscientific research. However, ECoG electrodes that use metal as a conducting material exhibit poor biocompatibility and can easily damage the brain tissue. In addition, the low transparency and incompatibility with magnetic field of the metal also limits their multimodal applications, such as the cooperation with optogenetics, two-photon, and MRI, which is of great significance in neuroscientific research.

To overcome the challenges, Prof. Zhang from the Changchun Institute of Applied Chemistry developed a hydrogel-elastomer neural interface (HENI) with PVA-artificial cerebrospinal fluid (ACSF) as the conductive layer and polydimethylsiloxane (PDMS) as the insulator[102]. It can be used as a subdural cortical electrode as illustrated in Figure 12A and B. In contrast to traditional metal electrodes, HENI electrodes offer remarkable biocompatibility and compatibility with MRI. It shows a potential to be integrated with optical imaging techniques due to the high transparency. The high translucency of the PVA-ACSF hydrogel allows the simultaneous acquisition of neuronal calcium signals and vascular signals beneath the electrode using two-photon microscopy. As a result, high-quality cortical neural signals with excellent spatiotemporal resolution can be recorded. This multimodal approach enables researchers to observe and analyze neuronal activity and dynamic vascular changes under various physiological or pathological conditions, which can provide novel insights and methods for the study of brain region interactions and neurovascular mechanisms.

Driven by the demands of multimodal implantable brain electrodes, our research team also developed a multimodal transparent conductive hydrogel electrode. The electrode is designed and fabricated with a polymer network comprising polyvinyl alcohol, hexadecyltrimethylammonium chloride, and hyaluronic acid (PVA@HACC@HA) through a freeze-thaw method as illustrated in Figure 12C-F[85]. No toxic or harmful cross-linking agents and initiators were used during the synthesis of the hydrogel to ensure

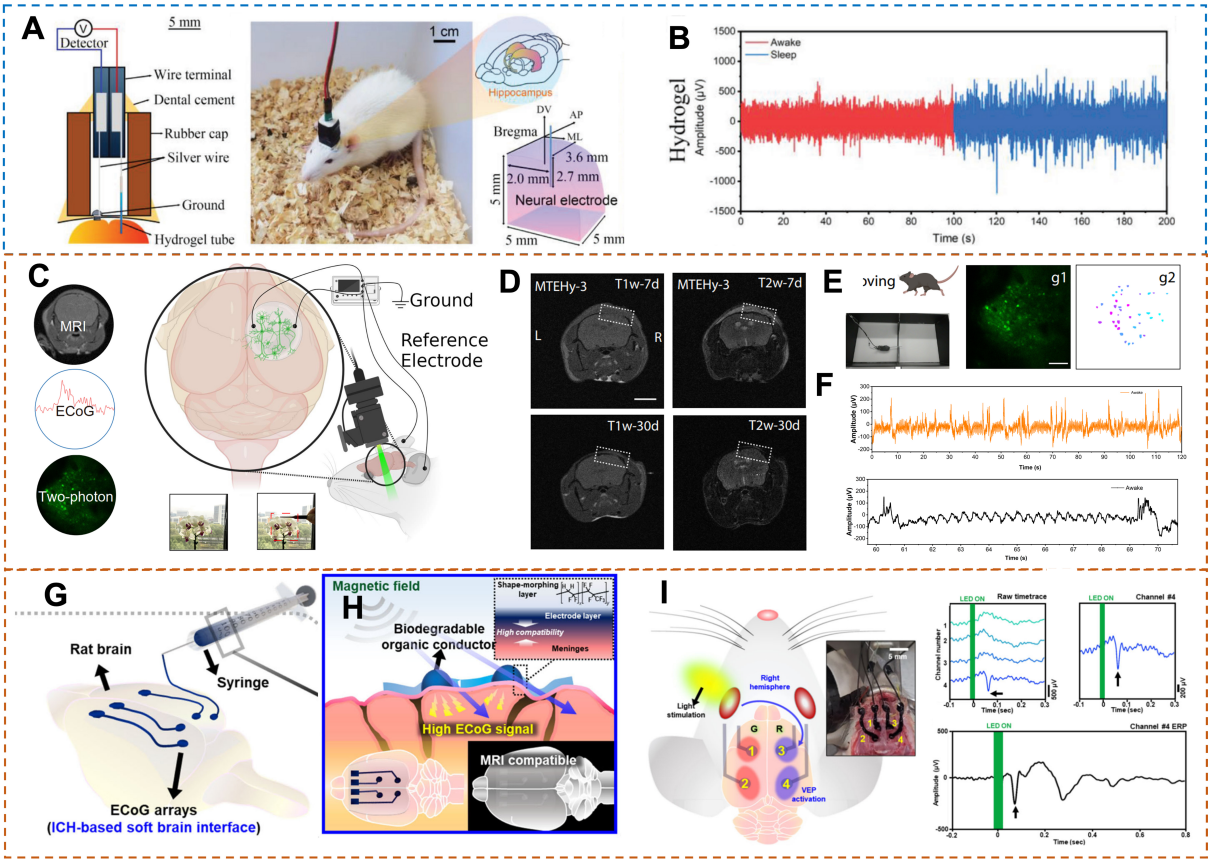

Figure 12. Multimodal implantable hydrogel interfaces. (A and B) Highly stretchable hydrogels as implantable electrodes for the recording of neural signals[102]; (C-F) *In situ* multimodal transparent electrophysiological hydrogel for *in vivo* miniature two-photon neuroimaging and neural signal analysis[85]; (G-I) MRI compatible ICH electrodes[76]. MRI: Magnetic resonance imaging; ICH: injectable conductive hydrogel.

biocompatibility. Also, the hydrogel, containing abundant water and ions, exhibits mechanical and chemical properties similar to those of biological tissues. As a result, it can significantly reduce neural inflammation reactions and damage to brain tissue. When the hydrogel is used as the electrodes, it can adhere tightly to brain tissue and exhibits low interface impedance with brain tissue (150 Ω at 1 kHz). In addition, there is a high transparency of the hydrogel with a transmission of 93% in the range of 300 to 1,100 nm, and no degradation is observed in the structure and electrochemical performance under exposure to light and electrical stimulation. As a proof of concept, this MTEHy-3 was used with MRI scanning technology, achieving a rapid and precise localization of brain regions using MRI scans. In brief, *in-vivo* MRI was conducted on the brains of mice after the hydrogel electrode was implanted on the surface of the cerebral cortex for seven and thirty days as shown in Figure 11D. In addition, the real-time two-photon images for the neuronal activity in resting and active states of the mice were also monitored benefiting from the high transparency of the MTEHy-3 electrode as shown in Figure 12E in conjunction with the two-photon imaging[85]. The ECoG signal with high SNR during rest and movement is measured and shown in Figure 12F.

Son at Sungkyunkwan University developed an injectable conductive hydrogel (ICH) based on the ionic cross-linking properties of hydrogels[76]. The ICH can be injected *in-situ* to form high-resolution array with a diameter less than 200 micrometers. In addition, it demonstrates high biocompatibility for both *in-vitro*

with a 95.9% cell survival rate and *in-vivo* with no inflammation or fibrosis. In detail, Figure 12G shows a schematic diagram of a brain interface based on ICH. Figure 12H depicts the ICH-based brain interface composed of ICH and a poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP) substrate in an MRI imaging setting. No artifact on MRI was observed because both ICH and PVDF-HFP are compatible with MRI. Figure 12I demonstrates the conformal and soft neural electrodes with a 4-channel ICH electrode for ECoG recording in a rodent model and clear visual-evoked potential signals from the visual cortex was observed. Therefore, due to the brain-like soft modulus and excellent ionic conductivity, the MRI-compatible ICH neural electrodes enable the stable monitoring of ECoG, even in the setting of response to visual stimuli. The ICH-based brain interface can be further extended to record neural responses from various sensory modalities, such as olfaction, touch, and hearing.

Multimodal implantable hydrogel interfaces represent a significant advancement in neural signal recording, particularly in overcoming the limitations of traditional metal electrodes, which can compromise biocompatibility and hinder integration with imaging, CT and MRI. Innovations such as HENIs offer remarkable transparency, flexibility, and compatibility with MRI and optical imaging techniques. These features provide a solution for simultaneous recording of spatio-temporal signals. Moreover, the development of self-expanding and biodegradable electrodes demonstrates a commitment to minimizing invasiveness, which facilitates a more comprehensive understanding of brain function by enabling the exploration of various sensory modalities while maintaining stable signal acquisition over extended periods. Overall, these multimodal interfaces are poised to transform neurotechnological research and therapeutic applications, which offers new insight into complex neural dynamics and interactions.

CONCLUSION AND OUTLOOK

In conclusion, the long-term monitoring of EEG, ECoG, and LFP or single-neuron activity holds immense significance for the study of brain science, artificial intelligence, and the diagnosis and treatment of brain-related disorders. The exploration of both non-invasive and invasive brain interfaces with diverse materials has been proposed. Among the materials, hydrogels have emerged as a promising interface material for neural electrodes due to their mechanical combability with biological tissues, exceptional biocompatibility, and high conductivity. It is expected that this review paper will serve as a valuable source of knowledge and provide researchers with a reference for the studies and developments in the field of brain signal monitoring.

Although hydrogel-based interfaces have emerged as a promising solution for the brain signal interfaces with superior performance, particularly in terms of biocompatibility, long-term stability and multi-channel monitoring, some key challenges remain for further exploration.

Biocompatibility

Although the high water content and adaptability of hydrogels enhance tissue compatibility after implantation, their biocompatibility can be limited by the synthesis methods and material components used, particularly due to potential toxicity or inflammation associated with cross-linking agents and surface chemistry, which may compromise long-term stability. Possible solutions include employing physical cross-linking techniques such as freeze-drying and thermal gelation, which allow for the formation of hydrogels through temperature and pH adjustments without the use of chemical cross-linkers, thus minimizing sources of toxicity. Additionally, utilizing naturally biocompatible cross-linkers such as alginate or chitosan can create a non-toxic environment suitable for long-term neural implantation. Moreover, incorporating anti-inflammatory molecules on the hydrogel surface, with controlled release during the initial implantation phase, may help mitigate early-stage immune responses.

Long-term stability

Long-term stability is of great significance for hydrogel electrodes in brain signal monitoring. This stability requires adequate mechanical, electrical and chemical properties. However, due to their high water content, hydrogels are susceptible to dehydration or swelling in difference humidity conditions, which can compromise the stability and quality of the signal. Potential solutions include designing complex network structures by incorporating an independent cross-linking network within the existing hydrogel matrix, to enhance mechanical strength and durability. Additionally, the use of solvent exchange methods or multi-solvent systems to create a stable oil-water mixture can help resist dehydration and swelling effects. Furthermore, embedding flexible polymers or microfibers within the hydrogel to form a multi-scale porous structure can improve fatigue resistance under prolonged mechanical stress, reducing structural damage caused by expansion.

Multi-channel integration

As neuroscience progresses, multi-channel neural electrodes have become crucial tools for investigating the mechanisms of brain activity and its spatial distribution. Multi-channel integration allows for high-density, precise acquisition of brain signals, which can provide researchers with detailed patterns of neural activity and insights into complex brain networks. However, utilizing hydrogels for multi-channel integration poses significant challenges, particularly in achieving high channel density and signal quality while ensuring flexibility and biocompatibility. Although some studies have embedded conductive channels within hydrogels to create preliminary multi-channel electrodes, they often do not meet the high-density requirements for practical applications. Possible solutions include employing micro/nanofabrication techniques compatible with hydrogels, such as laser etching and soft lithography, to construct high-density microelectrode arrays within hydrogels. These methods ensure precise channel distribution and minimize inter-channel interference. Additionally, electrochemical deposition can be used to coat conductive materials onto microelectrode surfaces, which enhances the overall conductivity of the array. In addition, creating multi-layered hydrogel structures, where each layer contains an independent conductive network, allows for channel isolation and reduces signal crosstalk. This layered design can further increase channel density. Besides, a modular design for hydrogel electrodes, with each module incorporating an independent multi-channel electrode array, allows for flexible arrangement and combination to meet specific monitoring needs across different brain regions.

Organogels

Organogels are emerging as a promising alternative to hydrogels, particularly in applications where the inherent limitations of hydrogels present challenges. Unlike hydrogels, which are often constrained by water solubility and swelling behavior, organogels can provide enhanced stability and reduced leaching of active compounds, thereby improving the efficacy and longevity of formulations. Moreover, they offer tunable properties through the selection of different gelators and solvents, which allows for precise control over their rheological and thermal characteristics. This versatility can address specific application requirements, such as bioactivity and biocompatibility, which are crucial in pharmaceutical and biomedical contexts. Additionally, organogels can mitigate issues related to microbial contamination and degradation, which are common challenges hydrogels face in certain settings.

Integration of hydrogel interfaces with machine learning for neural decoding

Machine learning algorithms excel in extracting patterns and features from complex datasets, which is essential for decoding neural signals obtained through hydrogel-based electrodes. By integrating hydrogel electrodes to record high-quality signals with machine learning, researchers can significantly enhance the accuracy and efficiency of neural signal interpretation. In addition, machine learning models can adapt to changes in neural activity over time, which provides a dynamic decoding capability. It can evolve with the

neurological condition of the patients. This adaptability is especially beneficial when used with hydrogel electrodes, which are applied in long-term monitoring scenarios. In addition, the combination of hydrogel electrodes and machine learning enables more personalized medical interventions. Algorithms can learn individual neural patterns and tailor stimulation protocols or therapeutic responses accordingly, potentially improving outcomes in neurological therapies.

DELARATIONS

Authors' contributions

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Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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