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Flexible and biodegradable electronic implants for diagnosis and treatment of brain diseases

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In the diagnosis and treatment of brain diseases, implantable devices have immense potential for intracranial sensing of brain activity and application of controlled therapy for providing feedback to the sensing. Flexible materials are preferred for implantable devices, as they can minimise implanted device–brain tissue mechanical mismatch. Moreover, biodegradable implantable devices can reduce potential immunological side-effects. Biodegradability also helps avoid the burdensome secondary surgery for retrieving the implanted device. In this study, we reviewed recent advancements related to the use of flexible and biodegradable type of implantable devices for the diagnosis and treatment of brain diseases. Representative cases of intracranial sensing and feedback therapy are introduced, and then a brief discussion concludes the review.

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Introduction

Over the years, with the rapid rise in life expectancy, the number of patients suffering from neurological disorders, such as Alzheimer's disease (AD) [1], Parkinson's disease (PD) [2•], and epilepsy [3], has also been increasing significantly. Moreover, brain tumour still remains one of the most fatal types of cancer [4], notorious for its extremely low survival rate [5]. Therefore, research related to the development of novel methods for the diagnosis and treatment of brain diseases has been among the key areas of interest for both scientists and clinicians [6]. However, due to the poor accessibility to the brain, the continuous and accurate sensing of the brain activity and the application of controlled therapy for providing feedback to the sensing can really been challenging [7]. The brain's natural protective barriers, including the skull and blood–brain barrier, restrict direct continuous monitoring of the brain condition and inhibit efficient systemic delivery of therapeutic moieties to the brain [8]. This is where the implantable devices can act as a potential solution for the effective diagnosis and treatment of brain diseases [9–11].

For the development of implantable devices, several factors, including constituent materials [12] and specific functions of the device [13,14], need to be carefully designed. In case of an implantable device, flexible and biodegradable materials are preferred for its development [15,16], since a mechanical mismatch [17,18] between the implanted device and the brain tissue as well as the long-term exposure of the brain tissue to abiotic materials can induce immunological side-effects [19] and/or lead to abnormal neural behaviour. If the implanted device is biodegradable, the patient does not need to undergo the costly surgery essential to retrieve the non-biodegradable device from the brain [20•,21]. Meanwhile, effective sensing [22] and therapy of brain diseases involve various high-performance device functions [20•]. These include continuous monitoring of electroencephalography signals [23] and precise sensing of pressure [24••], pH, and temperature [25] inside the brain. For effective treatment, feedback therapies [26] via controlled drug delivery [27••,28–30] as well as electrical [31] and optical [32••] stimulations to the target brain region are also essential.

To enable the development of such a device, implantable devices fabricated using flexible and biodegradable materials and equipped with diverse sensing and therapy functionalities are being developed [20•,33]. Particularly, while fabricating the device, electronic materials (e.g. conductor [34], semiconductor [35], and insulator [36]) that possess the essential properties, such as mechanical softness and *in vivo* biodegradability, are being increasingly used [37]. For example, ultrathin films of alkaline metals [38] (e.g. Mg, Ca) and transition metals [39] (e.g. Fe, Zn, Mo, and W) are being used as conductors, submicron-thick membranes of silicon [40] and metal oxides [37] are used as semiconductors, and thin layers of nitrides [41], oxides [42], and polymers [43] are used as insulators. Metal conductors exhibit high conductivities, however, have limitations such as fast dissolution rates [44]. The fast dissolution rate can induce locally high concentrations of dissolved metal ions that cause potential toxicity issues. Silicon nanomembranes (Si NMs) are typically used for high-performance deformable devices due to its superb material properties and low flexural rigidity. Nonetheless, Si NMs have distinct disadvantages such as the inconstant dissolution rate that is strongly affected by ambient pH, ion concentrations, and types of ions as well as their brittle mechanical properties. Polymers are commonly used for encapsulation layer and substrate owing to their long-term stability, but paradoxically this stability functions as a shortcoming regarding the whole biodegradation rate of the device. A brief summary of the biodegradable materials, classified on the basis of their roles in various types of implantable devices used for brain diseases, is presented in Table 1.

In this article, we have reviewed the recent advancements in the field of flexible and biodegradable types of implantable devices used for the diagnosis and treatment of brain diseases. Firstly, we reviewed the various implantable sensors used for monitoring brain activities and conditions, such as pressure [24••], electroencephalography signals [32••], strain [45•], temperature, pH, and chemical elements [25]. Then, we studied the use of implantable devices for the treatment of brain diseases via controlled drug delivery [27••] as well as by sending electrical [31]/optical [46] stimulations to the intended region of the brain. Finally, we concluded this review with a brief discussion about the future outlook of the flexible and biodegradable types of implantable devices.

Flexible and biodegradable electronic implants for intracranial brain monitoring

Neurophysiologic monitoring is important for the diagnosis and treatment of neurological disorders [47]. Although conventional neurophysiologic monitoring devices are being widely used for intraoperative monitoring [48], users still find it difficult to use these devices for continuous long-term brain monitoring [20•]. In contrast, a flexible and biodegradable type of implantable sensor has the potential to perform outlong-term postoperative brain monitoring [45•]. This has paved the way for the use of diverse kinds of flexible [49] and biodegradable [50] electronic materials for the development of various implantable sensors. In this chapter, such flexible and biodegradable intracranial brain monitoring devices have been studied.

Single crystal silicon nanomembranes are one of the most typical high-quality semiconductors used in the development of biodegradable sensors [51]. Silicon is a rigid material; however, its nanoscale form, such as Si NMs, exhibits high mechanical flexibility [52]. Moreover, the nanoscale thickness of the material facilitates the *in vivo* degradation speed of Si NMs [40]. For instance, a flexible and biodegradable intracranial pressure (ICP) sensor could be fabricated using Si NMs. The biodegradable ICP sensor, enabling real-time monitoring of the intracranial pressure (ICP), which is a key diagnostic factor [53,54] in cases of brain diseases, such as traumatic brain injury [55] and hydrocephalus [56], was implanted in the intracranial cavity of a rat (Figure 1a) [24••]. Because of its flexible texture, the ICP sensor was able to endure the applied pressure without any mechanical fractures and be retreated back to its original shape when the applied pressure was removed. Moreover, the ICP sensor duly detected the deformable Si NM's piezoresistive responses, which were dependent on the external pressure changes. Depending on the posture of the subject animal, the device successfully monitored the *in vivo* ICP changes (Figure 1b). The ICP was increased under the trendelenburg position (30°C head-down) and decreased under the reverse trendelenburg position (30°C head-up). 25 days after the implantation, the sensing function disappeared due to the biodegradation of the device. It was observed that a relatively long measurement time could be attained using the thermally grown SiO_2 insulation layer, which protects the sensing layer (Si NM) from biodegradation by biofluids.

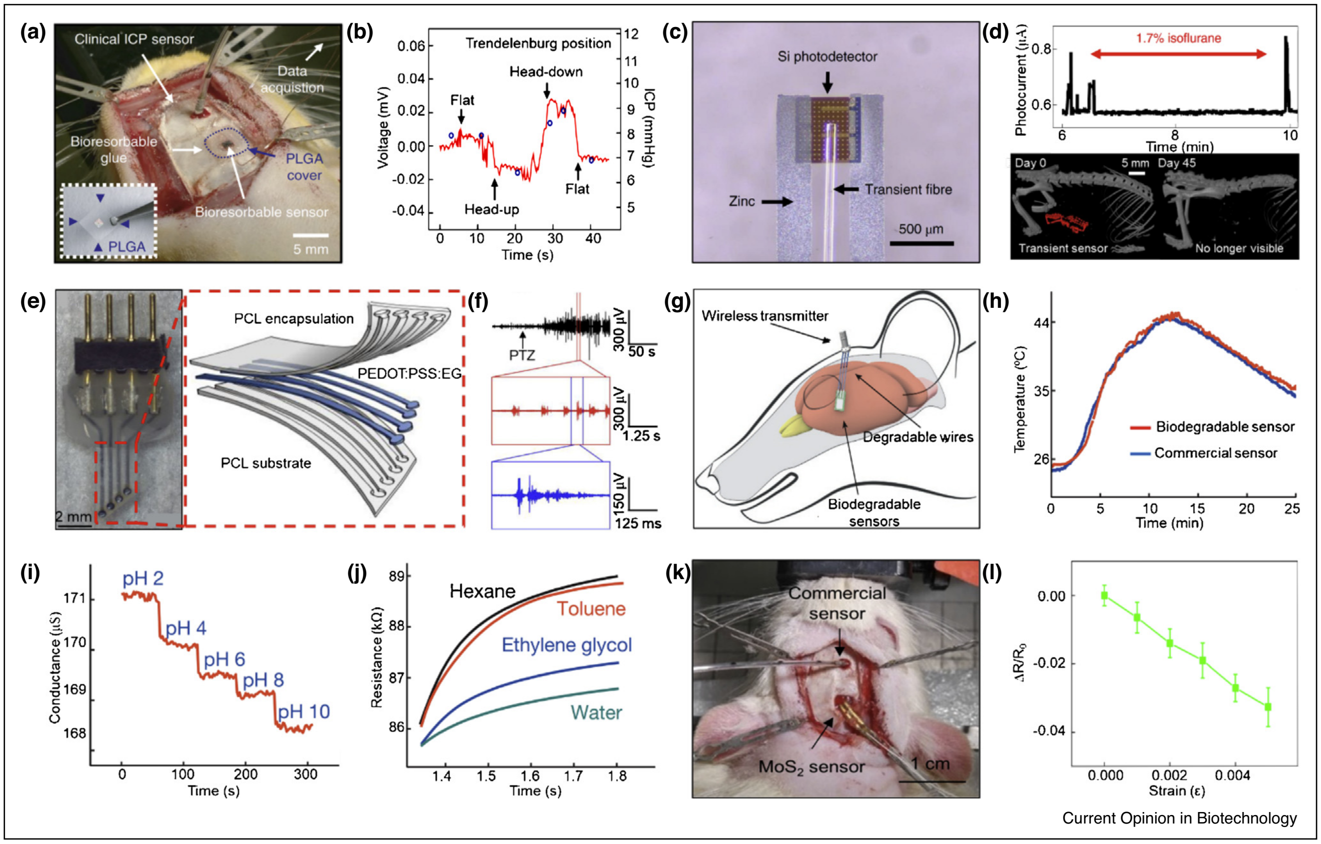
Interestingly, Si NMs can also be used to fabricate biodegradable photodetectors used for optical monitoring of neural activities. Bai *et al.* reported a biodegradable device composed of Si photodetector, Zn electrode, SiO_2

Table 1

Biodegradable materials classified as their roles in various types of implantable device for diagnosis and treatment of brain diseases

	Type		Conductor	Semiconductor	Insulator	Substrate/matrix	Ref
Diagnosis	Electrophysiology sensor	Electrical	PEDOT:PSS:EG	–	PCL	PCL	[44]
		Optical	Zn	Si NMs	SiO_2	PLGA	[32••]
	Pressure sensor		Mo, Cu	Si NMs	SiO_2	Si	[24••]
	Strain sensor		Mo	MoS_2	SiO_2	PLGA	[45•]
	Temperature/pH/chemical sensor		Mo	Si NMs	SiO_2	PLGA, Si	[25]
Treatment	Chemo/thermotherapy		Mg	–	–	PLGA/starch	[27••]
	Electrotherapy		Mg	Si NMs	SiO_2	PLGA	[31]
			Mg, FeMn		PCL	PCL, PLLA-PTMC	[66]
	Phototherapy		–	–	–	PLA	[46]

Figure 1



Flexible and biodegradable electronic implants for intracranial brain monitoring.
(a) Optical image of the biodegradable ICP sensor implanted in an intracranial cavity of a rat. **(b)** *In vivo* measurement of ICP of a rat in Trendelenburg and reverse Trendelenburg positions. Adapted with permission from Ref. [24••]. **(c)** Optical image of biodegradable photodetector for measurement of electrophysiological changes. **(d)** Photocurrent measured by the implanted photodetector in response to fluorescence modulated by neural calcium transients exhibits the effect of anesthetic induction (top). The photodetector is implanted in mice (bottom left) and degraded in 45 days after implantation (bottom right). Adapted with permission from Ref. [32••]. **(e)** Optical image of the biodegradable neural activity sensor (left) and schematic illustration of the constituents of the neural probe (right). **(f)** Epileptic activity recorded by the biodegradable neural probe after the injection of the drug. The red and blue box show an enlargement of the measured activity. Adapted with permission from Ref. [44]. **(g)** Schematic illustration of a biodegradable sensor implanted in the intracranial region of a rat for detection of temperature, pH, and biomolecules. **(h)** Measurement of intracranial temperature of a rat by the biodegradable sensor, compared with the measurement by a commercial temperature sensor. **(i)** Measurement of conductance variation depending on pH of surroundings near the biodegradable sensor. **(j)** Time-dependent resistance change measured by the biodegradable sensor with thermal actuation by Joule heating. The coefficients of thermal conductivity of hexane, toluene, ethylene glycol, and water are 0.12, 0.13, 0.26, and 0.60 W/mK, respectively. Adapted with permission from Ref. [25]. **(k)** Optical image of a biodegradable strain sensor using MoS_2 implanted in the rat. **(l)** Relative resistance change of the biodegradable strain sensor depending on the strain. Adapted with permission from Ref. [45•].

insulating layer, PLGA fibre, and PLGA substrate (Figure 1c). Subsequently, the device was used for the spectroscopic measurement of oxygenation, temperature, and Ca^{2+} [32••]. Consequently, the photocurrent signals recorded by the photodetector implanted in the mouse brain showed calcium suppression during the animal's anaesthetic induction with 1.7% isoflurane (Figure 1d top). Such real-time physiological monitoring can guide during surgical procedures and help in securing useful information required to plan drug dosages and rehabilitation protocols. Also, the device meets the clinically relevant timescales with respect to its degradation period (~45 days) (Figure 1d bottom).

Although alkaline/transition metals have been mainly used as a conductor in the biodegradable implantable devices due to their high conductivity, they have distinct limitations such as a short lifetime (a few days maximum) [44]. As a potential solution, conducting polymers can be used to extend the lifetime of the transient implants. Ferlauto *et al.* used a poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) mixed with ethylene glycol (EG) as the conductor in a flexible and biodegradable neural electrode array (Figure 1e). The neural activity of a mouse is successfully recorded before and after the injection of the convulsant drug through the transient neural probe, which is fabricated by using a polymer (e.g. PCL for insulator and substrate) (Figure 1f) [44].

Continuous monitoring of the brain temperature [57] and the precise measurement of the pH [58] in the brain are also important in the diagnosis of various brain diseases. For example, monitoring pH is important in the diagnosis of brain cancers, considering the low pH in the extracellular environment of tumor cells. A biodegradable electronic device was developed using Si NMs and Mo films used for sensing temperature, pH, and thermal properties of the intended region of the brain (Figure 1g) [25]. The accuracy of the device in sensing the brain temperature was observed to be similar to that of a commercial temperature sensor (Figure 1h). In addition, the device was able to measure the pH by gauging the conductance, which is inversely proportional to the pH (Figure 1i).

Sensing chemical elements is essential to diagnose AD and PD because the prognosis of such diseases is highly related to the concentration of neurotransmitters. Since thermal conductivity is an inherent feature of the materials, chemical sensing can be made through the measurement of the thermal conductivity. Coefficients of thermal conductivity of various materials can be calculated by measuring the rate of change in resistance after Joule heating (Figure 1j). However, the intracranial chemical sensing using an implantable device *in vivo* needs further improvements, because various biological elements in the brain environment interfere and prohibit the accurate sensing of the desired substance.

Although Si NMs have been known to be among the most widely used materials for flexible and biodegradable electronic implants [59], the use of other types of nanomaterials has also been witnessed over the years. For example, Chen *et al.* used a monolayer of molybdenum disulfide (MoS_2) for developing a flexible and biodegradable strain sensor [45•]. Thus, in this case, the device, which consisted of a monolayer of MoS_2 as a strain sensitive layer, Mo as an electrode, SiO_2 as an insulating layer, and PLGA as a supporting layer, was biodegradable. It was implanted in the brain of a rat and could make a conformal contact with the brain surface due to its ultrathin thickness (Figure 1k). Moreover, due to the extremely small flexural rigidity of the MoS_2 monolayer, the device was even able to detect minute strain changes (Figure 1l).

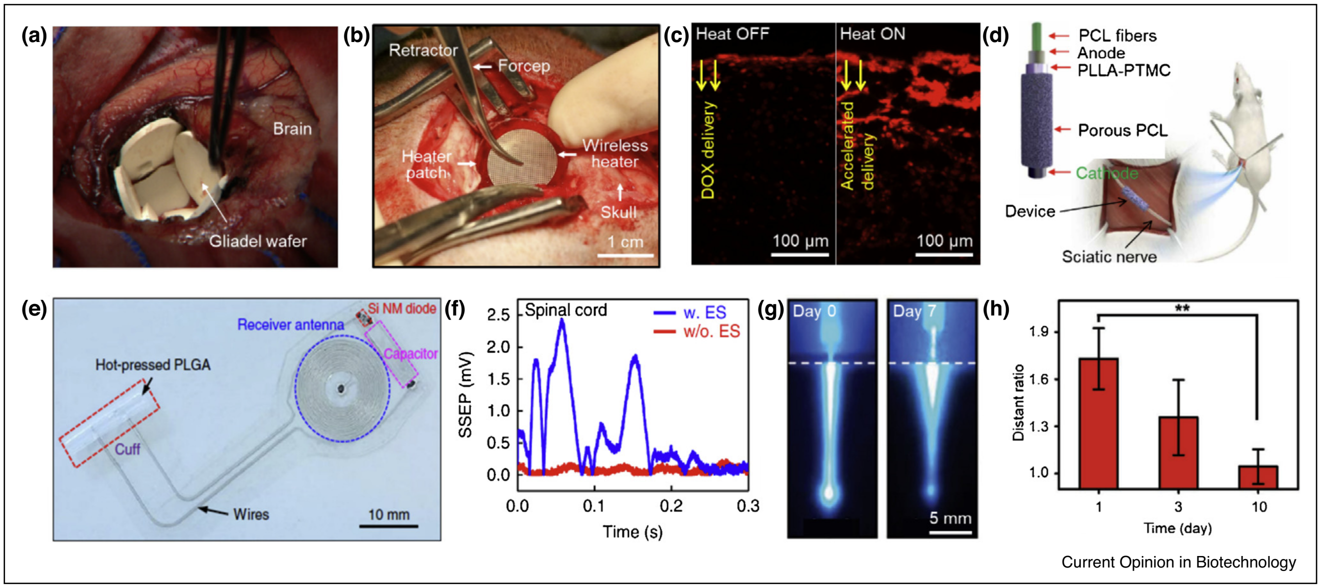
Since accurate sensing of the brain status externally is challenging due to the limited accessibility to the target brain tissue, intracranial sensing of electrophysiological signals [32••] and physiological conditions (e.g. pressure [24••], strain [45•], temperature, pH, and thermal properties [25]) by electronic implants helps decipher the status of the brain accurately. For example, monitoring intracranial pressure provides a diagnostic basis for infections, tumors, stroke, epilepsy, and hydrocephalus, and neurophysiologic monitoring can be used for the diagnosis of neurological disorders and traumatic brain injuries. Since tumor cells lower pH of their extracellular environment, pH sensing can be also used to diagnose the brain cancer. The detection of specific chemical elements is useful to detect various brain diseases such as AD, PD, and epilepsy, which are highly related to the concentration of neurotransmitters. As a result, the continuous intracranial monitoring of brain is important for the precise diagnosis of brain diseases [60] (e.g. brain tumor, traumatic brain injury, hydrocephalus, AD, PD, stroke, and epilepsy). After the accurate sensing of the brain status, the implantable devices can be used to diagnose the appropriate treatment essential to recover from the brain diseases [9].

Flexible and biodegradable electronic implants for treatment of brain diseases

Several intracranial treatment methods, including chemotherapy, electrotherapy, and phototherapy, have been found to be effective in the treatment of brain diseases [61]. The blood–brain barrier (BBB) acts as the major obstacle in the conventional systemic delivery of therapeutic agents to the brain [62]. The intracranial delivery of chemical drugs can help detour the BBB, thereby facilitating the obtainment of improved therapeutic efficacy [63]. Long-term electrical and/or optical stimulations to the brain, using the conventional rigid and non-biodegradable type of implantable device, could result in potential immunological side-effects due to the mechanical mismatch between the device and the brain tissue [64]. Thus, only the flexible and biodegradable electronic implants devoid of the aforementioned issues are being developed as an alternative. In this chapter, such flexible, biodegradable, and intracranial therapy devices have been discussed.

The drug-loaded polymeric wafer (Giladel® wafer, Arbor Pharmaceuticals, USA; Figure 2a) [65] is a representative example of the intracranial biodegradable implant used for localised drug delivery to the brain. Typically, it is implanted in the brain cavity after the surgical resection of the brain tumour. Then, the chemo-therapeutic drugs, which the polymeric wafer contains, are naturally released. This intracranial drug release can help prevent the recurrence of the brain tumour. However, there are several issues related to the wafer, such as its rigidity and limited penetration of drugs into the brain tissue, which still cause a hindrance in its effective application for the treatment of brain tumour.

Figure 2



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Flexible and biodegradable electronic implants for treatment of brain diseases.
(a) Optical image of the Gliadel wafer implanted into the cavity after surgical resection. Adapted with permission from Ref. [65]. **(b)** Optical image of a biodegradable patch integrated with electronics. **(c)** Fluorescence microscope images of the drug diffused from the patch into the tumor tissue in a mouse model *in vivo* without (left) and with external magnetic actuation (right). Adapted with permission from Ref. [27••]. **(d)** Schematic illustration of the exploded view of the self-electrified device (left) and the electrical stimulation to the scatic nerve using device (right). Adapted with permission from Ref. [66]. **(e)** Optical image of a biodegradable wireless electrical stimulator. **(f)** Measurement of a somatosensory evoked potential (SSEP) without (red) and with (blue) electrical stimulation. Adapted with permission from Ref. [31]. **(g)** Optical images of a PLA fiber in brain phantom before (left) and after (right) degradation for seven days. **(h)** Ratio of the moving distance with the optical stimulation and that without the optical stimulation at different time points. Adapted with permission from Ref. [46].

Lee *et al.* proposed a flexible and biodegradable patch-type electronic device (Figure 2b) [27••]. The flexible nature of the proposed device minimises its mechanical mismatch with the brain tissue. Mg was used to fabricate the flexible and biodegradable heater in the patch. Heat can be generated locally by the device in response to the external magnetic field. The generated heat facilitates deep penetration of drug molecules into the brain tissue and also accelerates drug release from the polymer reservoir in the patch (Figure 2c). The top encapsulation, which is composed of polylactic acid (PLA), suppresses the leakage of drugs in the cerebrospinal fluid (CSF). This, in turn, facilitates maximum delivery of the loaded drug to the brain and prevents potential side effects caused by the drugs in CSF. In accordance with the *in vivo* animal experiments conducted using xenograft mouse models, due to its characteristic favourable features, the device is capable of reducing the tumour volume substantially as compared to the control groups. However, the biodegradable property of the patch can be a drawback in consideration of the complete recovery from brain tumors. Electrotherapy is widely known to be effective in treating several neurological diseases, such as epilepsy and PD [66]. However, conventional electrodes have certain limitations as far as their use for electrical stimulation is concerned. These include a requirement of wiring and mechanical mismatch [67]. To overcome these challenges, electronic devices whose power can be supplied without wiring to the external power supply have been reported. One example is a self-electrified biodegradable device, which is designed for the electrical stimulation (Figure 2d) [66]. The device contains a miniaturized battery that enables the electrical stimulation during its biodegradation period. However, there is a limitation in that the electrical stimulation is possible only within the capacity of the biodegradable battery. Another approach is to use the wireless power supply to the flexible and biodegradable electronic implants [31]. The device consists of the Si NM diode, Mg/SiO_2/Mg capacitor, Mg antenna, Mg wire, and the PLGA substrate (Figure 2e). The antenna harvests power via radio frequency power transfer from the external energy source. Subsequently, the monophasic electrical pulse was delivered to the nerve through the cuff-type electrode, which was demonstrated in the spinal cord *in vivo* (Figure 2f). Although the device demonstrations in the brain have not been illustrated, the fully biodegradable wireless electronics have already exhibited their immense potential with respect to wireless intracranial electrical stimulations.

Because of its excellent spatiotemporal resolution, the optical stimulation with genetic modifications (i.e. optogenetics) has been drawing a lot of attention as a potential treatment for brain disease [68]. However, typical light sources, such as light-emitting diodes, are generally not composed of biodegradable materials [69]. Therefore, as a suitable alternative, a flexible and biodegradable optical fibre has been proposed for intracranial light delivery (Figure 2g) [46]. The optical fibre was fabricated using PLA, a biodegradable polymer, and its biodegradation was corroborated by the loss in light propagation. The applicability of the fibre was tested *in vivo*. After the injection of the virus, which genetically modifies excitatory neurons for optical responsiveness, the optical signal from the laser was transmitted to the site via the implanted optical fibre. It was observed that, as a result of the optical stimulation, there was a significant rise in the overall distance that the mouse moved on Day 1 (Figure 2h). However, the effect of the optical stimulation gradually decreased due to the biodegradation of the implanted fibre, whose size became much smaller on Day 10. The biodegradable implants for optical stimulations developed so far have relatively simple structures, such as a single-layer and single-function device, and thereby a more completely integrated device with multiple functional layers and composed of fully biodegradable materials needs to be developed.

The integration of sensing and feedback therapy is essential for the treatment of the brain disease [70]. However, unlike various other intracranial sensors, research related to the application of flexible and biodegradable type of implantable devices for the feedback treatment of brain diseases has been stunted. Many therapeutical approaches have been attempted for the treatment of brain diseases, but there have been a few treatment cases using the intracranial electronic implants due to many constraints related with the unique features of the brain. For example, the implantable treatment device should not involve any side effects. Consequently, the application of most such devices for the brain *in vivo* has not yet been observed. Accordingly, further research and development related to the various types of flexible and biodegradable electronics capable of facilitating the intracranial treatment (e.g. drug delivery, electrical stimulation, and optical stimulation) is still ongoing and more studies are still needed for the development of ideal intracranial treatment tools for brain diseases.

Conclusions and persisting challenges

In this study, the implantable devices have been considered as a novel solution for the diagnosis and treatment of brain diseases. This is because the natural protective barriers of the brain (e.g. skull and BBB) hinder the direct intracranial monitoring and systematic drug delivery to the brain. However, when it comes to the development of implantable devices, certain challenges have been observed, such as the mechanical mismatch between the implanted device and the brain tissue, immunological side effects in case of long-term intracranial implantation, and the high cost of surgery to retrieve the implanted device back from the brain.

In order to address these challenges, unconventional material and device approaches, using flexible and biodegradable materials, have been proposed for the fabrication of novel implantable devices. As a result, flexible and biodegradable electronic implants were developed, and their high performance and various device functions have been demonstrated through *in vivo* animal experiments. The specific device functions of these implants include precise sensing of electrophysiology signals and physiological conditions (e.g. pressure, temperature, pH, and chemical substances in the brain) and their ability to carry out feedback treatments via intracranial drug delivery and electrical/optical stimulations.

However, there are still many persisting challenges related to the effective application of these devices. Several biodegradable devices suffer from heterogeneous and non-simultaneous biodegradation, because of the different biodegradation rates of substances composing multiple layers of the device. From this point of view, more studies should be conducted to control and harmonize the biodegradation rates of the various biodegradable materials (Table 1) by adjusting the physical factors such as the thickness, crystallinity, and doping level. Such advances can be also helpful to prevent the unexpected toxicity issues, for example, potential cytotoxicity induced by the rapid degradation of alkaline metals. There are also remaining big hurdles with respect to their commercialisation. Although intracranial sensing has been successfully demonstrated in small animal (mouse or rat) models, there is a possibility that further demonstrations in the large animal models may reveal many unexpected clinical issues and biological obstacles. Furthermore, for future researches, limited candidates of biodegradable semiconductors, most of which include Si NMs currently, should be extended. Contrary to intracranial sensors, the application of flexible and biodegradable implants for intracranial treatment has not been explored much.

After the development of individual devices for intracranial sensing and treatment, their monolithic integration in case of multifunctional electronic implants, which can perform intracranial sensing, data storage, data transmission, processing, and are able to conduct feedback treatment, is another pressing challenge related to their application. Integration of wireless functions can lessen the burden related to the need to integrate various functional components. Therefore, future research efforts should be focused on device integration and optimisation in order to facilitate the development of flexible, biodegradable, and fully integrated implantable systems. Such future directions of research efforts for the development of flexible and biodegradable electronic implants are expected to play a significant role in the progress related to the diagnosis and treatment of brain diseases.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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