

Hydrogels in Neurological Disorders: Emerging Diagnostic and Therapeutic Applications

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Abstract: The clinical management of neurological disorders remains a major challenge worldwide, constrained by fundamental limitations in both diagnosis and therapy. Electroencephalography (EEG), the cornerstone of neurological assessment, is limited by low spatial resolution and inconsistent signal quality. Therapeutically, the blood-brain barrier (BBB) restricts drug delivery to the brain, resulting in subtherapeutic intracerebral concentrations. These convergent diagnostic and delivery bottlenecks underscore an urgent imperative for innovative materials and technologies. Hydrogels, characterized by biomimetic three-dimensional (3D) architectures, have emerged as a versatile material platform to bridge this gap. From a diagnostic perspective, hydrogels-based electrodes exhibit exceptional biocompatibility and low interfacial impedance, enabling high-fidelity EEG acquisition while minimizing insult to sensitive neural and skin tissues. From a therapeutic perspective, their 3D architecture provides versatile scaffolds for therapeutic agents, supporting high loading efficiency and programmable release profiles for neurological interventions. In this review, we first outline the physicochemical properties and fabrication techniques of hydrogels. We then discuss their applications, with particular emphasis on neural bio-electrodes, brain-computer interfaces (BCIs), drug delivery, and neuro-bioengineering. Finally, we examine the challenges impeding the clinical translation of hydrogels and outline prospective mitigation strategies. The integration of these functionalities is anticipated to advance closed-loop therapeutic systems for the precise management of complex neurological disorders.

Keywords: hydrogel, neurological disorders, flexible electrode, brain computer interface, drug delivery

Introduction

Neurological disorders represent a paramount challenge to human health,¹ progressively impairing fundamental neural dimensions including motor coordination, sensory perception, cognition, and emotional regulation.² Currently, neurological disorders are regarded as the second leading cause of death worldwide, with absolute mortality increasing by 39% and disability-adjusted life-years (DALYs) rising by 15% over the past three decades.³ Moreover, the continued aging of population and increased life expectancy have contributed to a concerning rise in the age-standardized incidence rates of neurological disorders, outpacing rates of other diseases globally.⁴ Nevertheless, the clinical management of neurological disorders remains constrained by critical bottlenecks in both diagnosis and therapy, necessitating transformative technological breakthroughs.

Hydrogels have emerged as a versatile material platform, defined by three-dimensional (3D) crosslinked polymer networks with exceptional water-retention capacity.⁵ This distinctive structural characteristic, combined with the versatility to tailor their physicochemical properties for specific applications under diverse conditions⁶ (Figure 1), enable them to uniquely bridge the gap between materials and biological applications.⁷ Structurally, hydrogels are broadly divided into natural polymers and synthetic matrices. Natural hydrogels generally exhibit superior biocompatibility, with degradation products comprising endogenous metabolites such as amino acids and monosaccharides,⁸ whereas synthetic hydrogels offer robust chemical stability and precise tunability of physicochemical properties.⁹ Functionally, these



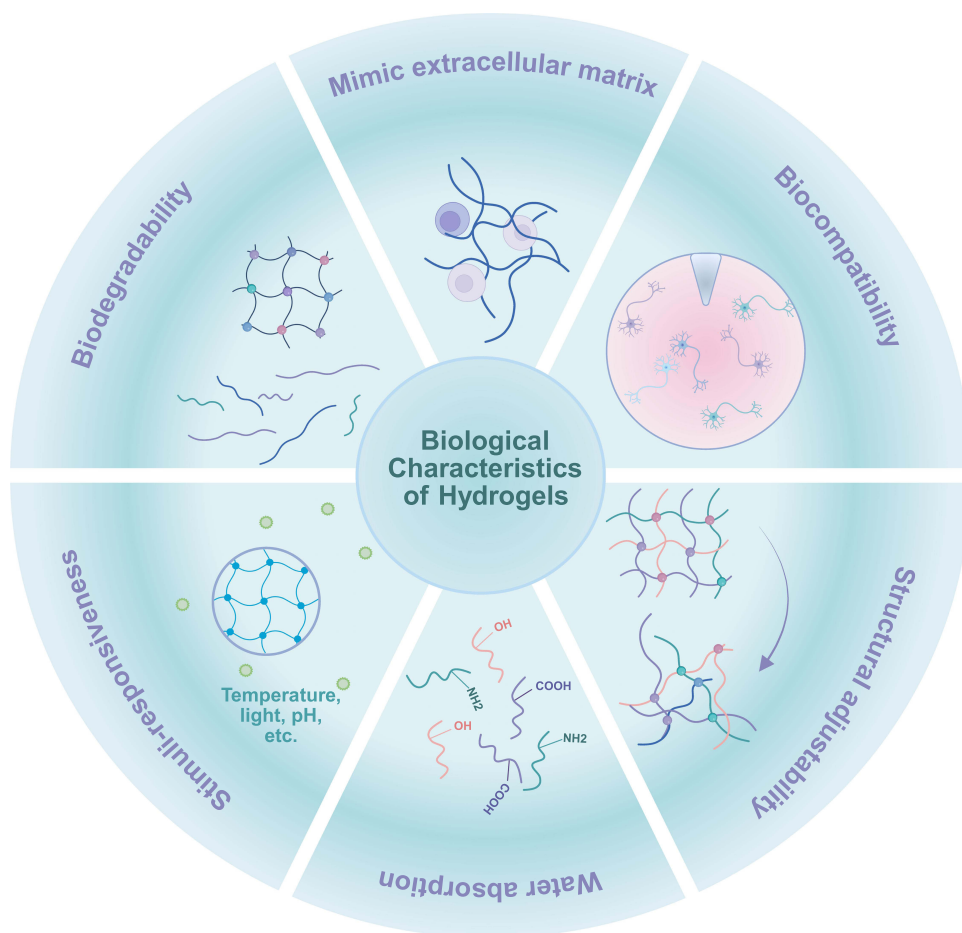


Figure 1 The biological properties of hydrogels.

systems are categorized into conductive and non-conductive networks. By integrating crosslinked networks with functional conductive nanocomposites,¹⁰ conductive hydrogels achieve hypersensitive acquisition of electrochemical signals.¹¹

In neuro-diagnostics, electroencephalography (EEG) is vital for capturing electrophysiological biomarkers of most neurological disorders.^{12–16} However, conventional non-invasive electrodes are frequently compromised by high contact impedance and motion artifacts,^{17,18} compromising their spatial resolution. Conversely, invasive electrodes achieve superior resolution yet are typically constructed from rigid metals or silicon, exhibiting a profound mechanical mismatch with soft brain tissue.¹⁹ Their elevated Young's modulus and acute geometries elicit chronic neuroinflammation and physical trauma.²⁰ Hydrogel-based electrodes offer a compelling solution to these challenges. On the one hand, characterized by a low Young's modulus and favorable biocompatibility, they inflict minimal trauma on neural tissue. On the other hand, abundant electrolytes entrapped within hydrogels matrix establish ionic-ionic interfaces with both skin and brain tissues, markedly lowering interfacial impedance. Furthermore, the inherent viscoelasticity and fluidity of hydrogels permit spontaneous adaptation to microscopic surface under applied pressure, generating intimate conformal contact that substantially improves signal quality.

With regard to therapeutic intervention, standard systemic administration of bioactive agents²¹ is severely compromised by the blood-brain barrier (BBB),²² necessitating supratherapeutic dosages that inevitably lead to side effects and systemic toxicity.²³ Although alternative strategies such as deep brain stimulation (DBS), vagus nerve stimulation (VNS), and surgical interventions provide symptomatic relief, they primarily attenuate pathological signal propagation without targeting underlying disease mechanisms. The distinct 3D architecture of hydrogels establishes a biomimetic reservoir that enables high-capacity loading of therapeutic agents, protects payloads from enzymatic degradation, and permits

spatiotemporally controlled release at the pathological site.²⁴ Furthermore, brain tissue engineering is a transformative strategy for functional restoration following severe central nervous system (CNS) injuries, providing biomimetic scaffolds to mitigate long-term sequelae.²⁵ By recapitulating the physicochemical properties of the native extracellular matrix (ECM),²⁶ hydrogel-based scaffolds can be functionalized with incorporated stem cells, adhesion motifs, growth factors, and biomolecules,²⁷ promoting cell proliferation, axonal guidance, and de novo tissue formation. Unlike circulating carriers such as nanoparticles and liposomes, hydrogel-based delivery systems can be retained at the therapeutic site to form a localized drug depot, achieving sustained release over weeks to months. By contrast, circulating carriers are susceptible to rapid clearance and exhibit limited stability.

Whereas existing reviews have largely catalogued hydrogel synthesis or addressed isolated facets of neuro-interventions, this review uniquely bridges flexible diagnostic interfaces, BBB-penetrating drug delivery, and regenerative neural engineering. Moreover, we identify critical gaps and novel opportunities in the field, aiming to provide a roadmap for their clinical translation and to inspire further research in neuroscience.

Basic Characteristic of Hydrogels

Source and Development

The development of hydrogels has a glorious history dating back over a century. In 1894, van Bemmelen innovated the term “hydrogel”.²⁸ Subsequently, in 1960, Wichterle and Lim developed the synthetic poly2-hydroxyethyl methacrylate (PHEMA) hydrogel, marking the first generation of hydrogel, which was applied in the production of hydrogel contact lenses.²⁹ Since their inception, hydrogels have experienced alarming growth across various fields and exhibit a wide array of applications. Currently, the diversity and quantity of hydrogels are considerable, and they can be categorized based on varying criteria.

According to sources, hydrogels can be classified into two primary categories: natural and synthetic types. Natural hydrogels, including collagen, gelatin, cellulose, hyaluronic acid (HA), chitosan, and others, are recognized for their inherent biocompatibility, bioactivity, and biodegradability.³⁰ For instance, the extracted collagen can be converted into hydrogels through pH and temperature stimuli via a self-fibrogenesis process under physiological conditions, which is recognized as a biomimetic substance mimicking the cellular microenvironment.³¹ It is important to note that natural types exhibit relatively weak stability, mechanical strength, and pose challenges in achieving precise formulations and drug loading. Synthetic hydrogels are synthesized through the polymerization of monomers that incorporate various polymers including polyethylene glycol (PEG),³² polyvinyl alcohol (PVA),³³ polyethylene oxide (PEO),³⁴ and poly-2-hydroxyethyl methacrylate (PHEMA).³⁵ These hydrogels can be tailored under different conditions, including chemical structure, arrangement, biological functions, and physicochemical properties.

As technology has evolved, stimuli-responsive hydrogels have emerged as a significant area of interest. These hydrogels are synthesized through the integration of stimuli-responsive molecular complexes and biomolecular units, enabling triggered and reversible transitions in structure and physical properties. Such transitions can be elicited by various physical or chemical stimuli, such as pH changes, chemical agents, light, temperature, magnetic fields, and electrical fields. Moreover, the incorporation of biomaterials consistently enhances their unique recognition properties and facilitates chemical modification.³⁶ This enhancement not only allows for responses to physical and chemical signals but also results in increased sensitivity to biochemical stimuli, such as enzymatic reactions³⁷ and levels of reactive oxygen species (ROS).³⁸ For example, tumor cells frequently deplete their blood supply to satisfy their energetic requirements, which cause permanent or transient deprivation of oxygen and nutrients. This deprivation leads to increased levels of ROS and the upregulation of antioxidant enzymes.³⁹ In response to this condition, cancer cells exhibit high rates of glycolysis, leading to the production of excessive lactic acid and a lower extracellular pH compared to normal tissues.⁴⁰ Given the altered metabolic profiles of cancer cells, Yi-Jun Jo et al developed a multi-stimuli responsive hydrogel to precisely control the release of doxorubicin (DOX). The hydrogel exhibited a rapid release of DOX under various conditions, including acidic environments (pH 5), reducing conditions (10 mmol DTT), oxidizing media (0.5% H₂O₂), and exposure to NIR irradiation.⁴¹ In vitro experiments indicated that multi-stimuli responsive hydrogel enhances the antitumor efficacy of DOX.

Table 1 Summary of the Hydrogel Component, Stimulus, Targeted Diseases and Related Treatment Agents of Some Typical Intelligent Stimuli-Responsive Polymers

Component	Stimulus	Diseases	Treatment Agents And Usage
Oligosulfamethazine-grafted gelatin ⁴²	PH Temperature	GBM	PTX Preventing the progress of Glioblastoma
Hydrophobic poly (propylene sulfide) TM ⁴³	ROS	TBI	Cur Promoting the regeneration and recovery of neurons
Phenylboronic acid-modified hyaluronic acid, Poly vinyl alcohol ⁴⁴	Glucose ROS	Stroke patients with diabetes	Stem cell-derived EVs Promoting angiogenesis, improving neurobehavioral recovery
Nanocellulose Chitosan ⁴⁵	PH Temperature	GBM	Neural stem cell Increasing the density of neural stem cell, killing tumor cell
CS-NAC SA ⁴⁶	The ethanol adsorption rate	Brain injuries caused by alcoholism.	TP Reducing liver and brain injuries in mice caused by alcoholism.
AgNWs Biocompatible collagen I gels ⁴⁷	Electrical	Brain tumor	RGD peptide-conjugated gold nanorods Providing photothermal therapy
Poloxamers 407 and 188 ⁴⁸	Temperature	Microwave-induced brain injury	Intranasal TET Alleviating microwave-induced brain damages
Nanoparticles and hydrogels ⁴⁹	ROS	Ischemia stroke	Atorvastatin calcium and β -nerve growth factor Reducing neuronal apoptosis, improving the rats' neurological deficits
DEX derivate Nanoparticles ⁵⁰	ROS	Depression	Olanzapine and amino borane Alleviating depression-like behaviors

Abbreviations: GBM, glioblastoma multiforme; PTX, paclitaxel; TM, triglycerol monostearate; TBI, traumatic brain injury; ROS, oxygen species; Cur, curcumin; EVs, extracellular vesicles; CS-NAC, sulfhydryl functionalized chitosan; SA, sodium alginate; TP, tilapia peptide; AgNWs, highly conductive silver nanowires; RGD, targetable Arg-Gly-Asp; TET, tetrandrine; DEX, dextran;

Despite extensive exploration of traditional hydrogels as carriers for molecules and cells, these materials often fail to effectively integrate with the defect site and lack the ability to adapt their behavior properties in response to the physiological and pathological conditions associated with disease. Intelligent, stimuli-responsive hydrogels facilitate precision interventions in neurological diseases by responding to changes in the brain's microenvironment, as summarized in Table 1.

Synthesis of Hydrogels

The distinctive three-dimensional architectures of hydrogels arise from chemically or physically cross-linked hydrophilic polymer networks (Figure 2). The selection of cross-linking method critically determines their structural parameters, including mesh size, swelling ratio, and permeability, which will be introduced subsequently.

Physical Crosslink

Physical crosslinking methods do not necessitate the use of crosslinking agents, providing advantages in convenience and non-toxicity. Advancements in science and technology have facilitated the development of diverse synthesis methods, including hydrogen bonding, anion-cation interactions, heating-cooling cycles, and freezing and thawing. Numerous natural hydrogels are constituted through self-assembly processes that involve physical crosslinking, despite their inherent instability and low mechanical strength resulting from the weak interactions between polymer chains.⁵¹

Hydrogen Bonding

Polymer chains typically contain numerous hydrogen atoms, which enable electrostatic interactions and the formation of hydrogen bonds among them, promoting the immediate assembly of hydrogels.⁵² For instance, Yan Wang et al developed a novel hydrogen-bonded polysaccharide hydrogel through the formation of strong intermolecular hydrogen bonds between ipsilateral hydroxyl groups.⁵³ It exhibited favorable mechanical strength, antibacterial ability, and excellent biocompatibility, all attributed to the dynamic and reversible linkages. Notably, the formation of hydrogen bonds in hydrogels is intrinsically governed by pH.⁵⁴ This pH-dependent dynamic enables hydrogels with dense hydrogen-

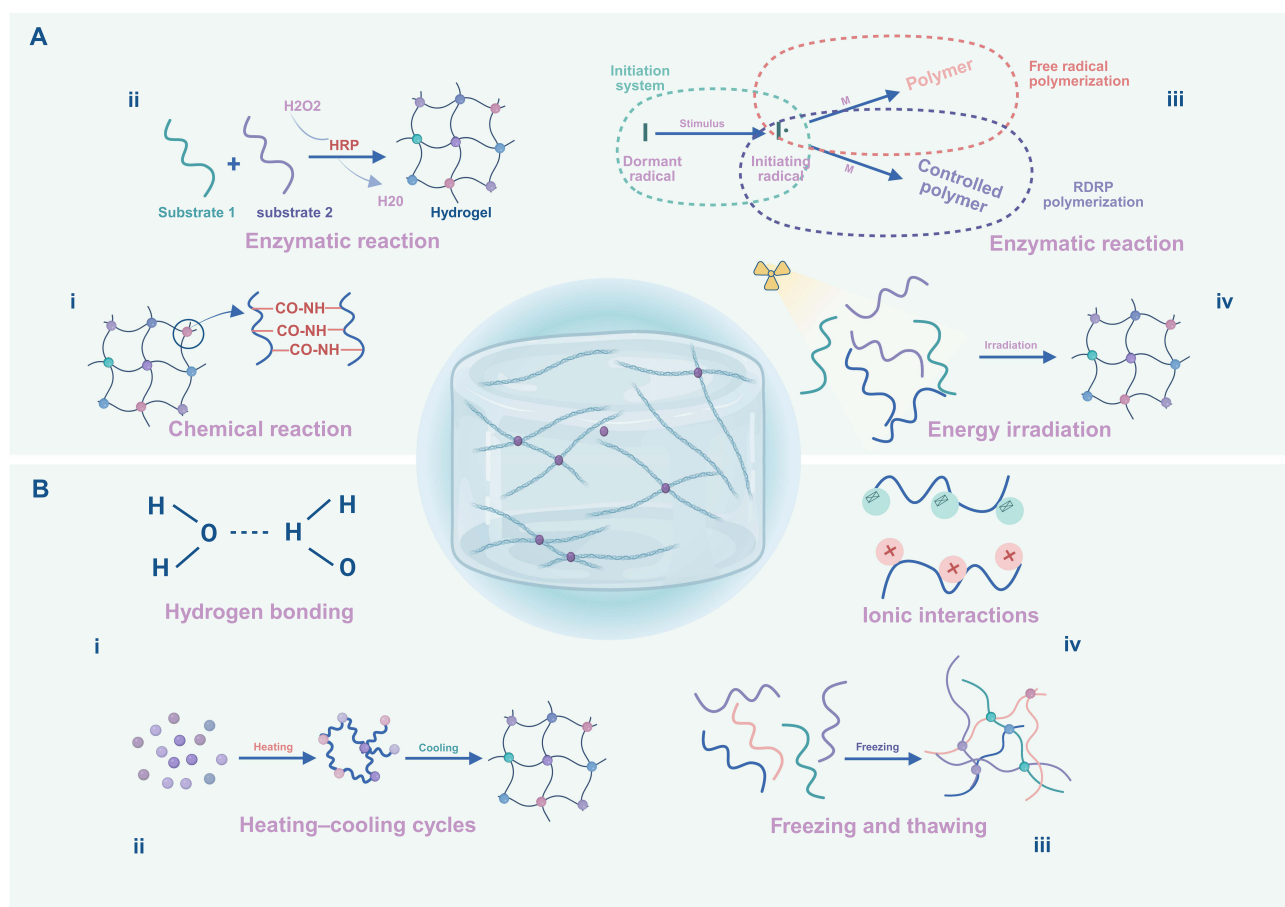


Figure 2 Hydrogel networks are typically categorized as chemically (A) and physically (B) crosslinked systems. Chemical crosslinking includes (Aii) chemical reaction, (Aiii) enzymatic reaction, (Aiv) energy irradiation; physical crosslinking includes (Bi) hydrogen bonding, (Bii) heating-cooling cycles, (Biii) freezing and thawing, and (Biv) ionic interactions.

bonding networks to exhibit programmable pH-responsive behaviors, a cornerstone for engineering smart hydrogels capable of autonomous adaptation to physiological pH fluctuations.

Ionic Interactions

It has been established that ions can participate in ion-dipole interactions with both polymers and water,⁵⁵ facilitating the formation of hydrogels. Moreover, ionic hydrogels generally display exceptional conductivity, rendering them suitable for applications in electricity collection equipment, such as electrodes. Wen Li et al utilized tannic acid (TA) to reinforce polyacrylamide (PAM) and sodium carboxymethyl cellulose (CMC) polymers to create a strain sensor for human-machine interaction (HMI) devices.⁵⁶ This hydrogel-based sensor exhibits optimal electromechanical performance and achieves a high motion recognition accuracy of 97.85%, characterized by high sensitivity ($GF = 4.03$), favorable linearity (0.997), and a low detection limit (0.5%).

Heating-Cooling Cycles

Heating-cooling cycles are essential for the dissociation of oligomers into monomers and the subsequent refolding process.⁵⁷ Initially, these cycles induce a coil conformation in the polymer chains, which, after additional cycles, result in the formation of double helices, stabilizing the hydrogel structure through the involvement of salt. Tingrui Lin et al combining heating-cooling cycles with γ -ray radiation methods to develop a novel agarose/Ti3C2Tx-crosslinked-polyacrylamide hydrogel.⁵⁸ In the experiment, the researchers mixed a solution of Ti3C2Tx nanosheets with agarose (AG), acrylamide (AM), and water in a glass vial. The mixture was heated to 90°C until it achieved homogeneity,

followed by cooling to room temperature. Following several cycles, a strain sensor hydrogel was produced, which exhibited superior mechanical properties with 4250% stretchability, and enhanced adhesion to various substrates, demonstrated by an adhesive strength of 1148 kPa to copper at 30 °C. These advancements make it an effective strain sensor in large-scale strain detection scenarios that require high sensitivity and adhesion.

Freezing and Thawing

During the freezing step, water solidifies while solutes and bound water remain in a liquid state. This freeze-concentration effect drives extreme polymer chain compaction. This condition results in high local concentrations and the occurrence of “proximity effects”, which facilitate physical entanglement and the formation of multiple hydrogen bonds.⁵⁹ Similar conditions for cross-linking are maintained during the thawing step, leading to the establishment of a three-dimensional polymer network characterized by unique wall and pore structures. The number of freezing–thawing cycles, freezing temperature and time significantly influence the structure and mechanical properties of hydrogels.⁶⁰ Zhengyu Gong et al prepared a hydrogel composed of poly (acrylamide-co-acrylic acid) (PAM-co-PAA) and polyvinyl alcohol (PVA) through copolymerization and freezing/thawing. They demonstrated that hydrogels created in this manner exhibit exceptional rapid recovery, superior fatigue resistance, and self-healing capabilities. These attributes arise from the integrated fatigue resistance and self-healing properties, which are measured at 1230 ± 90 kPa and 1250 ± 50 kJ/m³, respectively.⁶¹

Chemical Crosslink

Chemical methods leverage site-specific reactions between functional groups on polymer chains and multifunctional crosslinkers. This process induces irreversible covalent cross-links and excellent mechanical strength. Conventional chemical crosslinking strategies often rely on exogenous agents like epichlorohydrin (ECH) or glutaraldehyde, which pose dual challenges regarding the toxicity of cross-linking agents and uneven cross-linking distribution.⁶²

Radical Polymerization

The free radical polymerization (FRP) mechanism governs hydrogel network formation through four fundamental steps: initiation, propagation, chain transformation, and termination,⁶³ which enables precise spatiotemporal control over covalent network architecture. Recent breakthroughs in reversible deactivation radical polymerization (RDRP) techniques, such as atom transfer radical polymerization (ATRP), have revolutionized hydrogel synthesis by enabling precise control over network topology. Citing a case, Yerneni et al prepared a type of hydrogel using ATRP, a powerful and versatile RDRP process. They subsequently employed cholesterol-modified DNA tethers to functionalize the lipid membrane of exosomes for polymer grafting,⁶⁴ enabling the localized delivery of therapeutic exosomes for a duration of one month, which is longer than that of conventional exosomes.

Chemical Reaction

Chemical reactions occur between complementary functional groups or pendant hydrophilic moieties and polymers mediated by multifunctional crosslinking agents. Crosslinking agents feature multiple reactive termini that covalently conjugate with complementary functional moieties on hydrophilic polymers to orchestrate the assembly of three-dimensional polymeric networks. Junjie Qin et al designed a glucose-driven self-regulating hydrogel with resilient structure, using beta-cyclodextrin (β -CD) and ferrocene (Fc) as partial crosslinkers, and a chemical reaction network (CRN).⁶⁵ The designed supramolecular photonic hydrogel (SPH) has been successfully employed to detect glucose in human plasma and H₂O₂ in liver tumor tissue, yielding results comparable to those of commercial assay kits. However, it is crucial to highlight that a majority of crosslinkers often exhibit inherent cytotoxicity and environmental persistence due to non-degradable byproducts and ecotoxic leakage. Scientists are challenged to develop safer alternatives.

Enzymatic Reaction

Enzyme-mediated hydrogel synthesis emerges as a biocompatible paradigm shift, offering spatiotemporal control over gelation kinetics and network precision unattainable by conventional physicochemical methods.⁶⁶ This method is uniquely suited for polymers functionalized with enzyme-sensitive molecules. In recent decades, several technologies

have been developed, including enzymatic polymerization of monomers, enzymatic cross-linking of existing polymers, and enzyme-manipulated self-assembly of small molecules.⁶⁷ For instance, tyrosinase-mediated reactions were utilized to cross-link monophenol-modified glycol chitosan with hyaluronic acid, generating a bioactive hydrogel film.⁶⁸ This film has been demonstrated to regulate blood glucose levels in a type 1 diabetes mouse model following transplantation. Furthermore, enzyme-catalyzed crosslinking approaches, especially the horseradish peroxidase (HRP)-catalysed cross-linking approaches, are promising approaches for materialization, due to their high specificity and mild reaction conditions.⁶⁹ A notable advancement by Sara Baptista-Silva et al introduced a new horseradish peroxidase-mediated cross-linked hydrogel, composed of silk sericin.⁷⁰ This study validated the methodology and demonstrated potent anti-inflammatory efficiency, which can promote cell adhesion and massive cell colonization after 7 days of culture in an *in vivo* diabetic wound model.

Energy Irradiation

Energy irradiation method employs high-energy radiation, including X-rays, gamma rays, and electron beams to synthesis hydrogels via radiation-induced polymerization or crosslinking. For example, Maria Demeter et al reported an elaborate hydrogel based on collagen-poly (vinyl pyrrolidone) (PVP)-poly (ethylene oxide) (PEO) cross-linked by e-beam irradiation,⁷¹ Moises Bustamante-Torres et al presented a pH-sensitive hydrogels copolymerized by gamma rays to localized release of ciprofloxacin and silver nanoparticles (AgNPs).⁷² Compared to traditional methods, energy irradiation eliminates the need for cytotoxic chemical initiators, while enable controlled network architectures. Moreover, the materials can be sterilized using energetic radiation, integrating synthesis and sterilization simultaneously, reducing both costs and time.

Fabrication Techniques

3D Printing

In recent years, the proliferation of 3D printing technologies (Figure 3), particularly utilizing inks containing multiple macromolecules and biological components, have revolutionized the fabrication of customizable hydrogels. 3D hydrogel-forming extrusion (HFE) employs the computer-controlled, layer-by-layer dispensing of semi-solid polymeric solutions, dispersions, or pastes through programmable nozzles traversing (x, y, z) axes.⁷³ The chemical, mechanical, and stimulus-responsive properties of hydrogels can be tailored through the printing process. For instance, articular cartilage tissues connect articular surfaces to subchondral bones. However, due to its avascular environment and low cellular density, the capacity for regenerative restoration is limited. When damaged, articular cartilage extends into the underlying subchondral bone.⁷⁴ To promote tissue regeneration, Qi Li et al produced a flash bioinspired double-network hydrogel scaffold through 3D printing, encapsulating tissue-specific decellularized extracellular matrix (dECM) and exosomes deriving from human adipose mesenchymal stem cell (MSC).⁷⁵ The bionic hydrogel scaffolds promoted the attachment, spread, migration, proliferation, and differentiation of MSC, accelerating the simultaneous regeneration of cartilage and subchondral bone tissues in rat models.

However, ensuring printing quality poses significant challenges. The high-water content of hydrogels hinders achieving adequate printing accuracy and shape fidelity. Most hydrogel inks are influenced by gravitational forces and surface tension, which predisposes them to collapse or spread after printing.⁷⁶ More importantly, it is an insurmountable barrier to assure biocompatibility, non-toxicity, and appropriate mechanical properties in 3D-printed hydrogels 3D printing hydrogels adopted in biomedical engineering.⁷⁷

Electrospinning

Electrospinning is a sophisticated manufacturing technique that employs a high-voltage electrostatic field to convert polymer solutions or melts into ultrafine fibers, generally characterized by nanoscale diameters⁷⁸ (Figure 3). Typically, electrospinning setup includes a high-voltage power supply, a spinneret (a metallic needle), and a grounded collector. When a sufficient voltage is applied to the spinneret, the electrostatic forces surpass the liquid's surface tension, initiating a charged polymer jet that undergoes whipping and stretching in the electric field.⁷⁹ This process leads to solvent evaporation or melt solidification, ultimately producing a nanofibrous network

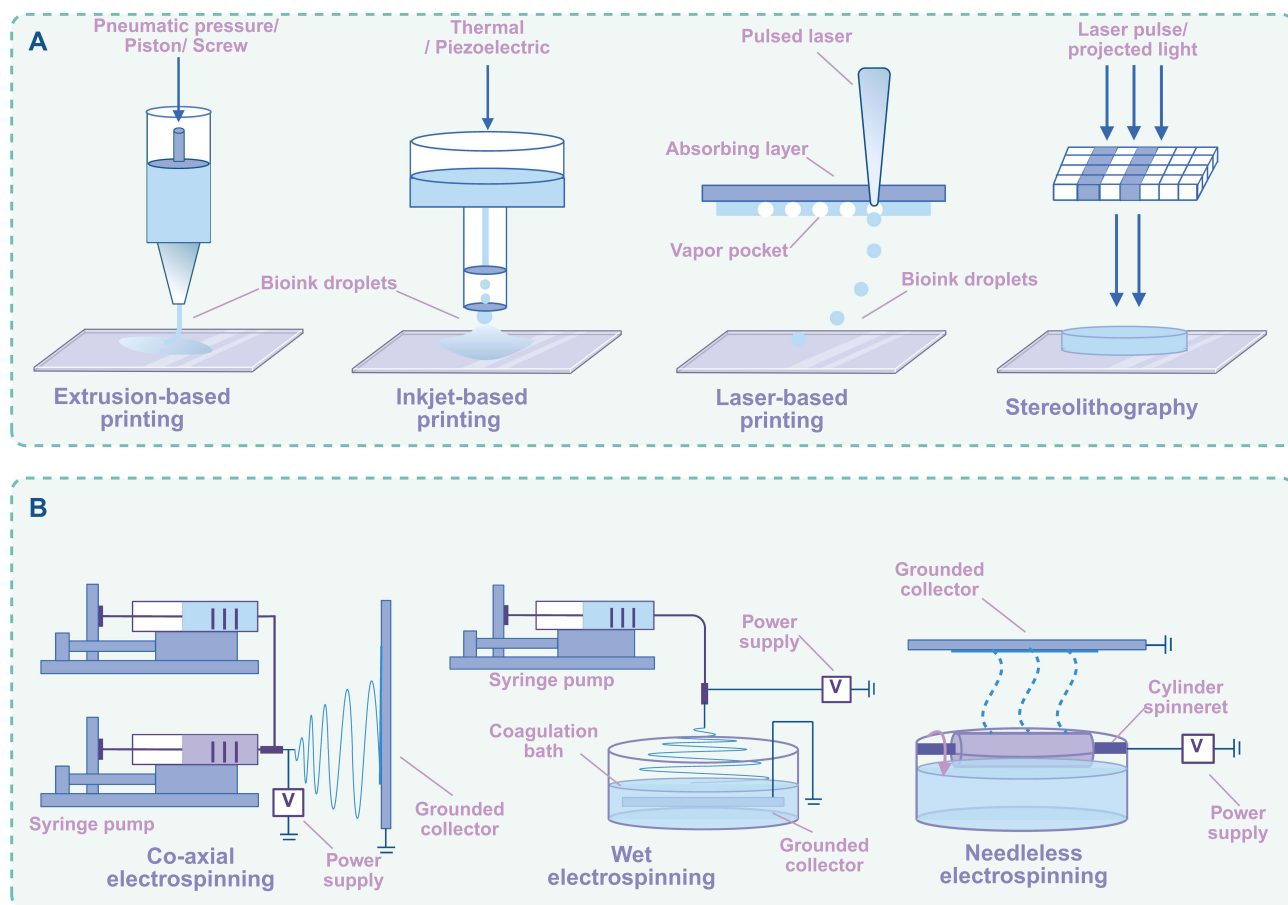


Figure 3 The synthetic methodologies for hydrogels, including three-dimensional (3D) printing (A) and electrospinning (B).

with exceptional properties, including high surface-to-volume ratio, controlled porosity, and tailored mechanical strength.

Similarly, the ability to precisely control fiber morphology and alignment through electrospinning provides a powerful tool for the fabrication of intricate hydrogel network. Moreover, the controlled nanofibrous architecture exhibits a rapid swelling response and faster shape recovery compared to bulk hydrogels. For instance, Shenglian Yao and co-workers incorporated carbon nanotubes (CNTs) into methacrylate acylated gelatin (GelMA) hydrogel to develop aligned conductive hydrogel fibers using rotating liquid bath electrospinning technique.⁸⁰ Compared to bulk hydrogels with irregular structures, the aligned hydrogel fibers supported the proliferation and aligned adhesion of PC12 cells, promoting the regeneration of neural fibers.

The integration of 3D printing and electrospinning technology can address some limitations inherent to each individual method, such as restricted cell migration resulting from the dense intertwining of electrospun fibers and the limited resolution associated with certain 3D printing techniques. For example, Sitian Liu et al presented an anisotropic multiscale cardiac scaffold achieved by combining the two methods. The 3D-printed micrometer-scale scaffold frames effectively mimic the interwoven anatomical structure of the myocardium, while the branched-aligned electrospun nanofiber network directionally guides cellular arrangements.⁸¹

Recording Neural Electrophysiological Signals

Neurons continuously generate and transmit electrophysiological signals. The EEG serves as the gold standard non-invasive modality for capturing the aggregate postsynaptic potentials from cerebral pyramidal cells. Currently, various devices for recording EEG signals have been developed, classified as invasive, semi-invasive, and noninvasive

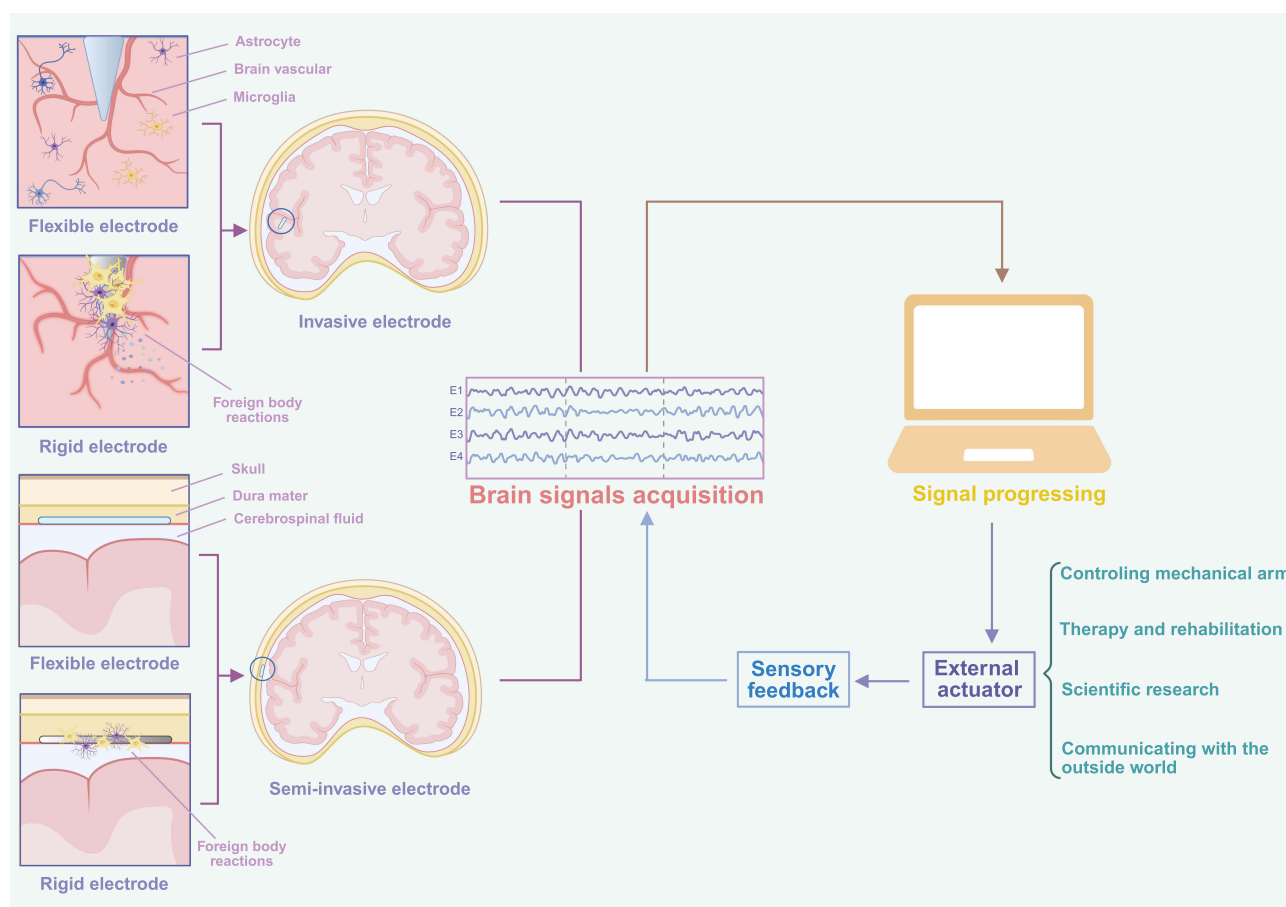


Figure 4 Schematic illustration of the closed-loop brain-computer interface (BCI) workflow.

installations. These devices authorize the interaction between biological system and external electronic devices, functioning as operational instructions for activating brain computer interface (BCI) systems (Figure 4). In recent years, flexible hydrogels have attracted considerable interest as viable alternative materials for neuro-electrodes and interface components, promoting the development of electrochemical biosensors.

Flexible Electrode Materials

Conductive materials are essential components of electrodes, forming the electrical connections between the neuron and external device. Metals are the most widely utilized electrode materials, primarily due to their superior electrical properties and chemical stability. Research has demonstrated that liquid metal conductors fabricated onto polydimethylsiloxane substrates can create highly stretchable neural electrode arrays with a resolution of 50 μm , which are particularly effective for neural recording.⁸² However, these electrodes face challenges related to biocompatibility with both brain tissue and our scalp, which can lead to inflammation and irreversible brain damage. The adaptation of bio-materials, particularly hydrogels, represents a visionary alternative to address this issue, as summarized in Table 2

Invasive Electrodes Materials

Invasive neural signal acquisition entails a deep penetration into brain tissues to record voltage potentials from individual neurons near electrodes with high precision and specificity. However, conventional metallic electrodes trigger a cascade of foreign body reactions (FBR)⁸³ when they contact with brain tissue. Furthermore, metals and semiconductors exhibit high rigidity, with Young's moduli in the tens of gigapascals, whereas brain tissues are significantly softer, characterized by Young's moduli in the kilopascal range. This disparity in mechanical properties can lead to irreversible brain damage and aggravate the inflammatory response. In the context of long-term recording, these rigid electrodes may be

Table 2 Classification and Comparison of Hydrogel-Based Electrodes

Classification	Interface	Core Advantages	Challenges	Applications
Invasive electrodes	Deep into the brain parenchyma	Capable of recording single-neuron action potentials and local field potentials; High SNR and mechanical adaptability.	The complex biochemical environment may accelerate the degradation of the hydrogel matrix, limiting chronic functional stability; Associated with acute trauma, intracranial hemorrhage, and infection risks during implantation; Long-term encapsulation can still trigger chronic neuroinflammation.	Utilizing low-voltage DC to synthesize implantable electro-gelation electrodes; Incorporating mechanically interlocked polyrotaxane into topological hydrogels to acquire brain neural information and conduct neuromodulation.
Semi-invasive electrodes	Typically placed on or beneath the dura mater	Directly bypasses the skin's primary barrier layer, achieving low contact impedance; Minimally invasive compared to deep implants.	Chronic exposure to the CSF environment introduces a spectrum of stability concerns such as swelling and dehydration; Requisite craniotomy or burr hole placement still incurs unavoidable risks.	Developing a novel PAAm hydrogel for permanent recording of brain cortex signals.
Noninvasive electrodes	Solely attached to the skin surface	Completely risk-free with no surgical barriers, and repeatable deployments; Flexible hydrogel networks could conform to microscopic skin wrinkling and topography.	The high impedance of the skull and stratum corneum dampens spatial resolution; The gel patch can easily displace relative to the skin under kinetic movement; Physically unstable and prone to dehydration.	Engineering a conductive hydrogel electrode with an asymmetrical bilayer structure that exhibits high biological and mechanical compatibility; Designed semidry double-layer hydrogel electrode could acquire EEG for up to 12 h and is ready for recycled use.

Abbreviations: SNR, Signal-to-Noise Ratio; DC, direct-current; CSF, Cerebrospinal fluid; PAAm, polyacrylamide; EEG, electroencephalogram.

encapsulated by microglia,⁸⁴ which can increase electrical impedance and compromise their biocompatibility and functionality. Furthermore, studies have demonstrated that, despite stringent aseptic implantation protocols, certain gut bacterial constituents might translocate to the brain following electrode insertion, compromising microelectrode performance and exacerbating chronic inflammatory responses.⁸⁵ Moreover, when inflammation escalates and implanted electrodes fail, they must be surgically removed, causing escalates damage. This scenario highlights the critical need for developing appropriate materials to overcome the limitations of invasive electrode systems.

Among flexible biomaterials, hydrogels are distinguished as a notably active and widely utilized class. For instance, Zhen-Kai Lin et al utilized low-voltage direct-current (DC) to synthesize implantable electro-gelation electrodes, by inducing sol-to-gel transitions in an aqueous reconstituted silk fibroin solution.⁸⁶ The electrode exhibits a high Young's modulus (11–150 MPa) under ex vivo conditions to facilitate penetration through brain tissue, while transitioning to a brain-tissue-matching lower modulus (50–3200 kPa) post-insertion to minimize mechanical mismatch-induced damage. Simultaneously, the controlled release of dexamethasone (DEX) interrupt astrocyte growth to reduce the inflammatory response. Additionally, microscale needle-like electrode technologies provide neural extracellular recording with a high spatiotemporal resolution while minimize tissue injuries by reducing the surface area of electrodes and increasing their number.⁸⁷ Zhenzhen Shen et al incorporated mechanically interlocked polyrotaxane into topological hydrogels to acquire brain neural information and conduct neuromodulation, enabling the continuous recording of neural local field potentials for eight weeks.⁸⁸

However, invasive hydrogel-based electrodes are subject to dual destabilization mechanisms, dehydration can degrade electrical conductivity and promote mechanical stiffening, whereas excessive swelling drives volumetric expansion and potential structural disintegration. Moreover, the simultaneous optimization of electrical conductivity, modulus matching, biocompatibility, and mechanical stability remains inherently challenging, necessitating judicious trade-offs among these competing requirements.

Semi-Invasive Electrodes Materials

Despite being considered the gold standard for diagnosing certain neurological conditions, invasive methods are not universally accepted for their unavoidable tissue trauma. Semi-invasive electrodes, commonly referred to as Electrocorticography (ECoG) electrodes, are small devices strategically placed on or beneath the dura mater. This procedure is typically performed before and during neurosurgical operations for epilepsy or brain tumors. Remarkably, due to the mild immune response, these electrodes can reliably record signals for many years after implantation.⁸⁹ Furthermore, ECoG electrodes are in direct contact with the brain and record the local field potential (LFP) from the cerebral cortex with high signal to noise ratio, fewer artifacts, and greater spatial specificity.⁹⁰ However, conventional semi-invasive electrodes do not conform to the intricate mechanical properties of the brain. Upon implantation, these electrodes can disrupt brain tissues and compromise the BBB, which may accelerate the formation of a glial sheath around the electrodes and thicken the dura mater.⁹¹ Moreover, while semi-invasive electrodes must be sufficiently flexible to maintain contact with the brain's convoluted surface, most electrodes lack the conformability. The loose connection between electrodes and the cortex can cause electrode displacement, potentially leading to inaccurate signal recordings and even misdiagnosis. Micromotion between the implanted electrodes and neural tissues may occur over time, primarily induced by vascular pulsations.⁹²

Hydrogel-based electrodes offer adequate conformability to the brain's curved and grooved surface, ensuring reliable neural signal acquisition. More importantly, hydrogels can absorb heat, avoiding local burns, lesions, and pain.⁹³ For instance, through the integration of MRI-based anatomical mapping, finite element analysis (FEA)-optimized mechanical design, and direct ink writing (DIW) 3D printing, an ultrasoft hydrogel electrode featuring a bioinspired honeycomb architecture was developed. Its bending stiffness matches that of brain tissue, ensuring excellent cortical integration and conformability.⁹⁴

Notably, the chronic exposure of semi-invasive electrodes to the cerebrospinal fluid (CSF) environment introduces a spectrum of stability concerns, ranging from uncontrolled swelling and dehydration-driven stiffening to inadequate conductivity and mechanical fatigue. Compounding these material challenges, the requisite craniotomy or burr hole placement still incurs unavoidable risks of hemorrhage, infection, and CSF leakage. Consequently, future investigations must judiciously address swelling restriction and interfacial adhesion optimization.

Noninvasive EEG Electrodes

EEG is the most widely used neuroimaging technique in clinical practice, due to its non-invasive nature, portability, ease of use, and lack of associated trauma. Typically, non-invasive electrodes can be categorized into three types: dry electrodes, semi-dry electrodes, and wet electrodes. Hydrogels can significantly enhance technological advancements by optimizing various types of electrodes for improved performance.

Wet electrodes, particularly those commonly used in EEG recording, are frequently preferred. Conventional gel electrodes incorporating Silver/Silver-Chloride (Ag/AgCl) materials and a conductive electrolyte gel are considered the gold standard for EEG signal recording,⁹⁵ due to their low intrinsic noise levels and skin-contact impedance. However, the use of conductive gels often results in adherence to patients' hair and skin, which are cumbersome and time-consuming for patients to clean. Moreover, while conductive paste promotes the formation of ion channels and guarantees stable signal acquisition progress, unintended leakage of paste can cause short circuits between adjacent electrodes.⁹⁶ Additionally, the water content in the gel inevitably evaporates over time, necessitating regular maintenance to preserve optimal signal quality for extended periods,⁹⁷ which does not allow for continuous long-term signal recording. Hydrogels are characterized by low impedance and a high signal-to-noise ratio (SNR), providing a stable and seamless interface between skin and wet electrodes. Moreover, hydrogel-based wet electrodes exhibit favorable electrical conductivity and are anticipated to enable long-term neuroelectric signal recording. Researchers have engineered a conductive hydrogel electrode with an asymmetrical bilayer structure that exhibits high biological and mechanical compatibility while remaining compatible with magnetic resonance imaging (MRI) and computed tomography (CT), obtaining high spatiotemporal resolution multi-dimensional brain information.⁹⁸

Unlike wet electrodes, dry electrodes eliminate the need for conductive gel and maintain stable contact with the scalp through external pressure. This offers advantages such as convenience, comfort, ease of operation, and stability.⁹⁹

Nevertheless, the primary disadvantage is their reduced conductivity and higher skin-electrode contact impedance, which makes them more susceptible to motion artifacts. The multichannel microneedle array (MMA) can penetrate the non-conductive stratum corneum to reduce electrode-skin contact impedance,¹⁰⁰ however, the potential breakage of microneedles within the skin may increase the risk of infection and inflammatory reactions. To address these issues, researchers have designed semi-dry electrodes, which combine the advantages of both wet and dry electrodes while mitigating their respective drawbacks. Semi-dry electrodes, which contain a minimal amount of electrolyte, can reduce electrode-scalp impedance to a level comparable to wet electrodes while avoiding hair contamination and the risk of short circuits.¹⁰¹ However, semi-dry electrodes also suffer from liquid evaporation, which can be mitigated by applying hydrogels. For example, Hailing Xue et al propose a semi-dry double-layer hydrogel electrode.¹⁰² This electrode comprises two distinct layers. The first layer is constructed from conductive, robust hydrogels, which provide low skin-electrode impedance and high durability, facilitating prolonged use. The second layer consists of adhesive hydrogels formulated to bond with various substrate materials through chemical anchors. The designed semi-dry electrode demonstrated comparable signal capture capabilities to wet electrodes in both N170 and P300 event-related potential (ERP) tests, while causing less harm.

Nevertheless, the inevitable evaporation of moisture from wet electrodes induces polymeric network shrinkage, aberrant electrolyte concentration, and elevated contact impedance. Moreover, the high-water content compromises mechanical robustness and tissue adhesion. Semi-dry electrodes partially reconcile signal quality with wearing convenience, yet struggle to maintain a constant and controllable electrolyte exudation rate under variable environmental conditions and interindividual skin differences. Future research must transition from single-parameter optimization to multi-physics design, developing environmentally adaptive intelligent hydrogel materials and optimizing dynamic impedance-matching algorithms to ensure long-term clinical utility.

Interface Materials

For implantable electrodes, the practical and economic approach involves decorating the basic electrode with functional coating materials, rather than developing new designs and configurations.¹⁰³ The electrode interface, where electrodes directly contact brain tissue, is crucial for the transmission of electrical signals. Functional coatings applied to the electrode surface enhance mechanical properties, biocompatibility, and durability.

Researchers have produced various coating materials, with hydrogels being a particularly favorable choice. For instance, Manuele Gori et al fabricated a sulfobetaine-based zwitterionic hydrogel as coating material for Polyimide (PI)-based intraneural electrodes. The PI surfaces were coated with a thin film of the hydrogel through covalent bonding to prevent the delamination of the hydrogel coating from the surface of neural electrodes.¹⁰⁴ The Young's modulus was 2.7 ± 0.24 kPa similar to brain tissue, minimizing the mechanical mismatch between electrodes and brain. Besides, the hydrogel coating was inspected and verified to successfully reduced adhesion and activation of fibrogenic and pro-inflammatory cells, ensuring the possibility of long-term implantation. Researchers created an organic subdural electrode composed of a hydrogel substrate and a patterned stretchable carbon fabric (CF).¹⁰⁵ The hydrogel substrate acted as a buffer layer between the rigid electrodes and soft brain tissues, mitigating the immune responses induced by foreign matter.

However, hydrogel-based coatings, while demonstrating excellent biological performance, inherently possess low electrical conductivity. The incorporation of electrically conductive materials, such as conductive polymers (CPs) and metal oxides, could address this issue by retaining the desired biological and electrical properties.¹⁰⁶ Sungjun Lee et al utilized poly (3,4-ethylenedioxythiophene): polystyrene sulfonate (PEDOT: PSS), alginate (Alg), polyacrylamide (PAAm), and CMC to synthesize a soft, tough ionic conductive hydrogel, which was subsequently covered with stretchable metal electrodes.¹⁰⁷ The coated electrodes demonstrated a reduction in impedance from 60 k Ω to 10 k Ω at 1 kHz and acute in vivo experiments successfully validated their success, demonstrating sensitivity and accuracy.

Working as Part of a Brain-Computer Interfaces

Brain-computer interfaces (BCIs), which enable interaction between the human brain and machines, have garnered global attention and are undergoing rapid technological advancement. BCIs generally utilize electrodes to continuously encode and decode brain signals, translating these into the desired output following analysis and processing. This technology has

diverse applications across multiple domains, such as the restoration of communication and motor function, the treatment of neurological and psychiatric disorders, daily life applications, and the gaming industry.¹⁰⁸

The Development of BCIs

Since Berger first discovered the human electroencephalogram in 1924,¹⁷ researchers have embarked on a longstanding effort to investigate electrical neuronal activity, establishing the foundation for the development of BCI systems. Real BCIs devices did not begin to emerge until the 1970s. During this period, Jacques J. Vidal pioneered the evaluation of the feasibility and practicality of using brain signals for human-computer interaction, coining the phrase “Brain-Computer Interface”¹⁰⁹ To date, BCI technology has evolved into a multidisciplinary field encompassing neuroscience, cognitive psychology, linguistics, artificial intelligence, philosophy, anthropology, robotics, and information technology.¹¹⁰ For example, chemotherapy-induced peripheral neuropathy (CIPN) is a detrimental side effect of neurotoxic cancer treatment, affecting quality of life and potentially disabling cancer survivors.¹¹¹ Sarah Prinsloo PhD et al proposed a closed-loop BCIs in which breast cancer survivors, who had undergone chemotherapy, were required to play a video game while their brain activity was monitored by electroencephalography. Both auditory and visual reinforcement were provided as the signal input command changed. The study demonstrated that the BCIs group reported significant symptom reduction and continuous improvement, exhibiting larger effect size differences compared to the placebo and waitlist control groups.¹¹² A typical BCI system operates in three stages. The first stage involves the acquisition of neuroelectric signals from the brain. The second stage focuses on analyzing and integrating these signals, followed by converting the input signals into predefined output commands through translation algorithms. The final stage involves the operation of external devices according to the command.¹¹⁰

BCIs can be categorized into invasive, semi-invasive, and noninvasive systems, according to the type of electrodes employed. Conventional rigid electrodes may cause or worsen brain damage, diminishing the efficiency and long-term viability of BCIs. Therefore, biocompatibility, electrical conductivity, and mechanical properties resembling those of soft brain tissue are crucial for the fabrication of high-performance devices.¹¹³ Multifunctional hydrogel bioelectronics have authentically established reliable and compatible Human-Machine Interface (HMI) platforms for high-quality bioelectronic recording. For example, Chiara Rinoldi et al designed a novel soft neural bio-interface made of polyacrylamide hydrogels loaded with plasmonic silver nano-cubes.¹¹⁴ This type hydrogel-based electrodes, characterized by their low electrical impedance (<3 k Ω at 10 Hz) and Young’s modulus (<10 kPa), conform well to the brain surface and maintain stability amidst the brain’s subtle movements. These properties render them particularly suitable for applications in neuroscience. Ju-Chun Hsieh et al¹¹⁵ focused on EEG-based long-term and wearable BCIs. They developed an enhanced PEDOT: PSS/PAMPS hydrogel EEG electrode exhibiting improved ionic and electrical conductivity, along with long-term stability and low electrode-skin interfacial impedance. The authors demonstrated that the designed hydrogel electrode could capture oscillatory rhythms in motor imagery protocols, a feature applicable to BCI-based functional electrical stimulation (FES) for motor rehabilitation.

What Can BCIs Do

BCIs capture neuronal electric activity and convert it into commands for a computer or other device, enabling the user to control mechanical arm solely through thoughts. Recent advances in BCI technology hold significant potential for applications ranging from entertainment¹¹⁶ to medical rehabilitation,¹¹⁷ particularly in treating neurological disorders.

The majority of neuropsychiatric diseases can cause irreversible brain damage, presumably leading to various complications. For example, stroke is the leading cause of paralysis, often resulting in upper limb impairments and speech disorders;¹¹⁸ Alzheimer’s disease can cause cognitive and memory impairment;¹¹⁹ spinal cord and brain injuries are significant risk factor for motor dysfunction.¹²⁰ BCIs are anticipated to restore or enhance brain functions impaired by debilitating disorders, as shown in Table 3.

Recently, researchers have successfully developed bidirectional BCIs that enable comprehensive communication between the brain and an actuator. Bidirectional BCIs enable not only the control of external mechanisms but also the delivery of somatosensory feedback by converting external sensor information into electric stimuli directed to the cortex.¹³⁰ The development of the reverse pathway requires diverse feedback methods to establish a closed-loop system.

Table 3 The Role of Brain Computer Interfaces in Neurological Disorders

BCIs Type	Disease Disorder	Method Purpose	Outcome
Noninvasive EEG ¹²¹	Chronic stroke Dyspraxia	Linking BCI technology with MI and FES feedback for motor recovery of the lower limbs.	Promoting long-lasting functional improvements in the gait speed, reducing spasticity, and promoting muscle contraction
Noninvasive EEG ¹²²	Neuropathic pain	Detecting signatures of neuropathic pain from EEG and SC	Demonstrating feasibility of real-time pain detection, and the effectiveness of a triggered combination of VR and TENS to decrease neuropathic pain
Noninvasive EEG ¹²³	Paralyzed Physical disabilities	Employing a complete phoneme-based imagined speech EEG BCI to offer a potential communication method	Allowing participants to successfully and reliably identify all 44 phonemes of the English language.
Invasive ECoG ¹²⁴	Amyotrophic lateral sclerosis	Using brain activity recorded to reconstruct and synthesize speech	Synthesizing commands from a vocabulary of 6 keywords to control a communication board for patients to communicate
Noninvasive EEG ¹²⁵	Stroke Upper limb motor dysfunction	Promoting the rehabilitation effect of upper limb motor dysfunction	Significant improvement in upper extremity motor function after 10 days of intervention
Invasive ECoG ¹²⁶	Spinal cord injuries Lower extremities paralysis	Using MI training to actuate assistive devices.	Decoding upper-limb MI is a feasible control signal for patients to achieve lower-limb motor control.
Noninvasive EEG ¹²⁷	Hemiparesis	Using visual cues to fulfill the motor intention using an activated robotic hand orthosis	Obtaining significant improvement in upper limb motor function after six weeks of training
Semi-invasive ¹²⁸ endovascular technique	Amyotrophic lateral sclerosis Bilateral upper-limb paralysis	Delivering recording electrodes to superior sagittal sinus to assess the safety and feasibility	Endovascular access to the sensorimotor cortex performed well with no serious adverse events and no vessel occlusion or device migration
Noninvasive EEG ¹²⁹	Traumatic cervical spinal cord injury sensorimotor dysfunction	Applying motor imagery training to acquire upper limb sensorimotor functional recovery	Patients gained better recovery of hand function compared with hand MI training not supported by BCI group

Abbreviations: EEG, electroencephalogram; BCI, brain computer interface; MI, motor-imagery; FES, functional electrical stimulation; SC, skin conductance; VR, virtual reality; TENS, transcutaneous electrical nerve stimulation; ECoG, electrocorticography.

For example, since vision provides limited feedback information, Sharlene N Fleshe et al applied tactile sensations generated by intracortical micro-stimulation of somatosensory cortex to enhance the completeness of feedback pathways.¹³¹ The authors reported that a bidirectional BCI system capable of eliciting tactile perceptions significantly improved the performance of an individual with tetraplegia using a robotic limb. This enhancement reduced the median time required to grasp objects from 20.9 seconds to 10.2 seconds. Bidirectional BCIs are expected to significantly restore or enhance human capabilities and are bound to become a mainstream technology in the future.

Functions as Biosensors

Beyond neural electrical signals, recent studies have demonstrated that hydrogels can also be engineered as biosensors to detect neurochemical signals or monitor motor function, enabling integrated diagnosis and management of neurological disorders. For instance, Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) in interstitial fluid (ISF) is aberrantly downregulated in patients with Alzheimer's disease (AD),¹³² representing a potential neural biomarker. By integrating GelMA hydrogel microneedles, effective transdermal penetration of the skin epidermis can be achieved, enabling quantitative assessment of ISF MALAT1 levels and providing a practical tool for early non-invasive diagnosis of AD.¹³³ A highly elastic and self-healing hydrogels conductor comprising catechol, alginate, and diatomite was fabricated as a stretchable triboelectric nanogenerator (TENG). This device harvests energy from human motion and

functions as a self-powered tremor sensor when applied to the skin, enabling detection and tracking of low-frequency vibrational movements in patients with Parkinson's disease (PD).¹³⁴

However, the high-water content and inherent softness of hydrogel-based biosensors are intrinsically incompatible with long-term stable performance. Additionally, conventional hydrogels suffer from insufficient mechanical strength and poor toughness, rendering them susceptible to fatigue cracking, permanent deformation, or conductive network disruption during motion detection. Future improvements necessitate interdisciplinary strategies, synergistically integrating materials design, structural engineering, and algorithmic optimization to progressively overcome these existing limitations.

Carrying Therapeutic Agents

The treatment of major neurological disorders heavily depends on therapeutic agents. However, these agents frequently fail to achieving effective concentrations in the brain. Administering excessive doses of drugs tends to cause irreversible side effects. The utilization of advanced carriers presents a promising opportunity. Various carriers have been developed using a range of materials, among these hydrogels have been rapidly evolved due to their unique properties (Figure 5).

The Treatment of Neurological Disorders

Hydrogels are capable of encapsulating hydrophilic drugs, enabling sustainable and controllable drug release. They can access brain tissues through invasive and non-invasive routes. For example, injectable hydrogels can deliver ASM to the epileptic focus. Specific conditions, such as electrical stimulation and pH changes, can modify the physical properties of these hydrogels, facilitating the controlled release of drugs over an extended period.¹³⁵ Here, focus on the intranasal

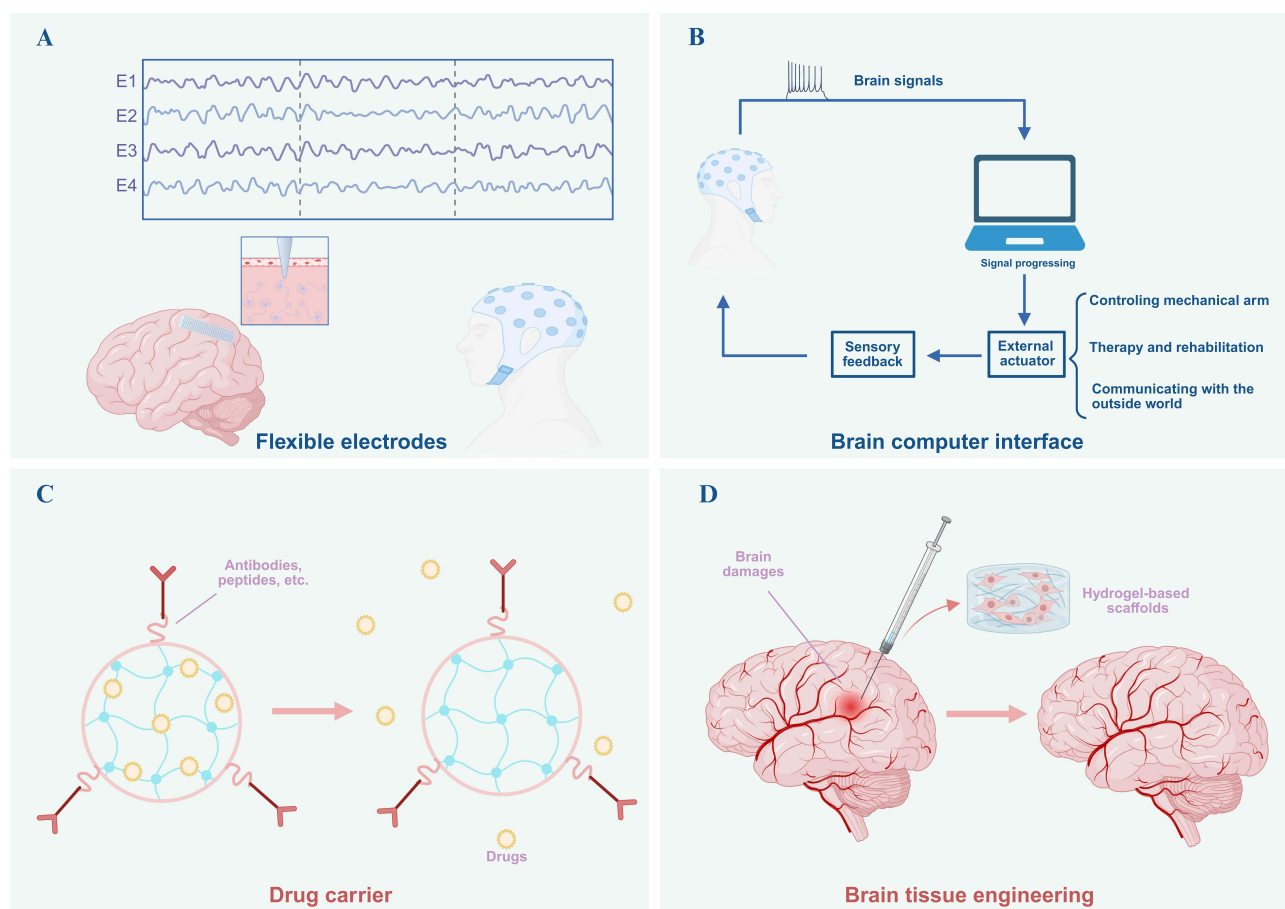


Figure 5 Biomedical applications of hydrogels, encompassing electrophysiological (EEG) signal monitoring (A), brain-computer interface (BCI) construction (B), drug delivery (C), and engagement in neural tissue engineering and repair (D).

administration pathway, heralded as a promising alternative for drug delivery. This method not only circumvents the BBB, ensuring effective intracranial concentrations, but also remains harmless.¹³⁶ The combination of intranasal administration with a hydrogel carrier is expected to usher in a new era in the treatment of neurological disorders. Yujing Liu et al have conducted a study on the treatment of AD using the combination of hydrogel technology and intranasal administration.¹³⁷ They developed a thermosensitive hydrogel by cross-linking carboxymethyl chitosan (CMCS) with aldehyde Pluronic F127 micelles, which were loaded with black phosphorus (BP) and methylene blue (MB). Researchers have demonstrated that the fabricated hydrogel alleviates neuroinflammation and improves cognitive function in mouse models of AD.

Conventional hydrogel delivery systems, characterized by micrometer-scale structures, are notably larger in size, which restricts their ability to cross BBB. Scientists have proposed a novel technique for manufacturing nanogels, by transforming hydrogel from microgels to nanogels. This method shows promise for allowing hydrogels to reach the smallest capillary vessels and cross the BBB due to reduced size. Furthermore, hydrogel carriers have limitations in encapsulating specific drug types, such as hydrophobic drugs, antibodies, and nucleic acids,¹³⁸ due to their hydrophilic nature and relative instability. Additionally, their mechanical properties are often weaker compared to other materials. This challenge can be addressed by synthesizing hydrogel nanocomposites, which integrate nanotechnology with hydrogel technology. Specifically, incorporating nanomaterials into hydrogels creates an interpenetrating network structure,¹³⁹ improves mechanical properties, and enhances drug encapsulation within a single delivery system. For example, the deep infiltration of glioblastoma multiforme (GBM) into the brain parenchyma limits efficacy of post-surgical treatment such as radiotherapy and systemic chemotherapy. Taegyu Kang et al developed an injectable thermos-responsive hydrogel nanocomposite.¹⁴⁰ At room temperature, the composite consists of a liquid solution comprising drug-loaded micelles and water-dispersible ferrimagnetic iron oxide nano-cubes, which is injected into the resected tumor site following surgery. At body temperature, the composite undergoes sol-gel transitions, serving as a soft, deep intracortical drug reservoir. In orthotopic mouse GBM models, the drug delivery system remarkably suppressed tumor growth and improved survival rates. It is important to distinguish between nanogels and hydrogel nanocomposites, as they are fundamentally different. A nanogel is essentially a pure hydrogel, while a hydrogel nanocomposite consists of a combination of hydrogels and nanomaterials.

Compared with other drug delivery vehicles, hydrogels offer distinctive advantages as intracranial drug delivery devices. They can be minimally invasively injected as a liquid at room temperature, then undergo rapid gelation upon reaching the intracranial target site to achieve precise cavity filling. Their 3D polymeric networks enable sustained and controllable drug release over weeks to months, circumventing the peak-trough fluctuations and systemic toxicities associated with systemic administration.¹⁴¹ When engineered as intelligent systems responsive to stimuli such as pH, temperature, or enzymes, they further permit spatiotemporally precise on-demand drug release. However, current research has yet to achieve ideal outcomes, as significant challenges persist, including insufficient stability, heterogeneous drug distribution, and imprecise controlled release. Consequently, interdisciplinary convergence remains imperative to ensure the safety of clinical translation.

Rehabilitation of Neurological Dysfunction After Injury

Both BCIs and brain tissue engineering aim to reconstruct neural function. BCIs primarily achieve this by controlling external devices, whereas brain tissue engineering focuses on the activation or inhibition of molecular pathways within the brain. In both approaches, hydrogels play a crucial role. As previously summarized, their functions in brain-computer interfaces have been outlined, followed by a discussion of their effects in neuro-prosthetic engineering.

Restoration of Neurological Functions

The CNS consists of complex neural networks that regulate a spectrum of physiological activities, ranging from basic autonomic processes to advanced cognitive functions. CNS insults or diseases can trigger a cascade of reactions, including rapid cell death and severe neuroinflammatory responses. These events cause substantial cerebral damage and irreversible functional loss, further contributing to the disintegration and collapse of intricate neural circuits and connections within the affected regions.¹⁴² Although surviving neurons can sprout new axons and form synapses,

reconstructing lost functions presents significant challenges, resulting in various complications. For example, during a stroke, neurological functions associated with the affected area are lost. After a few months, a partial recovery of nerve function typically occurs. However, approximately half of young stroke patients experience cognitive impairment, with around a quarter also suffering from aphasia.¹⁴³ The global pooled prevalence of post-stroke fatigue among survivors was as high as 46.79%.¹⁴⁴ In terms of specific deficits, the incidence rate of upper limb weakness (FAST score ≤ 8) is 35%, upper limb coordination impairment 46%, delayed recall impairment 41%, and upper limb sensation impairment 26%.¹⁴⁵

Brain tissue engineering seeks to recreate living, functional tissue, playing a crucial role in restoring brain function and cognitive health. This goal is achieved by employing biological scaffolds that provide a supportive environment for cellular growth and storage spaces for molecules. Hydrogels can mimic the extracellular matrix, providing a supportive environment for transplanted and host cells to adhere, proliferate, and differentiate, making them an ideal choice for scaffold fabrication. Additionally, hydrogels extend the half-lives of injected molecules and alleviate their adverse effects by confining them within the hydrogel matrix, minimizing burst release, rapid proteolysis, and unintended diffusion.¹⁴⁶ Over time, implanted hydrogel-based scaffolds gradually degrade and are replaced by the natural extracellular matrix synthesized by the neurons,¹⁴⁷ a process that is non-toxic and safe. To date, multiple hydrogel-based scaffolds have been fabricated and applied in the treatment of neurological disorders, as list in Table 4.

Establishing Brain-Like Tissue

Generally, scientists employed animal models and two-dimensional (2D) cell culture systems to study the mechanisms of the nervous system. However, there exist significant differences in the characteristics of neurodevelopment and neurological diseases between humans and animals, contributing to the poor translation of therapeutic agents derived from animal models to the clinic.¹⁵⁶ Additionally, traditional 2D cell culture models, like hippocampal slices, commonly reflect disease-related changes in a singular dimension, failing to preserve the intricate hierarchical structure of the brain and the dynamic interaction between cells and their environment.¹⁵⁷ Therefore, it is necessary to design 3D brain-like models that accurately replicate mimic the structure and composition of human brains. Hydrogel possess properties similar to the extracellular matrix of brain tissue, enabling the specific distribution and growth of cells when properly designed. This capability makes hydrogels an appealing support material for 3D brain organoids. For instance, Raimondi et al employed hydrogel-based semi-interpenetrating polymer networks to develop a millimeter-thick brain-like tissue model,¹⁵⁸ containing neurons and glial cells. The

Table 4 Summary of Hydrogel-Based Scaffolds Loaded with Cells or Molecules for Nerve Regeneration in Brain Tissue Engineering

Scaffolds	Cell/Molecule	Disease	Function/Outcome
EMC Heparin sulfate ¹⁴⁸	Nerve growth factor	Traumatic brain injuries	Promoting the formation of neural tissue in the defect area, maintaining the stabilization of BBB
SiP@PDA GelMA/ECM ¹⁴⁹	Schwann cells	Peripheral nerve injury	Regulating regenerative microenvironment for peripheral nerve repair
Silk fibroin ¹⁵⁰	Neural stem cells	Traumatic brain injury	Reducing the formation of cavities in the brain and the number of glial cells
Lipoic acid-iron ¹⁵¹	Lipoic acid-iron	Glioblastoma	Enhancing the efficacy of tumor-immunotherapy and promoted tumor ferroptosis.
H2S@SF ¹⁵²	Exogenous hydrogen sulfide	Traumatic brain injury	Inhibiting neuronal pyroptosis Alleviating brain edema and the degree of neurodegeneration
Nano-reinforced hyaluronic acid ¹⁵³	Neurotrophic factor mesenchymal stem cells	Parkinson's disease	Enhancing the mechanical properties of hydrogels, and therapeutic effects.
Artificial extracellular matrix ¹⁵⁴	Vascular endothelial growth factor	Stroke	Realizing incorporation and sustained release of drugs Enhancing angiogenesis and neurological recovery;
Gelatin hydrogel ¹⁵⁵	Epidermal growth factor	Intracerebral hemorrhage	Maintaining a tight interface with adjacent brain tissue and filling the ICH cavities without deforming brain tissue

Abbreviations: ECM, extracellular matrix; BBB, Blood brain barrier; SiP@PDA, polydopamine-modified silicon phosphorus nanosheets; GelMA/ECM, methacryloyl gelatin and decellularized extracellular matrix; H2S@SF, surface-fill H2S-releasing silk fibroin hydrogel; ICH, intracerebral hemorrhage.

model effectively reproduced the functional relationships with peripheral body districts and the key biochemical parameters of brain tissue.

Future Perspective

The true benchmark for advances in biomedical science lies in their successful integration into clinical practice. Despite the recent surge in hydrogel research and the proliferation of promising preclinical findings, challenges in clinical translation persist.

Hydrogels provide a highly biomimetic interface that minimizes disruption to brain tissue. However, the cross-linked networks of these materials are mechanically fragile, particularly natural hydrogels, limiting long-term implant durability. Conversely, synthetic hydrogels exhibit superior physicochemical stability and enable facile shape modulation alongside scalable manufacturing, positioning them as a dominant platform for future investigations. Furthermore, the potential for bioaccumulation of degradation byproducts such as metallic elements like copper and toxic cross-linking agents, poses a significant risk of chronic neurotoxicity. Future research should prioritize the long-term biostability and functional reliability of these devices. The degradation rate, mechanical properties, and potential for chronic inflammation of hydrogels must be rigorously assessed.¹⁵⁹ Additionally, hydrogels inherently exhibit limited intrinsic electrical conductivity. While the integration of nanomaterials, such as graphene oxide and carbon nanotubes, could enhance signal acquisition,¹⁶⁰ it often introduces heterogeneous phases within the matrix. The non-uniform distribution of these fillers can inadvertently elevate the Young's modulus and induce uneven electroosmotic flow, compromising the interfacial stability and long-term bio-compliance of the electrodes. Consequently, the central challenge lies in how to balance conductivity, transparency, and mechanical compliance while preserving biocompatibility.

Hydrogels are effective drug delivery systems enabling sustained drug release. However, the complex anatomy of brain poses challenges for precise targeting and delivery to pathological foci. Furthermore, the therapeutic efficacy of many current systems is tethered to passive stimuli-responsive kinetics, relying on localized fluctuations in pH or temperature.¹⁶¹ In the absence of such physiological triggers, the drug release profile may become unpredictable or suboptimal. Future efforts should concurrently enhance drug transport efficiency while modulating swelling rates to match brain tissue density, integrating molecular recognition moieties to enable precise controlled release, and ensuring long-term safety. At the fundamental research level, 3D brain-like models provide biomimetic platforms that recapitulate the multicellular complexity and anatomical architecture of the CNS. Due to the intricate structure of brain tissue and its highly nonlinear characteristics,¹⁶² there is an urgent need for advanced electrophysiological mapping of these hydrogel-integrated systems.

Despite challenges persist, the evolution of smart hydrogel systems offers a transformative vision for neuro-medicine. The synergy between material innovation and clinical necessity ensures that hydrogels will remain at the forefront of efforts to diagnose and treat neurological disorders.

Conclusions

Our review summarizes the fundamental physicochemical properties of hydrogels, with particular emphasis on their applications in the diagnosis and treatment of neurological disorders, including EEG signal acquisition and targeted therapeutic delivery. Furthermore, we critically analyze current research bottlenecks and discuss feasible solutions. Bioelectrode applications primarily rely on the ionic conductivity of hydrogels, enabling the transduction of ionic currents into measurable electronic signals. Conversely, drug delivery vehicles exploit the 3D network architecture to regulate mass transport, wherein mesh size dictates drug diffusion rates and swelling ratios modulate release kinetics. Recently, efforts have also been directed toward integrating these two modalities, yielding theranostic intelligent hydrogel systems.

However, translating these laboratory breakthroughs into clinical practice remains challenging. From a material perspective, hydrogel matrices inherently possess lower intrinsic electrical conductivity compared to conventional metallic or semiconductor elements, necessitating the integration of conductive additives to achieve desired electroactive properties. Biologically, the macromolecular size and complex hydrodynamics of many advanced hydrogel carriers

frequently impede their efficient transit across BBB, undermining targeted central delivery. Furthermore, current therapeutic validations are predominantly confined to preclinical animal models, which fail to replicate the pathophysiological complexity and microenvironmental dynamics of the human brain. Rigorous, long-term biosafety profiling, precise degradation kinetics, and large-cohort clinical trials are imperative.

Consequently, the clinical translation of hydrogel devices requires robust interdisciplinary collaboration across materials science, neuroscience, and engineering. Future work should advance biomaterial design, improve fabrication techniques, and optimize device interfaces to enable early diagnosis and precision therapy for neurological disorders.

Abbreviations

EEG, Electroencephalography; BBB, Blood-brain Barrier; 3D, Three-dimensional; BCIs, Brain-computer Interfaces; DALYs, Disability-adjusted Life-years; DBS, Deep Brain Stimulation; VNS, Vagus Nerve Stimulation; CNS, Central Nervous System; ECM, Extracellular Matrix; PHEMA, Poly2-hydroxyethyl Methacrylate; HA, Hyaluronic Acid; PEG, Polyethylene Glycol; PVA, Polyvinyl Alcohol; PEO, Polyethylene Oxide; ROS, Reactive Oxygen Species; DOX, Doxorubicin; YA, Tannic Acid; PAM, Polyacrylamide; CMC, Carboxymethyl Cellulose; HMI, Human-machine Interaction; AG, Agarose; AM, Acrylamide; PAM-co-PAA, Poly (acrylamide-co-acrylic acid); ECH, Epichlorohydrin; FRP, Free Radical Polymerization; RDRP, Reversible Deactivation Radical Polymerization; ATRP, Atom Transfer Radical Polymerization; β -CD, Beta-cyclodextrin; Fc, Ferrocene; CRN, Chemical Reaction Network; SPH, Supramolecular Photonic Hydrogel; HRP, Horseradish Peroxidase; PVP, Poly (vinyl pyrrolidone); AgNPs, Silver Nanoparticles; HFE, Hydrogel-forming Extrusion; dECM, Decellularized Extracellular Matrix; MSC, Mesenchymal Stem Cell; CNTs, Carbon Nanotubes; GelMA, Methacrylate Acylated Gelatin; FBR, Foreign Body Reactions; DC, Direct-current; DEX, Dexamethasone; ECoG, Electrocorticography; LFP, Local Field Potential; FEA, Finite Element Analysis; DIW, Direct Ink Writing; CSF, Cerebrospinal Fluid; Ag/AgCl, Silver/Silver-Chloride; SNR, Signal-to-noise Ratio; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; MMA, Multichannel Microneedle Array; ERP, Event-related Potential; PI, Polyimide; CF, Carbon Fabric; CPs, Conductive Polymers; PEDOT: PSS, Poly (3,4-ethylenedioxythiophene): Polystyrene Sulfonate; Alg, Alginate; PAAM, Polyacrylamide; CIPN, Chemotherapy-induced Peripheral Neuropathy; FES, Functional Electrical Stimulation; MALAT1, Metastasis-associated Lung Adenocarcinoma Transcript 1; ISF, Interstitial Fluid; AD, Alzheimer's Disease; TENG, Triboelectric Nanogenerator; PD, Parkinson's disease; CMCS, Carboxymethyl Chitosan; BP, Black Phosphorus; MB, Methylene Blue; GBM, Glioblastoma Multiforme; 2D, Two-dimensional; PTX, Paclitaxel; TM, Triglycerol Monostearate; TBI, Traumatic Brain Injury; Cur, Curcumin; EVs, Extracellular Vesicles; SA, Sodium Alginate; TP, Tilapia Peptide; AgNWs, Highly Conductive Silver Nanowires; TET, Tetrandrine; MI, Motor-imagery; SC, Skin Conductance; VR, Virtual Reality; TENS, Transcutaneous Electrical Nerve Stimulation; SiP@PDA, Polydopamine-modified Silicon Phosphorus Nanosheets; GelMA/ECM, Methacryloyl Gelatin and Decellularized Extracellular Matrix; H2S@SF, Surface-fill H2S-releasing Silk Fibroin Hydrogel; ICH, Intracerebral Hemorrhage.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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