Review Article

Determination of the Relationship Between the Flexibility, Materials and Sizes of Neural Probes and Their Effect on the Foreign Body Response

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ABSTRACT

Neural probes greatly assist us in our journey of learning about the brain by revealing the functioning of neurons. Probes are implanted in different areas of the brain to record data or to stimulate those sites. This detection and intervention of neural activity allows probes to diagnose and treat diseases. Probe technologies have advanced over time and opened new avenues in neural engineering. However, the appearance of a foreign object in the brain elicits a negative reaction that harms the brain and its components. To minimize this reaction, scientists utilize a variety of methods and designs that have yet to be perfected. This review aims to highlight the influence of neural probe designs on the foreign body response. This includes looking at existing types of probes and exploring their potential. The effects of different flexibilities, materials and sizes of neural probes will be examined using studies and research made by scientists to decipher what methods minimize the negative response the most. This paper also aims to identify the gaps in our current knowledge of this subject.

Keywords: Micro-electrodes; Neural probes; Foreign body response; Neural engineering; Biocompatibility

INTRODUCTION

The Foreign Body Response

Implantable neural probes cover a wide variety of solutions for many neurodegenerative diseases; however, the foreign body response (FBR) is an unavoidable process that occurs whenever any device is implanted into the brain. When an object is in the process of being implanted, the surrounding tissue is damaged. This triggers the inflammatory response which converts into a fibrotic response over a period of weeks to months (1). The insertion of implantable devices tears through the extracellular matrix, disrupts the blood-brain barrier (BBB), and punctures cell membranes (2, 3), illustrated in Figure 1. Rupturing the BBB can cause increases of hemoglobin, a protein that is responsible for providing tissue with oxygen (3). The insertion of an electrode can also damage blood vessels in the brain. Vascular damage

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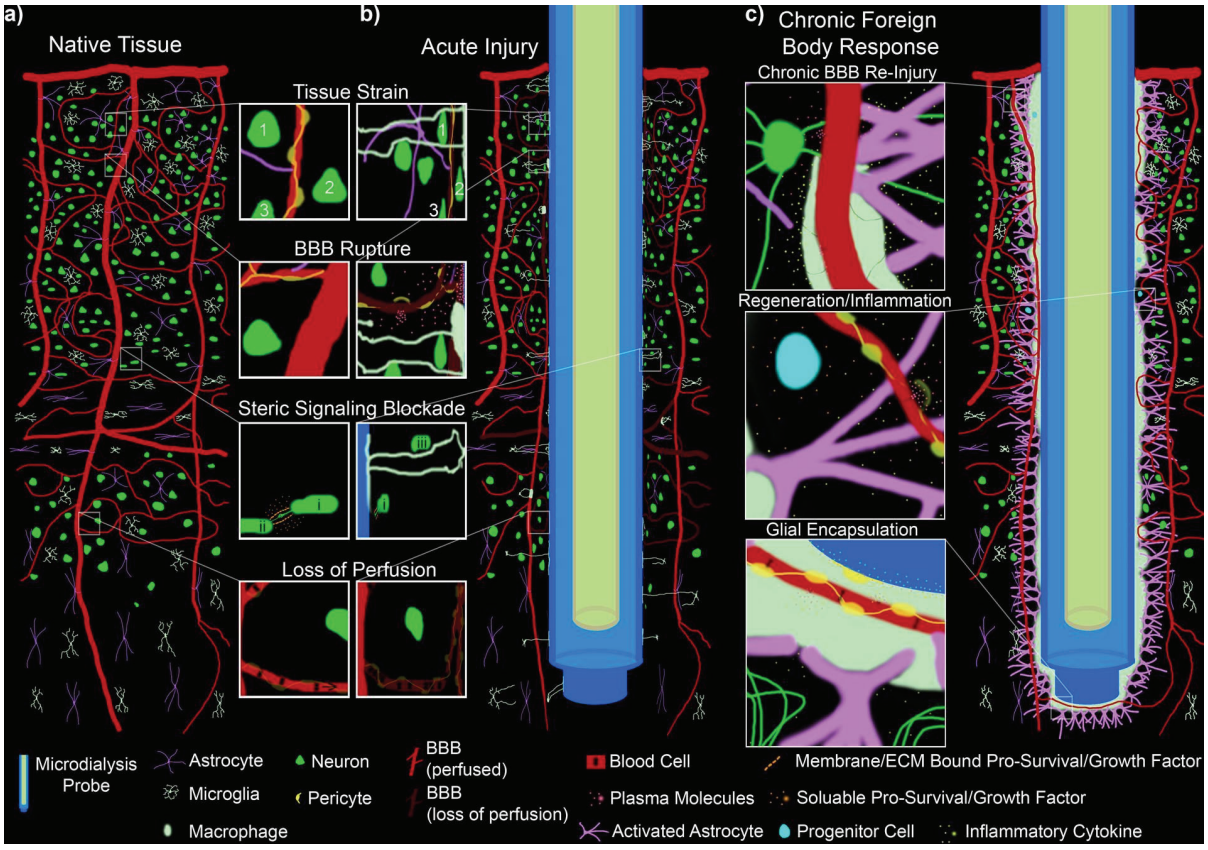

Figure 1. Cartoon of tissue inflammatory response. a) Tissue before insertion of implant; b) Acute injury caused by probe insertion includes increased tissue strain, BBB rupture, steric signaling blockade, and loss of perfusion; c) Chronic tissue reaction caused by probe insertion includes BBB re-injury, tissue inflammation, and glial encapsulation (3).

involves fluid displacement, dragging of blood vessels and eventual vessel severing (4). The most severe form of vascular damage is vessel rupture. Research shows that the penetration of a single large intracortical blood vessel results in significantly large BBB bleeding compared with the penetration of multiple small capillaries.

Pericytes also play a critical component of the BBB, as they reduce BBB permeability from periphery-derived harmful substances, while allowing the influx of nutrients. They also regulate blood flow and clear away neurotoxic waste products in the brain (3). Endothelial cells help sustain pericytes and maintain the BBB. Chronic BBB breakdown is associated with dysfunction in pericytes. Disruption of the BBB caused by the insertion of foreign objects activates nearby microglia. Microglia interlock with each other on the surface of the device and secrete proinflammatory cytokines and chemokines (4). These cytokines release proinflammatory factors which further recruit more microglia and macrophages to the site of injury (4). The layer of microglia forming around the implant starts to isolate and phagocytose the implant. When the macrophages successfully phagocytose the probe, the FBR reaction ends and the surrounding brain tissue slowly starts to heal from the injury (1). Often, the macrophages are not able to phagocytose the implant because of its large size, so the macrophages attempt to break down the implant and phagocytose the smaller fragments by releasing factors such as reactive oxygen species (ROS) (1). Small amounts of ROS and reactive nitrogen species (RNS) are generated by cells and are important regulatory mediators in the signaling process (4).

Some probes exhibit surface degradation and cracking when they are exposed to the inflammatory environment created by microglia in the brain. This may cause the implant to break and release toxic species into surrounding tissue (1). Some implants are designed to be inserted into the tissue and help with tissue regrowth. These devices often dissolve as the tissue heals. Although the desire

for neural implants is to perform for the lifetime of the patient, microglia and reactive astrocytes are observed at the implantation site when FBR transitions from the acute to the chronic stage (1).

The beginning of the chronic stage is characterized by the transition from an inflammatory to a fibrotic process. This stage involves the encapsulation of the device in a fibrous tissue that can act as a barrier between the implant and brain tissue. The FBR transitions into this phase over the course of weeks, and will remain active until the implant is removed or destroyed. During this transition, macrophages shift from a proinflammatory activation phenotype to a tissue generation phenotype (1). This shift is often observed as a part of the normal wound healing process, but these new macrophages support astrocytes and the encapsulation of the implant (1). Reactive astrocytes and microglia interlock around the implant and fill the space and begin to prune the dying cells (3), forming a new fibrotic tissue capsule. Cell proliferation and ECM deposition thickens the capsule over a period of 6 weeks until the implant is completely isolated from the surrounding tissue (1). This makes it difficult for the device to fulfill its therapeutic job and decreases signal sensitivity (1).

The FBR process described above can differ in different brain tissues because the brain is very heterogeneous and has different cellular populations for each compartment (1). In the central nervous system (CNS), the body exerts tight control over cell and molecule crossing from the bloodstream into the CNS (1). Here, FBR is driven by central nervous system (CNS) resident microglia and astrocytes. In peripheral nerves, FBR is driven by different cell types such as macrophages and fibrosis, driven by fibroblasts (1). Despite these differences, general principles of FBR still apply. This includes the formation of fibrotic capsules and inflammatory damage surrounding tissue.

Many factors contribute to brain FBR outside of surgical insertion, including the difference in brain tissue biomechanics and prosthetic material mechanics. Some of the most common materials used in the fabrication of neural probes are metals, polymers, and silica which are all relatively hydrophobic, causing probe surfaces to be susceptible to protein absorption (3). This following section will explore in depth how mechanical mismatch affects brain biocompatibility.

Biocompatibility and Mechanical mismatch

Mechanical strain on brain tissue caused by material softness mismatch between the implant and the tissue can lead to the upregulation of pro-inflammatory cytokines (3). Flexible devices can reduce chronic FBR by reducing tissue strain. Many characterization studies occur in rodent models instead of humans. Animal brains are less striated and less complex than human brains, therefore it is challenging to predict the elastic modulus and minimize micromotion at the implantation site (5). Neurosurgeons have reported regional variation in the stiffness of the brain (5) based on form and function, so complete integration of neural probes in the brain, without disruption, remains a high priority to address in this field, and has been so for years.

Because the elastic modulus of an electrode is much higher than that of brain tissue, the devices are slow to achieve mechanical and geometric adaptation with the tissue disturbance. Risks of infection and rejection are often present, and this causes instability and displacement of the electrode, which makes it difficult to achieve a safe and reliable connection with brain tissue (6). Tissue damage can be caused by displacement of electrodes after implantation. Glial scar separates damaged brain tissue from healthy tissue, prevents lymphocyte infiltration of the BBB, and eventually affects the quality of signal recording and the duration of signal acquisition (6). Materials with good biocompatibility include polymers (e.g., silicones, polyethylene and polyimide), metals (e.g, platinum and gold), and ceramics (1). Materials with a low Young's modulus include polyaniline, polyimide, parylene, SU-8, and two-dimensional carbon nanomaterials which display high electrical conductivity, flexibility, and good biocompatibility in a single atomic layer thickness (6).

COMMON VARIETIES AND MATERIALS OF ELECTRODES

Traditional metal and silicon-based probes elicit an immune response that can impede the goal of the implantation. More modern devices seek to minimize the appearance and effect of the foreign body response. Here are some commonly used materials, methodologies and strategies that researchers are implanting to address the hurdle of FBR.

Microwire electrodes and microelectrode arrays

Microwires are generally fabricated from stainless steel, tungsten wires, gold, platinum, and iridium (6). The metal wires have diameters of 20-50 μm. The ends of these probes have a bare plane or a conical tip. When the surface makes contact with neurons, their action potential and local field potential (LFP) signals can be recorded (6).

They are used to detect neuronal activity in animal brains. Some different designs include single-wire, tetrode, and multi-wire electrodes. The bending stiffness of metal microwires ranges between 10^{-4} and 10^{-3} nm (6). However, microwires record only through their exposed tip, so increasing the number of recording sites result in a larger electrode size and more significant tissue damage (6).

Silicon-based microelectrodes

Michigan-style arrays. Michigan-style microelectrodes are a commonly used electrode and was first reported by *Wise et al.* at the University of Michigan in 1970 (6). These are designed using an in-plane scheme with recording sites located within a single face of the microelectrode rod. The probe is fabricated primarily out of silicon with circular recording sites made of iridium or platinum with side lengths of tens of micrometers (5, 6). An advantage of the Michigan electrode is that they can be easily customized into a wide variety of configurations (5). The Michigan array records LFP signals and spikes in an animal's brain (6). Although results are variable, as one of the oldest MEAs, these probes are commonly observed to initiate the brain's inflammatory response (5).

Utah arrays. The Utah silicon-based microelectrode was developed by Richard Normann at the University of Utah to be used as a cortical visual prostheses (4). It uses an out-of-plane design with a body made of doped silicon and a tip made of a platinum or iridium based metal (5, 6). The device includes around 25 to 100 probes, each about 80 μm long and 1500 μm in diameter (6). This array is well suited for use in primate brains and is the only electrode that can be implanted into human brains, since it is the only MEA that is FDA approved (5, 6). Despite its success and small size, the mechanical mismatch between the probe and the brain limits performance capabilities of the electrode (6) (Figure 2).

Polymer electrodes

The mechanical mismatch between electrodes and brain tissue triggers the inflammatory response, therefore, flexible and conductive polymers such as

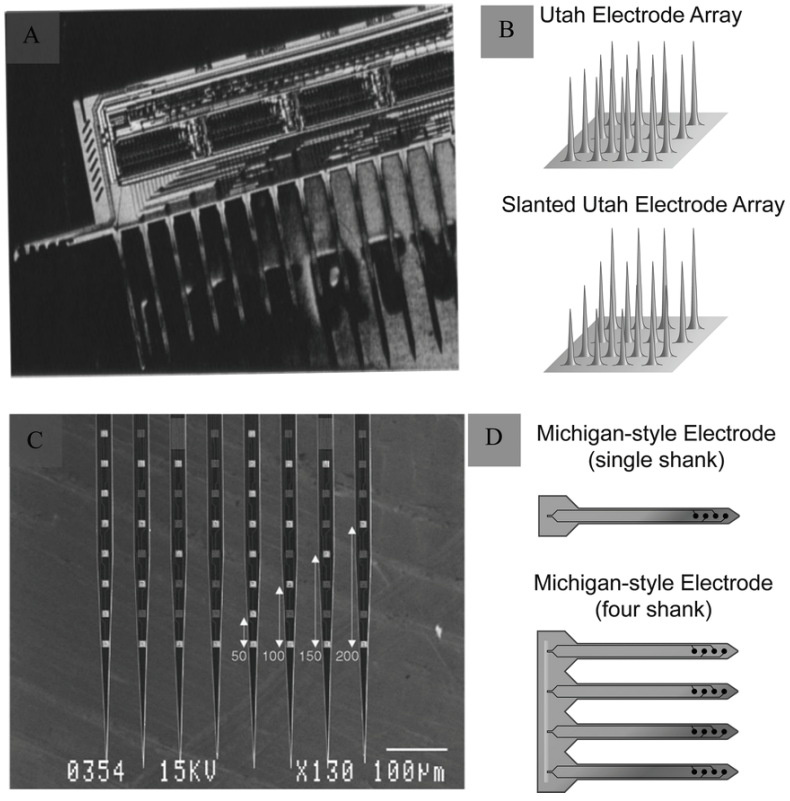

Figure 2. Michigan and Utah electrode schematics. (A) Michigan electrode. (B) Utah electrode schematic representations. (C) Utah electrode. (D) Michigan electrode schematic representations (6).

polyaniline, polyimide, and parylene that have low Young's modulus, have been introduced and studied (6). Polyacetylene, polyparaphenylene, polyaniline, polypyrrole, polythiophene, and SU-8 are all commonly used conductive polymers (6). The conductor part of the electrode is made of one or more metal layers, about 200-300 nm thick, located between the polymer substrate and the encapsulation layer (6). The characteristics of conductive polymers depend on the doping material and its electrical characteristics can be adjusted. Parylene devices are able to record single unit activity for a month up until a year; however, the electrical activity of polymer electrodes decreases over time due to their poor long-term stability (5, 6). Aside from a microglia sheath that appears the first week after implantation, Parylene devices are good for reducing tissue reactivity (5). Tracy Cui reported an ultra-soft polymer wire electrode designed to resolve mechanical mismatch (5). Over the course of 8 weeks, fewer microglia, macrophages, and reactive astrocyte biomarkers, glial fibrillary acid protein (GFAP) were found. In addition, there was less evidence of BBB leakage, cleaved caspase-3 and distortion of mature axons (5). Compared to the neurons around a stiff metal electrode, the neurons surrounding Cui's device experienced significantly less deformation. Ellis Meng's research group used a flexible parylene-based array to chronically record from the rat hippocampus (5). Meng's groups also developed a parylene sheath electrode that is implanted with the aid of an assistive microwire (5). This device was coated with bioactive components to enhance its biocompatibility and was able to detect activity for up to 50 weeks. It also contains perforations that allow brain tissue to invade the device and facilitate cellular signaling (5).

Seymour and Kipke published an article on a parylene-coated 'Michigan'-style device and reported that neuronal loss and gliosis were mitigated around the implant (5). Purcell and Seymour designed a hollowed-out, planar, parylene-coated probe (5). The probe was seeded with stem cells which initially decreased the intensity of the acute brain response, while increasing neuronal densities. However, after six weeks, the increase in neuronal density declines and more closely matches control conditions, as glial encapsulation begins around the devices (5).

Carbon-based electrodes

Carbon materials have good electrochemical stability, capacitive mechanism, chemical inertness, and biocompatibility (6). Their small size reduces immune reactions. Carbon-based nerve (CNT) fibers have good biocompatibility and can be used as coatings for nerve electrodes to enhance conductivity (6). Graphene has good mechanical and electrical properties, thermal conductivity, chemical stability and biocompatibility (6). It has a higher specific surface area than CNT and exhibits lower cytotoxicity at high concentrations. Chronically implanted carbon microthread electrodes (MTEs) minimize BBB disruption and tissue displacement provided stable recording for 5 weeks and are capable of single unit recordings (5). In 2012, Kozai and colleagues reported a carbon fiber-based recording electrode with sub cellular dimensions (5). This device is flexible and can be implanted into the cortex using an assistive insertion device. The MTEs showed improved tissue response compared to Michigan probes and has had greater interfacial neuronal densities (5). Lower accumulation of proximal astrocytes, microglia, and endothelial cells was observed at chronic timepoints. Paras Patel and Cynthia Chestek tested two tip coatings for MTEs: poly(3,4-ethylenedioxythiophene):p-toluene sulfonate (PEDOT:pTS) and poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) (5) proving that electrodes coated in PEDOT:pTS operated longer and were chosen for chronic *in vivo* characterization (5). The new design was coated in a layer of polyethylene glycol that would cover the electrodes during insertion, but dissolve as soon as it penetrates the brain. The results of this experiment showed neuronal survivability around the device and reduced FBR. In summary, the combination of material type, stiffness, flexibility and size all synergistically contribute to FBR, as discussed in Table 1. This next section explores those effects in greater detail.

MATERIAL FLEXIBILITY, SOFTNESS AND SIZE

Flexibility

Flexible probes first appeared in the 2000s in order to overcome mechanical mismatch (7). They are well suited for chronic recordings and can reduce the immune response while enhancing the device's stability to record action potentials of single cells for a long time (6, 7). Probes consisting of stretchable structures and materials, such as hydrogel, have the ability to adapt to changes in brain tissue because of the dynamic developmental process of the tissue (6). Natural biomaterials have an elastic modulus similar to that of brain tissue and are porous in structure. Nanomaterials come in abundant sources and have high mechanical strength, polymerization and crystallinity (6).

Polymer. Responsive polymer-based probes consist of

soft implants that are able to change their elastic modulus under physiological conditions. Polymers can be chemically or temperature activated, and can decrease their Young's modulus after insertion (7). *Nguyen et al.* [2014] reported the chronic neuroinflammatory response of implanted mechanically-adaptive intracortical microelectrodes (7). This study compared these microelectrodes to rigid silicon implants and poly(vinyl acetate)/tunicate cellulose nanocrystal nanocomposite implants, which is initially rigid but becomes compliant after implantation into the brain. The results concluded that the mechanically-adaptive intracortical microelectrodes reduce the inflammatory response when compared to stiffer implants. *Simon et al.* [2017] reported the development of an intracortical probe with a tunable elastic modulus (7). In this study, the probe's biocompatibility *in vitro* and its sustainability for *in vivo* cortical recording in rats for over 2 months was demonstrated. *Shoffstal et al.* [2018] performed *in vivo* experiments to observe the neuroinflammatory response of implanted thiol ene-based shape memory polymers (SMPs) with bare silicon implants and SMPs-coated Si implants (7). The immunohistochemistry analysis of rat tissue after 16 weeks showed that astrocytic scarring was reduced for the coated implants. *Zátonyi et al.* [2019] reported a probe composed of a custom thiol ene/acrylate thermoset polymer (7). It was successfully inserted into rats without any problems with probe buckling and without the use of any insertion shuttles. The device was able to record single-unit activity. *Zátonyi et al.* [2019] studied the mechanical features of implants with softening polymer samples (7). The probe was observed to change its elastic modulus from 2 GPa to 300 MPa when exposed to physiological conditions (body temperatures) in a ten minute timescale (7).

- **Polyimide**

  Polyimide is one of the most used polymeric substrates when fabricating probes, but the characterization of these devices is limited. Loren Frank's group demonstrated a flexible polyimide device that was capable of recording activity for over 5 months (5). The trace metals consisted of titanium or gold with either platinum or iridium recording sites.

  Polyimide is classified into two classes: photosensitive and non-photosensitive. *Freitas et al.* [2021] reported a flexible probe fabricated with a photosensitive and low-temperature cured polyimide (7). The use of lower curing temperature reduced the thermal oxidation of the metals on the probe's substrate. *Takeuchi et al.* [2004] reported a 3D flexible multichannel array fabricated of non-photosensitive polyimide that successfully recorded

Table 1. Advantages and limitations of probe materials

Types/Material of Neural Probe	Advantages	Limitations
Microwire electrodes Typically 20–50 μm in diameter (6).	Has multiple simple designs. Has good corrosion resistance (6).	Limited bending stiffness and number of recording sites (6). Associated with inflammatory tissue response.
Silicon-based electrodes	Wide variety of configurations (5). Well suited for primate brains (Utah arrays) (5). Biocompatible, can utilize multiple recording sites.	Relatively hydrophobic (3). Associated with inflammatory tissue response. Mechanical mismatch between tissue and probe.
Polymer electrodes	Good tissue integration and biocompatibility. Able to be fabricated in a way in which they are soft and flexible. Can be temperature or chemically activated (7). Elicits a smaller immune response in tissue. Low Young's Modulus (6).	Relatively hydrophobic (3). Water absorption leads to tissue compression (3). Challenging to implant due to probe buckling (7). Degrades electrochemical performance of electrodes over time (conductive polymer coatings) (6).
Carbon-based electrodes	Good biocompatibility, high specific surface area, elicits smaller immune responses in tissue (6). Low Young's Modulus (6).	Brittle and susceptible to cracking (8). Limitations in lifespan and electrical conductivity (8).

spontaneous neural signals from the visual cortex (7). *Xiang et al.* [2014] reported a ultra-thin flexible probe made of non-photosensitive polyimide with four gold microelectrodes (7). To facilitate implantation, a biocompatible and biodegradable maltose layer was coated on the probe and later dissolved by bodily fluids. The carbon nanotube coated gold microelectrodes improve recording by decreasing the impedance of the microelectrodes. This device was able to record spontaneous neural activity from the hippocampus (7). *Pimenta et al.* [2021] reported a high density, double-layered, closely spaced gold electrodes, also made of non-photosensitive polyimide (7). The double layer design allowed for a higher number of electrodes to be implemented and added additional stiffness to avoid probe buckling. The device was able to record spontaneous neural activity from the cortex with high signal-to-noise ratios (SNR) and reduced acute trauma. *Vomero et al.* [2022] reported that large polyimide flexible probes lead to more cellular and molecular changes in the tissue interface that do not affect the recording quality, at least within 12 weeks, as compared to thinner polyimide probes (7).

- **Parylene**

  Parylene is a widely used substrate. *Kuo et al.* (2013) reported a parylene-C neural probe with a 3D sheath structure and platinum microelectrodes (7). The sheath structure allows neurotrophic factors to promote neural tissue ingrowth after implantation. *Zhao ZG et al.* [2018] reported a flexible neural probe based on a parylene tube shank with an 18.2 mm length with gold electrodes (7). This device was able to reach deep brain structures and allowed for recordings of LFP data from the amygdala, one of the deepest brain regions.

Microfluidic flexible neural probes. Some therapeutics are used to treat neurological diseases, such as depression and epilepsy, and neurodegenerative diseases, such as Parkinson's disease and sensory organ abnormalities (6, 7). Standard injection of drugs for treatment is hampered by the BBB, since the majority of drugs have large molecules that cannot cross the barrier (7). A solution to this problem is known as convection-enhanced drug delivery (CED). This is the direct infusion of a drug into brain tissue by utilizing neural probes. This method reduces negative effects on healthy tissue and organs. In the early 2000s, there was a development in silicon micromachining-based microfluidic devices to accomplish CED (7). Polymeric probes with microfluidic channels reduce neural tissue trauma. *Metz et al.* [2004] performed a characterization of microelectrodes and microchannels through impedance spectroscopy measurements and flow experiments, respectively (7). The microfluidic system allows the liquid to be locally delivered with precise control of the amount.

Microfluidic channels can improve the stiffness of a probe by filling the channel with rigid material. *Takeuchi et al*. [2005] presented a parylene neural probe integrating a microfluidic channel and a gold microelectrode inside the microchannel (7). The microchannel was filled with PEG, a polyether compound that is solid at room temperature and dissolves when it comes in contact with brain tissue. This temporarily increased the stiffness of the probe and avoided probe buckling during implantation.

There are limitations to microfluidic devices that must be recognized in order to achieve the best results while minimizing brain trauma (7). These include the necessity for the probe to be aligned parallel with the insertion direction, which minimizes the probability of tissue damage and backflow. There must be a precisely controlled flow rate because high flow rate can cause cell damage. Microfluidic probes also need a backside external system with external pumps and tubing connectors (7).

Other flexible probes. There are multiple methods for increasing probe flexibility, some of which are demonstrated in Figure 3 and the following examples. *Altuna et al.* [2012] presented an SU-8-based probe with planar gold electrodes that record the action potentials and LFP data from the dorsal hippocampus (7). *Chung et al.* [2019] reported a flexible interface with an ultra-high density of electrodes (7). Nanoelectronic flexible interfaces were also presented by *Luan et al.* [2017] and *Tchoe et al*. [2022] (7).

Limitations and Solutions. One of the main limitations of flexible probes is how difficult it is to implant into the brain. However, there are methods to overcome this issue. The use of an auxiliary introducer tool like stainless steel wire, coating the probes with an absorbable molecule such as maltose, PEG, saccharose, and hydrogels to temporally confer more rigidity, and by increasing the thickness of the probe with a polymeric multilayering to make the body of the probe more robust (7).

Concerns regarding the fabrication of flexible devices include how to maximize the number of recording sites per shaft. *Böhler et al.* [2023] reported multilayer polyimide probes with a high density of platinum -recording sites that were capable of performing long-term and stable recordings (7). *Wang HM et al.* [2022] used a polyimide

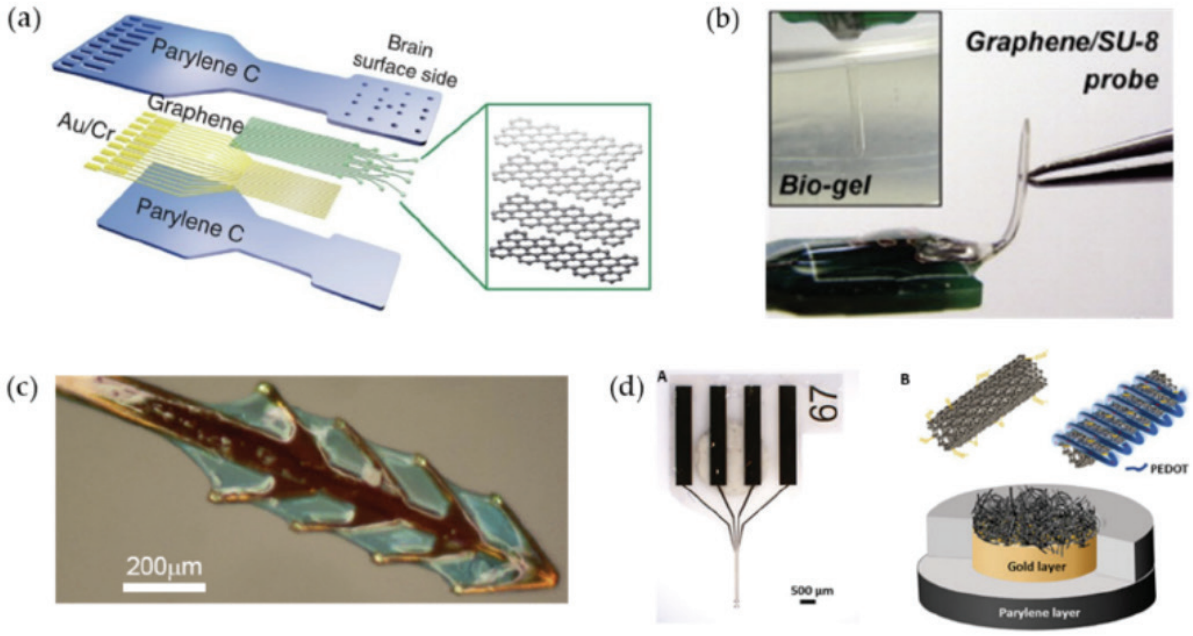

Figure 3. Different manufacturing methods used to increase probe flexibility. (a) Schematic of an electrode with flexible parylene probes. (b) Optical micrographs of a flexible SU-8 probe with 90° bending. (c) Microscope image of a fishbone-shaped polyimide probe. (d) Using nanomaterial PEDOT-CNF to improve electrode performance: A–Optical micrograph of the probe. B–Schematic diagram of the PEDOT-CNF composite deposition (9).

neural probe coated with polypeptides to improve its biocompatibility (7). Polypeptides can also serve as drug carriers due to its micromorphology. *Chin et al.* [2022] reported a flexible microelectrode array coated with a hydrogel (pHEMA) that reduces the mechanical mismatch between the probe and brain tissue (7). The integration of more functionalities of a device can improve the quality and reliability of received data.

The flexibility of an electrode may be improved by reducing the cross-sectional area of the device and reducing the elastic modulus of the material. While increasing the length of a device can improve its flexibility, it is not practical, as the implantation location is a fixed point (3). Flexible devices tend to buckle during the insertion process as it penetrates pia mater and may be deflected to a new location. When dealing with the possibility of leakage of insulation layers and the fragility of electrical traces, materials have to be durable at the subcellular level (3). To deal with this issue, the cross-sectional area of devices is often increased but increasing the cross-sectional area decreases the flexibility achieved through a decreased elastic modulus. This leads to problems including tissue strain and more significant insertion injuries. Certain polymers expand when hydrated, making these electrodes susceptible to an increase in the volume of the device (3).

Bending stiffness and softness

Softer devices or a reduced Young's modulus may improve issue integration. Polymer, hydrogel and nanocomposite-based materials can all be used to fabricate softer devices. Parylene-C and polyimide are used because their Young's modulus is reduced compared to that of metal and silicon electrodes (5). A softer device interface can be created by coating the probe in a substance like hydrogel. Some electrodes start as a rigid object but shift into a softer material after implantation in order to minimize the inflammatory response. An example of this are polyvinyl acetate structures, which allow changes in the compliance of electrodes (5). The biomimetic nanocomposite incorporates a low modulus polymer and cellulose-based nanowhiskers that swell when they are hydrated (5). Bioresorbable interfaces that use biocompatible structures that are compliant with and support the environment of neurons improve acute FBR effects. Biologically active compounds like silk and fibroin that are derived from enzymes and chondroitinase

can be used as a solution to mechanical mismatch issues by using the enzyme to dissolve the layers of scar tissue surrounding and isolating the probe (5).

Size

Reducing the dimensions and elastic modulus of an electrode may increase its flexibility. Decreasing the volume of the devices lowers the mechanical strain it applies on the brain, which reduces pressure on transmembrane channels and pumps (3). A larger device exerts more force onto brain tissue, which can activate the calcium-dependent extracellular signal-regulated protein (ERK) pathway (3). ERK mediates the increase of a type of proinflammatory cytokine which can lead to inflammation in the surrounding tissue. A study comparing two types of stainless steel sham electrodes using a tethered design demonstrated this (10). One probe had a diameter of 50 μm, and the other had a diameter of 200 μm. The results of the study indicated that implants with large diameters elicit a more severe and significant tissue response. According to the data, those tissue reactions lasted for at least 12 weeks. Despite the advantages, decreasing the size of an electrode also decreases its yield strength, which makes the device susceptible to mechanical failure (3).

PROGRESS AND FUTURE DIRECTIONS

Device failure often occurs at chronic timepoints, so it is difficult to identify the problem and optimize implant design to accommodate FBR. A common goal while working with neuronal implants is trying to achieve a higher similarity in terms of mechanical properties, size and shape, with the brain. The most effective strategy to reduce FBR is by designing implants that minimize brain tissue damage. FBR is caused by tissue trauma, and the severity of implantation trauma is linked to the severity of the resulting FBR. The implantation of a device initiates cellular immune response pathways leading to FBR, then tissue trauma around the device furthers inflammation and worsens FBR (1). Brain tissue experiences continuous motion at various rates and length scales, due to the host's breathing, blood pumping, movement and locomotion (1). Once the device is implanted into the brain, the device also becomes subject to this movement. The mechanical mismatch between the mechanical properties of implant and brain tissue leads to a variability in how the two interact in response to constant motion (1). When the implant fails to move in sync with the tissue, the compression and sliding along the interface damages the surrounding tissue. This leads to inflammation, which only worsens FBR, and can permanently damage surrounding tissue (1). Implementing a flexible implant for a chronic time period may achieve a lower degree of FBR and tissue damage. This is a particularly useful strategy as highlighted in the next section for neuroprostheses implanted in nervous tissue, one of the softest tissues in the body.

The Neuralink array has 3072 sensing sites spread across 96 soft filaments (6). The filament moves together with brain tissue and the device reduces neural damage and glial scar formation. Micro-flexible electrodes, nerve tassel electrodes, and syringe electrodes can reduce the inflammatory response during device implantation and change into a substance with a Young's modulus similar to that of brain tissue upon insertion (6). A way of fabricating electrodes into living tissue is by injecting gel into the body and forming a soft and conductive polymer gel that reduces tissue rejection (6). Sheet and reticular structures are developed to adapt to the shape of brain tissue (6). Hydrogels are commonly used in tissue engineering and drug delivery because they can be customized to mimic biological tissue in terms of water content and mechanical properties (6). It is a substance that reduces the possibility of rejection because it has viscosity, elasticity and other mechanical properties similar to the brain's mechanical properties. *Cullen et al.* developed "living electrodes" by encasing living cortical neurons within soft hydrogel cylinders to record and modulate brain activity (6). The substrate of a device is a main cause of the inflammatory response, so improving the biocompatibility of the substrate is a good option to reduce rejection reactions (6). Some methods to achieve this are through surface coating, doping, layer-by-layer self-assembly techniques based on electrostatic attraction, and covalent grafting. *Bahareh et al.* improved the biocompatibility of MEAs by coating the electrode surface with PEG and parylene-C polymers (6). Electrode arrays based on carbon fibers with silk support have been shown to elicit a reduced glial reaction (6). Research showed that encasing a silicon microelectrode array with a thick hydrogel coating reduced the chronic stage of FBR by 16 weeks (6). Another study demonstrated an array supported by a biocompatible and soluble material, PEG (6). Once implanted in the brain, PEG dissolves into a fluid, which allows electrodes to detach and move freely in brain tissue. *Spencer et al* reported PEG hydrogels with tunable thickness and elastic moduli can be applied to probes to reduce the strain caused by micromotion(6). *Seker et al.,* reported a nano-pourous gold surface coating that reduces astrocyte coverage while maintaining normal neuron coverage (6). Doping bioactive absorbent molecules with biomaterials

saves time and solves the problem of surface adhesion (6). Grafting and nanomaterials are used to mitigate adverse biological reactions(6). Research indicated that implanted microelectrodes coated with silicon nanopillars enhances neuron survival compared to those with a microstructured surface (6).

In order to design a neural probe that minimizes FBR the most, the mechanical properties of the probe need to match the properties of the brain as closely as possible. This includes softness, bending stiffness, elastic modulus and shape. To achieve this, we must learn more about the 3D structure of the brain and its mechanical properties. The properties of a probe must also be studied both individually and together to find the limits of the probes. Studies have to address all the mechanical properties, size, shape synergistically in order to fabricate a probe that can accommodate its limits and be as biocompatible as possible.

CONCLUSION

In summary, the foreign body response activated by implantable neural electrodes is an unavoidable process, but can be minimized by implementing the properties of different materials and electrodes to create a biocompatible device. The electrodes can minimize FBR using a variety of different ways, most commonly by making the devices more flexible, smaller, or using flexible and biocompatible materials. Choosing a flexible polymer substrate to use in an electrode can decrease the severity of the inflammatory response, but no matter how soft or flexible a probe is, FBR cannot be avoided (1). Research can be conducted on the long-term effects of FBR, on long-term safety and efficacy of neural probes, and strategies to maintain device performance and overcome impedance. The limits of the size or flexibility of a probe are still unclear, differ for each material and may become a limitation when conducting research with neural probes. An investigation of the synergistic effects of softness, bending stiffness, size and shape is important when trying to minimize FBR to allow devices to record for as long as possible.

DECLARATION OF CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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