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Research Article

SOFT BIOELECTRONICS FOR BRAIN NEURAL RECORDING AND THERAPY

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Abstract

The human brain is a complex organ responsible for controlling bi-directional signals between the peripheral and central nervous systems through a complex network of neurons. Despite significant research efforts, many brain diseases and disorders remain poorly understood, and effective treatments are lacking. Recent advances in neurotechnology, including bioelectronic devices that can record and stimulate neural activity in the brain, have played a crucial role in addressing these challenges. However, conventional bioelectronic devices face significant challenges due to the mechanical mismatch between soft brain tissue and the rigid electrode. This review paper discusses the limitations of conventional bioelectronics to record brain neural activity and emphasizes the importance of the mechanical properties of device materials and dimensionality. Furthermore, it highlights the latest research on different types of bioelectronic technologies, including flexible, stretchable, and intrinsically soft bioelectronic devices available for monitoring and modulating brain activity and their advantages and limitations. By highlighting recent advancements and exploring potential future developments, this review paper provides a comprehensive overview of the current state of the art in flexible and stretchable bioelectronic technology for brain monitoring and therapeutic application.

Keywords: Soft bioelectronics, Device materials, Neural interface, Neural recording, Neuromodulation.

INTRODUCTION

The human brain is the most complex organ in the body, responsible for controlling bi-directional signals between the peripheral and central nervous systems through a complex network of neurons(M. Lee *et al.,* 2019). Despite decades of research, many brain diseases and disorders remain poorly understood, and effective treatments are lacking. Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, psychiatric disorders such as depression and schizophrenia, oncological diseases such as brain tumors, and neurodevelopmental disorders such as autism and ADHD are all examples of conditions that affect the brain and can severely impact a person's quality of life (H. Li *et al.,* 2020). In recent years, advances in neurotechnology have played a crucial role in addressing these challenges by enabling the monitoring and modulation of brain activity. These technologies include a range of bioelectronic devices that can record and stimulate neural activity in the brain. Neurorecording techniques, such as electroencephalography (EEG), epicortical electrocorticography (ECoG), and intracortical encephalography (ICE), have significantly enhanced our understanding of pathological symptoms and allowed us to comprehend brain signals and neuromodulation to date. These techniques have been used to investigate the relationship between neuronal signals and external cognitive function, identify biomarkers for brain diseases, and develop new treatments for brain disorders(Sunwoo *et al.,* 2020). Despite these advances, conventional bioelectronic devices face significant challenges, mainly due to the mechanical mismatch between brain tissue and the electrode. The dissonance exists between the soft and curvilinear brain tissue in which ion controls the signal transmission and the bulky and rigid electrodes fabricated with inorganic materials in which electrons serve as a transmitter.

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Furthermore, the implantation of rigid devices may serve as a chronic stressor for the brain tissue, resulting in significant mechanical damage (Cho *et al.,* 2022). Recent advances in soft bioelectronics have led to the development of stretchable and soft electronic devices which can reduce the mechanical mismatch between the device and the brain tissue and thus conform to the contours of the brain. These developments have opened new possibilities for monitoring and modulating brain activity and have the potential to revolutionize our understanding of the brain and its disorders (Koo *et al.,* 2021) In this review paper, we will discuss the limitation of conventional bioelectronics to record brain neural activityand emphasize the importance in mechanical property of device materials and dimensionality. Also, latest research on the different types of bioelectronic technologies includingflexible, stretchable, and intrinsically soft bioelectronic devicesavailable for monitoring and modulating brain activity and highlight their advantages and limitations. By highlighting recent advancements and exploring potential future developments, this review paper aims to provide a comprehensive overview of the current state of the art in soft bioelectronic technology for brain disorders.

Conventional bioelectronics in neurotechnology

Penetrating electrodes made of silicon – such as the Utah electrode array and Michigan electrode array have been conventionally used to monitor vigorous neural activity(Chen *et al.,* 2021). The close contact with the targeted neuron enables recording with high accuracy. However, the limitation of these electrodes lies in the poor bending stiffness of the material, which leads to the mismatch between the electrode and soft brain tissue, especially in the case of long-term attachment (Hong and Lieber, 2019). One of the primary considerations is the low Young's modulus of the electrode. If the electrode is not sufficiently flexible, the quality of the signal may be reduced due to mechanical inequity with the soft tissue. Additionally, miniaturization of the electrode is

important for precise measurement and minimization of brain damage during insertion(Chen *et al.,* 2021). The elastic modulus can be driven by the following equation where σ and ε respectively refer to stress and strain (Eq. 1).

$$E = \frac{\sigma}{\varepsilon}$$

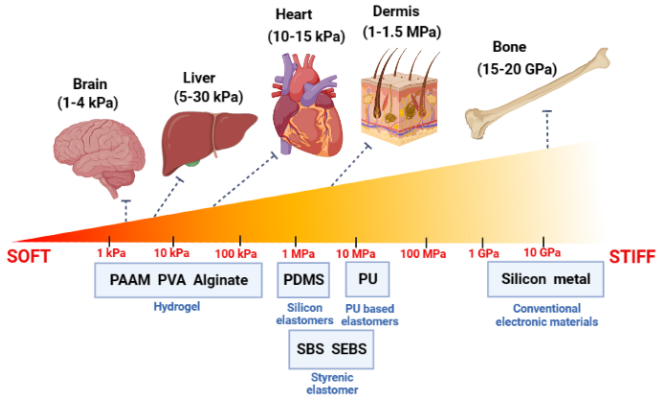

Figure 1. Elastic moduli of different types of biological tissue and device materials

The elastic modulus is a gauge of how much a substance opposes modifications in its dimensions when subjected to forces of tension or compression. Substances that require less effort to achieve the same alteration in size are considered softer because of their lower elastic moduli. It is inevitable that the conventional rigid neural probes made of silicon would cause a mismatch with brain tissue(Koo *et al.,* 2020), since the elastic modulus of the former is 150 GPa whereas the latter ranges from 100 Pa to 10 kPa (Figure 1). It implies that offering materials with a similar level of softness to the brain surface would result in far less stress on the tissue when interfacing with it, even with the same amount of strain. This poses a significant hurdle for achieving seamless integration between the device and human body, particularly with bulky and rigid devices chronically implanted or in contact with target tissues or organs (Li *et al.,* 2020).

induce severe inflammatory responses.There is debate about whether implantable electrodes can provide steady and consistent neural signals that validate the risks of implantation and the long-term presence of a foreign object inside the brain(Sunwoo *et al.,* 2020). As a result, rigid materials of conventional electronic devices can be a chronic stressor in which cause significant damages to brain tissue as well as inconsistent signal recording.On the other hand, bioelectronics made of soft materials can reduce those side effects (Figure 2b).

Soft Bioelectronics

Flexible and stretchable electronic devices: Soft bioelectronics has made significant contributions to neuroscience and neurotechnology by using unconventional materials, customized fabrication processes, and novel device designs. The focus has been on reducing mechanical, chemical, and electrical mismatches between biotic and abiotic systems to create soft devices that can record electrical signals or provide electrical/chemical stimulation to the nervous system. These devices have been shown to function effectively over long periods without causing significant biological or mechanical damage. The ability of a structure to deform or conform to a curvilinear surface under an applied force is known as bending stiffness. The effective bending stiffness (k) can be expressed in the form of $k \propto Et^3$, with *E*and t referring to the elastic modulus and thickness, respectively(Chen *et al.,* 2021). The formula shows that a lower elastic modulus of the constituent material or a thinner device structure necessarily results in more bendable electronics. This reduction in thickness improves the softness of the material without affecting its electrical properties. Thus, ultrathin materials can serve as a good neural signal recorder with minimal mechanical differences from brain tissue in terms of flexural rigidity(Chiang *et al.,* 2020). The softness of these ultrathin materials also allows for long-term recording with stable spatiotemporal resolution. Micro- and nano-fabrication technologies make it possible to produce ultrathin devices that are more flexible by decreasing their bending stiffness.

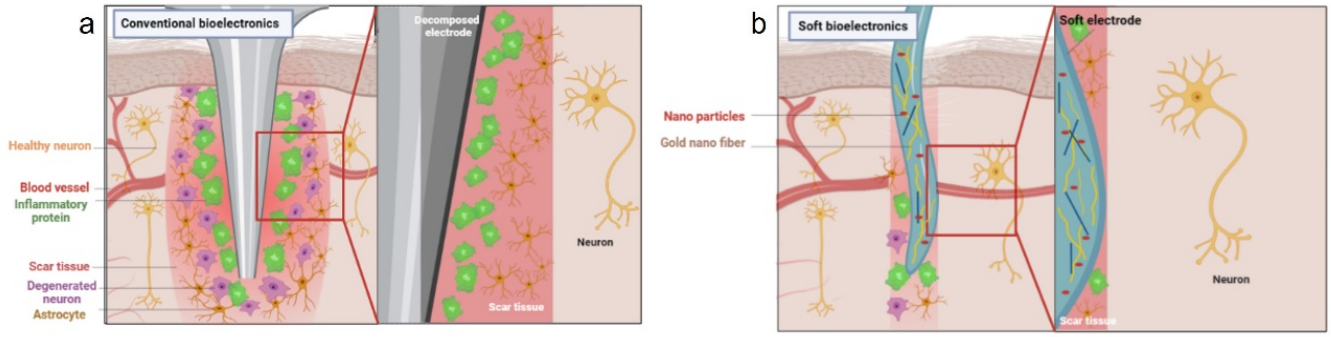

Figure 2. Schematic of an inflammatory reaction caused by the injection of the intracortical recording device. a) The use of conventional rigid intracortical electrodes triggers an inflammatory response, leading to the recruitment of astrocytes and inflammatory proteins at the implantation site. It results in the formation of a considerable amount of scar tissue around the electrode and thus the transmission of electrophysiological signals is hindered as degenerated neurons obstruct the signals originating from active neurons. b) The decreased mismatch between a soft unconventional intracortical bioelectrode reduces an inflammatory reaction as compared to a conventional rigid bioelectrode

Moreover, implantation of neural devices can cause symptoms such as elevated pressure, hemorrhage, and breakdown of the blood-brain barrier, while nonfunctional glial cells and astrocytes recruited around the implant can interfere with brain-electrode interfacing(Chiang *et al.,* 2020) (**Figure 2a**). In particular, the mechanical mismatch of rigid implants can

This can improve the adherence and integration of neural probes with targeted neural tissue by inducing less stress on adjacent neural tissue. The flexibility of the electronic circuit is also important for improving the chronic stability of the interface (**Figure 3a**).

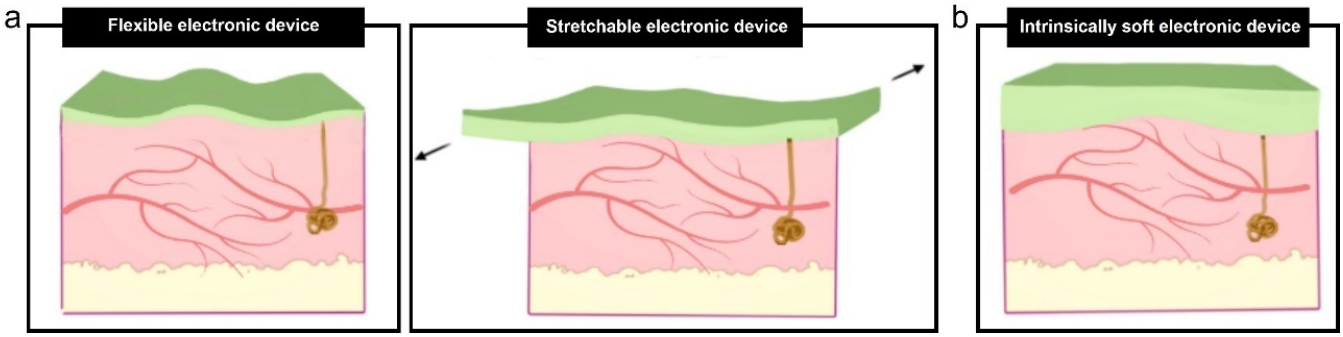

Figure 3. Schematic illustration of (a) flexible, stretchable, and (b) intrinsically soft electronic devices placed on biological tissue

The stretchability can be achieved through two conceptually different strategies: materials innovation and structural design (Koo *et al.,* 2020). Materials innovation involves the use of elastomeric and ductile materials that exhibit either reversible, linear elastic responses or plastic deformation without fracture under large strains. These materials have been employed in the fabrication of functional stretchable electronics. Structural design involves geometrical designs that distribute global strain via geometrical openings or introduce out-of-plane displacements by fabricating devices on pre-strained substrates, resulting in buckling interconnects. Mesh structure optimizes the flexibility of ultrathin devices by allowing maximum deformability of the device. Line-shaped design enables stretching in multiple directions and is thus more applicable for various uses than the large film-shaped device. Furthermore, Liu et al. developed syringe-injectable electronics based on a mesh-like design and sub-micrometer thickness (Liu *et al.,* 2015). Due to the deformability and recoverability of the structure, the device can fit into the syringe and return to its original state after injection. The multiple channels allowed the recording of brain activity in the hippocampus of anesthetized mice across 16 channels. The device is mechanically soft and thus compatible with brain tissue, which led to minimal chronic immunoreactivity over a period of 5 weeks. This outcome demonstrates greater biocompatibility than the conventional silicon probes, which are known to cause gliosis and quickly lose their recording function.

Intrinsically soft electronic device: Elastomers have soft mechanical properties that allow them to easily integrate with biological tissue (Shim *et al.,* 2021). They consist of long, crosslinked polymer chains that can be stretched as the tangled chains unwind. The elasticity of the material is necessary for conformal integration with dynamically deformable biological tissues, such as skin, heart, and the brain. The mechanical properties of elastomers including Young's modulus and stretchability are determined by the crosslinking of the elastomer backbone chains. A higher density of strong crosslinking makes the elastomer stiff and tough, whereas a lower density of weak crosslinking makes the elastomer soft and easily breakable. Also, elastomers have moduli that are comparable to those of tissues, and some hydrogels even have moduli that are close to or lower than that of the brain. Some biological tissues have non-linear stress-strain relationships and viscoelasticity, which involves stress relaxation and energy dissipation. Using elastomers that have a nonlinear strain-stress relationship and viscoelasticity can minimize the mechanical mismatch between the device and the biological tissue (**Figure 3b**).

To enhance the functionality of elastomers for use in bioelectronics, alternative methods are necessary in addition to controlling crosslinking or incorporating chemical functional groups in the polymer chain. One strategy is to incorporate functional fillers into the elastomer, which can produce elastomers with conducting properties. The fillers are responsible for the electrical properties, while the elastomer acts as a supportive and structural medium to maintain the 3D arrangement of the fillers. This technique is commonly used to improve the electrical properties of elastomers. Conductive nanomaterials, such as metals and carbon-based materials are used as fillers to improve the electrical properties of elastomers for bioelectronics (Joo *et al.,* 2020).

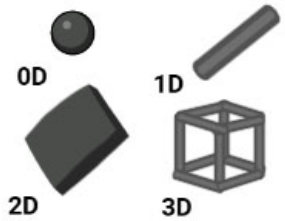

Figure 4. Types of nanomaterials classified into dimension

Nanostructured materials can be classified based on their morphology, ranging from zero dimension (0D) to three dimensions (3D) (**Figure 4**). These materials possess unique properties that differ from their bulk counterparts due to the localization of electrons in nanometer-sized materials, which leads to a strong dependence of band gaps on the size of the nanomaterials (quantum confinement effect) (Cho *et al.,* 2022). Additionally, the surface-area-to-volume ratio of nanostructured materials increases dramatically in the nanometer domain, resulting in a significant enhancement of their chemical reactivity. For instance, nanoparticles, nanowires, or nanoflakes are dispersed in the elastomer matrix to form percolation networks that transport charges. The networks can withstand deformation, as some connections may break but new ones are generated, preserving electrical pathways. The formation of a percolation network in elastomers is influenced by the shape of the fillers (Lee *et al.,* 2021). Aluminum oxide particles, which are 0D fillers, remain separate from each other, while carbon fibers, which are 1D fillers, can create a percolation network without affecting the elastomer's soft mechanical properties, even at the same volume percentage. Generally, 1D fillers are better at forming percolation networks without altering the elastomer's mechanical properties. Nanoscale fillers, such as CNTs, can form more stable and denser percolation networks than larger fillers because they are more numerous in the elastomer

matrix. Therefore, nanoscale fillers are commonly used as functional fillers in elastomer composites.

Neural recording and neuromodulation

Flexible and soft electronics forneuron *in vitro:* The ability to measure single neuron level action potentials and to record over long period maintaining high temporal resolution is vital for comprehending the dynamics of neural circuits, including its development, learning process, and memory formation, which are valuable in long-term studies in neuroscience. Although conventional electrical neural interfacing methods, such as intracellular and extracellular electrophysiological recording techniques, lack specificity, they offer new opportunities for monitoring neural activity at the cellular level when coupled with flexible electronics. For instance, the patch clamp technique, considered the gold standard for electrophysiology, enables researchers to isolate a single targeted neuron or ion channel for in-situ recordings of its electrical behavior (Kruskal *et al.,* 2015). This technique can uncover the cellular or subcellular biophysics of the brain. On the other hand, extracellular recording allows for large-scale recordings through multiple channels and can provide additional information for reconstructing the interactions between neurons at the circuit level. Flexible electronics are typically flat and used as 2D substrates for cell cultures, but they cannot fully model 3D interactions. Bioinspired flexible electronics, like the 3D nanoelectronic scaffold (nanoES), offer a promising platform for 3D cell cultures (Cohen-Karni *et al.,* 2009). The nanoES includes silicon nanowire FETs and has a porous structure that allows cells to interpenetrate. 3D nanoES/tissue hybrids enable stable 3D recording of local field potentials. Bioinspired flexible electronics offer a promising platform for 3D recording and manipulation of cellular activities. Feiner et al. integrated a porous electronic mesh with drug-containing polymers for simultaneous activity recording and modulation (Feiner *et al.,* 2016). The drugs in the polymers could be spatially released by electrical stimulation to regulate tissue functions, such as promoting cell migration in vitro.

Spheroids and organoids are commonly used as models for studying human development and diseases as they can recreate complex features of 3D microenvironments found in living organisms. Li et al. developed a method called the cyborg organoid, which involves integrating mesh electronics throughout an entire organoid during organogenesis using cell-cell attraction forces (Li *et al.,* 2019). The method involves embedding mesh electronics within a coculture of human mesenchymal stem cells and human-induced pluripotent stem cells. The mesh electronics was designed with a serpentine structure that allowed it to accommodate large volume changes during organogenesis, with in-plane stretchability of up to 30% and an out-of-plane compressibility several times smaller than its initial volume. The mesh electronics was embedded uniformly throughout the organoids and could stably monitor the evolution of field potentials of cardiomyocyte cells during organogenesis due to their seamless interfaces.

Flexible and soft electronics for brain *in vivo:* The main techniques for recording electrophysiological signals are EEG, ECoG, and ICE (**Figure 5**). Each technique uses specific electrodes designed for purposes and integrates with different target tissues depending on the type of signal being recorded. For example, EEG records signals from the scalp, ECoG from the dura mater, and ICE from the intracortical region. These methods differ in terms of signal amplitude, spatiotemporal resolution, and invasiveness. EEG has low amplitude and resolution but is less invasive, while ICE has high amplitude and resolution but is more invasive. ECoG sits in the middle of EEG and ICE in terms of its characteristics. When the distance between the electrode and the target neuron increases, the extracellular potential amplitude decreases, making it challenging to filter low amplitude signals like EEG from surrounding noise. Therefore, more invasive recording methods like ICE may be preferred in certain circumstances.

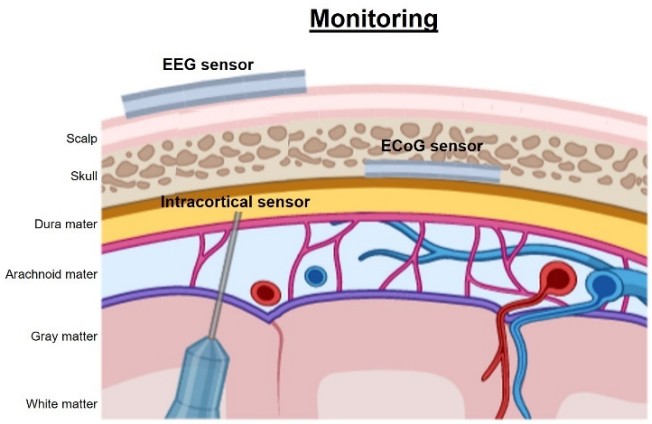

Figure 5. Various medicinal applications of soft unconventional bioelectronics. Schematic of EEG sensor situated on the scalp, ECoG sensors positioned on the dura mater beneath the skin, and intracortical sensor placed within cortical tissue

To overcome the challenges associated with ICE sensors, researchers sometimes combine two or more materials to minimize mismatches and maintain functional advantages. Nam et al. developed an injectable ICE electrode using a composite of a supramolecular β-peptide-based hydrogel and conductive carbon nanotubes (CNTs) to mimic the mechanical and chemical properties of brain tissue (Nam *et al.,* 2020). This hydrogel composite was soft enough to reduce mechanical damage to the cortex while also being stiff enough to penetrate the brain tissue during insertion. The resulting electrode showed a low modulus of 1,500 Pa, similar to that of brain tissue. The injectable device was implanted in a chronic epileptic mouse model and produced high-quality ICE recordings due to the large surface area of the composite, the ionic interface of the hydrogel, and the high conductivity of the CNTs. The hydrogel composite electrode showed significantly lower inflammatory responses after 12 weeks of implantation compared to a conventional metal electrode. Although the morphology of the hydrogel composite electrode was significantly altered due to its flexibility, it remained stable due to the high stability of the β-peptide and did not interfere with cerebral blood flow. Flexible electronics also allows the conforming interface with the curvilinear shaped surface, allowing for high-fidelity ECoG recordings. Khodagholy et al. suggested an adaptable platform for ECoG that makes use of a flexible substrate called parylene and utilizes electrodes made of poly (3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) to lower impedance (Khodagholy *et al.,* 2011). The technique has important implications for clinical settings, such as recording signals and synthesizing audible speech by decoding the kinematic and sound representations encoded in human cortical activity. Since traditional ECoG arrays which typically measure local field potential on the surface of the brain have reached a limit in terms of single-neuron level

recordings, conformable ECoG platform utilizing flexible substrate has been developed to address the issue. For example, the Neurogrid platform designed for stimulation of biological brains enables the recording of single neuron action potentials as well as high spatial resolution across the cortical surface, through the minimized size. The device allows the electrical coupling between the electrode and cortical neuron, improving the mechanical conformation to the curved brain surface and thus resulting in an enhanced extracellular action potential amplitude recording.

On the other hand, less invasive techniques such as EEG, which is placing electrodes on the scalp rather than the actual brain tissue, present challenges in maintaining high spatial resolution and conformal contact. The stretching of elastic skin causes delamination of the device which increases the impedance (Hong *et al.,* 2019). In addition, the long-term attachment of the device may cause skin irritation. The development of novel soft electrodes has greatly improved electrophysiological recording techniques such as EEG. One example is the fractal geometry electrode developed by Norton et al. which consists of ultrathin gold electrodes on an elastomeric film (Norton *et al.,* 2015). This electrode is highly flexible and soft, allowing it to conform to the shape of the auricle and mastoid bone for long-term, high-fidelity EEG recordings without the need for electrolytic gels. Advanced electrotherapies use electrical stimulation to either regulate or improve specific neural activities, and soft bioelectronics can be especially valuable for this purpose (**Figure 6**).

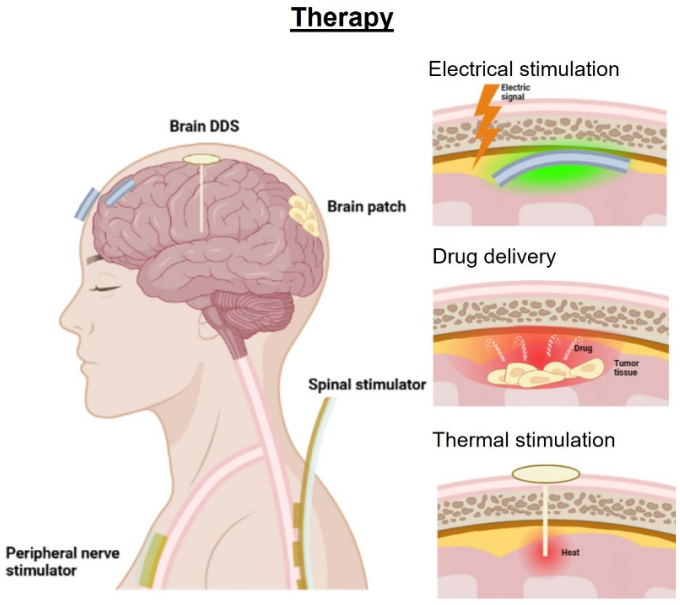

Figure 6. Various therapeutic application in brain using soft bioelectronics. Soft electrodes can support electrotherapy by giving out electric signal, thermal actuation via a heating device injected into an intracortical area, and drug delivery via flexible electronic-assisted brain patches for treating brain tumors

An example of a soft neural interface device is the e-dura implant, which mimics the shape and mechanical properties of the dura mater (Wenger *et al.,* 2016). The implant consists of a soft silicone substrate and stretchable gold interconnects that reduce mechanical mismatch with brain tissue and maintain stable electrical conductivities. Moreover, the soft electrodes are covered with a platinum-silicone composite to minimize chemical and electrical disparities. In experiments on rats, the e-dura was biocompatible over a prolonged period and stimulated the spinal cord without significantly deforming neural tissue. In one study, the e-dura was implanted in a paralyzed rat and its electrical stimulation allowed the rat to walk, and had dependable therapeutic effects during rehabilitation. In another study, the e-dura was combined with a computed protocol that replicated natural motor neuron activation during locomotion, and the spatiotemporal neuromodulation provided by the e-dura improved overall locomotion quality in paralyzed adult rats. Chemotherapy has been used for treating neural diseases for a long time, but the usual administration routes like oral intake or injection fail to deliver the required amount of drug to the target brain sites due to drugs spreading non-specifically to other organs and being unable to cross the blood-brain barrier. To overcome this, local drug-delivery systems (DDS) have been developed to control chemotherapy doses at the desired site and minimize side effects(J. Lee *et al.,* 2019). However, conventional DDS are mechanically incompatible with brain tissues due to their rigid properties. Soft bioelectronics can be an effective and controllable solution for providing long-term chemotherapy to neural tissues. Intracranial soft DDS can also deliver drugs directly to extracellular fluids, bypassing the blood-brain barrier and increasing drug efficacy.

Conclusion

In conclusion, neurotechnology has significantly advanced our understanding of brain activity, and its potential for developing new treatments for brain disorders cannot be overstated. However, the conventional bioelectronic devices' mechanical mismatch with brain tissue limits their use, and their implantation can cause damage to the brain tissue. Soft bioelectronics represent a significant breakthrough in the field and have the potential to overcome these limitations. The review paper has highlighted the advantages and limitations of different types of bioelectronic technologies and emphasized the importance of mechanical properties of device materials and dimensionality. Further research is needed to develop safe and effective soft bioelectronics for neuromodulation, which will revolutionize our understanding of brain disorders and lead to better treatments. Overall, the review paper has provided a comprehensive overview of the current state of bioelectronic technology for neural recording and neuromodulation.

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