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Recent advancements in Micro-engineered devices for surface and deep brain animal studies: A review

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ABSTRACT

Developing technologies for understanding the functioning of the brain and treating neurological disorders is an important area of research in neuroscience. Devices that form the neural interfaces have a significant contribution in progressing this field. Technological advancements driven by microfabrication techniques and materials innovation have led to the developing of a new class of engineered microelectrode devices. These miniaturized devices provide seamless neural interfaces as demonstrated successfully in animal models. Depending on the brain region to be studied and the application involved, surface and depth micro-engineered devices have been developed for recording or stimulating electrical signals. These devices have also shown potential to be used to treat neurological disorders such as epilepsy and parkinsonian. Strategies such as nanowires as electrode materials and polymer as flexible substrates have proven to help minimize the anti-inflammatory response and maximize the density of microelectrodes. This article provides a detailed overview of the recent developments in micro-engineered surface and depth neural devices used in various animal models.

1. Introduction

Neural Interfaces using micro-engineered devices (MEDs) have enabled clinicians to treat different neurological disorders (e.g., Parkinson's disease) [1]. Understanding how a brain function is of utmost importance in neuroscience. Spatial and temporal recordings of the electrophysiological information from the brain enable us to fulfill the desired objective. Recording of the electrophysiological signals was reported in the 1940s in human subjects using metal wires but is insufficient to understand the brain's functioning as it has vast neuronal circuitry [2]. Electroencephalography (EEG) is the oldest and widely used for investigating the brain, which utilizes electrical signals recorded from the array of electrodes attached to the scalp [3]. It provides a high temporal and low spatial resolution of the brain signals [4]. On the other hand, electrocorticography (ECoG) provides high temporal and high spatial resolution signals than EEG [5]. ECoG signals are recorded from the electrodes placed on the brain's cortical surface, usually kept under the dura. Epileptic seizures are successfully detected in a rat's brain using ECoG arrays [6]. ECoG signals are also used for real-time functional mapping of the cortex, as reviewed by Hill et al. [7] elsewhere. The innovation of materials and advances in micro-electromechanical systems (MEMS) based fabrication processes enabled the researchers to fabricate a wide variety of ECoG arrays that record and stimulate signals on the animal brain in recent years with a high density of electrodes [8–13]. EEG electrode arrays record electrophysiological signals from the scalp. ECoG electrode arrays can record electrophysiological signals from the cortical surface. These electrode arrays have a limitation of exploring or modifying the electrophysiological activity in the deeper regions of the brain [5].

In this context, depth electrodes are needed to record and/or stimulate the deeper areas of the brain using electrical signals. Various experiments are conducted, such as stimulation of the targeted brain areas, subthalamic nucleus, and pedunculopontine tegmental nucleus using metal microwires, resulting in improved conditions for diseases such as Parkinson's disease (PD) in animal models as stimulation protocols need to be tested in animal models before bringing it on to humans [14–16]. The advancements in MEMS-based technologies enabled researchers to fabricate miniaturized and dense electrodes [8]. The first-ever MEMS-

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based neural MED was reported in the 1970s for recording electrical signals from the cortex of a cat's brain, a well-known Michigan electrode array [17]. Researchers have developed several surface MEDs [9–13,18–20] and depth MEDs to fulfill various objectives such as the number of electrodes, compliance with the anatomical shape and targeted region, to stimulate or record electrical signals in the particular area of interest [21–30]. MEDs are fabricated as single shank single electrode, single shank multi-electrode, multi shank single electrode, and multi-shank multi electrodes depending on the application and target area. Each electrode can act as a recording or stimulation site. Multi-shank architectures help record signals from different brain regions simultaneously. For example, the Utah electrode array has a multi-shank architecture with one electrode per shank [31]. In contrast, shanks with multiple electrodes were developed by Shin et al. [32] and Wang et al. [33]. Apart from signal recording and stimulation, microneedles can also be used for delivering drugs at the targeted locations by incorporating microfluidic channels in such devices [32,34,35].

Surface or deep brain MEDs are made using conventional materials such as silicon (Si) or silicon on insulator (SOI) results in a higher neuroinflammatory response [36]. As an alternative, flexible materials using polymers such as Parylene C [37–39], polyimide (PI) [40–42], and polydimethylsiloxane (PDMS) [43–45]. These materials were extensively explored for developing soft neural devices that would cause minimal damage during and after electrode implantation [46]. Biocompatibility of materials used to develop neural devices is another crucial factor to be considered since foreign body response sets in immediately after implantation of the neural MED [46]. Further, the recording/stimulating electrodes are fabricated with the help of biocompatible materials such as Gold (Au), Platinum (Pt), Iridium (Ir) [23]. A few research groups have exploited carbon composites and polymer material as recording or stimulating electrodes in their MED design [47–49]. Lee M et al. reviewed soft and high resolution neural probes for chronic recording or stimulation [50]. Materials and various approaches required for flexible bioelectronic systems are reviewed elsewhere [51]. Cogan SF has reviewed different electrical requirements and characterization methods for recording and stimulation electrodes [52]. Lecomte A et al. reviewed mechanical aspects of chronically implantable neural probes [53]. In recent times, a chronically implanted microelectrode array on the motor cortex region of a human subject is used to record the electrophysiological signals. These signals are further decoded and sent as an input to the neuromuscular electrical stimulation system, which provides isolated finger movements [54]. Deep brain stimulation is clinically established as an effective therapy for patients suffering from several neurological disorders. The research community is working towards the development of MEDs by changing the electrode's architecture that improves the efficiency of the stimulation [55]. Research is progressing faster towards the development of chronic implantable neural devices in humans suffering from several neurological disorders. Understanding the neural interfaces from a deployment perspective (Cortical surface or deep brain) would also help the scientific community in a better way. As depicted in Figure 1, this review focuses on different MEDs (rigid and flexible MEDs) as neural interfaces

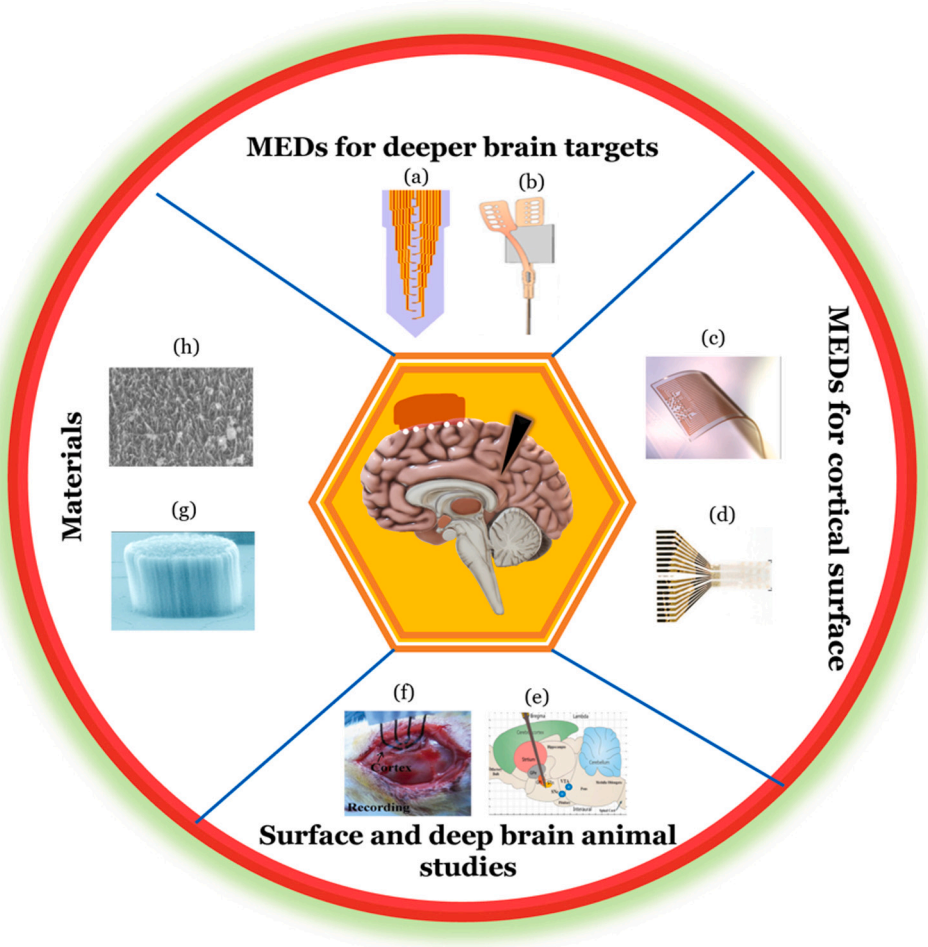

Fig. 1. Schematic representation of: MEDs for deep brain studies (a) [117], (b) [136]. MEDs for cortical surface studies (c) [45], (d) [77]. Schematic representation of depth MED penetrating the rat brain (e) [113], Image of the rat brain with surface MED (f) [83], and Images of materials (g) Adapted with permission from [49]. Copyright 2006, American Chemical Society, (h) [104].

in animal studies, majorly rodent models, by categorizing the discussion into MEDs for cortical surface and deep brain in vivo studies. This review emphasizes (a) criteria for choosing a material used in MEDs, (b) fabrication processes involved, and (c) region of deployment of a MED in the brain. In a few cases, the motive behind electrode design architecture and the necessary reason for the study is mentioned.

2. MEDs for cortical surface studies

Electrocorticography (ECoG) recordings are used during Awake Craniotomy to improve the resection of tumors without causing damage to functional cortex regions of the brain. ECoG plays a vital role in identifying resectable tumor regions along with the epileptogenic region. Although scalp electroencephalogram (EEG) can also perform a similar task with minimal invasion, EEG suffers from a poor signal-to-noise ratio (SNR).

2.1. MEMS-based hybrid (rigid and soft) devices for cortical surface studies

The substrate and electrode material in contact with the tissue used in MEDs need to be biocompatible [56], flexible [49,50], should have a low thermal coefficient [59] and have a conformal contact with the brain tissue to effectively stimulate or record the electrophysiological signals from the brain tissue [46]. Large area (80 mm × 80 mm) subdural ECoG recording electrodes are useful in clinical scenarios such as mapping epileptic foci on the cortical surface with a high degree of spatial resolution compared to EEG [9]. The Utah Intracortical electrode array was one of the early reported rigid MEDs [31]. This MED has 100 shanks of length 1.2 mm, where only the tip is conductive. These shanks are penetrated to record electrophysiological signals from the visual cortex region of a feline, and it proved to be better than the existing EEG recording arrays at those times [31]. But the limitation of the Utah electrode array is that it records only laminar information from the brain

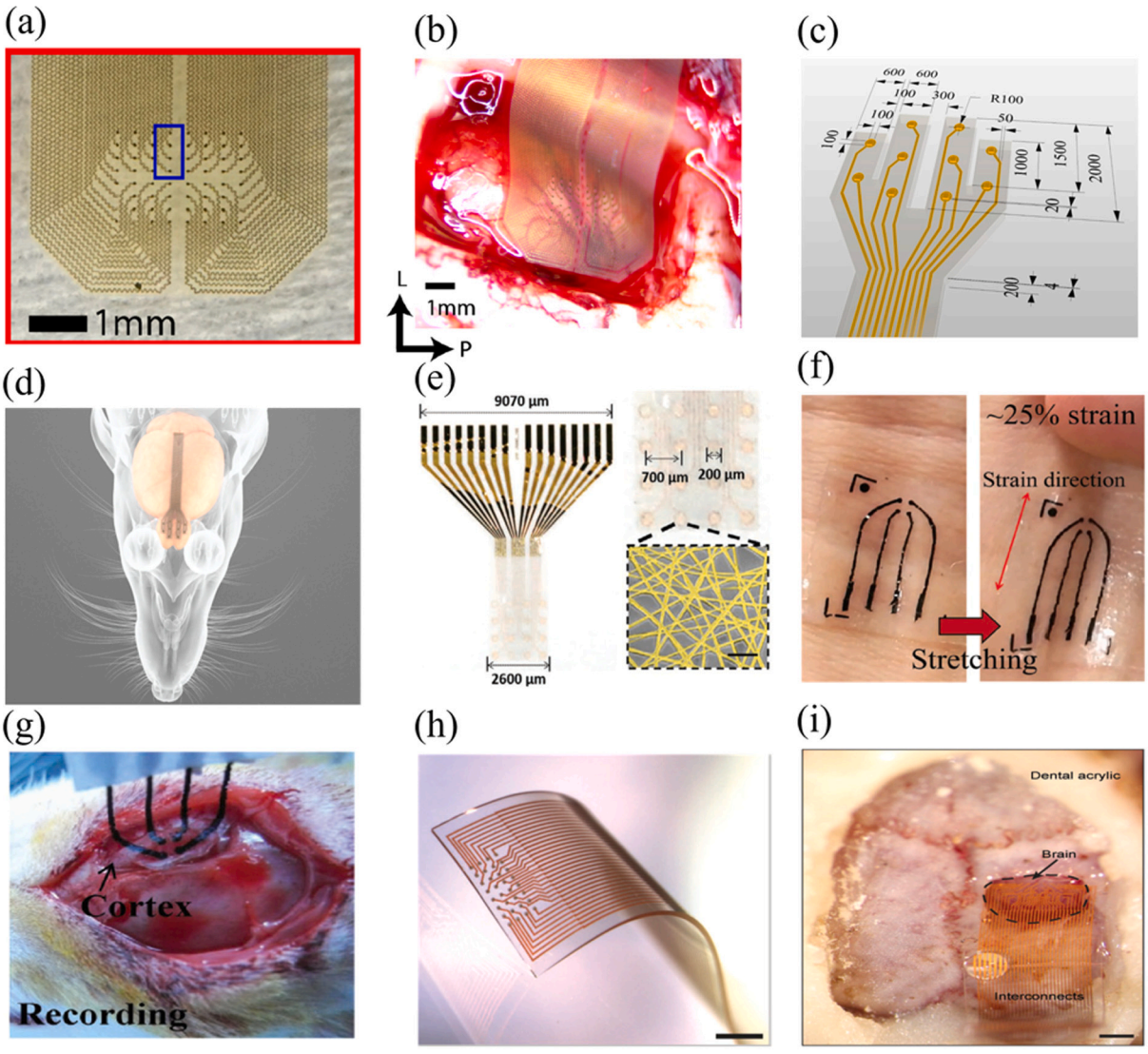

Fig. 2. Surface MEDs for animal studies. (a) Image of the SiC array electrodes for surface recording from a rat's brain, (b) Image of the SiC ECoG array implanted on the rat's primary visual cortex [11]. (c) Schematic representation of hybrid PDMS-Parylene C with electrode contacts (circular shape), (d) Schematic representation of hybrid PDMS-Parylene C with electrode contacts implanted on a rat for recording from olfactory bulb [76]. (e) Optical image of ECoG array made of Au Nano network with 16 recording sites, and SEM image can be found at the bottom and yellow represents Au Nano network. Scale bar, 5 µm [77]. (f) Image of the all-polymeric electrodes placed on the wrist and stretched all-polymeric electrodes with 25% strain, (g) Image of the four-channel all-polymeric electrodes placed on rat brain [83]. (h) stretchable 32 electrodes embedded in PDMS. Scale bar, 1 mm, and (i) Image of the rat's brain after placing stretchable 32 electrodes embedded in PDMS. Scale bar, 1 mm [45]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

area of 4 mm × 4 mm. Mismatch in mechanical properties between brain tissue and rigid substrates causes various scenarios such as tissue damage, triggering an inflammatory response that affects chronic recording [34,54]. In this regard, hybrid devices that incorporate silicon as an active material for fabricating high-density electrodes and a polymer substrate for improved interface with brain tissues offer an alternative for large area active electrodes with high spatial resolution. In one of the first such attempts, Viventi et al. [9] reported an actively multiplexed microelectrode array with 360-channels. With transistors fabricated using doped silicon nanomembrane of thickness 260 nm and PI as a substrate, a bendable multi-electrode array with an active area of 10 mm × 9 mm was developed and implanted in a feline brain's visual cortex region. Apart from high-density electrodes, the hybrid-rigid approach has another utility of providing seamless connector assembly to neural probes [10]. A dedicated connector assembly for interfacing the neural probe with a neural recording system requires a flat and rigid surface such as silicon, where the connectors can be die bonded. This approach was reported by Tolstosheeva et al. [10] Wherein, monolithic integration of the rigid silicon platform to the flexible electrode was achieved during the fabrication process. Silicon carbide (SiC) is alternate material that can be used to develop neural recording devices due to its attributes such as chemical inertness, biocompatibility, and feasibility with microfabrication processes. In a report by Diaz-Botia et al. [11] using heavily doped SiC with Titanium/gold (Ti/Au) as contact electrodes were fabricated on a silicon carrier wafer with a sacrificial silicon oxide layer. Freestanding SiC devices were obtained by etching the sacrificial oxide layer and were mechanically supported by PI film spin-coated and then patterned. The final SiC electrodes array (Fig. 2a) was implanted in a rat's brain (Fig. 2b), and ECoG recordings were obtained from the visual cortex region.

Another approach to developing a hybrid platform for electrophysiological signal recording or stimulating is to use bioresorbable materials. Several reports are published on bioresorbable materials that can dissolve over time without affecting the normal functioning of the body and prevent a second surgery for device extraction could find potential applications in neural studies [61–64]. These are an emerging class of materials that degrade enzymatically or by the process of hydrolysis when implanted, without causing any damage to the surrounding tissue and biological function of the body [61]. The low thickness doped silicon nanomembranes (~300 nm) offer controlled dissolution by hydrolysis and compatibility with microfabrication processes. Hence, they are suitable for such applications. Using a combination of silicon nanomembranes and a bioresorbable polymer, poly(lactic-*co*-glycolic acid) (PLGA), Yu et al. [65] developed a 64-channel bioresorbable device that can be used for recording ECoG signals from a rat model. This device is fabricated on an SOI substrate, using standard MEMS processing techniques, and later transferred onto a PLGA substrate to obtain the final device configuration.

2.2. Flexible devices for cortical surface studies

The popular silicon-based substrate materials such as Si, SiO_2, and noble metals such as Au, Pt have very high elastic modulus (~60–300 GPa) [66] compared to Brain tissue (e.g., rat) (~0.1–1.2 MPa) [52,53]. It is challenging to meet flexibility requirements for chronic recording with rigid materials [34,54]. To overcome this problem, flexible materials such as Polyimide (PI), Parylene C, Silk [35–37,55,56] [38–40,57–60], and other polymers [50,61], are used as substrate materials extensively. PI and Parylene C are the preferred polymer materials for use as a substrate in flexible ECoG devices, mainly because of their biocompatibility and compatibility with the existing microfabrication processes [12]. PI substrate offers high thermal stability, mechanical toughness, and flexibility and has been extensively used to develop flexible electrodes for surface recordings. Tuning the film thickness of PI substrate (from 100 μm to 2.5 μm) offers a method to improve the conformability of the device to the wrinkled surface of the brain cortex, leading to improved signal recording [35]. Therefore, PI-based devices have been extensively reported in recent years [9,71–75,77]. However, thin layers of Parylene C and PI pose difficulties in handling the devices during the fabrication process [76], and polymers cannot be subjected to high-temperature processes during fabrication [36]. PDMS suffers poor adhesion to metal layers. The PDMS-Parylene C hybrid layer has been used to overcome these limitations [76]. In this work by Lee et al., convex metal-coated PDMS-based microstructures are fabricated for ECoG recording. Molds are created in Si/SiO_2 wafer using lithography followed by Reactive Ion Etching (RIE), PDMS microstructures are obtained by replica molding. Ti/Au recording electrodes and contact pads were deposited using e-beam evaporation and then patterned using lithography, followed by metal etching. As shown in Fig. 2c, the protruding convex structures resulted in conformal contact of the recording electrodes with the dura matter above the olfactory bulb of a rat's brain (Fig. 2d). By nanopatterning, transparent neural electrodes can be developed using metals like Au. In a report by Seo et al. [77], a template of polymethyl methacrylate (PMMA) nanofibers was used to obtain Au nanonetwork that resulted in high optical transparency. This was achieved by first patterning photoresist on a colorless PI film-coated Si wafer with aluminum (Al) as a sacrificial layer. Chromium/gold (Cr/Au) was then thermally evaporated, followed by electrospinning of PMMA nanofibers, which served as a hard mask for Au nanopatterning. Dry etching followed by Photoresist (PR) removal was done to pattern Cr/Au and electrode opening. Another layer of the colorless PI was then deposited for passivation, and finally, the fabricated devices were released from the Si carrier wafer, realizing the device (Fig. 2e). For neural recording, the device is placed between the primary somatosensory and motor cortex. A confirmatory test to distinguish between signal and noise and absence seizure was generated by administering gamma-Butyrolactone. Table 1 summarizes the use of various MEDs in different brain regions in recent years.

Organic materials like Poly(3,4-ethylenedioxythiophene) doped with polystyrene sulfonate (PEDOT:PSS) offer an alternative for the electrode material, apart from conventional materials like Au, Pt, or Ir. There are multiple advantages of organic materials. For example, their ionic conduction is better than the metal electrodes due to their lower electrochemical impedance. This improves the detection of even low amplitude brain signals, constituted by ions like Na^+ and K^+, thus improving overall SNR [70,79–81]. In a report by Schander et al. [82], a 202-channel PEDOT:PSS coated electrode array was fabricated on a PI film coated on top of an oxidized Si wafer as a carrier wafer. After the patterning of Ti/Au electrodes, the second layer of PI is coated for passivation and then patterned using lithography and RIE. A thicker Au layer (3 μm) is deposited on contact pads and electrode regions for soldering and improved electrode stability during recording, respectively. To make the region of the electrical contacts compatible with the Omnetics SMD connector, a part of the PI coated Si carrier wafer was retained. At the same time, the rest was etched selectively by using lithography followed by the deep reactive ion etching (DRIE) process. Onto this rigid contact socket of Si, Omnetics SMD connectors were soldered. In the final step, PEDOT:PSS was deposited on the Au electrodes using the electropolymerization process. The fabricated electrodes are chronically implanted on the epidural region above the primary visual cortex of two macaque monkeys, and signal reliability was gauged by monitoring impedance spectroscopy data. To improve the stretchability of neural probes, creating wavy structures is an effective strategy. In a report by Qi et al. [83], a combination of intrinsic mechanical robustness and wavy microstructures of polypyrrole (PPy) was used to develop highly stretchable neural probes. The process of fabrication began with a patterning photoresist on an Indium Tin Oxide (ITO)-coated glass substrate. PPy was deposited on the patterned areas using electropolymerization, and then PPy nanowires were grown on the patterned regions. Thereafter, the photoresist was removed, and a half-cured pre-strained PDMS film was covered on the patterned PPy electrodes, and then the PDMS film was released from the strain after

Table 1
Summary of MEDs used for cortical surface studies from recent years.

Target region	Substrate material	Electrode material/ Dimensions	Comparative analysis	Number of electrodes/ electrode spacing	Reference
The sensorimotor cortex of a rat's brain	Parylene C	Ti_3C_2 Mxene and Au / 50 μm × 50 μm	Ti_3C_2 Mxene exhibited a four-fold reduction in interface impedance and higher SNR compared to Au electrodes	18 (Surface electrodes)/ 300 μm pitch	[85]
Three different places on the somatosensory barrel cortex of a rat's brain	Polyimide	Two arrays: Porous Au with electrodeposited PEDOT: PSS and PEDOT: Nafion / Diameter: 140 μm (porous Au)	Conformal contact with tissue, higher CIL	32 electrodes in each array / ~590 μm pitch along one axis, ~450 μm pitch along another axis	[78]
Rat's olfactory bulb	PDMS and Parylene C hybrid layer	Ti/Au / 100 μm × 100 μm × 20 μm (convexly protruded)	Conformal contact with the tissue and handling of the substrate layers is easy	10 electrodes on four arms / ~600 μm pitch (Along a single arm)	[76]
Somatosensory cortex (S1) of a rat's brain	Polyimide	Glassy Carbon or Pt with electrodeposited PEDOT: PSS/ Diameter: 300 μm	Higher SNR of Glassy Carbon compared to Pt	12 per array/ ~960 μm pitch	[18]
Sensory/motor cortex of a rat's brain	Polyethylene Terephthalate/ Indium Tin Oxide (or) polyimide	Ti/Pt /Diameter: 100 μm	Conformal contact with the tissue, handling thin films of polyimide poses a challenge	36 electrodes in each sample/ 470 μm pitch along one axis and 200 μm pitch (alternate rows were used for the study) along another axis	[86]
The primary motor cortex of a rat's brain	Parylene C	Ti/Pt / 1 mm × 1 mm (electrical contact area) (or) 130 μm × 300 μm (electrode opening)	Conformal contact with tissue	24 (four rectangular strips are used)	[87]
Recording field potentials from barrel cortex, and stimulation is performed on the motor cortex of a rat's brain	Polyimide	Porous Graphene/ 250 μm × 250 μm	Low interface impedance and higher CIL	64/ 500 μm pitch	[88]
Left primary sensory cortex of a rat's brain	Polyimide	Cr/Silver/Cr/Au / Diameter: 50 μm (at the tip of the electrical contact)	Conformal contact with tissue	32/ ~560 μm pitch	[89]
Regional boundary between primary somatosensory (S1) cortex and motor (M1) cortex a mouse's brain	Polyimide	Cr/Au nanonetwork/ Diameter: 200 μm	Low interface impedance	16 channels/ 700 μm pitch	[77]
Cortical surface of a rat's brain	Silk	Cr/Au/ Diameter: ~150 μm	Very good conformal contact	24, 49, and 100 channels/ ~500 μm pitch along one axis and ~ 830 μm pitch along another axis	[90]
Somatosensory cortex of a rat's brain	PDMS	Au-coated TiO_2 nanowires/ ~ 50 μm × 50 μm	Stretchable electrode grids	32/ 200 μm pitch	[45]

complete curing. The peeled-off device was 100% stretchable without any increase in the device resistance (Fig. 2f). Fabricated devices were implanted in a rat's brain (Fig. 2g), and signals were recorded for the normal and epileptic condition from the visual cortex region. Composite materials offer the advantages of the constituent elements and have become popular in making ECoG recording electrodes. Another way of using these composites is to coat the standard Si flank-like recording electrodes [84]. The idea is to improve the adhesion with the neural tissues, decrease the inflammatory response, and improve the electrical signal recording. Similarly, composites can be made using conventional material Au with a biocompatible metal oxide Titanium dioxide (TiO_2) to obtain electrodes (Fig. 2h) for chronic neural recording [45]. Being solution-processable, such composites can be solution cast onto any desired substrate and then patterned using standard lithography. The hydrophobic nature of the device can be observed in Fig. 2i.

3. MEDs for deep brain studies

MEDs are designed to stimulate and/or record signals from deeper brain regions, such as the subthalamic nucleus (STN) and pedunculopontine nucleus (PPN). As an example of application, depth electrodes, when used for deep brain stimulation (DBS) [91,92], which involves stimulating a particular region of the brain using an electrical pulse, have been helpful in treating patients suffering from PD [93,94]. Apart from STN, various brain regions are also exploited for stimulation to achieve multiple objectives [93]. In this regard, different microelectrode architectures are fabricated using MEMS-based processes for stimulating and/or recording neural signals from different regions of the brains of animal models. In recent years, the MEMS-based fabrication processes have yielded miniaturized structures (10^{-9}–10^{-6} m or lower orders) with good fidelity [8]. Towards this end, the scientific community has used different fabrication processes to develop various device architectures required to fabricate neural MEDs to understand various brain functions.

3.1. Rigid MEDs for deep brain studies

Si-substrate is conventionally used to fabricate neural MEDs because of its thermal stability, mechanical strength, and chemical compatibility with various MEMS processes [94]. Several neural depth MEDs are fabricated for potential use in animal models to record electrophysiological signals from different regions of the brain [28,95–104]. Recording the signals with high spatial and temporal resolutions gives a better understanding of the functionality of the brain. Silicon, a conventional material for fabricating MEMS-based devices, has been extensively used to develop high-density neural recording devices, where each probe has multiple electrode sites [21,32,102,103]. In a recent study, a Neuropixel with 384 recording channels has been used for recording signals from various brain regions. The main objective of this design is to cover a larger volume of the neuronal population with reasonably high spatiotemporal resolution. The activity of seven hundred isolated neurons was recorded simultaneously from different brain regions of an awake mouse by using two such devices [27]. In addition to the electrical recording sites, MEDs with L-glutamate sensing sites have also been fabricated to record the chemical activity among the neurons because neurons communicate both chemically and electrically

in central nervous systems [99]. In this design, Pt/Ti electrode sites were patterned using a lift-off process on an oxidized silicon wafer. Further reduction of the electrode impedance was achieved by electrodeposition of the platinum nanoparticles onto the electrodes. Since the impedance of platinum nanostructures was shown to have two orders of magnitude lesser than untreated platinum [104]. This device was implanted successfully, and signals were recorded from the striatum of a rat's brain. In another work, depth MED was fabricated with a microfluidic channel in addition to electrodes [98].

For a recording electrode, low electrode-tissue impedance is required for quality recordings [46,66]. The cables that connect the neural device with the electronics module need to be flexible to avoid tissue damage due to the force applied by micromotion of the brain and thus hinder the performance of electrode recording [105–109]. To overcome these, A. Schander et al. [26] integrated flexible ribbon cable made of biocompatible material monolithically on wafer level with the Silicon probe. In this way, the mechanical coupling of the recording device with the skull is reduced. Recording electrodes are made of Ti/Au coated with PEDOT: PSS, and action potentials are recorded from the deeper regions of the rat cortex. Another approach to fabricate neural device is by using amorphous silicon carbide (a-SiC) as a substrate material with 16 penetrating shanks with a cross-sectional area of less than 60 μm^2 [110]. Because of its lower cross-sectional area, the a-SiC penetrating neural device reduces the foreign body response and tissue damage [46]. The device successfully recorded spontaneous neural activity from basal ganglia from the zebra finch and the motor cortex of a rat [110]. Despite these advances in micro-engineered depth electrodes, it remains challenging to understand neuronal circuit interactions from the large distributed network of neurons in the brain and monitor coordinated activation between neurons.

In work by Rios et al. [25], implantable MED is fabricated with 1024 electrodes in a volume of 0.6 mm^3 to record electrophysiological signals from the hippocampus of an awake mouse. With increasing electrode sites, the electrode area needs to be reduced to keep the overall device dimensions to a minimum. The reduction of electrode area increases the electrode impedance, resulting in poor signal recording [46]. This issue can be resolved using in situ amplifiers beneath each electrode [97]. This was achieved in a report by Lopez et al. [97]. A CMOS neural probe with 455 electrodes with in situ amplifiers was fabricated with 52 simultaneous channel readout connections. The width of the metal interconnects used to connect electrodes and bond pads also need to be optimal, as decreasing the width of interconnects increases the capacitive coupling between metal interconnect lines [97]. The electrophysiological signals were recorded successfully by implanting the device in a rat's brain from the thalamus and cortex regions.

It is advantageous to have multiple shanks with multiple electrodes on each shank to obtain information on different layers from different regions simultaneously to understand activated coordination between neuronal networks. In a recent work by Shin et al. [32], a depth MED with four shanks (Fig. 3a) of different lengths were fabricated. Each shank had eight electrodes, and the shank length was determined as per the anatomical shape of the brain's hippocampal region. In addition, one of the shanks in this device consisted of a microfluidic channel for drug delivery, microelectrodes for neuronal recording, and a waveguide. This MED was used to record electrophysiological information from hippocampus CA1 and CA3 regions of a rat's brain. Apart from recording, stimulating specific regions of the brain, such as the internal globus pallidus and the subthalamic nucleus using electrical signals, has proven to improve patients suffering from certain neurological disorders, such as PD [111,112]. Focused efforts from the research community have been developing MEDs with stimulation capability to carry out experiments on various targets in animal models [113,114]. Zhao et al. [113] fabricated a MED to stimulate the subthalamic nucleus and record electrophysiological signals from the basal ganglia region by

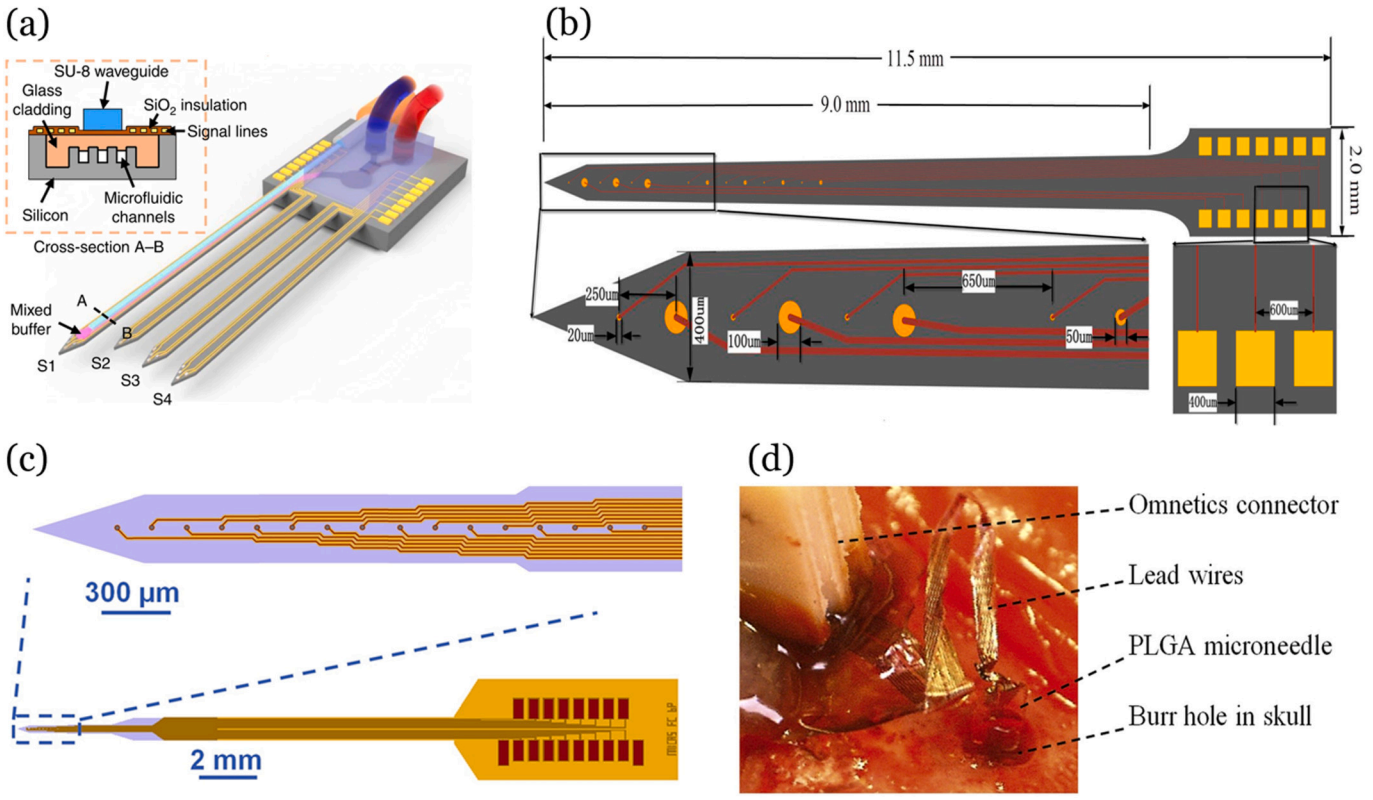

Fig. 3. Recently developed rigid and flexible MEDs for deep brain animal studies. a) Schematic representation of multifunctional multi-shank rigid MED with inset showing cross section of one of the shanks [32]. b) Schematic representation of rigid MED with electrode array [113]. c) Schematic representation of flexible MED bonded to PLGA, and d) Image of the rat's brain during implantation [117].

simultaneously using a dual-sided microelectrode array (Fig. 3b). To fabricate this MED, electrodes and interconnect lines (Cr/Au) are patterned on an oxidized Si wafer by lithography, followed by a lift-off process. Patterned metal is insulated by depositing the silicon dioxide layer using Plasma Enhanced Chemical Vapor Deposition (PECVD) technique. Finally, the electrode sites and bond pads area are exposed using DRIE. A limitation to the rigid MEDs is the mechanical stiffness of the substrate material that poses a risk of injury during implantation or post-implantation to the brain tissue. This injury can trigger an immune response and glial scar formation, adversely affecting the chronic recording [50]. To resolve this issue, in recent years, researchers have explored different flexible materials for use in neural MEDs.

3.2. Flexible MEDs for deep brain studies

Polymers such as Parylene C, PI are generally used as substrate materials in neural MEDs because of their biocompatibility [66], lower Young's modulus than conventional substrate materials such as Si, SOI, and their compatibility with microfabrication techniques [34,54]. In the work by Chung et al. [115], polyimide is used as substrate material, and Cr/Au is used as an electrode material. For polyimide processing, it needs to be deposited or spin-coated on rigid substrates such as Si, Glass (carrier substrates) to perform MEMS processing techniques. Chung et al. [115] spin-coated polyimide on a glass wafer. Cr/Au electrodes are patterned by the wet etching process. The surface roughness of the Au electrodes is modified using the RIE technique with optimal conditions to lower electrode impedance. While inserting the flexible device in the brain, buckling effects were observed [116,117,118]. To overcome these effects, a mechanical shuttle or a brace material that dissolves over time to coat the substrate is used to improve the stiffness temporarily [52,119]. In work by Ceyssens et al. [117], MED was fabricated using PI as substrate with 0.06 mm^2 cross-sectional area (Fig. 3c). Platinum/Iridium Oxide (Pt/IrO_x) was used as the electrode material to record local field potentials (LFPs) and spontaneous spikes from the somatosensory cortex region of the rat brain. This MED was thermally bonded to a layer of bioresorbable material PLGA to properly insert this device into the rat's brain (Fig. 3d).

In another work, Xue et al. [118] reported the fabrication of a porous

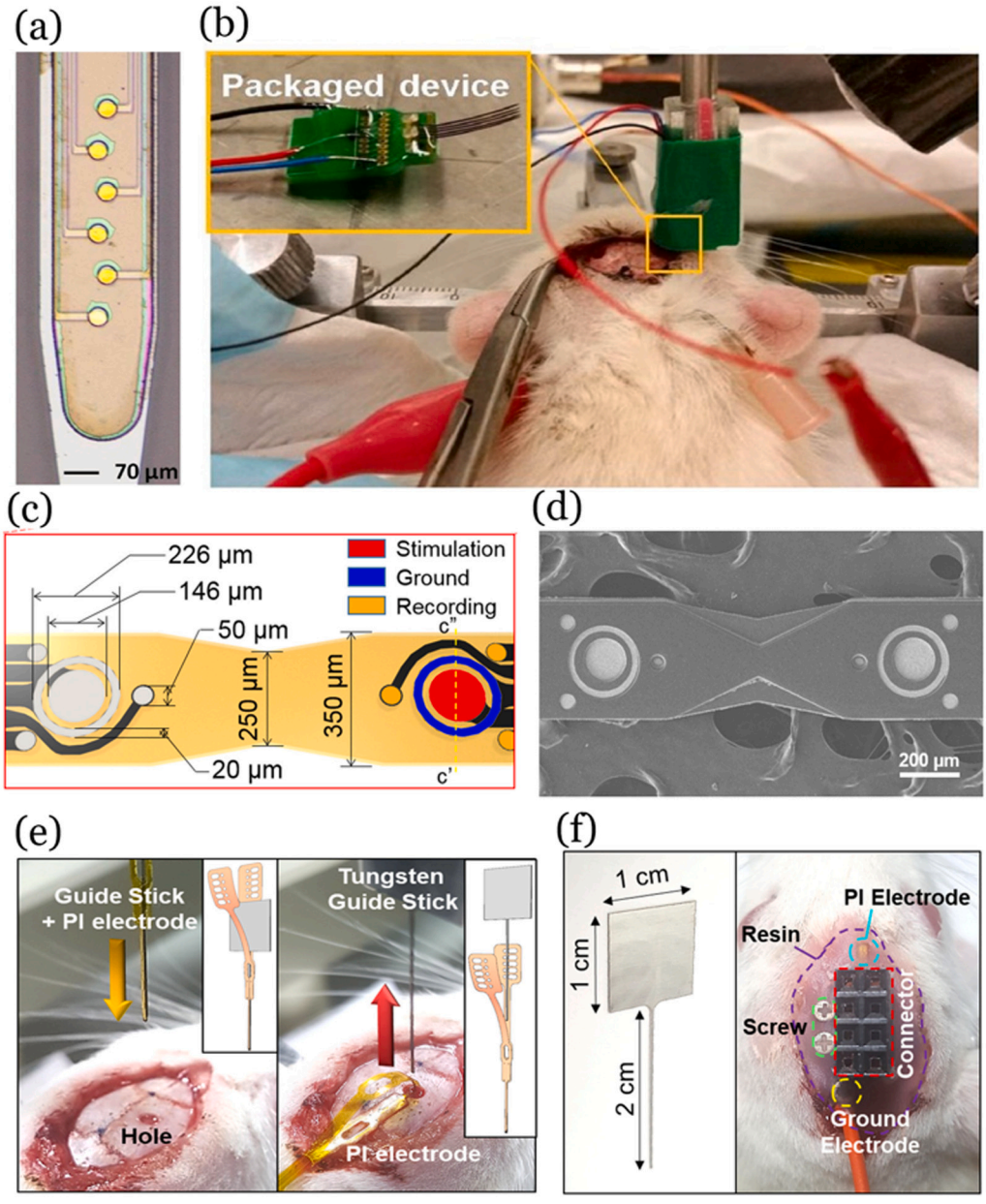

Fig. 4. Schematic representations, SEM image, Implantation images of MEDs for deep brain animal studies. (a) Photomicrography image of porous-Si MED with circular Au electrodes, (b) Image of the rat during implantation of porous Si depth MED, inset shows the packaged device integrated with necessary electronic modules [118]. (c) Schematic representation of the tip of the flexible MED for deep brain stimulation and recording electrodes, (d) SEM image of the fabricated probe tip, (e) Insertion method used for inserting flexible depth MED using Tungsten guide stick as a mechanical shuttle, and (f) Image of the Tungsten guide and completion of implantation with necessary components [136].

Si PI-based probe for neural recording. In this design, porosification of Si (PSi) is done using an electrochemical process [119], followed by deposition and patterning of polyimide layer (acts as substrate material once PSi dissolves), Ti/Pt, and another layer of PI (for passivation) using commonly used MEMS-based fabrication methods (Fig. 4a). The device is then packaged and implanted in the rat's brain, as shown in Fig. 4b. Since PSi dissolves within seven days [118], the PI layer in contact with the neural tissue does not give rise to any significant tissue immune response and glial scar formation compared to other rigid substrates [120]. This device successfully recorded LFPs from deeper regions of the rat's cortex. Since the brace materials dissolve over time, implanting the device at the desired location requires exceptional skills for the precise placement of the device such that the electrodes come in contact with the tissues at the chosen location. Implant movements are observed if the devices are implanted using rigid shuttles from the implanted site even though the shuttles are decoupled successfully [121]. A polysiloxane acrylate (PSA) based device was fabricated by Jung et al. [122] to resolve this issue. The additional advantage of using PSA is that it is compatible with conventional microfabrication techniques. Two components as precursors are used along with poly (ethylene glycol diacrylate) to facilitate tunable Young's modulus of the PSA (415 MPa - 1.34 GPa). However, the optimum value of Young's modulus of the PSA, to enable penetration in the brain tissues without causing them any damage, needs to be evaluated. During seizure activity, this device successfully recorded LFPs from the intracortical region at a 1.2 mm depth from the somatosensory surface of the mice.

Electrophysiological information flow between multiple brain regions is essential to understand the activated coordination between the neurons during brain stimulation. Therefore, devices with multiple shanks have been fabricated to record signals simultaneously from various regions of the brain. Primary considerations while fabricating such a device include keeping the width of the shank as small as possible to minimize the tissue damage and optimum stiffness to ensure penetration into the brain tissue. To fulfill these requirements, Wang et al. [33] fabricated a neural probe using a Parylene C as a substrate material and a biodegradable polymer (polyethylene glycol) as a brace material to temporarily increase stiffness in order to avoid the buckling effect during insertion of the flexible device [117,118]. In this work, Wang et al. [33] fabricated sixty-four electrodes with eight electrodes per shank. Conventional MEMS processes such as CVD and electron-beam deposition (a Physical Vapor Deposition process) were used to deposit Parylene C and Pt layers, respectively. Lithography, followed by DRIE and RIE processes to obtain the final device. Finally, polyethylene glycol is braced with the Parylene C probe with the help of PDMS mold, which can improve the mechanical stiffness of the flexible Parylene C device to penetrate the brain tissue [123]. This device was used for recording electrophysiological signals from the hippocampus of a rat's brain.

Stimulation of the targeted area in the brain improves neurological disorders such as PD, dystonia, and tremors [94,112,124–126]. But, the mechanism of the DBS is not fully understood as it is likely to act via several neuronal networks in the brain [127,128]. In this context, several researchers have carried out experiments on DBS in animal models to stimulate electrical signals and record electrophysiological signals simultaneously. A 14.9 mm long flexible neural device with 16 electrodes was fabricated by Lai et al. [126] using MEMS-based processes to stimulate the thalamic region, and evoked somatosensory potentials were recorded from a rat's brain. Another flexible material, Parylene C, is used as a substrate material in work by Castagnola et al. [127], Parylene C material is deposited using CVD at 700 °C onto a Si wafer (the final device was peeled off from the Si wafer). Circular Ti/Au electrodes were patterned using a lift-off process. Again, Parylene C was deposited on top of the patterned Ti/Au layer to passivate the interconnects. Electrode contact sites and contact pads were opened by using dry etching of the Parylene C layer. The signal-to-noise ratio of the recordings from the hippocampus brain region of the mice was compared for both cases and was higher in the case of PEDOT:PSS coated electrodes than non-coated electrodes. For a stimulating electrode, a higher reversible charge injection limit (CIL) is one of the essential requirements [44,64]. PEDOT:PSS has a higher CIL compared to noble metal Pt [128,129], because of which it has been frequently used as a coating material to the electrodes in their design [18,42,67–69]. Stimulation of the brain using electrical signals results in induced temperature changes which is an important consideration to avoid adverse effects of DBS [130,131,132]. Wang et al. [133] fabricated a temperature sensor to monitor induced temperature changes, and stimulation electrodes fabricated with Cr/Au material. Another challenge during brain stimulation is that the stimulating electrode may activate the unintended tissues in the neighboring regions of the target area. Improper design of electrode architecture may activate unintended tissue, leading to several adverse effects [134]. To enable the desired volume of tissue activation [135], J.H. Kim et al. [136] fabricated an extra ring-shaped ground around each stimulating electrode site, as shown in Fig. 4c-d. This grounding resulted in limiting the volume of tissue activation within the boundary of the ground electrode when stimulation is performed. Since PI requires mechanical support, it needs to be spin-coated over rigid substrates such as Si-wafers for the MEMS-processing, and the spin-coated layer can be released from the rigid substrate chemically or mechanically once the device is fabricated. In addition, platinum was chosen as an electrode material because of its high CIL over conventional noble metals [52]. Electrodes were fabricated on multilayers to reduce the width of the device, which in turn reduces tissue loss and iatrogenic damage [124,137,138]. Since PI is a flexible substrate, the flexible device was inserted into the rat's brain with the help of a tungsten guide as a mechanical shuttle, as shown in Fig. 4e. The device was integrated with necessary electronic components (Fig. 4f) for deep brain studies.

DBS has been used in clinical practice for more than two decades [139]. Commercially available DBS for humans have cylindrical electrodes, and generally, contacts are linearly stacked up, separated by some distance over a cylindrical substrate material [140]. The same electrode lead dimensions are used for stimulating different regions of the brain. Even if there is an error in the electrode placement by 1 mm, it has an adverse effect. This is because some of the targeted regions for DBS, such as the pedunculopontine nucleus or the STN, are relatively smaller. These DBS leads may stimulate a large population of neurons around the lead [141]. In this scenario, directional DBS has become a popular idea to direct the current to the intended target instead of conventional omnidirectional stimulation [141]. In the study by Connolly et al. [141], planar arrays of thin size compared to traditional leads used for human DBS were fabricated and assembled on a cylindrical carrier to achieve conformality. The electrode arrays were chronically implanted in globus pallidus and subthalamic regions of two parkinsonian non-human primates (NHPs). It was observed that directional stimulation consumes less power and increases the therapeutic window than omnidirectional stimulation [142]. In addition, various MEDs used for deep brain studies are summarized in Table 2. In the future, more pre-clinical trials are expected to be performed based on directional DBS on animal models and NHPs to improve the clinical therapy used for treating different neurological disorders using DBS.

4. Conclusions and future scope

In research, neural MEDs are widely used on animal models to carry out preliminary experiments to understand the brain's functioning and identify the regions of the brain associated with different neurological disorders. MEDs are fabricated by considering several important aspects such as (i) biocompatibility of the materials used, (ii) Young's modulus comparable to that of brain tissues, (iii) mechanical flexibility to achieve better conformality, (iv) Geometrical considerations such as area of the electrode, length of the shank for deep brain regions, (v) number of electrodes per device, (vi) electrical aspects such as low interface tissue impedance for recording quality signals, and (vii) high CIL for a

Table 2
Summary of MEDs used for deep brain studies from recent years.

Target region	Substrate material	Electrode material/ Dimensions	Comparative analysis	Number of electrodes/ electrode spacing	Reference
The sensorimotor cortex of a rat's brain (Insertion depth of 2.5 mm)	Polyimide	Pt /IrO_x/ Diameter: 18 μm	Good conformality of the device, risk of electrode displacement from the desired target region	16/ 150 μm pitch	[117]
The striatum of a rat's brain	SOI	Ti/Pt / Diameter: 15 μm (electrophysiological site) and 60 μm × 125 μm (amperometric signal site)	The rigid substrate may cause local tissue irritation	14/ 80 μm pitch (between electrophyoplogical sites) and 170 μm pitch (between amperometric signal sites)	[99]
Thalamus (5.4–6 mm ventral of the dura mater) and the cortex of a rat's brain	Silicon	Ti/TiN stack layer/ 5 to 30 μm (Variable diameters of electrodes)	CMOS compatible, rigid substrate may cause local tissue irritation	455/ 35 μm pitch	[97]
Inserted into the cortical tissue of the sensory motor area in the rat brain	Polysiloxane acrylate (PSA)	Cr/Au/ Diameter of ~20 μm at the end	A mechanical shuttle is not needed during surgery	8 channels/ ~60 μm pitch between the center of the electrode tips	[122]
Subthalamus region of the rat's brain	Polyimide	Ti/Au and Ti/Pt for recording and stimulation, respectively/ Diameters of 50 μm, 146 μm, Ground electrode: 226 μm (outer diameter of annular ring), 166 μm (inner diameter of the annular ring)	Good conformality of the device with the tissue, localized stimulation.	5 (one group) /center to center distance between recording and stimulation electrode is ~180 μm	[136]
CA1 and CA3 regions, CA1 and DG regions of the hippocampus of a rat's brain	Parylene C	Pt / diameter of 30 μm (exposed electrical region)	Good conformality of the device with the tissue, Multi region recording	64 per device/ 70 μm pitch	[33]
Hippocampal CA3 and CA1 regions of a mouse's brain	SOI	Ti/Ir/ 19 μm × 19 μm	May cause local tissue irritation due to rigid substrate, Multiregion recording	32/ ~25 μm pitch	[32]

stimulating electrode. In addition to these, the materials used in MEDs must be compatible with different MEMS-based fabrication processes. In this review, we have presented recently developed MEDs discussing the materials used therein and fabrication techniques employed, and various animal studies in which these MEDs were deployed. The goal of the researchers remains to find the MEDs that meet the mentioned requirements to obtain optimal performance. For example, Brain-Machine Interface presented by Elon Musk and Neuralink has a neural interface with 3072 gold electrodes coated with PEDOT:PSS and Iridium oxide, respectively. Electrodes coated with PEDOT:PSS showed less impedance compared to IrOx coated electrodes [13]. In another study, PEDOT:PSS electrodes were used to monitor the human brain in an intraoperative environment, replacing existing ECoG arrays [80]. Currently, PEDOT:PSS is extensively used as a coating material for electrodes because of its reasonably low electrode impedance (especially small electrode dimensions) and a higher CIL. There exist different deposition techniques for PEDOT:PSS such as spin-coating, electrodeposition, etc. Electropolymerized PEDOT:PSS has shown great behavior during cyclic voltammetry and stability experiments compared to spin-coated PEDOT:PSS [143]. In an observation by another research group, electrodeposited PEDOT:PSS using galvanostatic method (constant current) on Pt is prone to delaminate, especially with the increased thickness. Whereas, Potentiodynamic (cycling potential) method of electro polymerization of PEDOT:PSS on a glassy carbon is found to be homogeneous (morphology) and reproducible [18]. This observation is consistent with another reported work [144]. The growth and properties of PEDOT:PSS strongly depend on the underlying layer on which it is deposited. Also, different materials such as PEDOT:Nafion, Graphene, Mxenes, Glassy carbon are used as electrode materials in animal models, but the suitability to clinical therapies needs to be well established.

Further, Neural interfaces made of bioresorbable materials are drawing interest among the scientific community. Since bioresorbable materials dissolve over time, the need for retrieval surgery can be avoided. Millions of people worldwide suffer from diseases that lead to paralysis, in which the pathway between the brain and the muscles is disrupted. Chronic in vivo studies can record the functioning of the brain in real-time. These studies will help clinicians in better understanding various neurological disorders to facilitate effective treatments. High dense recordings need to be performed, but it poses a challenge in terms of supporting electronics required for processing those recordings. With the advancements in neural interfaces and microscopic Application Specific Integrated Circuit (ASIC) technologies that help in signal processing and wireless transmission, a patient with paralysis may use the Artificial Intelligence enabled microchip implanted on the brain to operate the smartphone or computers without using the fingers. These types of studies are successfully performed on some Non-Human primates (NHPs). Currently, clinical trials need to be performed on humans. These studies can be extended to several other neurological disorders. Also, electrode-tissue integration has been a challenge for long-term recording or stimulation. Research is progressing towards developing regenerative neural interfaces, where the seamless integration between neurons and implanted MEDs could be possible. The application of tissue engineering strategies may help to improve the integration of neural interfaces with the surrounding tissues. Using this, the ultimate goal of understanding brain functioning seems to be achievable and can lead to the establishment of effective clinical protocols for various neurological disorders.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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