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Review

Biomaterials for neuroengineering: applications and challenges

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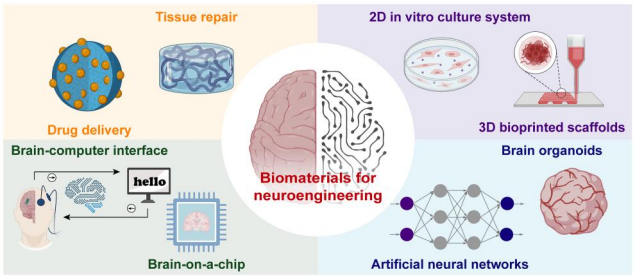
Abstract



Neurological injuries and diseases are a leading cause of disability worldwide, underscoring the urgent need for effective therapies. Neural regaining and enhancement therapies are seen as the most promising strategies for restoring neural function, offering hope for individuals affected by these conditions. Despite their promise, the path from animal research to clinical application is fraught with challenges. Neuroengineering, particularly through the use of biomaterials, has emerged as a key field that is paving the way for innovative solutions to these challenges. It seeks to understand and treat neurological disorders, unravel the nature of consciousness, and explore the mechanisms of memory and the brain's relationship with behavior, offering solutions for neural tissue engineering, neural interfaces and targeted drug delivery systems. These biomaterials, including both natural and synthetic types, are designed to replicate the cellular environment of the brain, thereby facilitating neural repair. This review aims to provide a comprehensive overview for biomaterials in neuroengineering, highlighting their application in neural functional regaining and enhancement across both basic research and clinical practice. It covers recent developments in biomaterial-based products, including 2D to 3D bioprinted scaffolds for cell and organoid culture, brain-on-a-chip systems, biomimetic electrodes and brain–computer interfaces. It also explores artificial synapses and neural networks, discussing their applications in modeling neural microenvironments for repair and regeneration, neural modulation and manipulation and the integration of traditional Chinese medicine. This review serves as a comprehensive guide to the role of biomaterials in advancing neuroengineering solutions, providing insights into the ongoing efforts to bridge the gap between innovation and clinical application.

Keywords: biomaterials; neuroengineering; nanopattern; organoid; 3D printing; brain-on-a-chip

Introduction

Neuroengineering, an interdisciplinary field at the intersection of neuroscience and engineering, aims to develop technologies for understanding, repairing and enhancing neural systems [1–4]. The ultimate goal of neuroengineering is to address neurological disorders and enhance brain function, thereby offering hope to millions who suffer from conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), as well as brain and spinal cord injuries [5–11]. The last decades have witnessed much progress in biomaterials including polymers [12–17], metals [18, 19] and nonmetallic inorganics [20, 21], which has led to rapid progress of pertinent medical devices [22, 23] and drug delivery systems [24–26]. In addition, neuroengineering has made significant progress, taking advantage of or stimulated by the development of various biomaterials. Biocompatibility is a key issue for an implant [27, 28]. Extensive investigations have been made to study cell-material interactions [29–31] using a series of advanced techniques such as surface patterning [32–37].

However, the complexity and sensitivity of neural tissues pose significant challenges to developing effective treatments and interventions. Despite substantial progress, neuroengineering faces several critical challenges that impede its advancement [38–40]. One of the primary hurdles in advancing neuroengineering is the current inadequate understanding of the complex interplay between the biological, physical and chemical properties of brain tissues. The brain's intricate architecture and complex

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biochemical environment necessitate the development of biomimetic tissues and tunable biomaterials that can accurately replicate the microenvironment required for neural repair and regeneration [2, 9, 40]. Several significant strides in this area utilized organ-on-a-chip technology to model neural environments, providing a more accurate platform for studying neural repair mechanisms [41]. Secondly, biomacromolecules, such as extracellular vesicles, proteins, polysaccharides and DNA, play crucial roles in the structure and function of neural tissues [42]. However, the interactions of these macromolecules within neural tissues lack comprehensive support from physical and chemical theories. Understanding these molecular interactions is vital for designing biomaterials that can effectively interface with neural tissues. The integrating insights from chemical science and biophysics to develop advanced biomaterials can support neural function and repair [43–46]. Thirdly, the dynamic activities within neural tissues, including neuronal electrical activity, protein translation and DNA synthesis, are fundamental to life and neural function. Studying these dynamic processes requires innovative methods, such as the development of *in vivo* probes and advanced imaging techniques, to observe and understand these processes in real-time [47]. These tools are essential for gaining insights into neural function and dysfunction, paving the way for novel therapeutic strategies [48, 49]. Moreover, despite advances in our understanding of neural networks, the mechanisms that underlie neural connectivity and information transmission remain elusive. Neuromorphic engineering, along with the development of artificial synapses, is critical for accurately simulating the fundamental structures and functionalities of neural networks. These technologies are designed to replicate the connectivity and functionality of neural networks, thereby providing a deeper understanding of the brain's processes for information processing and transmission [50–55]. Finally, the development of treatments for neurological diseases is also hindered by the limitations of current pharmacological approaches. There is a pressing need for innovative strategies that combine biomaterials with therapeutic agents to enhance treatment efficacy. By engineering biomaterials capable of delivering therapeutic agents directly to the site of neural damage or disease, we can enhance the efficacy of neurological therapies and offer more effective treatment options for patients. The integration of biomaterials in neuroengineering holds significant promise for addressing the complex challenges of brain science. By advancing our understanding of brain tissue properties, enhancing our ability to model and study neural environments, and developing new therapeutic strategies, we can make substantial progress in treating neurological disorders and improving neural health [56, 57].

In this review, we initially provide an overview of the significance of developing innovative biomaterials within the realms of neuroscience and neuroengineering. We then comprehensively summarize the recent advances in applications of novel biomaterials from basic and clinical research for the exploration of neural active process and therapeutic purposes in neurological diseases and injuries, including the use of brain organoids, biomimetic simulated inductive materials, neuromorphic devices, human–computer interactions, as well as the strategies for blood–brain barrier (BBB) and sustained drug release (Figure 1). Through this comprehensive analysis, the review highlights the potential applications of biomaterials, which could revolutionize neuroengineering and significantly advance the treatment of neurological injuries and diseases.

Neuroengineering: a fast-developing interdisciplinary field

Neuroengineering is a rapidly developing interdisciplinary field that focuses on issues related to the interplay among biology, technology, materials science and medicine in a revolutionary manner with respect to the past [58]. Neuroengineering and neuroscience, with their focus on the neural network at the cellular and molecular levels and the integration of biomaterials, are making significant progress. This interdisciplinary approach offers promising applications for enhancing the recovery of cognitive, sensory and motor functions in individuals with neurological disorders, impacting both basic research and clinical practice. A rapidly emerging topic within this field is 'biomaterials in neuroscience and neuroengineering', which highlights interdisciplinary efforts aimed at restoring, modulating, and regenerating neurofunction in both healthy individuals and patients afflicted by neurological disorders [59].

Neuroengineering and neuroscience

Recent advancements in neuroscience are not only inspiring innovations in neuroengineering but are also being reciprocally informed by them, fostering a synergistic evolution in both fields. The primary challenge in neuroscience lies in deciphering the complex systems of the brain and the central nervous system (CNS) under both physiological and pathological conditions [60]. Neuroengineering, on the other hand, primarily aims at repairing and replacing neurofunctional recovery in clinical strategies, which puts it in a unique intellectual position to provide experimental and theoretical tools to decode the mysteries of neuroscience, such as translating neural network activities and molecular events in the CNS into complicated behaviors, thereby promoting the development of neuroscience [61]. With the development of a variety of novel technical and computational tools, neuroengineering enables a dialogue with the brain and nervous system, ranging from primary neuron cultures *in vitro* and brain organoids *ex vivo* to the CNS of live animals or even humans *in vivo* [62–64]. Moreover, neuroengineering products, such as biosensors, multi-electrode arrays, memristive devices and bidirectional brain–machine interfaces, not only extend our ability to communicate with the brain and nervous system by recording and analyzing but also push the boundaries into modulating and potentially manipulating the electrical activities of neurons and the intricate interactions within neural networks [65–68]. More specifically, it has been indicated that neuroengineering has three primary areas of interest with respect to studying neuroscience [69]: (i) to quantitatively investigate the mechanisms underlying cognitive, sensory and motor systems encoding and information processing with novel technological tools at various scales. This approach spans from the genetic level to synaptic interactions, from cellular activities to network dynamics, and extends to the comparison between biological neural systems and their artificial counterparts; (ii) to functionally modulate, manipulate, and even perform reverse engineering of the CNS at cellular, synaptic and molecular levels; (iii) to design and implement innovative biomaterials and devices aimed at repairing the CNS and even replacing parts of the brain under pathological conditions, particularly in non-fatal TBI, spinal cord injuries and neurodegenerative diseases [70–78].

Neuroengineering and biomaterials

Biomaterials represent a critical field of research in neuroengineering. They are novel, engineered substances that are designed to interact directly with living systems, or as components of complex

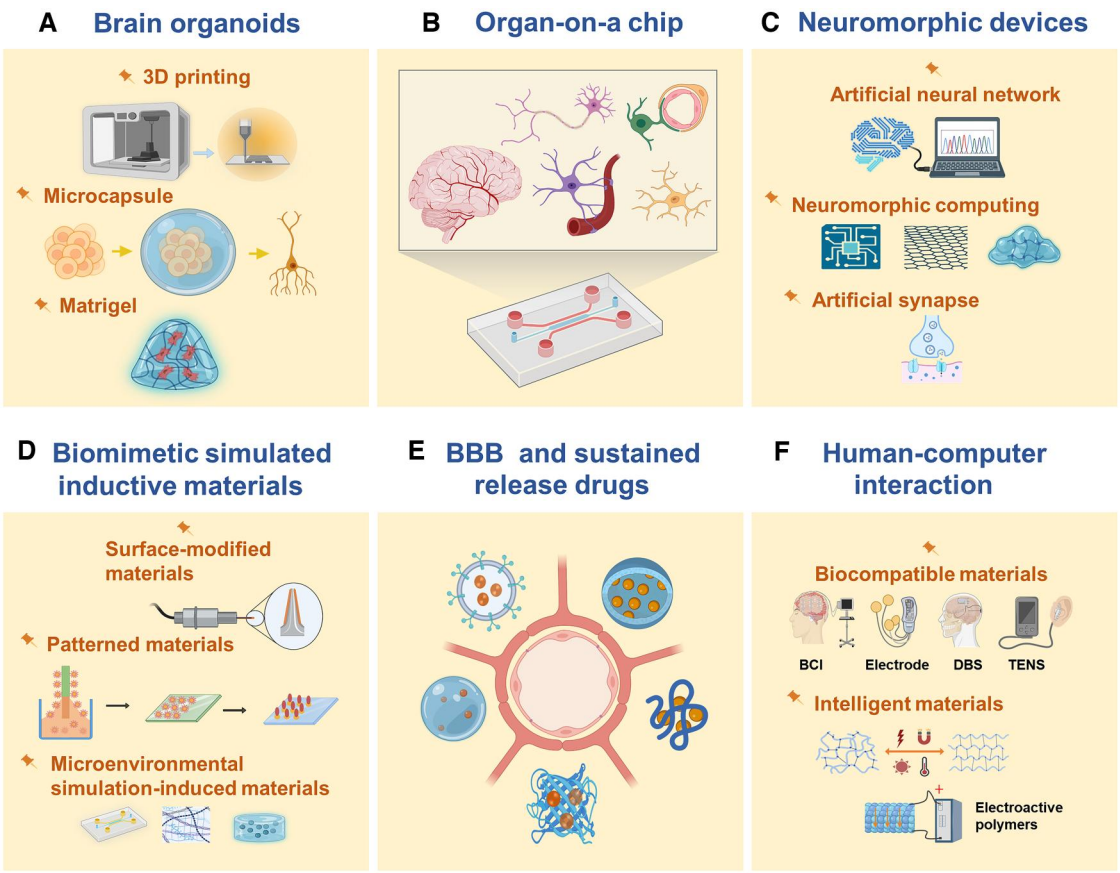

Figure 1. The application of biomaterials in neuroengineering. (**A**) Brain organoids: 3D printing has been applied to make human brain tissue. Matrigel helps grow these tissues. Specially treated mouse stem cells in a gel bead turn into nerve cells more effectively. (**B**) Organ-on-a-chip: the 'brain on a chip' combines brain-like tissue with tiny chips to mimic the human brain. It helps scientists' study how the brain develops and reacts to diseases and drugs outside the body. (**C**) Neuromorphic devices: These devices copy how neurons and synapses work, creating artificial networks that can advance a new type of computing. (**D**) Biomimetic simulated inductive materials: Patterns on glass with gold are made by using a special process. Adding tiny particles and molecules to this pattern improves how well electrodes pick up nerve signals. These materials also mimic the body's environment to help nerve cells grow. (**E**) BBB and sustained release drugs: advanced materials like nanomedicines and special gels are applied to help drugs get past the brain's protective barrier and release slowly. (**F**) Human–computer interaction: This area focuses on using safe and smart materials to create new ways to diagnose and treat brain-related diseases. (Created with BioRender.com.)

devices or systems, to facilitate therapeutic or diagnostic procedures for neurological injuries and diseases. The gratifying advancements of biomaterials are revolutionizing the methodologies through which neuroengineering interfaces with the nervous system. The integration of novel biomaterials in neuroengineering has advanced the field of neuroscience, transcending traditional morphological and functional studies to focus on the repair, replacement, modulation and manipulation of the CNS. This evolution is particularly significant in the context of cognitive, sensory, and motor functions.

Theoretically, biomaterials can be classified into biodegradable and non-biodegradable types. Biodegradable biomaterials, such as drug carriers, delivery systems and tissue scaffolds, are designed to degrade after serving their intended purpose [79]. In contrast, non-biodegradable biomaterials, including neural electrodes and CNS shunts, are engineered to maintain functionality over an extended period, potentially indefinitely [80–88]. In recent years, there has been a significant increase in interest towards the development of novel biomaterials for neuroengineering applications. This includes materials such as silicones, lipids, natural polymers and synthetic polymers. These biomaterials have been developed in various forms to accommodate specific applications within the field [89–93]. However, there are still several challenges that must be addressed in the next decade [69, 94]. Firstly, it is crucial to optimize the physical, chemical and biological properties of novel biomaterials to develop the next-generation interfaces that facilitate seamless integration between artificial systems and the nervous system [95]. Secondly, there is a critical need to develop flexible and wireless implantable neural bioelectronics that possess biocompatibility, minimal invasiveness, longevity and scalability. These devices should be capable of performing neural stimulation, modulation and manipulation [96, 97]. Thirdly, the development of a new generation of 'organ-on-a-chip' systems is imperative for neuroregeneration, with a focus on replicating the microenvironment of nerve tissue to facilitate the study and promotion of neural repair processes. Fourthly, the development of smart biomaterials with sub-nanoscale precision is essential to facilitate bidirectional communication and to induce specific molecular, synaptic and cellular reorganization within neural networks. This approach aims to achieve accurate and precise manipulation of the CNS, which is driven by both endogenous factors and material properties. Figure 2 presents the close relationship between biomaterials and neuroengineering.

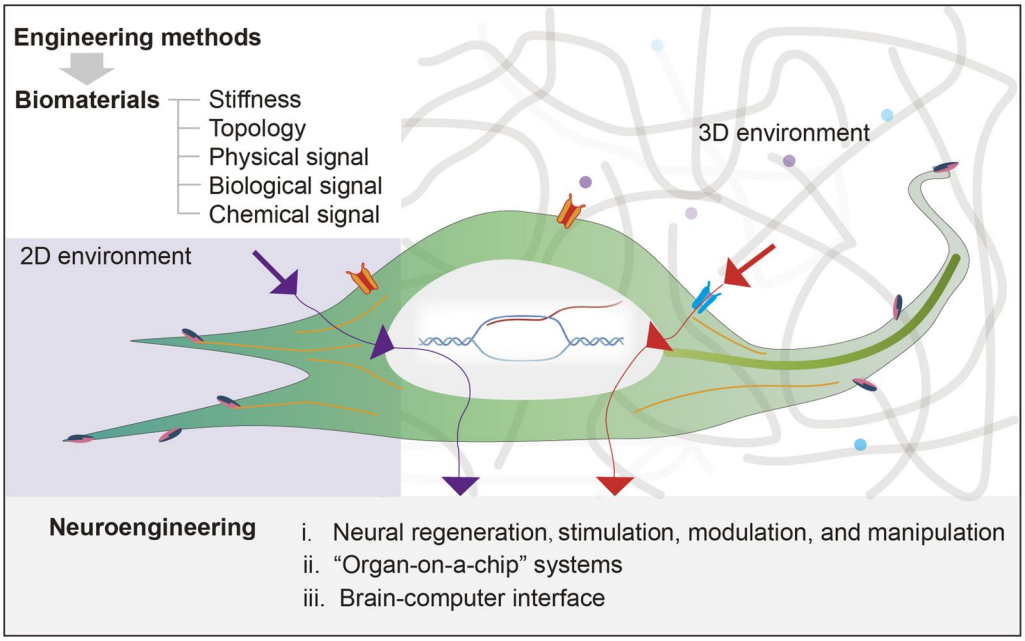

Figure 2. The close relationship between biomaterials and neuroengineering. The close relationship between biomaterials and neuroengineering is a pivotal area of research, as it involves the development and application of biomaterials designed to interact with the nervous system. This interdisciplinary field is crucial for creating innovative solutions for neurological disorders and injuries, including (i) neural regeneration, stimulation, modulation and manipulation; (ii) brain-on-a-chip systems; (iii) brain–computer interface.

Applications of biomaterials for neuroengineering

Brain organoids: 'brain-on-a-chip'

The 'brain-on-a-chip' system offers a promising approach to neural regeneration in living organisms by mimicking the critical spatiotemporal microarchitecture of neural-neural and/or neural-glial communications, as well as neural ECM [98, 99]. The integration of this novel system, which recapitulates neural cells on organ-level structures and functions, offers unprecedented benefits across a spectrum of applications in both basic research and clinical practice. These benefits include the development of human *in vitro* models for both healthy and diseased brains, enabling in-depth investigations into the fundamental mechanisms and developmental patterns of CNS development and neurological diseases. Furthermore, it facilitates drug development by streamlining toxicity screening and therapeutic target identification, and it holds promise as a potential alternative to traditional animal testing methodologies. Scientists propose that the implantation of a 'brain-on-a-chip' system may offer innovative possibilities by modulating the differentiation of NSCs and promoting neural regeneration, thereby potentially enhancing neural function in patients with neurological injuries and diseases (Figure 3) [100]. The combination of neuroengineering and chip research primarily concentrates on critical aspects such as axonal growth, the integrity and function of the BBB, the development of neurospheres, and the engineering of three-dimensional or layered neural tissues (Table 1) [101–107].

3D printing

Most recently, the focus of basic and clinical research on regulating microenvironments has been primarily on synthetic substrates, from 2D cell cultures to 3D bioprinting cell and organoid cultures (Figure 4A) [166–170]. The 3D multicompartment organotypic microphysiological systems representative of the BBB have been developed. *In vitro* neurovascular unit systems offer a promising platform for investigating the intricate interactions between neurons and the cerebral spinal fluid (CSF) compartment. These systems incorporate a realistic blood-surrogate supply and venous return mechanism, which is essential for mimicking the *in vivo* environment. Additionally, they often include circulating immune cells and the choroid plexus, key components of the neurovascular unit that play significant roles in maintaining CNS homeostasis. These systems successfully recapitulate all three critical brain barriers, including the BBB, brain–CSF barrier and blood–CSF barrier. This comprehensive replication is essential for studying the complex interactions between the brain's vasculature, the cerebrospinal fluid, and the immune system, as well as for evaluating the permeability and transport mechanisms across these barriers. Impressively, these novel technological platforms represent a convergence of multiple disciplines, including advanced microfluidics, cell culture techniques, analytical instrumentation, bioinformatics, control theory, neuroscience and drug discovery methodologies. They also incorporate 3D mapping technologies to visualize the distribution of nanoparticles within the vascular and perivascular regions at the cellular level, providing a detailed understanding of nanoparticle dynamics in these critical areas [171]. Moreover, these sophisticated *in vitro* systems are capable of replicating critical neurobiological processes, including chemical communication, molecular trafficking, cellular uptake and the penetration of the BBB through receptor-mediated transcytosis. Besides, they also can model inflammatory responses within the brain, providing a comprehensive platform for studying neuroinflammatory conditions and the transport of substances across the BBB [172, 173].

Matrigel

The BBB is a highly specialized and selectively permeable interface that is composed of a unique arrangement of endothelial cells, astrocytic endfeet and pericytes. This intricate structure forms a critical barrier that isolates the CNS from the systemic circulation. The BBB plays a pivotal role in bidirectionally

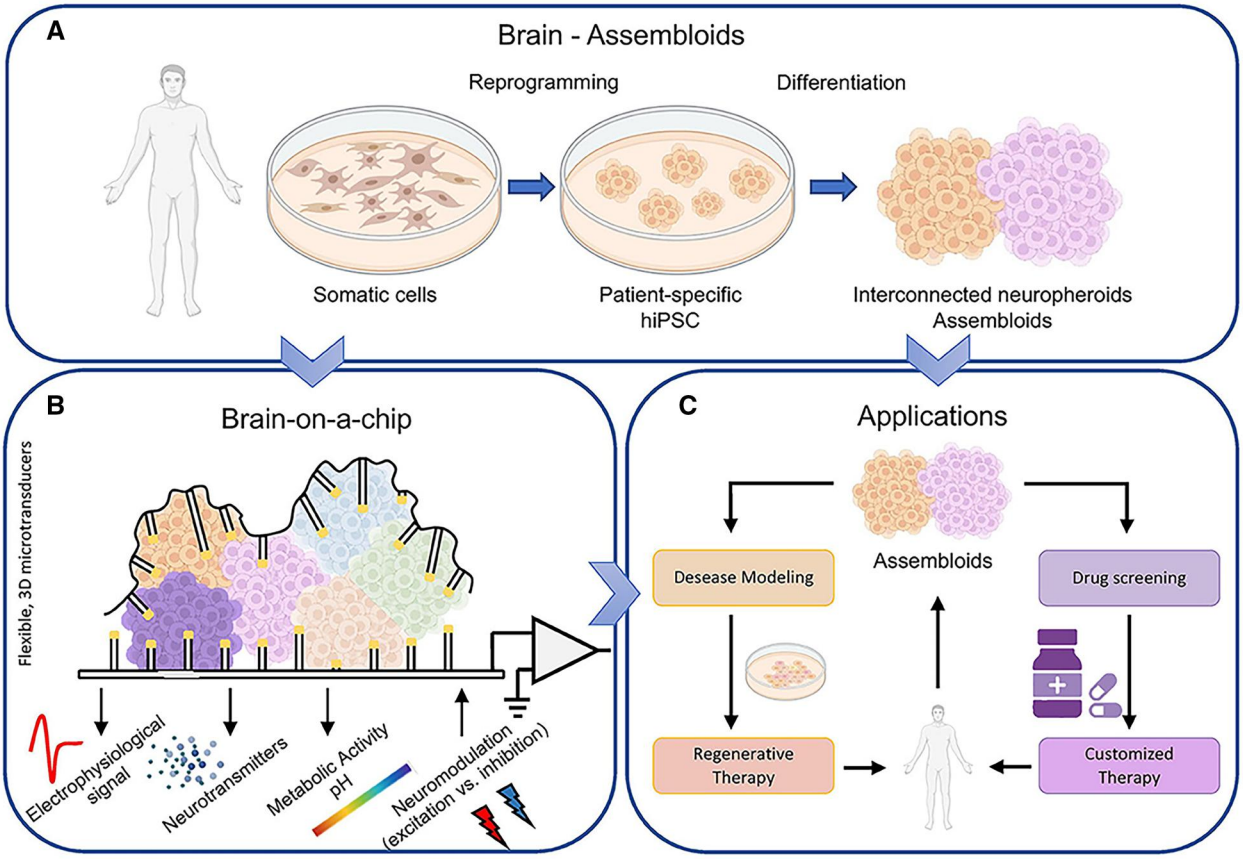

Figure 3. Brain-on-a-chip overview. (**A**) The reprogramming of human somatic cells into induced hiPSCs facilitates the differentiation into various neuronal types while preserving essential topological features of the brain, including its 3D architecture, adequate heterogeneity and modular connectivity. Consequently, this approach enables the *in vitro* cultivation of interconnected neurospheroids and assembloids. (**B**) Coupled to microtransducers, these systems are capable of recording the electrophysiological activity of the biological structures and monitoring other pertinent parameters, including neurotransmitter concentrations and fluctuations in metabolic activity. Furthermore, such devices should possess bidirectional functionality, enabling them to modulate electrophysiological activity through the application of either excitatory or inhibitory stimuli. (**C**) An accurate biological model of the brain, such as this, can be utilized not only for fundamental scientific research but also for drug screening, enabling the development of personalized and patient-specific therapies. Additionally, it facilitates the study of the pathogenesis of brain disorders *in vitro*, thereby aiding in the identification of potential therapeutic solutions. Reproduced from Ref. [108] with permission of Frontiers, © 2022.

regulating the trafficking of ions, molecules, and cells between the brain and the blood. This regulation is essential for maintaining the precise chemical environment and homeostasis within the CNS, which is crucial for proper neuronal function and overall brain health [174]. However, the BBB capacity to restrict the entry of peripheral inflammatory cytokines, immune cells and neurotoxic factors into the to restrict the CNS may become severely impaired under various pathophysiological conditions, such as trauma and neurological diseases [175]. The innovative microfluidic 'BBB-on-a-chip' platform offers a cutting-edge tool for investigating the BBB function with mechanical and biochemical modulation (Figure 4B) [176]. This platform, integrated with microfluidic technology, incorporating advanced microfluidic technology, facilitates real-time monitoring and analysis of human NSC-derived neurons, astrocytes, oligodendrocytes and a functionalized microvascular barrier in a designed physiological niche. It offers advantages such as the capacity for high-throughput screening, precise control over fluid velocity, low cell consumption, long-term culture and high integration on an organ-level basis [177–179].

The polydimethylsiloxane (PDMS) elastomer is widely utilized owing to its high resolution, flexibility, optical transparency and biocompatibility [180]. In some 'BBB-on-a-chip' systems, a porous membrane is integrated between two layers of PDMS, thereby partitioning the channel into distinct compartments (Figure 4C) [181]. Similar to Transwell models, cells are cultured on either side of the membrane, with the fluid composition and flow rate being independently adjustable [182]. In the advancement towards 2.5D cell culture systems, several 'BBB-on-a-chip' models have integrated hydrogels as supportive matrices. The design of the lumen in 'BBB-on-a-chip' systems primarily employs two techniques to isolate liquids from the hydrogel. The phase guide technique, widely utilized in commercial organ-on-a-chip platforms, exemplified by the OrganoPlate® from Mimetas Company, involves the injection of a hydrogel into one channel of an interconnected multichannel device [183, 184]. The presence of a phase guide in the initial channel retains the hydrogel within that channel, thereby creating a direct interface with the adjacent channel, where endothelial cells are cultured. In this context, the fluidic chamber for cell culture is composed of several biomaterials, including the hydrogel and the substrate that supports the microfluidic device [185–191]. To prevent the mixing of materials, an alternative strategy involves the direct creation of a lumen within the hydrogel, employing techniques such as viscous fingering or needle molding [192, 193]. An alternative approach involves the introduction of gold nanorods into a collagen hydrogel, enabling the direct writing of channels via the application of a laser beam. This process thermally denatures collagen

Table 1. The biomaterials-based 'brain-on-a-chip' system and their application.

Brain-on-a-chip	Cell type	Biomaterials	Integrated sensors/electrodes	Culture time
Neuron-based	EM-HCC	PDMS	—	34 h [109]
	hDRGNs	Polystyrene	Microelectrode array	23 d [110]
	hECNs	PDMS	Microelectrode array	14 d [111]
	ER-HCC glial cells from rat brain	PDMS	—	20 d [112]
	iPSC-NSCs, iPSC-neurons and iPSC-derived astrocytes	OrganoPlate	—	7 d [113]
	mECNs	PDMS	—	7 d [114]
	hNSC lines from both healthy and PD patient	Pelican	—	24 d [115]
Oligodendrocyte-based	mESCs	PDMS	—	14 d [116]
	rDRGNs OPCs from P0 to P2 rat brain	PDMS	—	39 d [117]
	Primary neurons from the E16 embryonic rat forebrain, as well as oligodendrocytes and astrocytes from the cerebral hemispheres of P0–P2 rat pups	PDMS	—	29 d [118]
	Primary cortical OPCs from P2 to P4 rats; DRG neurons from P4 rats	PDMS	Microelectrode array	12 d [119]
	DRGNs from E15 embryonic rat or E13 embryonic mouse OPCs from P1 mouse brain	PDMS	Electrodes	24 d [120]
	OPCs from P1 mice; DRG neurons from E13 mice	Carbon black containing PDMS	Blue LED array	24 d [121]
Astrocyte-based	Primary cortical neurons from E18 rats; cerebral cortical astrocytes from P0 to P2 rats	PDMS	—	15 d [122]
	mECNs astrocytes from P1 to P2 mouse cortical regions	PDMS	—	28 d [123]
	Astrocytes from adult rat brains	PDMS	High-speed pressure servo	5 d [124, 125]
	Primary astrocytes from mice	NA	An electrical stimulation system, comprising two electrodes positioned centrally within the culture chamber, is utilized for the discharge of electrical signals	Less than 1 d [126]
	Mouse astrocytes	NA	—	Less than 1 d [127]
Microglia-based	Primary microglial cells from P1 to P2 rats and mice; murine N9 microglia cell line	PDMS	—	1 d [128]
	Primary hippocampal neurons from E17 rat pups; microglial cells from postnatal rat pups	PDMS	—	14 d [129]
	ER-HCC microglial cells from P3 to P6 rat or mouse cortex	PDMS bonded to poly-D-lysine patterned glass	—	7 d [130]
	Human microglial cells from fetal brain tissue	PDMS	—	9 d [131]
	Murine microglial cell line BV2; C6 cells from rat brain glioma	PDMS	—	2 d [132]
	Adult male rat	Silicon-parylene hybrid	Open architecture electrode array	28 d [133]
Synapse	Primary hippocampal cells from P1 to P2 rats	PDMS	—	17 d [134]
	Primary rat cortical neurons and astrocytes	PDMS	Microelectrode array	27 d [135]
	Primary hippocampal neurons from P0 to P2 rats	PDMS	—	42 d [136]
	rECNs	PDMS	—	28 d [137]
	mECNs and EM-HCC	PDMS	—	21 d [138]
	ER-HCC	PDMS	—	17 d [139]
	mECNs and striatal neurons from E15.5 mcie, and $Hdh^{CAG140/+}$ or $Hdh^{Q111/+}$ mice	PDMS	—	18 d [140]
	mECNs and striatal cells from E14 mice	PDMS	—	15 d [141]
	iPSCs from human primary lymphocytes	PDMS	—	42 d [142]
	hESCs	PDMS	—	55 d [143]

(continued)

Table 1. (continued)

Brain-on-a-chip	Cell type	Biomaterials	Integrated sensors/electrodes	Culture time
BBB	Human brain endothelial cell line hCMEC/D3	PDMS	Electrodes for TEER measurement	7 d [144]
	b.End3 endothelial and C8D1A astrocyte cell lines	PDMS	Electrodes for TEER measurement	7 d [145]
	b.End3 endothelial cell line	PDMS	Electrodes for TEER measurement	4 d [146]
	b.End3 endothelial and C8D1A astrocyte cell lines	PDMS	Electrodes for TEER measurement	7 d [147]
	b.End3 endothelial cell line	PDMS	Electrodes for TEER measurement	6 d [148]
	BMECs and astrocytes from P1-P2 mice	PDMS	Electrodes for TEER measurement	4 d [149]
	Br-Bend5 murine endothelial brain cells	PDMS	Electrodes for TEER measurement	5 d [150]
	b.End3 endothelial and C8D1A astrocyte cell lines	PDMS	—	14 d [151]
	b.End3 endothelial, C8D1A astrocyte and mouse pericyte cell lines	PDMS	Electrodes for TEER measurement	21 d [152]
	$CD34^+$ cells from human umbilical cord blood, human $CD4^+CD45RO^+$ Th1 cells, incubated with pericyte-conditioned medium	PDMS	—	6 d [153]
	iPSC-ECs, pericytes and astrocytes from the human brain	PDMS	—	7 d [154]
	Human BMEC line TY10, hBPC line and hAst	OrganoPlate	—	9 d [155]
	Human brain endothelial cell line hCMEC/D3 human astrocytes	PDMS	Electrodes for TEER measurement	4 d [156]
	b.End3 endothelial cell line U87 glioblastoma cells	IP-DiLL photoresin	Electrodes for TEER measurement	5 d [157]
	dhBMECs (BC1 and iPS12 cell lines from healthy human, KW01 cell line from MS patient and AD6 cell line from AD patient)	PDMS	Electrodes for TEER measurement	6 d [158]
	hCMEC/D3 cell line; ReNcell VM human NPCs with familial AD mutations	PDMS	—	16 d [159]
	HUVECs ACM	PDMS	—	5 d [160]
	Rat brain endothelial cell line RBE4 ACM	PDMS	—	4 d [161]
	HUVECs, rat brain astrocyte cell line CTX-TNA2 and murine metastatic breast cancer cell line Met-1	PDMS	—	4 d [162]
	Human brain endothelial cell line hCMEC/D3 primary human astrocytes	PDMS	—	4 d [163]
	HUVECs, human brain endothelial cell line hCMEC/D3, rECNs and astrocytes from P0 to P2 brain cortices	PDMS	—	14 d [164]
	hUVECs, rECNs, astrocytes	PDMS	—	10 d [165]

ACM, astrocytic conditioned medium; b.End3, brain-derived endothelial cells.3; BMECs, brain microvascular endothelium cells; BV2, mouse microglia cell lines; C6, glioma cell lines; C8D1A, marine cerebellar microglia cell lines; CTX-TNA2, rat astrocyte cell lines; DRG, dorsal root ganglion; E, embryonic; EM-HCC, hippocampal cells derived from embryonic mice; ER-HCC, hippocampal cells from embryonic rat; hAst, human astrocyte; hBPC; human brain pericyte cell; hBMECs, human brain microvascular endothelium cells; hCMEC-D3, human cerebral microvascular endothelial cells, D3; hDRGNs, human dorsal root ganglion neurons; hECNs, cortical neurons from human embryos; hESCs, human embryonic stem cells; hNSC, human neuroepithelial stem cell; hUVECs, human umbilical vein endothelial cells; IP-DiLL, IP-Dip-in laser lithography; iPSCs, induced pluripotent stem cells; LED, light emitting diode; mECNs, cortical neurons from mouse embryos; mESCs, marine embryonic stem cells; N9, marine microglia cell lines; NA, not available; NPCs, neural progenitor cells; NSCs, neural stem cells; OPCs, oligodendrocyte precursor cells; P, postnatal; PD, Parkinson's disease; PDMS, polydimethylsiloxane; RBE4, rat brain vascular endothelium cell lines; rDRGNs, rat dorsal root ganglion neurons; rECN, cortical neurons from rat embryos; ReNcell VM, human neural progenitor cell lines; TEER, trans epithellal electric resistance; Th1; T helper 1 cell; TY10, human brain microvascular endothelium cell lines; U87, human glioma cell lines.

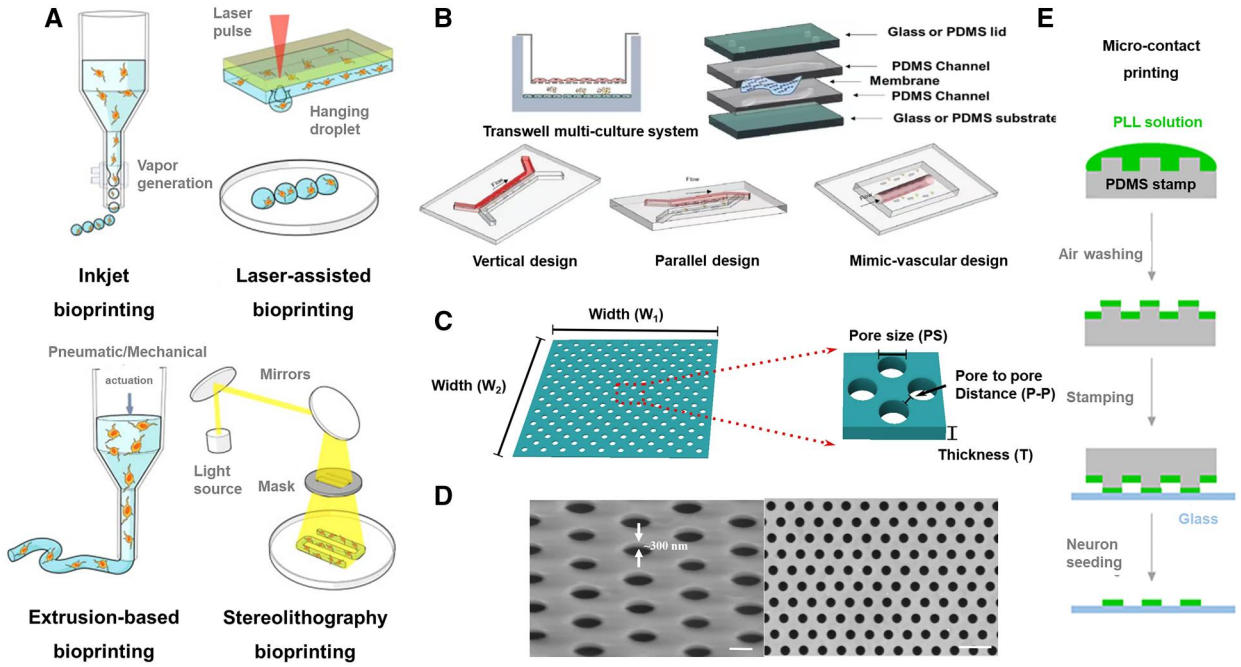

Figure 4. Schematic diagram of 3D bioprinting and 'BBB-on-a-chip' systems. (**A**) 3D bioprinting technologies for neural tissue bioprinting. Reproduced from Ref. [105] with permission of AIP Publishing, © 2022. (**B**) The BBB model development and 'BBB-on-chip' design. Reproduced from Ref. [176] with permission of MDPI, © 2021. (**C**) Tree dimensional sketch of a porous PDMS membrane specifying the adopted terminology: pore size (PS), pore to pore distance (P-P), thickness (T) and area ($W_1 \times W_2$). Reproduced from Ref. [181] with permission of Nature Publishing Group, © 2018. (**D**) Top view and 60°tilted representative SEM images of a UPP membrane with 3 μm pore size and 300 nm thickness. White arrows demonstrate the ultrathin thickness of the membrane (≈300 nm) (scale bar = 10 and 4 μm, respectively). Reproduced from Ref. [196] with permission of John Wiley and Sons, © 2020. (E) Brief procedure to micro-contact printing for fabricating microdot arrays. Reproduced from Ref. [212] with permission of Frontiers, © 2016.

fibers with high spatial and size resolution [194]. However, barriers also face limitations in brain-on-a-chip applications due to their intrinsic hydrophobicity, which may lead to non-specific adsorption of proteins and hydrophobic analytes [195]. To address this issue, an ultrathin porous parylene-C membrane has been developed for the chip, featuring an optimized pore size and arrangement, enhanced porosity (up to 25%), precise thickness (down to 300 nm) and controlled surface etching. These characteristics increase surface roughness, thereby promoting direct cell adhesion under varying flow conditions (Figure 4D) [196]. In a murine BBB-on-a-chip model, a nanofabricated membrane has demonstrated a high correlation coefficient (0.98) between the BBB permeability of a range of hydrophobic and hydrophilic drugs and their respective *in vivo* values [197]. Furthermore, microfluidic BBB models have been validated for their ability to closely mimic the *in vivo* BBB, exhibiting a dynamic environment and comparable permeability coefficients in response to histamine exposure within a relatively thin cultured membrane [145, 198].

Microcapsule

Various biomaterials play a crucial role in the fabrication of microfluidic chips and significantly influence key factors, such as the flow dynamics within neural networks, the size of neurospheroids, and the reprogramming and differentiation of neural stem cells [199]. Axonal sprouting and outgrowth from the proximal stumps, as well as the establishment of new connections with the distal stumps, represent primary challenges in the field of neural regeneration. To address these challenges, numerous studies have focused on designing microfluidic chips that promote axonal growth. These chips employ innovative strategies to provide directional guidance cues for axons and to stimulate the formation of axon branches. For example, microchannels or microgrooves designed for spatial neural guidance, with dimensions ranging from tens of nanometers to 10 microns in width, can effectively direct axonal growth and facilitate the formation and development of axons [200–204]. Furthermore, biodegradable guide channels fabricated from poly(lactic-co-glycolic) acid (PLGA) have been demonstrated to significantly influence glial growth factors and Schwann cells, thereby impacting peripheral nerve regeneration [200]. Surprisingly, the latest microfluidic protocols have enabled the visualization and quantification of axon growth on a chip-based platform [205–207]. These guidance cues establish an artificial neural microenvironment conducive to axonal regeneration [207]. Furthermore, the successful regeneration of axons is also indicated by the formation of axon branches, which is a critical aspect of the neural repair process. A substantial body of evidence from basic research supports the reliability and sensitivity of various biomaterial-based microdot array chip protocols in promoting axonal branching in artificial microenvironments, demonstrating the effectiveness of these protocols in terms of both spatial and temporal aspects (Figure 4E) [208–213].

Biomimetic simulated inductive materials

The traumatic damage of the nervous system, such as TBI, spinal cord injuries and peripheral nerve injuries, as well as neurodegenerative conditions like AD, pose remarkable challenges, as current methods for neural repair and regeneration remain inadequate [214, 215]. Neural function regaining based on neural repair and regeneration is the most promising therapeutic strategy for such neurological injuries and diseases. The clinical effectiveness of traditional microsurgical techniques, such as tensionless epineural sutures and autologous nerve grafting, is still limited due to factors such as nerve length availability and the

development of unfavorable neural complications such as neuroma formation and Wallerian degeneration [216, 217].

Scientists have discovered that induced pluripotent stem cell (iPSC) differentiation plays a crucial role in neural repair and regeneration, including the repair and replacement of defective and damaged tissues. During this process, the microenvironment surrounding the cells, which includes the extracellular matrix (ECM), cytokines and tissue-specific cells collectively referred to as a niche, is one of the critical factors. Specifically, the biological functions of neurons and glia in the living CNS are dynamically and bidirectionally regulated by their microenvironment, which encompasses physical, chemical and biological signals. These signals are imparted by neighboring cells and the ECM [218–220]. Dysregulated neural microenvironment is increasingly recognized as a major obstacle to neural repair and regeneration in neurological damage and diseases and has also been identified as a key factor in the progression of several neurological diseases and injuries. These aberrant microenvironments can be accurately recapitulated *ex vivo* using biomaterials-associated designs, tailored for patient-specific applications [221, 222]. By applying a variety of novel biomaterial technologies to mimic the complexity of the *in vivo* neural microenvironment *in vitro*, research on neural cell behavior has been revolutionized. This approach enables researchers to direct a specific neural (stem) cell type towards a desired phenotype, such as a particular state of differentiation, metabolism, proliferation, survival or functionality, thereby facilitating the study of neurological diseases and injuries. Recently, the focus of both basic and clinical research in microenvironmental regulation has primarily centered on synthetic substrates, ranging from 2D cell cultures to 3D bioprinting of cells and organoids [223].

Patterned materials

Micropatterning, which is a conventional approach, lays the groundwork and provides seminal insights for synthetic substrates in 2D cell cultures (Figure 5A) [224–227]. Specifically, micropatterning enables the precise deposition of ECM proteins onto glass surfaces. Subsequently, non-adhesive regions are introduced to compartmentalize cells, thereby confining single or multiple cells to adhesive islands of predefined sizes and shapes. Typically, non-adhesive regions are created on gold-coated substrates using PDMS elastomeric stamps, which can either release or induce the formation of protein-resistant polymer brushes. Alternatively, these regions can be formed by polymerizing non-adhesive precursors through a photomask [228, 229]. Subsequently, the cell-repellent pattern is immersed in a solution containing ECM-like proteins, such as fibronectin, collagen I and laminin. This process facilitates the transformation of the remaining areas into adhesive patterns through protein absorption. Consequently, cell spreading is restricted on the small, isolated islands, which narrows the distance between focal adhesions and induces a more relaxed cytoskeletal state (Figure 5B and C). Typically, these 2D substrates have been utilized to elucidate the mechanical control underlying the balance between epidermal stemness and differentiation, endothelial proliferation and apoptosis, and the differentiation of mesenchymal stem cells (MSCs) [226, 230, 231]. However, 2D cell cultures on rigid, uniform surfaces do not accurately represent the physiological environment and are incapable of replicating the complex cascade of genetic, environmental, biochemical and physical events that transpire during neurodevelopment and in neuropathological conditions [232]. Alternatively, 3D culturing of stem cells, neural progenitors, neurons, and glia within engineered biomaterials has shown superior biomimetic characteristics compared to 2D culture systems by effectively recapitulating both cell-cell and cell-ECM interactions [233–237]. Therefore, traditional 2D cell cultures are no longer regarded as the premier approach in the field of neuroengineering. Instead, the research focus has shifted towards examining neural cells under physiological *in vitro* conditions. This involves utilizing a complex and soft 3D environment enriched with multiple ECM components, diverse neural cell types and soluble growth factors, all of which

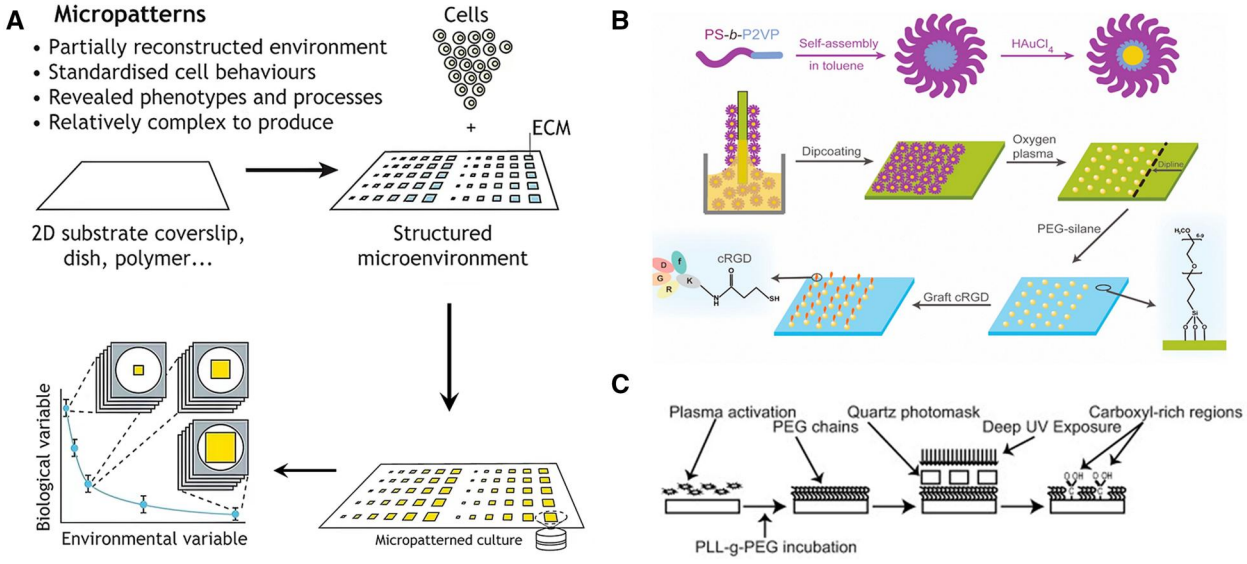

Figure 5. Schematic diagram of micropatterning. (**A**) Micropatterning provides the opportunity to independently control various aspects of the cellular environment, including substrate composition, mechanical properties, geometry and topography. Certain micropatterning techniques are also capable of modulating these variables in a dynamic manner. Reproduced from Ref. [224] with permission of the Company of Biologists, © 2021. (**B**) Fabrication procedure of the RGD nanopattern using block copolymer micelle nanolithography. Reproduced from Ref. [241] with permission of Elsevier, © 2020. (**C**) Scheme of protocol for transferring carboxyl-rich micro-patterns onto glass coverslips. Reproduced from Ref. [229] with permission of Public Library of Science (PLoS), © 2019.

are designed to emulate the natural cellular niches [238]. Notably, 3D culture systems offer several novel advantages, including the ability to modulate stiffness within the physiological range, undergo rapid and non-toxic gelification reactions, incorporate biodegradable or labile crosslinks that promote physical network remodeling, and exhibit enhanced cell adhesiveness [239]. These properties contribute to the disruption of the culture patterns *in vitro*. Neural cells cultured within 3D systems typically exhibit a departure from the tumor-like behaviors characteristic of 2D cultures, instead transitioning into a growth-arrested state. They acquire apico-basal polarity and self-organize to form structures that more closely resemble native tissue architecture [240]. Furthermore, the primary role of ECM stiffness and mechanotransduction in the transition from 2D to 3D cultures is also implicated in neural cell fate determination. This process is facilitated by the progressive addition of fibrillar collagen, which influences cellular behavior.

Surface-modified materials

Acupuncture, a vital component of Traditional Chinese Medicine (TCM), involves stimulating specific anatomical points using techniques such as needling, moxibustion, cupping and acupressure. This practice has a long history, spanning thousands of years in China and other Asian countries. Acupuncture serves as a complementary therapy for a broad spectrum of conditions, encompassing pain, itching, nausea and vomiting, fatigue, neuropathy, anxiety, depression, obesity, sleep disturbances and extending to neurological injuries and diseases [242–244]. Traditional acupuncture needles are commonly crafted from materials such as gold, silver, copper or stainless steel. Nevertheless, advancements in biomaterial science have led to the introduction of alternative materials that possess superior conductivity. These materials are utilized not only in the construction of traditional acupuncture needles but also in the development of aciform sensors, which are capable of measuring various signals and neurotransmitters. Early research has investigated the application of acupuncture needles as biosensors for the detection of lactate. In these studies, the sensing membrane of the needle was coated with a polymer by immersing it in a polymer solution [245]. However, because the modification is performed through adsorption, controlling the membrane thickness on the needles remains a challenge. More importantly, the polymer coating applied during the modification process is prone to detaching from the needle body upon insertion. Furthermore, the rough surface and unstable infrastructure of these modified needles also compromise their reproducibility and stability. Therefore, there is a pressing need for the development of novel acupuncture needles that feature a stable and thin membrane. A variety of innovative biomaterials have been developed to serve this purpose [246–248]. In a pioneering study, homogeneous and stable layers of gold (Au) nanoparticles and graphene were successfully deposited on the tip surface of acupuncture needles. This represented the inaugural application of an electrochemical method to modify the surface of acupuncture needles with nanomaterials, resulting in the fabrication of a graphene-modified acupuncture needle. This needle was introduced as a robust sensing interface for electroanalytical applications, offering enhanced sensitivity and selectivity for the determination of local pH levels and dopamine concentrations (Figure 6A) [245]. Another study reported on the modification of an acupuncture needle with an iron-porphyrin functionalized graphene composite, which was utilized for the real-time monitoring of nitric oxide (NO) release at acupoints. The functionalized needle facilitated

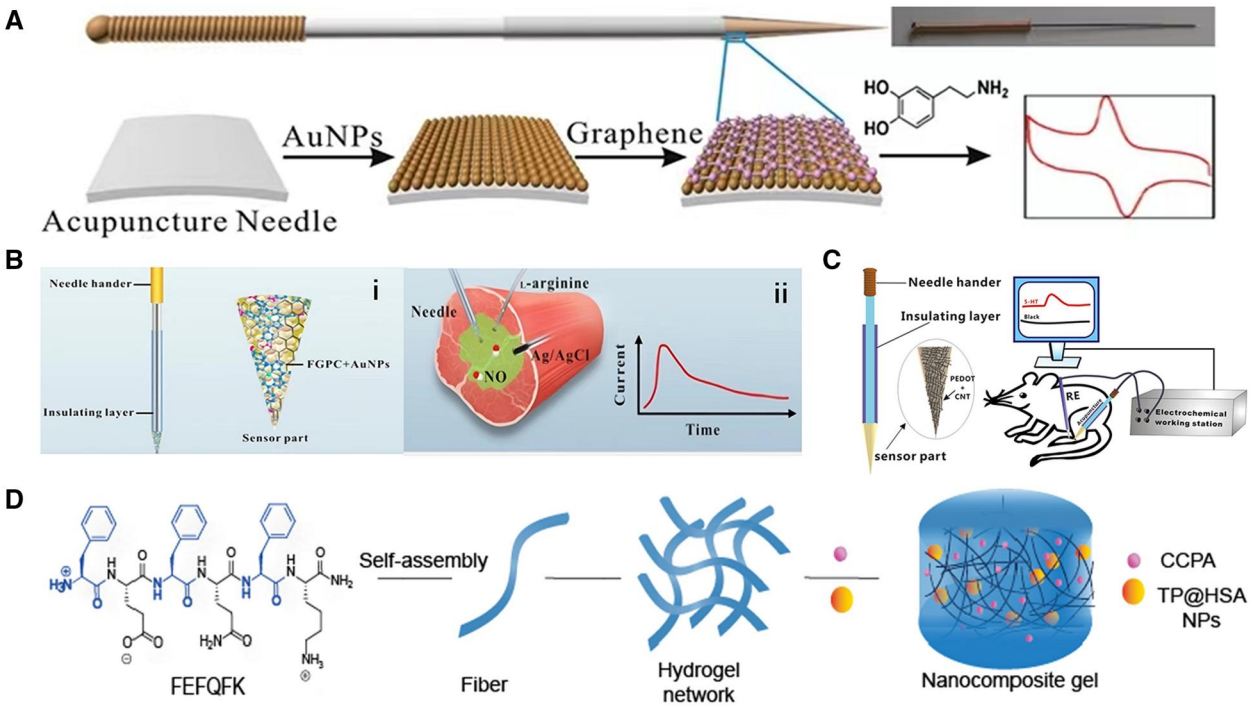

Figure 6. Schematic diagram and application of surface-modified materials. (**A**) The fabrication process for the preparation of the G-an and the detection of DA by the G-an. Reproduced from Ref. [245] with permission of Springer Nature, © 2015. (**B**) (i) Schematic diagram of the FGPC/AuNPs/acupuncture needle. (ii) Schematic diagram of real-time NO measurement in acupoint ST 36 stimulated by L-arginine. Reproduced from Ref. [249] with permission of Springer Nature, © 2017. (**C**) Schematic diagram of real time and *in vivo* monitoring of 5-HT by means of the PEDOT/CNTmodified acupuncture needle. Reproduced from Ref. [250] with permission of Springer Nature, © 2016. (**D**) Schematic representation of construction of nanocomposite hydrogel. Reproduced from Ref. [257] with permission of Springer Nature, © 2021.

specific and sensitive detection, as well as real-time monitoring of nitric oxide (NO) *in vivo*, owing to the favorable catalytic properties of iron-porphyrin and the exceptional conductivity of graphene (Figure 6B) [249]. Additionally, they introduced an extremely stable microsensor by modifying the surface of acupuncture needles with carbon nanotubes (CNTs) stabilized using poly(3,4-ethylenedioxythiophene) (PEDOT). This modification was applied to the tip surface of the needles for the purpose of real-time monitoring of serotonin (5-HT) levels *in vivo* (Figure 6C). Furthermore, the modified needle exhibited high selectivity for the detection of various inflammatory mediators and electroactive molecules [250]. Raman spectroscopy, an analytical tool in chemistry, offers molecular structural fingerprints through the analysis of vibrational modes. The design and fabrication of nanostructures with surface-enhanced Raman scattering (SERS) activity have positioned SERS as an analytical tool capable of ultrasensitive detection, suitable for qualitative or semiquantitative analysis [251]. Gold nanoshell-coated acupuncture needles, combined with polystyrene, can absorb SERS-active nanomaterials for the detection of interstitial fluids upon body insertion [252]. The novel SERS-active needles, integrated with glucose oxidase (GOx) as a signal converter, 4-mercaptobenzoic acid (4-MBA) as a signal reporter and microporous polystyrene, can detect glucose concentration *in vivo*. This approach may serve as a universal strategy for *in vivo* SERS detection of small biomolecules, utilizing SERS-active needles integrated with appropriate enzymes and corresponding reporters [251].

An essential aspect of acupuncture involves the manual manipulation of needles post-insertion to induce a 'Qi' response. However, a significant challenge in acupuncture is the reliance on subjective patient feedback for needle manipulations, as there are currently no quantitative, objective standards. To address this clinical issue, some researchers have made attempts. For instance, a force sensor, specifically the Nano-17 titanium model, was affixed to the acupuncture needles to measure various rotational frequencies and lifting-thrusting movements following the insertion of the needles into phantom tissue [253]. Furthermore, the development of porous acupuncture needles with hierarchical micro- and nanoscale conical pores on their surface has demonstrated increased efficacy in psychiatric treatments and a reduction in pain sensation levels when compared to conventional needles [254].

Acupoint injection therapy and acupoint catgut embedding therapy represent innovative approaches wherein herbal extracts, liquid medications or absorbable biomaterial sutures are introduced into acupoints to elicit prolonged therapeutic effects [251, 255]. Nanoparticle-based drug delivery systems constitute a promising strategy for enhancing the targeting and delivery efficiency of pharmaceuticals while minimizing adverse effects. A prior study prepared biodegradable poly(D, L-lactide-co-glycolide) nanoparticles loaded with bee venom (BV-PLGA-NPs), demonstrating a more sustained analgesic effect when compared to traditional bee venom injections at acupuncture points [256]. In the practice of acupoint catgut embedding therapy, commonly utilized thread types encompass medical catgut, absorbable surgical sutures and medicated sutures. Drawing inspiration from the utilization of nanobiomaterials in TCM, nanosilver threads have been incorporated into acupoint catgut embedding therapy. Nanosilver, owing to its antibacterial properties, demonstrates superior efficacy in reducing inflammatory responses compared to traditional catgut [251]. Intriguingly, several studies have reported on the feasibility of embedding acupoint nanocomposite hydrogels, such as nanoparticles combining triptolide with human serum albumin and 2-chloro-N (6)-cyclopentyl adenosine, for the treatment of rheumatoid arthritis (Figure 6D) [257]. Other hydrogels have been designed for treating myocardial ischemia-reperfusion injury [258]. Furthermore, hydrogel and cryogel biomaterials, fabricated from glycol chitosan and incorporating a novel biodegradable Schiff base crosslinker along with dysfunctional polyurethane, have been developed to promote healing in diabetic skin wounds [259].

Microenvironmental simulation of induced materials

Hydrogels, as innovative biomaterials, exhibit potential as synthetic substrates for 3D cell and organoid cultures [260–268]. The applications of these materials have expanded significantly, attributable to their versatile and highly tunable properties, as well as advancements in biomaterial technologies [269–276]. Hydrogels play a significant role in neuroengineering and regenerative medicine, facilitating the formation of a favorable ECM protein composition, as well as desired levels of stiffness, viscoelasticity, substrate topography (e.g. roughness and curvatures), and fibrosity (Figure 7) [82, 223, 277–280]. These capabilities make hydrogels valuable tools for studying cell behavior *in vitro* and for developing therapeutic strategies *in vivo*.

Hydrogels can be categorized into synthetic hydrogels, including poly(acrylamide) and poly(ethylene glycol) and natural polymer hydrogels, such as type I collagen, fibrin, hyaluronic acid (HA) and alginate. Hydrogel networks are commonly synthesized and modified through various polymerization and crosslinking reactions. These processes commence with either synthetic monomers or macromers, or with natural polymers that have been modified, resulting in 3D polymeric meshes that are stabilized by covalent bonds and physical entanglements [281]. The mechanical properties of hydrogels can be modulated by adjusting the polymer density and/or the crosslinker concentration. The ability to tune mechanical and biocompatible properties, coupled with their high water content, makes the physical characteristics of *in vitro* hydrogels analogous to those of the *in vivo* ECM [282]. Among synthetic hydrogels, those based on polyethylene glycol (PEG) are particularly versatile and biocompatible, making them well-suited for use in 3D cell culture systems [283]. PEG-based hydrogels can be functionalized with a variety of functional groups, which facilitates diverse polymerization reactions for the crosslinking of hydrogels. This modification allows for the incorporation of protease-sensitive and adhesive peptides [284]. Multi-arm PEGs provide precise control over the degree of crosslinking and biofunctionalization [220, 285, 286]. Methacrylated HA hydrogels are functionalized with both methacrylate and maleimide groups. These hydrogels are crosslinked by protease-degradable oligopeptides through Michael-type reactions and subsequently UV photopolymerized to form a crosslinked network after cell encapsulation [287, 288]. Moreover, HA hydrogels enable the independent co-presentation of various adhesive motifs, including N-cadherin and arginine-glycine-aspartic acid (RGD). alginate hydrogels, upon incorporation with RGD peptides and low molecular weight PEG spacers, exhibit viscoelastic properties [289]. Interestingly, while alginate is non-degradable within mammalian cells, the substrate still permits stress relaxation and the exertion of traction forces by cells. This is due to the presence of weak, ionic crosslinks between alginate chains, which are susceptible to modification by cellular forces. Furthermore, scientists have developed a functional pH-responsive immunoregulation-assisted neural regeneration strategy that offers a delivery system mediated by microenvironment-responsive immunological regulation, providing an alternative for the treatment of acute SCI [290]. Table 2 provides a summary of hydrogel-based biomaterials and their applications in neuroengineering, specifically for the

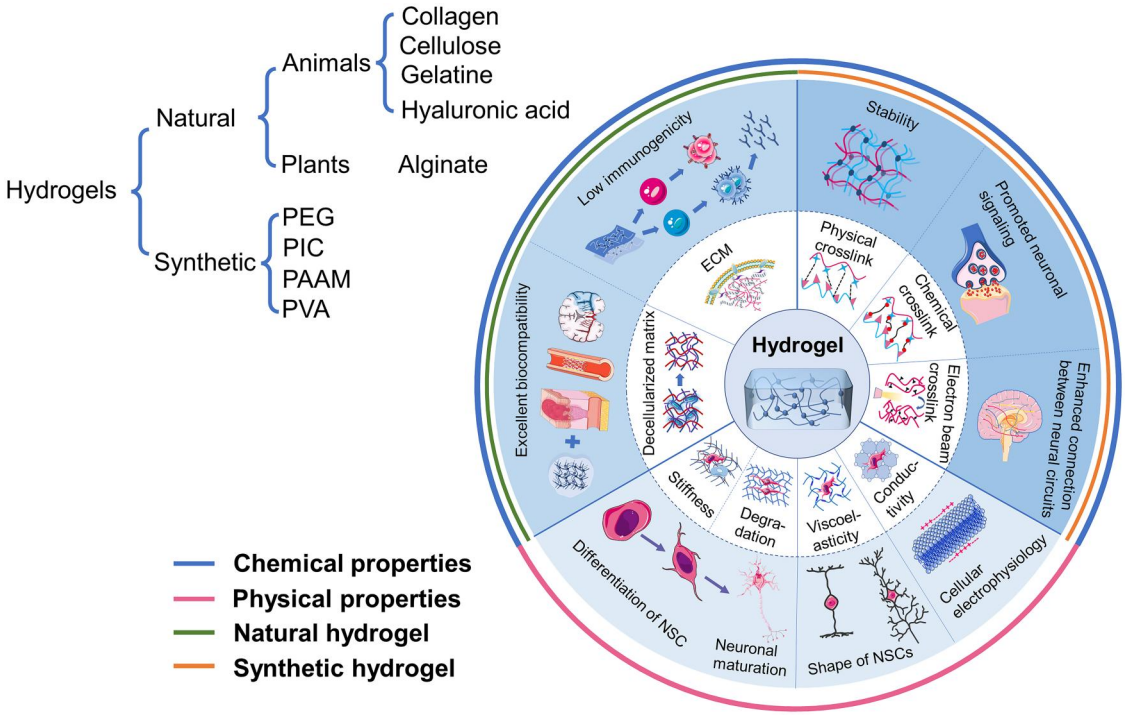

Figure 7. The classification and their properties of hydrogels. Natural hydrogels, such as collagen, chitosan, cellulose, gelatine, hyaluronic acid and alginate, are derived from biological sources and are known for their biocompatibility and biodegradability. They exhibit porosity, which is beneficial for cell infiltration and nutrient exchange, and have swelling properties that can be controlled by their chemical structure. Synthetic hydrogels, including PEG, PIC, PAA and PVA-based materials, offer customizability, controlled degradation rates and a wide range of mechanical properties. They can be engineered to be responsive to various stimuli, such as temperature, pH and light, and provide reproducibility and scalability in production. The choice between natural and synthetic hydrogels depends on the specific requirements of the application, with natural hydrogels often preferred for their biocompatibility and biodegradability, while synthetic hydrogels offer more control over their properties and can be tailored to specific needs.

cultivation of 3D neural cells and organoids in both *in vitro* and *in vivo* settings.

Others

In addition to the biomaterials previously discussed, conductive polymers, graphene, CNTs, and piezoelectric scaffolds have emerged as promising candidates for neural repair and regeneration. Their appeal lies not only in their unique physical and chemical properties but also in their biomaterial attributes, such as processing flexibility, the ability to promote neurite sprouting and outgrowth, and the potential for functionalization with chemically or biologically relevant molecules (Table 3).

Neuromorphic devices

Artificial synapse and artificial neural network

The development of a high-density parallel artificial synapse and neural network that can process large amounts of complex information while consuming minimal power in varied realistic environments is a top priority for researchers worldwide. To this end, scientists are investigating a range of biomaterials, encompassing both organic and inorganic substances, to augment the efficiency and integration of artificial synapses and neural networks [389, 390]. Due to their unique electrical, optical, mechanical, magnetic, thermal and chemical properties, nanomaterials have been extensively utilized in the development of artificial synapses and neural networks. These nanomaterials, such as nanoparticles, CNTs, nanowires, graphene and its derivatives, as well as 2D materials, have shown significant potential in the advancement of artificial synapses and neural networks (Figure 8A). Numerous studies have documented the defining characteristics of nanomaterials utilized in the construction of these systems [389–391]. These features include: (i) nanoconfinement effects for ensuring their electrical properties; (ii) the capacity to emulate biological synapse functionalities, encompassing short-term memory, long-term memory, and spike-timing-dependent plasticity (STDP); (iii) energy consumption characteristics that emulate those of biological synapses result in minimal energy expenditure; (iv) ultrathin channels that facilitate rapid heat dissipation; (v) the ability to support high-density integration, an essential factor in the development of practical and functional computation systems; and (vi) additional benefits including stability, stretchability, flexibility, biocompatibility and transparency. Taken together, these attributes are crucial for the development of advanced materials suitable for various applications, particularly in the field of bioengineering and wearable technologies. Table 4 provides a comprehensive summary of the characteristics of artificial synapses and neural networks that are based on biomaterials. It also details their synaptic behaviors, highlighting the relationship between material properties and functional performance.

Neuromorphic computing

Emerging neuromorphic sensory computing through inotropic devices has proposed a promising platform for simulating the sensing and computing functions of living organisms. This approach highlights representative concepts of both low-level and high-level sensory computing and introduces significant material and device breakthroughs [430]. In recent work, we reported on the utilization of lead-free perovskite $CsBi_3I_{10}$ as a photoactive material for the fabrication of organic synaptic transistors featuring a floating-gate structure, marking a novel approach in the field [431]. The devices are capable of sustaining an I_{light}/I_{dark} ratio

Table 2. Biomaterials with hydrogel method and their application in neuroengineering for 3D neural cell and organoid cultures *in vitro* and *in vivo*.

Biomaterials	Cell type	Applications
Natural polymer hydrogels		
Type-I collagen [291]	Embryonic rat NSCs and NPCs	Functional synapses and neural network formation in a 3D matrix
Type-I collagen/hyaluronic matrix [292–295]	Rat DRG	Promotion of axon regeneration
	Embryonic and adult mouse NSCs	Enhancement of NSCs and NPCs survival, proliferation and differentiation
	Human EnSCs	hEnSCs-derived motor neuron differentiation
	Gingiva-derived GMSCs	Promotion of development or differentiation towards NCSCs and/or SCPCs
Type-V collagen/LAM [296]	Rat sciatic nerves	Promotion of Schwann cell spreading and proliferation, as well as neurite outgrowth
Alginate [297–299]	Adult rat NSCs	First demonstration of the influence of mechanical modulus on NSC differentiation in a 3D scaffold
	Murine ESCs	Improvement of early neural differentiation
Alginate/GG/LAM [300]	Human iPSC-derived NPCs	Facilitation of cell differentiation
Chitosan [301–303]	Embryonic rat NSCs	Demonstration of the role that substrate topology plays in regulating the differentiation and proliferation of NSCs in chitosan hydrogels
	NSC-34, PC12	Promotion of cell differentiation towards a specific type of neuron
Hyaluronic acid [304–306]	Ventral midbrain-derived mouse NSCs	The distinct mechanical properties, such as stiffness and elasticity, significantly influence the differentiation of NPCs into astrocytes or neurons
	Human iPSC-NPCs	Facilitation of neurite outgrowth and spontaneous neural differentiation
Gelatin [307–312]	Human iPSC-derived neural cells	Gelatin-based hydrogel for building spinal cord organoids
	Rat primary cortical neural cells	Gelatin-based GelNB-PEGdiSH for generating compliant free-standing neural constructs
	BMSCs and NSCs	Increasing the NSCs differentiation towards neurons and oligodendrocytes
	NSCs and MSCs	Promotion of cell proliferation, migration and differentiation
	Murine BMSCs	Promotion of cellular viability, neural differentiation and neurotrophin secretion
Fibrin [313]	Adipose tissue-derived MSCs	Promotion of cell proliferation and differentiation into neurons
Synthetic polymer hydrogels		
Mixture of PEG and PLL [314–316]	Mouse postnatally isolated NSCs	Mechanical modulation of crosslinked hydrogels (PEG/PLL) that impacts NSC migration and differentiation
	Human ESCs-derived NPCs, endothelial cells, MSCs and microglia/ macrophage precursors	Neural construction with diverse neuronal and glial populations, interconnected vascular networks and ramified microglia
MoS2/GO/PVA [317]	NSCs	Promotion of NSCs into neuron differentiation and inhibition of astrocyte development with high anti-inflammatory effect *in vitro*
PVA-SA-VAPs [318]	NPCs	Facilitation of NPC differentiation into neurons, astrocytes and oligodendrocytes
PVOH-Ca [319]	Human ESCs-derived neuroepithelial organoids	Human ESC-derived neuroepithelial organoids
IKVAV-RADA16 SAPs [320]	Primary mouse NSCs	SAP 3D culture for neural tissue
	Rat NSCs	Encapsulated NSCs support and glia astrocytes formation reduction
Fmoc-SAPs [321]	Mouse cortical NPCs	Cell transplantation
SDF1-SAPs [322]	Human iPSCs	Tissue-specific hydrogels for neural repair
RADA16-RGD [323]	Human ADSCs	Promotion of spinal cord injury repair
UCMSC-bFGF-ECM-HP [324]	UCMSCs	UCMSC-bFGF-ECM-HP hydrogel for neural regeneration
PEDOT [325]	NSCs	Promotion of neuronal regeneration
CS-PANI [326]	Rat ADSCs, PC12 cells	Neural priming of ADSCs
Porcine DNM microspheres [327, 328]	Schwann cells and PC12 cells, primary NSCs and NPCs	Favorable viability and adhesive properties, cell extension promotion and proliferation enhancement

(continued)

Table 2. (continued)

Biomaterials	Cell type	Applications
Products		
Cellink Bioink ® [329]	Human iPSCs-derived NSCs	3D bioprinting for human iPSC-derived NSC differentiation
MatriGrid ®/ NeuroGrid® [330]	Primary rat cortical neurons, iPSCs	Neural cell applications
HyStem ® [331]	Human iPSCs	3D bioprinting for human iPSC differentiation

A, alanine; ADSCs, adipose mesenchymal stem cells; bFGF, basic fibroblast growth factor; BMSCs, bone marrow-derived mesenchymal stem cells; CS, chitosan; D, aspartic acid; DNM, decellularized peripheral nerve matrix; DRG, dorsal root ganglion; G, glycine; GG, gellan gum; GO, graphene oxide; ECM, extracellular matrix; EnSCs, endometrial stem cells; ESCs, embryonic stem cells; GMSCs, mesenchymal stem cells; HP, heparin-poloxamer; iPSCs, induced pluripotent stem cells; LAM, laminin; MSCs, mesenchymal stem cells; MoS_2, molybdenum sulfide; NCSCs, neural crest stem-like cells; NPCs, neural progenitor cells; NSCs, neural stem cells; PANI, polyaniline; PEDOT, poly(3,4-ethylenedioxythiophene; PEG, poly(ethylene glycol); PLL, poly(L-lysine); PVA, polyvinyl alcohol; PVOH-Ca, poly(vinyl alcohol)-calcium salt; R, arginine; RGD, arginine-glycine-aspartate; SAPs, self-assembling peptides; SCPCs, Schwann cell precursor-like cells; SDF1, stromal cell-derived factor-1; UCMSCs, umbilical cord mesenchymal stem cells.

Table 3. Other biomaterials and their application in neuroengineering for neural cell cultures *in vitro*.

Biomaterials	Cell type	Applications
Conductive polymers		
PPy (DBS) [332]	Human NSCs	Facilitating differentiation of human NSCs into neurons with long neurites and great branching
PPy-PLLA [333]	PC12	Adjusting the alignment of cellular neurites along the fiber axis or in response to electropotential gradients
CS/PPy-PLLA/PCL [334]	PC12	Promoting cell differentiation and axon outgrowth
PLLA fibers/PPy nanoparticles coated with laminin, fibronectin, collagen [335]	PC12	Enhancing neurite adhesion, alignment and elongation
PEDOT-PSS and DMSO-PEDOT-PSS [336]	NG108-15	Supporting neurite sprouting
Oligo-EDOT-PCL [337]	iNSCs	Enhancing the differentiation of NSCs into neurons by promoting neurite elongation and branching
Carbon nanotubes		
MWCNT-PEGDA [338]	NSCs	Promoting NSC proliferation and early neuronal differentiation
PU/Silk-MWCNTs [339]	S42 and PC12	Promoting neural growth, proliferation, differentiation and spontaneous neurite outgrowth
PLGA/MWCNTs [340]	PC12; DRG; Schwann cells	Supporting the cellular response of nerve cells, including cell proliferation, differentiation, neurite outgrowth and myelination by the application of electrical stimulation
PCLF-graphene-CNT-MTAC [341]	PC12	Promoting cell growth, neurite extension, proliferation
Hierarchical helical carbon nanotube fiber [342]	Artificial ligament	Bone-integrating anterior cruciate ligament replacement
Piezoelectric scaffolds		
PVDF [343, 344]	Rat spinal cord neurons	Promoting neurite growth and branching
	PC12	Inducing neuritogenesis of PC12 cells
PVDF-TrFE [345, 346]	NSCs	Promoting neuronal differentiation
	DRG	Stimulating neurite outgrowth
PVDF-TrFE/BaTiO3 [347]	SH-SY5Y	Enhancing ultrasound-mediated cellular viability, differentiation and neurite growth
PLLA [348–352]	PC12	Promoting cellular adhesion and differentiation
	SH-SY5Y	Promoting cellular viability, proliferation, glucose and lactic acid metabolism, as well as guiding neurite outgrowth
	Chick DRG and rat Schwann cells	Guiding neurite elongation and Schwann cell migration along the proper alignment of fibers
	iNSCs	Promoting cellular adhesion, growth, proliferation and guiding neurite outgrowth
GO-coated PLLA [353]	PC12 and Schwann cells	Promoting proliferation and NGF-dependent differentiation and proliferation
Graphene-based materials		
Graphene films [354]	Murine hippocampal cells	Boosting of neurite sprouting and outgrowth
Laminin-coated graphene films [355]	NSCs	Promoting biocompatibility, adhesion, proliferation and differentiation towards neurons and astrocytes
rGO PLCL microfibers [356, 357]	NSCs	Regulating the differentiation of NSCs into neurons and the subsequent formation of dense neural networks
3D-graphene foams [358, 359]	NSCs	Enhancing NSCs differentiation towards astrocytes and neurons
Laser-Scribed rGO [360]	Rat primary neurons	Promoting cellular adhesion, survival and neurite elongation

(continued)

Table 3. (continued)

Biomaterials	Cell type	Applications
Ginseng-rGO sheets [361]	NSCs	Accelerating the differentiation of NSCs into neurons
Electrospun PCL and graphene nanocomposite [362]	MSCs	Enhancing differentiation of MSCs into dopaminergic neurons
Silk/GO micro/nanofibrous scaffold [363]	NG108-15	Enhancing metabolic activity, proliferation and neurite outgrowth
FRGO and PRGO powder and film scaffold [364]	Neuron	Promoting DA differentiation and preventing cell death
Choline-functionalized Injectable GO Hydrogel [365]	Neuron	Promoting neurite outgrowth, stabilizing microtubule networks and enhancing the expression of neural markers
3D porous rGO foams scaffold [366]	Neuron	Supporting the ingrowth of myelinated vGlut2^{+} axons within rGO scaffolds
GO-PLGA hybrid nanofibers [367]	NSCs	Enhancing neuronal proliferation and differentiation *in vitro*, as well as protecting NSCs from oxidative stress
GO/Polycaprolactone nanoscaffold [368]	Neuron	Facilitating functional and morphological recovery in peripheral nerve regeneration
rGO-GelMA-PCL hybrid nanofibers [369]	Neuron	Promoting both sensory and motor nerve regeneration, as well as facilitating functional recovery in rats
rGO-coated ApF/PLCL scaffold [370]	SCs	Enhancing SCs migration, proliferation and myelination *in vitro* and promoting nerve regeneration *in vivo*
Graphene-based materials		
P(3HB)/graphene nanoplateletes composite [371]	Neuron	Promoting neuronal growth and maturation
Hydrogenated graphene [372]	Neuron	Promoting neuronal adhesion, network maturation and neuronal activity modulation
rGO-coated polycaprolactone fibrous scaffold [373]	SCs	Increasing proliferation and expression of NGF in Schwann cells
Chitosan-graphene oxide scaffold [374]	Neuron	Facilitating the recovery of neurological functions after spinal cord injuries
Silk/Gelatin scaffold [375]	Neuron	Increasing neuronal adhesion, differentiation and neurite elongation
Polyurethane-Graphene Nanocomposite [376]	Neuron	Enhancing neurovascular regeneration and peripheral nerve regeneration
Graphene collagen cryogel scaffold [377]	Neuron	Inducing neuronal differentiation, promoting immune-modulatory secretion, and enhancing cellular growth and migration in organotypic culture of the spinal cord
Graphene/silk fibroin scaffold [378]	Neuron	Promoting neurite outgrowth
Aminated GO scaffold [379]	Neuron	Inducing neurite elongation and branching in cortical neurons
Electrospun PCL/gelatin/graphene nanofibrous mats [380]	P12	Enhancing PC12 cells attachment and proliferation
N-cadherin-graphene oxide-based scaffold [381]	Neuron	Stimulating neuronal growth and intracellular transport processes
GNPs and MWCNTs and chitosan scaffold [382]	Neuron	Promoting differential neural cell adhesion and neurite outgrowth
3D-Printed PCL/rGO Conductive Scaffold [383]	Neuron	Inducing neural differentiation
Collagen-coated 3D graphene foam [384]	MSCs	Facilitating differentiation into DA neurons from MSC
rGOaCNTpega-OPF-MTAC composite hydrogel [385]	P12 cells	Enhancing proliferation and spreading of PC12 cells, as well as stimulating neurite development
GOa-CNTpega-OPF hydrogel [386]	Neuron	Increasing electrical conductivity and stimulating neurite development
GO and rGO mat [387]	ADSCs	Promoting neurogenic differentiation
Graphene-Polyacrylamide Hydrogel [388]	Neuron	Facilitating the development of synaptic activity

ADSCs, adipose derived stem cells; $BaTiO_3$, barium titante; Cs, chitosan; DA, dopamine; DMSO, dimethyl sulfoxide; DBS, dodecylbenzenesulfonate; DRG, dorsal root ganglion; EDOT, oligomers of 4-ethylenedioxythiophene; FRGO, full reduced graphene oxide; GNPs, graphene nanoplatelets; iNSCs, induced pluripotent stem cell-derived neural stem cells; MTAC, [2-(methacryloyloxy)ethyl]trimethylammonium chloride; MSCs, mesenchymal stem cells; MWCNT, multiwalled carbon nanotubes; NG108-15, analogue neuronal cells; NGF, nerve growth factor; NSCs, neural stem cells; OPF, oligo(polyethylene glycol fumarate); PC12, neuron-like rat phaeochromocytoma cells; PCL, poly(caprolactone); PCLF, poly(caprolactone fumarate); PEDOT, poly(3,4-ethylenedioxythiophene); PEGDA, poly(ethylene glycol) diacrylate; P(3HB), poly(3-hydroxybutyrate); PLCL, poly (l-lactic acid-co-caprolactone); PLGA, rPoly(lactic-co-glycolic acid); PLLA, poly-L-lactic acid; PPy, polypyrrole; PRGO, partially reduced graphene oxide; PVDF, polyvinylidene fluoride; PVDF-TrFE, polyvinylidene fluoride trifluoroethylene; PSS, polystyrenesulfonate; PU, polyurethane; rGO, reduced graphene oxide; s42, Schwann cells line; SCs, Schwann cells; SY-SY5Y, neuroblastoma cell line.

of 10^3 for 4 h and exhibit excellent stability over a 30-day test period, even in the absence of encapsulation. Synaptic functions have been successfully emulated. Notably, the combination of the organic semiconductor's favorable charge transport characteristics and the exceptional photoelectronic properties of $CsBi_3I_{10}$ enables the realization of synaptic performance at operating voltages as low as −0.01 V, a feature that is uncommon among floating-gate synaptic transistors (Figure 8B). Furthermore, we have constructed artificial neural networks. We propose a novel method capable of simulating synaptic weight values in a multi-digit format, thereby facilitating complete gradient descent. This approach has been demonstrated through

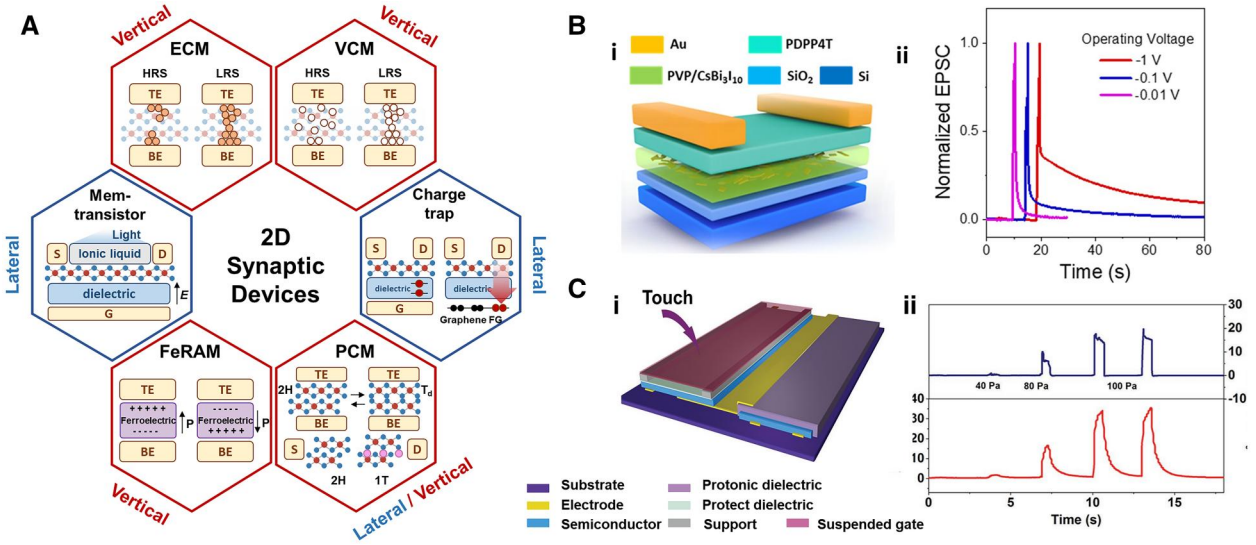

Figure 8. Schematic diagram of artificial synapses. (**A**) Types of 2D materials-based synaptic devices. Reproduced from Ref. [390] with permission of John Wiley and Sons, © 2021. (**B**) (i) Schematic of the CsBi3I10-based organic synaptic transistor. (ii) EPSC triggered by an optical pulse at different VDS varied from −0.01 to −1 V. Reproduced from Ref. [431] with permission of American Chemical Society, © 2021. (**C**) (i) Schematic diagram of dual-organic-transistor-based tactile-perception element (DOT-TPE). (ii) The relative changes in current for pressure-sensitive transistors under varying pressure conditions, as well as the corresponding postsynaptic current responses of the synaptic transistors, were investigated. Reproduced from Ref. [432] with permission of Whiley-VCH, © 2017.

image recognition tests, which exhibit impressive recognition accuracy rates of 91% for supervised learning and 81% for unsupervised learning classifications. These results demonstrate the significant potential of floating-gate organic synaptic transistors in the realm of neuromorphic computing. Additionally, we have developed light-stimulated synaptic transistors utilizing natural carotene in conjunction with organic semiconductors [432]. In this synaptic transistor, we have successfully realized several functions that closely resemble those of biological synapses, and we have achieved an ultra-low power consumption of 3.4×10^{-18} J (Figure 8C).

Human–computer interaction

Despite of neural repair and regeneration, neural modulation and manipulation are other therapeutic strategies for neurological injuries and diseases. Biomimetic electrodes, peripheral nerve interfaces and brain–computer interfaces are the cutting-edge frontiers in this framework [433, 434]. Advancements in biomaterials-based neural electrodes and interfaces have led to the development of unique materials with tailored chemistry, shape, size and texture. These features enhance electrical and mechanical properties, as well as biocompatibility, resulting in improved electrode longevity and performance [435]. A variety of biomaterials have been utilized in the construction of electrode and interface substrates. Initially, microwires and glass micropipette electrodes were employed to target specific brain regions. However, neural prosthetic devices have since evolved to encompass silicon shafts and more intricate micromachined silicon and polyimide flexible recording systems. These advanced systems enable the monitoring of neuronal networks with improved temporal and spatial resolution [436, 437]. Figure 9 shows the application and their characteristics of brain–computer interfaces. Table 5 summarizes the biomaterials that have been utilized for neural electrodes and interfaces.

Biocompatible materials

The first generation of neural electrodes primarily comprises microwires fabricated from conductive metal wires, including stainless steel, platinum, gold, iridium and tungsten. However, the inherent limitations of microwire electrodes have limited their clinical applicability. Transcutaneous wire connections pose an increased risk of surgical complications. Additionally, the forces and movements associated with tethered electrodes can introduce bias in recording, and the microwires are susceptible to bending during the implantation process. Therefore, micro-electromechanical systems (MEMS) electrodes, which can be crafted into intricate structures through microfabrication techniques, have been introduced as the next generation of neural electrodes. Silicon MEMS-based arrays, exemplified by the Michigan electrode and the Utah array, have transcended the technical limitations associated with microwire electrodes. These arrays offer significant advantages, including an increased number of recording sites, expanded recording layers, and the capability for long-term recording, all within a relatively compact form factor (Figure 10A) [435, 467, 468]. Furthermore, these arrays address the challenges arising from the mechanical mismatch between the rigid, planar nature of silicon electrodes and the compliant, curved surfaces of brain tissues [435]. However, the potential for these arrays to induce local inflammation has garnered significant attention, particularly as their successful application in neural recording and stimulation has become more widespread.

Intelligent materials

Novel neural prosthetic devices, such as neural interfaces with minimal chronic tissue inflammation, have been developed not only for neural recording but also for neural stimulation and manipulation. In the pursuit of enhancing electrode-tissue interactions and minimizing chronic immunological responses, various biomaterial-based strategies have been employed to modulate

Table 4. The biomaterials-based characteristics of artificial synapses and neural network and their synaptic behaviors.

Catalog	Active biomaterials	Ion/dielectric biomaterials	Synaptic behaviors
Nanoparticle	Pentacene embedded with Au nanoparticles	SiO_2	PPF, STP, STD, LTP, LTD and STDP [392–395]
	Self-assembled IZO	P-doped nanogranular SiO_2 films	PPF (∼180%) and STP [396–398]
	Nanoscale Ag particles in Si medium	NA	STDP [399]
CNT	Single-wall carbon nanotube	PEG	PPF (120%) and STDP [400]
	Single-wall p-type carbon nanotube	In-doped Al_2O_3	PPF (141%) [401]
	Single-wall p- and n-type carbon nanotube	Al_2O_3	LTP and LTD [402]
	Single-wall carbon nanotube	SiO_2	LTP, LTD and STDP [403]
		Poly (pyromellitic dianhydride-co-4,4′-oxydianiline)	PPF (304%) and STP [404]
Nanowire	TiO_x	NA	LTP, LTD and STDP [405]
	TiO_2	NA	STP, LTP and STDP [406]
	Sb-doped SnO_2	PEO/$LiClO_4$	PPF (430%) and STP [407]
		Chitosan	PPF (380%) and STP [408]
	P3HT	PS-PMMA-PS	PPF (162%), STP, STD, LTP, LTD and STDP [409]
Graphene	Twisted bilayer graphene	AlO_x	STP, STD, LTP, LTD and STDP [410, 411]
	Graphene oxide	SiO_2	STP and LTD [412]
	IZO	KH550-GO	PPF (266%), STP, LTP and LTD [413]
2D material	Exfoliated 2D multilayer MoS_2 flakes	PVA	PPF (367%) and STP [414]
	Exfoliated MoS_2 flakes	SiO_2	STP, STD and LTP [415]
	Polycrystalline CVD-grown mono-layer MoS_2	SiO_2	LTP, LTD and STDP [416]
	Exfoliated quasi-2D α-MoO_3	EMIM-TFSI	PPF (∼114%), STP, STD, LTP and LTD [417]
	Black phosphorus	POx	LTP, LTD and STDP [418]
	Exfoliated 2D perovskite single crystals	NA	PPF (∼150%), STP, STD and LTP [419, 420]
	Vertical MoS_2 double-layer memristor	Cu/Au	STDP [421]
	2D monolayer MoS_2 atomic sheets	Au/Au	Memristive switching [422]
	2D WS_2 nanosheet-based memristor	Pd/Pt	PPF and STDP [423]
	MoS_2	hBN/Au	LTP and STDP [424, 425]
		Li	LTP [426]
	Vertical 2H-$MoTe_2$- and $Mo_{1-x}WxTe_2$	$Al_2O_3/MoTe_2$	Memristive switching [427]
	2D-SnSe film	Au/NSTO	PPF, LTP, STP and STDP [428]
	MoS_2/PTCDA	NA	PPF, LTP, STP and SRDP [429]

ACM, astrocytic conditioned medium; b.End3, brain-derived endothelial cells.3; BMECs, brain microvascular endothelium cells; BV2, mouse microglia cell lines; C6, glioma cell lines; C8D1A, marine cerebellar microglia cell lines; CTX-TNA2, rat astrocyte cell lines; E, embryonic; EM-HCC, hippocampal cells derived from embryonic mice; ER-HCC, hippocampal cells from embryonic rat; hAst, human astrocyte; hBPC; human brain pericyte cell; hBMECs, human brain microvascular endothelium cells; hCMEC-D3, human cerebral microvascular endothelial cells, D3; hDRGNs, human dorsal root ganglion neurons; hECNs, cortical neurons from human embryos; hESCs, human embryonic stem cells; hNSC, human neuroepithelial stem cell; hUVECs, human umbilical vein endothelial cells; IP-DiLL, IP-Dip-in laser lithography; iPSCs, induced pluripotent stem cells; LED, light emitting diode; mECNs, cortical neurons from mouse embryos; mESCs, marine embryonic stem cells; N9, marine microglia cell lines; NA, not available; NPCs, neural progenitor cells; NSCs, neural stem cells; OPCs, oligodendrocyte precursor cells; P, postnatal; PD, Parkinson's disease; PDMS, polydimethylsiloxane; RBE4, rat brain vascular endothelium cell lines; rDRGNs, rat dorsal root ganglion neurons; rECN, cortical neurons from rat embryos; ReNcell VM, human neural progenitor cell lines; TEER, trans epithellal electric resistance; Th1; T helper 1 cell; TY10, human brain microvascular endothelium cell lines; U87, human glioma cell lines.

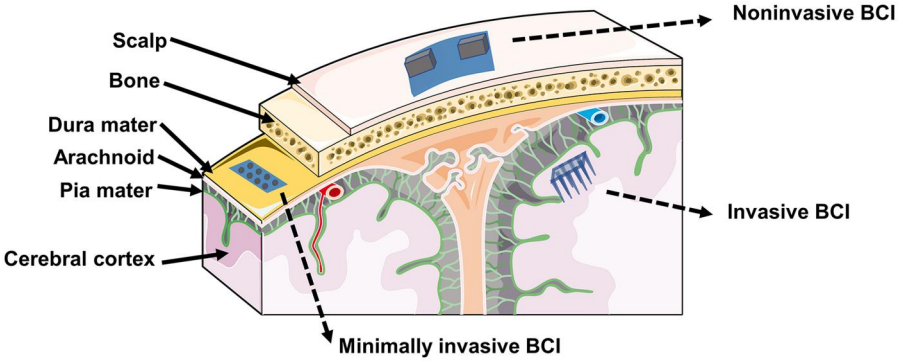

Figure 9. The application and their characteristics of brain–computer interfaces. Brain–computer interfaces (BCIs) can be divided into three main categories: (1) Noninvasive BCI: This type can decode scalp EEG signals. However, it suffers from fast signal attenuation and difficulty in signal extraction. (2) Minimally Invasive BCI: This type decodes cortical surface EEG signals, which have a higher signal-to-noise ratio. (3) Invasive BCI: This type decodes intracortical EEG signals, offering advantages such as fast conduction and strong signals, but it carries a risk of infection.

Table 5. The biomaterials for neural electrodes (arrays) and interfaces and their applications.

Type of composite biomaterial	Examples	Applications
Neural electrodes (arrays)		
Single microwire [435, 438]	Glass or polyimide insulated microwires	Improving neural recording duration
Microwire array [439, 440]	S-isonel- or Teflo)-coated tungsten or stainless steel	Improving neural recording duration with 3D array
Single nanowire FET [441]	Quartz/Silicon	Neural circuits mapping in acute brain slices
Vertical nanowire array [442, 443]	Silicon-on-insulator	Intracellular interfacing to neuronal circuits
Michigan electrode [444–447]	Silicon w/silicon dioxide/nitride	Chronic neural recording
Utah array [448]	Silicon coating materials: Parylene-C	Long-term stimulation and recording
Other Silicon microelectrode array [449, 450]	Silicon-on-insulator wafer, polyimide	Encouraging favorable long-term biocompatibility reactions at the tissue-electrode interface
Flexible array [451, 452]	Polyimide-platinum-polyimide, silk-supported PI array, silk array	Acute and chronic neural recordings *in vivo*
RGD nanoarrays [453]	RGD peptides on the PEG on the glass background	Designing cell-selective nanomaterials potentially used in cell screening
Neural interfaces		
IPNs of hydrogel [454]	PVA/PAA	Improving the electrode-tissue interface
Hydrogel/CP [455, 456]	Alginate/PEDOT, alginate/Ppy, PVA-(Hep-MA)/PEDOT and chitosan/Ppy	Acute neural recording
Hydrogel/CNT [457, 458]	PEGDA/SWCNT and agarose/ CNT	Chronically implantable neural electrodes and long-term neural recording devices
CP/CNT [459–462]	PEDOT/MWCNT, Ppy/ SWCNT, Ppy/MWCNT, MWCNTs/PEDOT:PSS	Neural recording with improving microelectrode stabilities
CNT/Non-conducting polymer [463, 464]	MWCNT/PVA, SWCNT/ laminin	Minimizing the immune response to neural electrodes
Graphene/CP [460, 465]	Graphene oxide /Ppy, graphene oxide/PEDOT	Biosensing and neural interfacing
Graphene/hydrogel [466]	Graphene/PDMAA	Neural tissues

CP, conducting polymers; CNT, carbon nanotubes; ECoG, electrocorticogram; FET, field-effect transistor; Hep-MA, heparin methacrylate; IPNs, interpenetrating polymer networks; MWCNT, multiwalled carbon nanotubes; NA, not available; PAA; poly(acrylic acid); PDMAA, poly(N,N-dimethylacrylamide); PDMS, polydimethylsiloxane; PEDGA, poly(ethylene glycol) diacrylate; PEDOT, poly(3,4-ethylenedioxythiophene); PEG, poly(ethylene glycol); PI, polyimide; Ppy, polypyrrole; PSS, poly(styrene sulfonate); PVA, poly(vinyl alcohol); RGD, arginine-glycine-aspartate; SWCNT, single-walled carbon nanotubes.

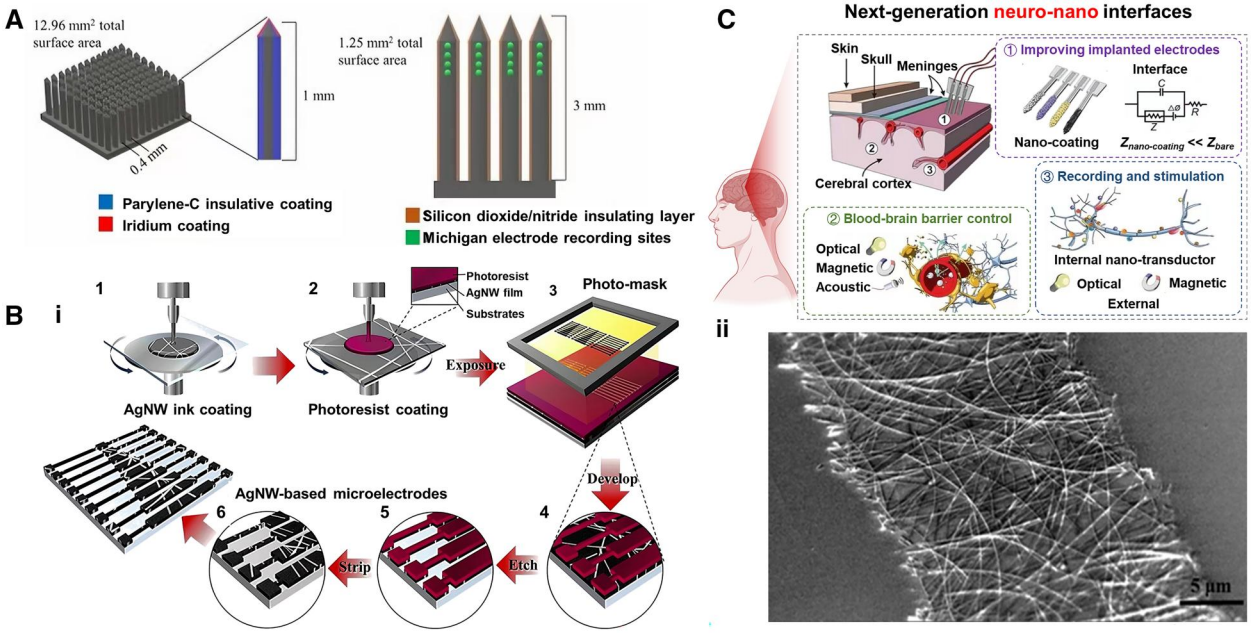

Figure 10. Schematic diagram of nerve electrodes. (**A**) Schematic detailing the Utah MEA configuration and schematic detailing the Michigan MEA configuration. Reproduced from Ref. [468] with permission of Wiley-VCH, © 2019. (**B**) (i) Schematic illustration for fabrication of silver nanowire (AgNW)-based microelectrodes using a photolithographic process. (ii) SEM images of silver nanowire-based microelectrodes. Reproduced from Ref. [479] with permission of American Chemical Society, © 2014. (**C**) The next-generation neuro-nano interfaces. Reproduced from Ref. [471] with permission of John Wiley and Sons, © 2017.

Table 6. The advantages of electroactive nanomaterials in neural interfaces.

Nanomaterials	Advantages	Representatives
Conducting polymers	(i) Entrap and release drugs and biomolecules; (ii) be functionalized with bioactive molecules and proteins; (iii) be able to transfer the electrical charge from ions in living tissue to electrons in an electrode; (iv) alter the electrical, chemical and physical properties of the surface to mediate the cellular response.	Ppy, PANI, PT and PEDOT [480, 481]
Carbon nanotubes	(i) High electrochemically accessible surface area, ranging from 700 to1000 m^2/g; (ii) high mechanical strength, with an elastic modulus of approximately 0.64 TPa for an individual nanotube; (iii) excellent thermal conductivity, with individual MWNT exceeding 3000 W/m·K; (iv) high electronic currents, up to 109 A/cm^2.	SWCNTs and MWCNTs [482–484]
Graphene	(i) High mechanical strength and chemical stability; (ii) high elastic modulus, approximately 1.0 TPa; (iii) remarkable thermal conductivity, approximately 3000 W/m·K; (iv) high electron mobility, approximately 200 000 $cm^2/V·s$; (v) excellent electrical conductivity, with a specific value to be provided; (vi) low resistivity, approximately 10^{-6} Ω as a substrate at room temperature; (vii) optical transparency, stable crystalline structure and a well-defined energy band structure.	Graphene [485–490]
Silicon nanowires	(i) Improved sensitivity; (ii) outstanding spatial resolution and SNR due to their high surface-to-volume ratio; (iii) smaller neuron-nanowires electrode distance, typically less than 50 nm.	2D and 3D NWFETs [441, 491–493]
Hybrid nanomaterials	(i) Reduced mechanical mismatch at the neural tissue interface; (ii) increased stability and biocompatibility; (iii) maintaining the functionality of the electrode.	Hydrogel [494, 495]

MWCNTs, multiwalled nanotubes; NWFETs, nanowire field-effect transistors; PANI, poly(aniline); PEDOT, poly(3,4-ethylenedioxythiophene); Ppy, poly(pyrrole); PT, poly(thiophene); SNR, signal-to-noise ratio; SWCNTs, single-walled nanotubes.

the immune response at both molecular and cellular levels [469]. To achieve better integration and modulate the chronic inflammatory response, modifying the physical, chemical and biological properties of the neural probe surface has been the primary strategy in this context [470–472] (Figure 10B). The biomaterials-based surface modifications of neural interfaces include both biological (e.g. coating with peptides, HA and growth factors) and non-biological modifications (e.g. conducting polymers, hydrogels and CNTs) [10, 231, 468, 473–478]. The application of neural electrodes and interfaces for recording, stimulating and manipulating neural activity still faces several challenges in both *in vitro* and *in vivo* settings. First and foremost, there is a necessity to design and develop novel biomaterials that can form seamless neural interfaces, characterized by a high degree of sensitivity. Second, there is a requirement for a high degree of electrode sensitivity, particularly for the detection of single-unit action potentials, which typically exhibit signal amplitudes in the microvolt range. Third, long-term stability is imperative. The primary obstacles in this field include achieving biocompatibility to prevent immune responses, ensuring the durability of the electrode-tissue interface over time and maintaining the fidelity of neural signals despite tissue encapsulation and electrode corrosion. Fourth, the development of innovative biocompatible biomaterials that emulate the characteristics of neural tissue is crucial for minimizing inflammation and ensuring long-term functionality. To address these challenges, researchers are exploring the preparation of electroactive nanomaterials, such as silicon nanowires and CNTs, as well as the integration of conductive polymer nanostructures within neural interfaces (Figure 10C). Innovative biomaterials of this nature may facilitate a significant advancement in the realms of neural recording, stimulation and manipulation. Table 6 summarizes the advantages of electroactive nanomaterials in neural interfaces.

BBB and sustained release drugs

TCM has gained significant attention for its potential in preventing and treating neurological diseases and injuries, particularly through the use of herbs or herbal extracts, acupuncture and catgut embedding. Nanomedicines are drug nanoparticles obtained by nanoscale processing of the active ingredients or active substances of herbal medicines. Nanomedicine carriers primarily encompass lipid-based nanoparticles such as liposomes, polymeric NPs, inorganic NPs and natural carrier NPs. The application of biomaterials in acupuncture aims to extract both biochemical and physical signals. For instance, the integration of materials like gold nanoparticles, graphene and CNTs into acupuncture needles enables the monitoring of neurotransmitter levels in the body. Specifically, these enhanced needles can detect dopamine, NO and 5-HT. Furthermore, the integration of nanoscale six-axis force sensors with acupuncture needles allows for precise measurement of the pressure and twist angle during needle insertion. This advancement facilitates more accurate and controlled acupuncture treatments. In addition to these developments, innovative therapies have emerged. For example, the incorporation of silver nanowires in acupoint catgut embedding therapy has been shown to mitigate inflammatory responses and enhance local drug delivery. Similarly, the application of bee venom-loaded nanoliposomes in acupoint injections has demonstrated the potential in reducing allergic reactions and minimizing toxic side effects (Figure 11).

A variety of herbs, herbal extracts, formulas, and decoctions have shown beneficial neuroprotective effects, improving neural function in various neurological injuries and diseases (Table 7). The neuroprotective mechanisms of these herbal compounds are diverse, often involving antioxidant and anti-inflammatory activities that protect neurons from oxidative damage and inflammation, which are key factors in the pathogenesis of neurodegenerative diseases. These natural treatments offer a promising avenue for the development of novel therapeutic strategies in neurorehabilitation and the prevention and treatment of neurodegenerative diseases. However, the application of TCM is significantly hindered by several factors, including complex formulations, single administration methods, poor water solubility, low bioavailability, and limited targeting capability. Recently,

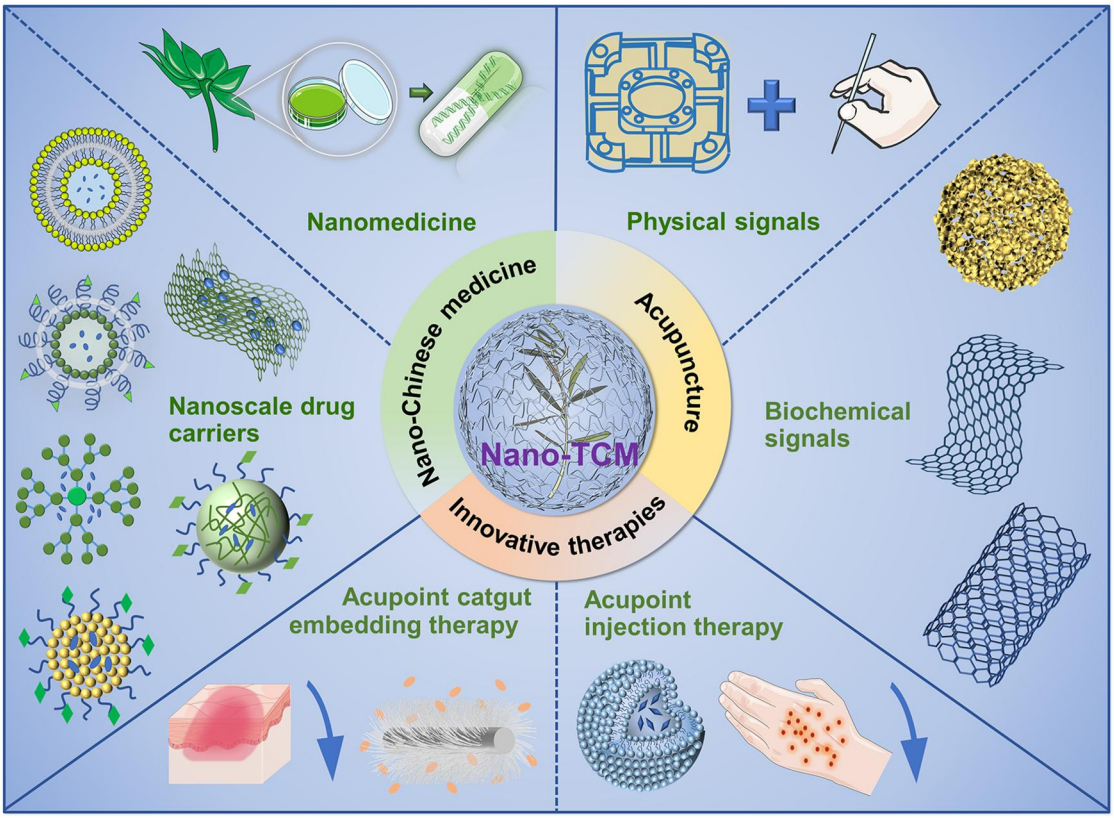

Figure 11. The clinical application of nano-TCM. The clinical application of nano-TCM involves the integration of nanotechnology with TCM to enhance the therapeutic potential of TCM components. This includes using nanoparticles for targeted and controlled drug delivery, which can improve the bioavailability, solubility and stability of TCM extracts. Nanomedicine can also increase the absorption of medicinal components by altering their size and surface properties, leading to enhanced efficacy and reduced toxicity. Nano-acupoint applies extremely fine needles made from nanomaterials that can be used for acupoint stimulation. These nanoneedles can potentially penetrate the skin with less pain and with higher precision than conventional needles. Moreover, equipped with nanosensors, these needles can detect subtle changes in the skin's electrical properties, temperature or the release of biochemical markers. This capability enables real-time monitoring of the body's response to acupoint stimulation, providing valuable feedback that can guide the treatment process.

biomaterials have increasingly been utilized in the field of neurorehabilitation and the treatment of neurodegenerative diseases to address pharmaceutical challenges, owing to their ability to mimic the ECM for cell growth and tissue regeneration, scaffolding for cell and drug delivery, excellent biodegradability, tailored stiffness and the potential for sustained-release effects [496–505]. These advantages may shift the limited modern medicine view on TCM application in clinical practice. Therefore, a new concept of nano-TCM has been proposed that involves low-dimensional materials, bioactive ingredients, bioactive parts, medicinal biomaterials or complex prescriptions smaller than ca. 100 nm in at least one dimension [251]. Persistent efforts have been dedicated to enhancing the physical, chemical and biological properties and characteristics of natural TCM, which exhibits neuroprotective, anti-inflammatory, and anti-oxidative effects. For instance, a previous study formulated *panax notoginseng saponin* into a hydrophobic dispersion with slow-release properties. Subsequently, *panax notoginseng saponin* was enclosed within *bletilla striata* polysaccharide/alginate microspheres to improve the encapsulation rate [506]. In another study, a thermosensitive hydrogel based on chitosan and gelatin was utilized as a delivery vehicle for *ferulic acid*. This hydrogel, characterized by its porous structure, was designed to facilitate a sustained release of *ferulic acid* (Figure 10A) [507]. Additionally, a composite of electrospun nanofibers, consisting of polycaprolactone and collagen hydrolysate, was developed and loaded with *ferulic acid*. This composite was designed to facilitate a continuous release of *ferulic acid* and to promote cellular proliferation and favorable morphology [508]. Furthermore, the investigation of an HA-decorated chitosan nanoparticle, loaded with *ferulic acid* and aerosolized, was conducted as a strategic combination of drug, nanocarrier, and delivery device for effective control of chronic inflammation [509]. Various strategies have been devised to enhance the release and delivery of *ferulic acid*, utilizing nanocomposite platforms that include nanogels and micelles [510], 3D hybrid scaffold [511], modified water soluble chitosan and poly (γ-glutamic acid) polyelectrolyte multilayers films [512], thermosensitive gelatin/chitosan/glycerol phosphate hydrogel [513], and chitosan-coated poly(ε-caprolactone) electrospun biomaterials [514]. Similarly, several approaches, such as chitosan microspheres, 3D printed alginate-cellulose nanofibers, guanidine-chitosan thermo-sensitive hydrogel, pH-responsive HA-, PLGA-, silica-, graphene-based nanoparticles and chitosan/hydroxyapatite cement, as well as gelatin nano-fiber and silk fibroin scaffolds, were applied to improve biocompatibility, drug delivery and sustainable release for *curcumin* [515–529], *puerarin* [530–536], *matrine* [537, 538], *ampelopsin A* [539], *tanshinone IIA* [540–546], *salvianolic acid B* [547–549], *astragaloside IV* [550, 551], *magnolol* [552–555], *scutellarin* [556–558], *honokiol* [559–566], *borneol* [567–573], *paeonol* [574, 575], *tetramethylpyrazine* [576, 577], *artesunate* [578–584], *byakangelicol* [585] and *berberine* [586, 587].

Table 7. The catalog of neuroprotective effects in TCM.

Catalog	Neurological diseases or animal model	Applications
Herbs		
Acanthopanax polysaccharides [588]	CIRI model in rat	Enhancing the antioxidant capacity of brain tissue and suppressing the overproduction of inflammatory cytokines
Ilex pubescens [589–592]	FCI/R and MCAO/R model in rats and mice	Enhancing cerebral ischemic tolerance and presenting neuroprotective effect
Carthamus tinctorius L. [593, 594]	MCAO model in rat	Regulating neural apoptosis and MMPs
Dracocephalum moldavica L. [595]	MCAO model in rat	Presenting anti-oxidation and anti-inflammation
Kudiezi injection [596]	ACI in patient	Inhibiting pro-interleukin production and promoting anti-inflammation
Gastrodia [597, 598]	MCAO and MCAO/R model in rat	Modulating the antioxidant system and antiapoptotic genes and protecting the permeability of BBB
Sophora japonica [599]	Symptomatic hemorrhoids in patients	Improving symptoms and decreasing the incidence of important clinical events
Ganoderma lucidum [600, 601]	LPS-induced BV2 cells	Presenting anti-neuroinflammatory activities
	MCAO/R model in rat	Presenting anti-oxidative and anti-inflammatory effect
Panax notoginseng [602]	Neonatal HI model in rat	Reducing neuronal damage, suppressing neuronal apoptosis and inhibiting astroglial reactive response
Rabdosia rubescens [603, 604]	MCAO model in rats and BIT model in mice	Stimulating endogenous protective mechanisms and alleviating injury to nerve cells in the hippocampus and cortex of the brain
Rhizoma pinelliae pedatisectae [605]	MCAO model in rat	Alleviating oxidative neuronal injury, inflammatory responses and neuronal apoptosis
Herbal extracts		
Ferulic acid [606]	OBI model in rat	Presenting the anti-oxidative and protective effects
Cholalic acid/Hyodeoxycholalic acid [607, 608]	OGD model *in vitro*	Protecting NVU morphological integrity and function *in vitro*
	LPS-treated mice	Preventing LPS-induced microglial inflammation
Curcumin [609]	OGD PC12 model *in vitro*	Increasing cell viability and presenting an antiapoptotic effect *in vitro*
Schisandrin A and B [610]	Adult mice	Enhancing adult DG neurogenesis and improving the survival and maturation of DG neurons
Puerarin [611]	SAH model in mice	Attenuating neurological deficits and reducing BBB disruption
Matrine [612]	AD model in mice	Inhibiting microglial activation and NADPH oxidase expression
Ampelopsin A [613]	SID model in mice	Enhancing neurocognitive and neuroprotective effects on intrinsic neuronal excitability and associated behaviors
Icariside II [614, 615]	Human AMSCs	Inducing hAMSCs to differentiate into dopaminergic neuron-like cells
	LPS-treated mice	Attenuating LPS-induced neuroinflammation
Tanshinone IIA [616]	LPS-treated U87 cells	Attenuating LPS-induced neurotoxicity and neuroinflammation
Salvianolic acid B [617]	MCAO model in rat	Presenting neural protective effects
Astragaloside IV [618]	LPS/MPP and PD model in mice	Preventing dopaminergic neurodegeneration and inhibiting astrocyte senescence
Salvianolic acid B and puerarin [619]	MCAO model in rat	Improving neurological function and anti-oxidation
Magnolol [620]	AD model in mice	Improving cognitive deficits, suppressing neuroinflammation, amyloid pathology and synaptic dysfunction
Scutellarin [621]	MCAO model in rat	Decreasing oxidative damage and reducing apoptotic cell death
Honokiol [622]	CRS model in mice	Inhibiting proinflammatory cytokines and endoplasmic reticulum stress
Borneol [623]	MCAO model in rat	Presenting long-term improvement of sensorimotor functions by reducing loss of dendritic spines

(continued)

Table 7. (continued)

Catalog	Neurological diseases or animal model	Applications
Paeonol [624]	Diabetic rats	Preventing neuronal damage, lowering demyelination and leukocyte infiltration
Brazilein [625]	SNI model in mice	Inhibiting the excessive expression of free radicals and promoting myelin regeneration
Tetramethylpyrazine [626]	AD model in mice	Alleviating neuronal apoptosis and injury
MLC901 [627]	VCIND patients	Benefiting the existing impairment in executive function
MLC601 [628]	TBI patients	Improving the clinical neuro-outcome
β-Asaron [629]	MCAO model in rat	Ameliorating brain damage
Artesunate [630]	CIRI model in mice	Suppressing oxidative and inflammatory processes
Rhizoma drynariae [631]	Scopolamine-induced learning and memory impairments in mice	Regulating the neuronal apoptotic system and oxidative stress
Formula and decoction		
Modeifed Shengyu decoction [632]	TBI model in rat	Reducing the expression of inflammatory cytokines and inhibiting the activation of microglial cells and astrocytes
Shaoyao-Gancao decoction [633]	CIRI model in rat	Ameliorating brain damage
Danshen-Chuanxiong-Honghua [634]	MCAO model in rat	Reversing cognitive impairment and providing neuroprotection by inhibiting microenvironmental inflammation and promoting neurogenesis in the hippocampus
Xueshuantong [635]	AD mice	Enhancing the neuro-functions
Huangjiao granules [636]	CIRI model in rat	Reducing the degree of neurological deficits
Weinaokang [637]	BCCAO model in mice	Inhibiting nitrative injury and modulated the ultrastructure of CMECs
Gueichih-Fuling-Wan [638]	CIRI model in rat	Inhibiting cellular apoptosis and neuroinflammation
Herbal formula FBD [639]	CIRI model in mice	Limiting PMNs infiltration and neurotoxicity
Naoxintong [640]	OGD/R EA.hy926 cells *in vitro*	Preventing the formation of thrombosis and reducing inflammation
Tao-Hong-Si-Wu-Tang [641]	MCAO model in rat	Inhibiting inflammatory responses, preventing the formation of apoptosis and suppressing platelet activation
Dengzhan Shengmai capsules [642]	AD model in mice	Protecting against cognitive defects, inhibiting the acceleration of Aβ aggregation into fibrils or protofibrils and reducing the levels of soluble Aβ oligomers
Yokukansan [643]	CIRI model in rat	Presenting anti-inflammatory protective effect
Danggui-Shaoyao-San [644, 645]	AD model in mice	Ameliorating the amyloidosis and neuronal degeneration
	CFA model in mice	Enhancing descending pain inhibition and reducing peripheral long-term inflammation
Refined Qingkailing Injection [646]	MCAO model in rat	Protecting brain tissue and BBB against ischemic stroke
Baimai san [647]	Diabetic rats	Protecting the peripheral neuron

ACI, acute cerebral infarction; AD, Alzheimer's disease; AMSCs, amniotic mesenchymal stem cells; BBB, blood–brain barrier; BCCAO, bilateral common carotid artery occlusion; BIT, brain ischemic tolerance; CMECs, cortical microvascular endothelial cells; CRS, chronic restraint stress; CIRI, cerebral ischemia/reperfusion injury; DG, dentate gyrus; EA.hy926, human vein umbilical endothelial cells; FCI/R, focal cerebral ischemia/reperfusion; HI, hypoxic-ischemic; LPS, lipopolysaccharide; MCAO/R, middle cerebral artery occlusion/reperfusion; MMPs, matrix metalloproteinases; MPP, 1-methyl-4-phenylpyridinium; NVU, neurovascular unit; OBI, oxidative brain injury; OGD, oxygen-glucose deprivation; OGD/R, oxygen-glucose deprivation-peoxygenation; PC12, neuron-like rat phaeochromocytoma cells; PD, Parkinson's disease; PMNs, polymorphonuclear leukocytes; SAH, subarachnoid hemorrhage; SID, scopolamine-induced dementia; SNI, sciatic nerve injury; TBI, traumatic brain injury; TCM, traditional Chinese medicine; U87, human astrocytoma cells; VCIND, vascular cognitive impairment no dementia.

Challenges and future perspectives

Biomaterials architectures with sub-nanoscale precision

The intricate complexity of the CNS has posed a remarkable challenge for researchers for decades. Nevertheless, the extraordinary advances in biomaterials and nanotechnology offer new insights, tools, and products to better probe the CNS, comprehend its functioning, and cure neurological injuries and diseases. The small size of nanomaterials, typically less than 1 μm, facilitates their delivery throughout the body and into cells by enabling them to cross the plasma membrane. While different neural cells, such as neurons, microglia, astrocytes and oligodendrocytes, exhibit varying lipid and protein compositions in their plasma membranes, nanomaterials are internalized in a size-dependent manner. This internalization occurs via endocytosis pathways, including clathrinid-mediated endocytosis, caveolae-mediated endocytosis and phagocytosis. The surface chemistry of nanomaterials significantly influences their effectiveness, as it can be tailored to selectively bind to biomolecules present on the cell membrane. This selectivity is crucial for targeting either

normal or diseased brain tissue or CSF. Thus, it is feasible to selectively and efficiently deliver circulating nanomaterials to specific targets by conjugating cell-specific targeting ligands or antibodies to their surfaces. Concurrently, the surface of nanomaterials can be chemically modified, for instance, through PEGylation, to enhance their circulation time within the body and to avoid rapid clearance by the liver or kidneys. In addition, nanomaterials can be synthesized with a variety of compositions, both inorganic and organic. These distinct compositions confer unique advantages, as they endow the nanomaterials with specific physicochemical, thermal, electrical, magnetic, mechanical and optical properties [648–651].

However, new generations of biomaterials on the sub-nano scale have revealed unexpected properties and advantages for neuroengineering. The physiochemical surface properties of the biomaterials (or ECM) on the sub-nano scale (typically less than 2 nm) are crucial for controlling stem cell regulatory signals, and these signals can direct the fate of stem cells. A previous study investigated the influence of sub-nano, nano and submicron surface features on bone marrow MSCs integrin activation and differentiation. The results indicated that both pure nanoscale and nano-submicron hybrid scales of titanium surface features were sufficient for activating integrin-ligand protein interactions. However, only the nano-submicron hybrid titanium surface features significantly accelerated subsequent osteoblast differentiation. This acceleration was observed in primary mouse bone marrow stromal cells and other stem cells [652, 653]. Live cell analysis of human bone marrow MSCs on transparent titanium surfaces demonstrated that rapid cytoskeletal reorganization induced by nanoscale surface features led to high expression of genes associated with the osteoblast phenotype [654, 655]. These findings demonstrate the advantages of sub-nano topography on stem cell dynamics. Such advantages are not only crucial for understanding the fundamental aspects of stem cell behavior but also provide valuable insights for the smart design of effective surface structures. These structures can potentially accelerate advancements in the field of neuroengineering [656, 657]. On the robust foundation of nano-inspired research, the rational design and application of sub-nanoscale biomaterials will likely facilitate the development of innovative methodologies and technologies. This advancement has the potential to significantly push the boundaries of neuroengineering [658].

Integration of neuroengineering with multidiscipline

Multidisciplinary research holds great promise in revealing the complex mechanisms that determine brain function in health and disease. In the framework of neuroengineering, the close collaboration of biomaterials with neuroscience, engineering, neurobiology, nanotechnology, computation and artificial intelligence (AI) opens the door to radical new approaches to understanding brain function and treating neurological injuries and diseases [659, 660]. For instance, neuroscience and neurobiology provide the general rules for neural change in structure and function in health, neurological injuries and diseases. Engineering lays the basic theoretical foundations for selecting appropriate cell sources, performing effective cell modification, and using proper supportive matrices. Nanotechnology enables the development of innovative tools for engineering and manufacturing biomaterials at the atomic and molecular scales. Moreover, AI algorithms facilitate the analysis and inference of big data, allowing for a more applicable understanding of complex interactions among innumerable variables in systems that involve the synthesis or use of biomaterials [661–663]. Therefore, the broader prospects in science and technology, combined with specific and immediate opportunities to enhance our understanding of the brain and expand our clinical treatment options, converge to create numerous promising avenues for multidisciplinary research in the future.

Future biomaterials for precisely targeted neuroengineering

In the field of neuroengineering, neural regeneration can be facilitated by the implantation of 3D scaffolds. These scaffolds are populated with progenitor cells and constructed from a range of biodegradable materials, including polymers, hydrogels and HA. Such materials enable the targeted integration of cells at CNS sites [664–667]. The ‘precise targets’ required for neural regeneration involve the following factors [668–673]: (i) the direction of regenerative neurite outgrowth post-transplantation must be meticulously controlled to ensure effective integration into the host brain tissue’s signaling pathways; (ii) the network architecture should be designed to be heterogeneous, aiming to replicate the injured site’s architecture to facilitate functional restoration; (iii) the neural tissue should be composed of appropriate cell populations that mimic the original tissue, thereby promoting the recovery of function; and (iv) the innervation of the newly developed regenerative neural tissue remains a fundamental challenge in engineering fully functional organs or neuronal scaffolds, particularly after vascularization. Taken together, play a pivotal role in the regeneration and formation of neural circuits. They facilitate the integration of iPSCs or primary neurons into scaffolds. These scaffolds can be designed with artificial brain regions on chips and pre-defined synaptic architectures, which are essential for the development of functional neural networks. This approach generates a multi-layered network that, upon transplantation into the brain, establishes synaptic connectivity with a precisely controlled ‘target’ network.

Neurorobotics for personalized precision neurorehabilitation

The advancement and integration of neurorobotics, a dynamic and rapidly evolving field that integrates the landscape of neuroengineering, robotics and AI, has garnered significant academic attention and is poised to revolutionize the field of personalized precision neurorehabilitation [674]. This interdisciplinary approach combines advanced technologies to develop innovative solutions for neuroscience research, diagnosis, and treatment, with a particular focus on enhancing the effectiveness of rehabilitation strategies for individuals with neurological conditions. It offers direct brain–machine communication [675, 676], robotic assistance in physical therapy [677, 678], AI-driven diagnostics and personalized treatment plans [679], adaptive learning for real-time therapy adjustments [680, 681], telerehabilitation for remote patients [682, 683], gamification to boost patient motivation [684], and extensive data analysis for treatment refinement [685]. Furthermore, neurorobotics also employs predictive analytics to optimize recovery and ensures patient safety through monitoring [686, 687]. However, as this field continues to evolve, ongoing research is essential to refine technologies, ensure safety and efficacy and address ethical considerations such as data privacy and autonomy [688].

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