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Implantation of electronic visual prosthesis for blindness restoration

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Abstract: Loss of sight significantly degrades the quality of human life. Various methods for restoring the vision of blind patients have been studied and range from biological ways to electronic devices. Ever since a visual prosthesis device demonstrated that electrical signals have the beneficial effect of generating phosphenes, their subsequent development has progressed rapidly. Implantation of an electronic prosthetic device in a visually-impaired person allows the individual to recognize the phase and movement of an object. In addition, several commercially approved prosthetic devices have demonstrated successful long-term stability. However, there are some challenges that need to be solved. In this work, we assess the current technology levels of retinal prosthesis devices (categorized by implant location), and then suggest possible directions for future retinal prosthesis devices.

1. Introduction

Blindness is one of the most severe problems that degrade the quality of human life, rather than any other disease or disorder [1,2]. According to the World Health Organization (WHO), 285 million people worldwide suffer from vision loss, and 39 million of them are completely blind [3]. From a medical perspective, total blindness is defined legally as a corrected visual acuity of 20/200 or worse. Vision loss is usually a consequence of eye disease such as retinal degeneration or glaucoma [4,5]. For example, senile retinal degeneration, which occurs in elderly patients, results in the gradual loss of various types of retinal cells, leading to irreversible loss of vision. However, it is impossible to prevent the pathogenesis of ophthalmologic disease because of strong genetic factors and there is no effective treatment for blindness [6–8].

To improve the quality of life for total blindness patients, numerous efforts focused on visual restoration have been made over the past few decades [9–12]. Clinical trials involving gene therapy [13–16], stem cell transplantation [17,18], and electronic prosthesis [11,19–22], are in progress and several have shown positive results that may lead to future research on artificial vision. Gene therapy strategies include modification of retinal cells that contain a genetic defect (e.g., RP patient and certain types of AMD patient) or reactivation of remaining vision-related cells at the late stages of disease. Clinical tests have shown that gene therapy can delay retinal degeneration, as intended. However, gene therapy is limited to being a temporary treatment for the delay of disease if the ratio of damaged photoreceptors exceeds a certain level, and sufficient verification and clinical trials have not yet been performed [23–25].

In stem cell therapy, retinal pigmented epithelial cells are transplanted into the eyes of blind retinal degenerative patients and replace the existing cells [17]. However, as with gene therapy, this method has problems that it has less effect on severe patients since apoptosis may be continued in case of the end stage of the disease [26]. Therefore, for these patients, including

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those who suffer from total blindness, a prosthetic device that can replace vision itself is needed, and electronic devices that can serve as a bionic eye are being actively studied by many research groups.

A retinal prosthesis, also called a bionic eye, is fabricated based on the principle of converting an external light signal into an electric signal that is transmitted to the human optic nerve, which allows a person to perceive the electric signal as light [27,28]. In 1755, LeRoy et al. discovered that electrical stimuli elicit a sensation of light in the eyes of a blind person [29,30]. This phenomenon is called "phosphene", which is characterized by the experience of perceiving light in the absence of actual light stimuli [31]. Since then, research has hardly progressed due to the limitations of actual clinical trials; it was not until 1966 that the first human trials could be conducted [2,27]. Due to the breakthroughs in technologies for the fabrication of implantable electronic devices, retinal prostheses have undergone considerable development over the last few decades. Electronic retinal prosthetic devices have not only been tested in animal trials but have also been implanted in total blindness patients who need their treatment. Although the ultimate goal of retinal prosthesis is to generate a device that is very small but yet capable of enhancing vision without the need of additional equipment, users must wear a very bulky ancillary device in current stage [32,33].

In this work, we introduce electronic retinal prosthesis devices that have been developed by various research groups and suggest future directions for the continued development of retinal prosthesis. Electronic retinal prosthesis devices can be placed either in the brain, optic nerve bundle, retina, or subretinal space to provide direct electrical stimulation, and clinical trials are currently being conducted (Fig. 1) [14,34–36]. Some of these devices are commercially available and their effectiveness has already been verified [19,32,37]. We will comprehensively emphasize such devices as shown in Table 1, and evaluate their practicality. We are confident that the advancement of this technology will contribute immensely to an improved quality of life for blind people in the future.

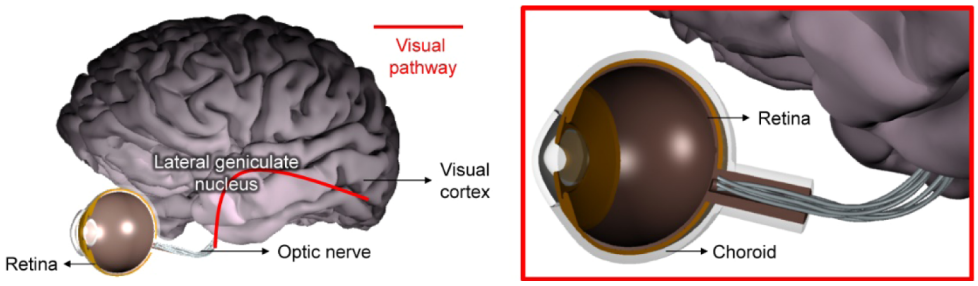

Fig. 1. Visual prosthesis along the visual pathway

Table 1. Visual prosthesis devices and applications

Device	Country	Institute	Approach	Stimulating electrode			Clinical trial	Reference
				No. Array	Dia-meter	Pitch		
N/A	USA	Schmidt Team	Visual cortex	38	37.5 μm	500 μm	Light perception	[38]
N/A	USA	University of Utah	Visual cortex	100	100 μm	400 μm	-	[39]
N/A	USA	Illinois Institute of Technology	Visual cortex	192	30 μm	500 μm	-	[40]
N/A	Belgium	Universite Catholique de Louvain	Optic nerve	6-30	1-5.5 mm	-	-	[41]
N/A	Japan	Osaka University Medical School	Optic nerve	3	0.5 mm	0.5 mm	-	[42]
OpticSELINE	Switzerland	Ecole Polytechnique Federale de Lausanne	Optic nerve	12	50 μm	200 μm	-	[35]
C-Sight	China	Peking University	Optic nerve	18	150 μm	2.5 mm	-	[43,44]
POLYRETINA	Switzerland	École Polytechnique Fédérale de Lausanne	Epietinal	2215	80 and 130 μm	150 μm	-	[10]
Argus I	USA	Second Sight	Epiretinal	16	260-520 μm	800 μm	20/3240	[6,45]
Argus II	USA	Second Sight	Epiretinal	60	200 μm	525 μm	20/1260	[32,46]
EPI-RET3	Germany	RWTH	Epiretinal	25	100 μm	500 μm	Light perception	[33,47]
N/A	Germany	Fraunhofer Institute for Biomedical Engineering	Epiretinal	24	70 μm	750 μm		[48]
MARC	USA	North Carolina state University	Epiretinal	100	-	-	-	[49]
IRIS II	France	Pixium Vision	Epiretinal	150	-	-	-	[50,51]
BRI	USA	BRIP	Subretinal	15	400 μm	-	-	[52]
Alpha IMS	Germany	Retina Implant AG	Subretinal	1500	50 μm	70 μm	20/546	[22,53–55]
ASR	USA	Optobionics	Subretinal	5000	9 μm	-	20/400	[56,57]
PRIMA	France USA	Pixium Vision & Stanford University	Subretinal	142	20 μm	75 μm	-	[58–61]
N/A	Taiwan	NTHU-NCTU	Subretinal	16	75 μm	490 μm	-	[62]
STS	Japan	NIDEK	Supra-choroidal	49	500 μm	700 μm	Light perception	[63]

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2. Visual cortex

2.1. Brain cortex for visual prosthesis

The possibility of using electricity to restore the sight of blind people was first proposed following the discovery that electricity causes a sensation of light [12,27]. In 1966, experiments were started on the subject of electrical stimulation of the human visual cortex. (Figure 2a) However, experiments at that time were at a basic level and physiological complexity made it difficult to conduct further studies [27]. Visual signals are processed by cells of the retina and are sent to the brain via the optic nerve. The optic nerve sends neural signals to the visual cortex through the LGN (lateral geniculate nucleus). The researchers suggested that more complicated phosphenes can be recognized by blind subjects because the neural signals along to the visual pathways of the cortex are much complicated and expanded compared to that of the distal sites [64]. In addition, risks associated with the cerebral cortical device, such as intracranial hemorrhage and infection, and the lack of implantable devices made the clinical application of such devices difficult.

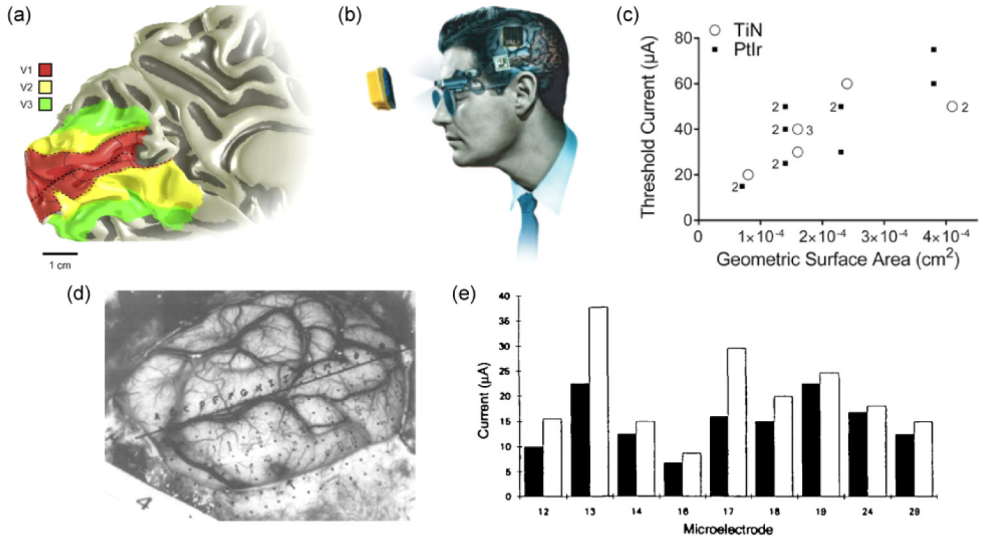

Fig. 2. Visual Cortex stimulation. (a) Medial view of the occipital cortex showing location of V1, visual area 2 (V2), and visual area 3 (V3), based on retinotopic mapping experiments with functional magnetic resonance imaging (fMRI) [73]. (b) A conceptual design of an intracortical visual prosthesis [40]. The threshold current versus geometric surface area for electrodes. TiN coated electrodes are indicated by open circles and uncoated PtIr electrodes are indicated by solid squares [69]. (d) Photograph of exposed surface of the right visual cortex of the blind subject. The overlaid dots, at ~2.4 mm spacing, were reference points for surface stimulation [38]. (e) Comparison of threshold currents of nine microelectrodes using cathodic-first (closed bars) and anodic-first (open bars) stimulation. Stimulation parameters: F = 200 Hz, PD = 200 us, TL = 250 ms [38]. Reproduced with permission from Ref. [73], copyright 2010 Elsevier Ltd and [40], copyright 2003 Wiley and [74], copyright 2010 Elsevier Ltd and [38], copyright 1996 Oxford University Press.

2.2. Visual cortex stimulating devices

Early experiments by Brindley, Dobell, and others showed that visual cortical stimulation leads to phosphenes (Fig. 2(b)) [27,36,65,66]. Brindley and Lewin obtained independent phosphenes from subjects capable of recognizing phosphenes corresponding to 80 cortical surface electrodes [36,65–67]. However, due to the relatively large surface of the electrodes, the threshold current for

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generating phosphenes was very high (Fig. 2(c)) and the resolution of the generated phosphenes was low [68,69]. After this initial experiment, a device with a penetrating electrode array was studied in order to fabricate high resolution cortical devices [39,70–72].

In 2003, Philip Troyk's research team (Illinois Institute of Technology, USA) reported an animal model for research on a visual prosthetic of the cerebral cortex [40]. In the existing visual prosthetic research field, research has been conducted that was focused on the biostability of hardware, since animal models cannot provide linguistic reports of visual perception. The research team modeled a visual prosthesis study of the cerebral visual cortex using a new animal psychology test to compensate for the lack of linguistic reports. The modeled cerebral cortex visual stimulation device is comprised of external components, including an external camera, a video processing module and coil, an implantable stimulation module, and an implantable electrode array. Penetrating microelectrode arrays surround the cortical surface and are connected to a fully implanted electronic stimulator module via a lead wire cable. Power for device operation and wireless communication of the stimulation module is accomplished through an inductive link through the skin. The transmitter coil on the surface of the scalp is driven by an external transmitter connected to a video processing system in which a real-time video camera provides visual input. In terms of the anatomy and function of the visual cortex, experiments were conducted with a rhesus monkey as a subject, because of its similarity with humans. Although at a preliminary stage, this study showed that animal models can be used in prosthetic studies to complement components of the linguistic report. However, additional development and testing are needed to understand the proper interpretation of psychophysical results and the ultimate limitations of the model [40].

The Schmidt team studied the validity of visual prosthesis using microstimulation of the visual cortex of people who were completely blinded by glaucoma. (Figure 2(d)) Experiments were performed by implanting an IrOx penetrating microelectrode into the right visual cortex of the subject near the occipital pole, and various phosphene results were reported, ranging from pinpoint to disk-shaped. The Schmidt team improved phosphene recognition results by replacing the long pulse train length (TL: 3,000 ms) with 10 shorter ones (TL: 200 ms) (Fig. 2(e)). Resolution was improved by using intercortical microelectrodes for cortical stimulation instead of surface electrodes. Penetrating electrodes at intervals of 500 μm formed individual phosphenes, but not at 250 μm. This resolution was five times higher than the resolution that was normally achieved. In addition, the threshold current value of phosphene formation was reduced by more than two-fold. The potentially large microelectrode density and low power consumption requirements of intercortical microelectrodes, as compared to surface stimulation, are favorable to this type of visual implant. However, issues with control of electrode insertion depth and brain tissue damage still remain, and additional studies of blind people are needed in order to optimize the stimulation parameters and test complex image recognition [38].

3. Optic nerve

3.1. Optic nerve stimulation

In several studies, electrical stimulation of the peripheral visual system and the visual cortex was performed [2,35,43]. Certain parts of the brain, including the visual cortex, are responsible for the final processing of visual signals. Visual signals are transmitted to the brain by traveling through a bundle of optic nerves that extend from behind the eyeball to the brain. For the restoration of vision, electrical stimulation was directly applied to the optic nerve bundles. As with visual cortex stimulation, only a few clinical trials have been conducted because the procedure requires head surgery to stimulate the deepest part of the human nerve system [35]. The electrical device that is used to stimulate the optic nerve usually targets the intracranial sections of optic nerve bundles [75]. This electrical device is composed of two parts: one is an implantable device that provides stimulation, in which a self-sizing spiral cuff-shaped electrode surrounds the optic nerves behind

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the eyeballs. The other part is an external signal processing device that is connected to cables that transmit electrical signals to the device through the back side of the ear.

3.2. Optic nerve stimulating devices

Attempts to restore visual acuity by applying an electrical signal to a blind person's visual pathway, particularly the optic nerve, were initiated using a spiral-shaped electrode to stimulate the intracranial optic nerve [76]. A schematic image of the device is shown in Fig. 3(a), and the position of the electrode that surrounds optic nerves is clearly depicted. Figure 3b shows photographs of a typical visual prosthesis used for optic nerve stimulation. An early model of prosthesis was plate type that had several rigid penetrating electrodes composed of platinum-iridium alloy, which was further developed into a device with a cuff shape with self-sizing functions. This device, which was designed for RP patients, is expected to have a beneficial effect on patients who lost the majority of their retinal cells because of the disease. Furthermore, it may be more effective for advanced RP patients because a certain portion of ganglion cells and bipolar cells remain intact even on the retina of a terminal RP patient; that is, retinal device (epiretinal, subretinal device) can damage those remained cells. The device was implanted into a 59-year-old female patient, and nerve stimulation experiments were performed two days after the implantation. The research group conducted an experiment to assess the location of phosphene. The patient's head was carefully fixed and the orientation of the device was also fixed for calibration in which the direction of the pupil during stimulation was checked. During

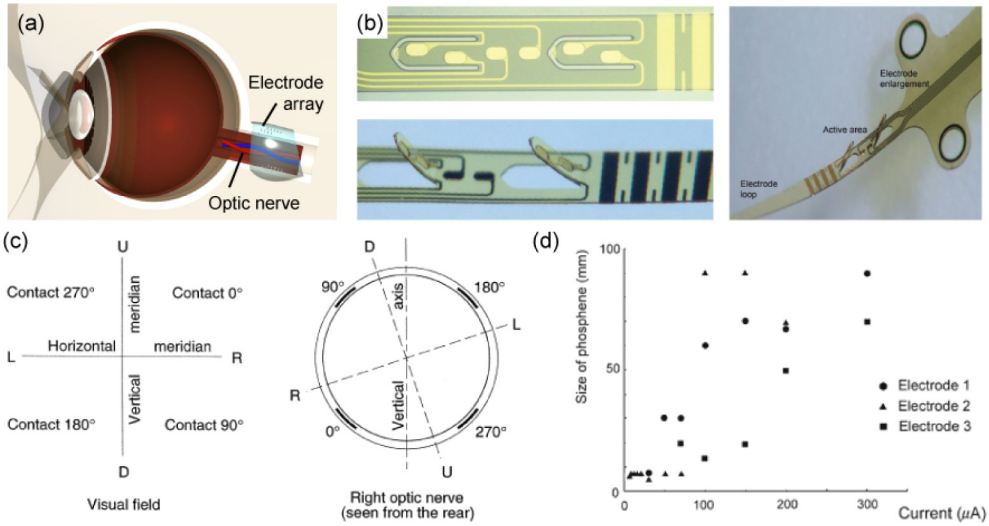

Fig. 3. Optic nerve stimulation. (a) Schematic image of penetrating optic nerve electrical stimulation system. (b) Photographs of OpticSELINE cuff-shaped stimulating electrode device. Reproduced with permission from Ref. [35]. (c) Retinotopic organization of the volunteer's optic nerve. Reproduced with permission from Ref. [76], copyright Elsevier. The probable position of the 4 contacts (labeled 0°, 90°, 180°, and 270°) around the optic nerve is indicated on the right; on the left, the quadrant–contact relationship refers to the position in the visual field of phosphenes elicited when stimulating through a given contact. (d) The relationship between the size of the perceived phosphenes and the electrical stimulation. The sizes of the perceived phosphenes were significantly larger with higher electrical currents (Spearman rank order correlation: electrode 1 $r = 0.865$, $P < 0.05$; electrode 2 $r = 0.706$, $P < 0.05$; electrode 3 $r = 0.893$, $P < 0.05$). Reproduced with permission from Ref. [42], copyright Springer Nature.

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118 days, a total of 1,465 phosphene locations were identified with four contact electrodes, and the correlation between visual field location and optic nerve stimulation location was verified. Figure 3(c) shows the retinotopic organization of the subject's optic nerves [41,44,76]. There was an angle difference of approximately 20 degrees between the anatomically verified human vision and experimental results from optic nerve stimulation. Results of this experiment showed that the expression of phosphene results from electrical stimulation has a specific trend, which was a very encouraging result.

Based on these experimental achievements, optic nerve stimulation clinical trials that tested electrode position, signal threshold, and shape or size of phosphenes were conducted. Tano group (Osaka University Medical School, Japan) investigated the efficacy and safety of artificial vision based on direct optic nerve stimulation [42]. A 35-year-old female RP patient with no light perceptions in her right eye was enrolled in the study. She had lost her vision 4-years earlier. The duration of the stimulus pulse was 0.25 ms/phase with a frequency of 40-320 Hz. As shown in Fig. 3(d), the phosphenes generated by optic nerve stimulation through the electrodes were roughly distributed and their sizes were significantly larger with a higher electrical current, from 5 to 300 μA.

4. Epiretinal prosthesis

4.1. Epiretinal device

The epiretinal device, which is the most general type of retinal prosthesis, is implanted on the ganglion cell layer, which is attached to the topmost part of the retina [77]. Implantation on the retina is performed with a form of weak pressure on the retina, which allows direct stimulation of ganglion cells [78,79]. Conventional devices capture an image through an external camera or a photodetector, then transmit the photographs to the epiretinal device after several signal processing and image compensation steps [78,80]. These devices are usually connected with cables and wires to facilitate effective electrode stimulation. The advantage of an epiretinal device is that it is easier to perform the surgical procedure to upgrade the device, and it does not require subsequent surgery as compared to the aforementioned visual cortex stimulation or optic nerve stimulation methods [81]. While the previously mentioned methods, such as visual cortex stimulation and optic nerve stimulation, required the resident doctor to reside because of the sensitive implantation site, the retinal device is relatively stable and is easy to commercialize. Moreover, the commercialized epiretinal device can control the stimulation electrode wirelessly, which means it allows the patient to control the intensity of phosphene that he or she wants to obtain using wireless operation; therefore, it is easy to personalize and customize the device for individual patients.

Epiretinal approaches have been studied by many academic and industrial groups, confirming that dot-like electrical stimulation on the retina surface (i.e., ganglion cells) causes visual perception and elucidates phosphenes. At the beginning of the study for epiretinal approach, a human trial conducted by Humayun et al. (University of Southern California, USA, [28,82,83]) verified that the patient recognized phosphene resulting from electrical stimulation by the electrode array. Rizzo and Wyatt's team implanted a 10-μm-thick thin-film microarray in six human subjects and suggested the possibility of developing future retinal prosthetic devices.

4.2. Epiretinal device with human trials

Argus (Argus I and Argus II, Second Sight Medical Products, Inc., USA) is the most well-known and commercially initiative epiretinal device and was the first to be approved by the FDA (Argus I) and to be approved by US and European clinical trials (Argus II) as the retina prosthetic device [32,33,37]. Argus I was transplanted into six subjects between 2002 and 2004. Argus I consists of a 4 by 4 electrode array with a range from 260 to 520 μm, total 16 platinum electrode, on the

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retina surface. Figure 4(a) presents the schematic illustrations of the basic structure of Argus I device, and Fig. 4(b) shows the fundus image of their stimulating electrode on the retina surface which consists of 16 electrodes in 4×4 array. This stimulating device of Argus I transmits signals from the external device with a cable that extends from the inside of the eyeball to the backside of the ear. After the implantation of Argus I, subjects were able to distinguish objects and detect the movement of the moving bars throughout trainings [80,83]. However, they could not recognize more complicated shapes or arbitrary shapes, suggesting there is a limitation to the resolution of the electrode array. In 2015, the Humayun group investigated the 10-year chronic effects of the Argus I device [84]. A 55-year-old male patient confirmed the surgery prognosis 10 years after transplantation of Argus I, and it was found that the distance between the electrode and the retina was approximately 290 μm, which means approximately 30 to 40 μm away from the retina over time compared to the distance when the electrode was just implanted (Fig. 4(c)), which caused the increase of the electrical stimulation threshold current. Fortunately, it is confirmed that physical or biological degradation had not occurred, and phosphene expression and the ability to detect objects were maintained.

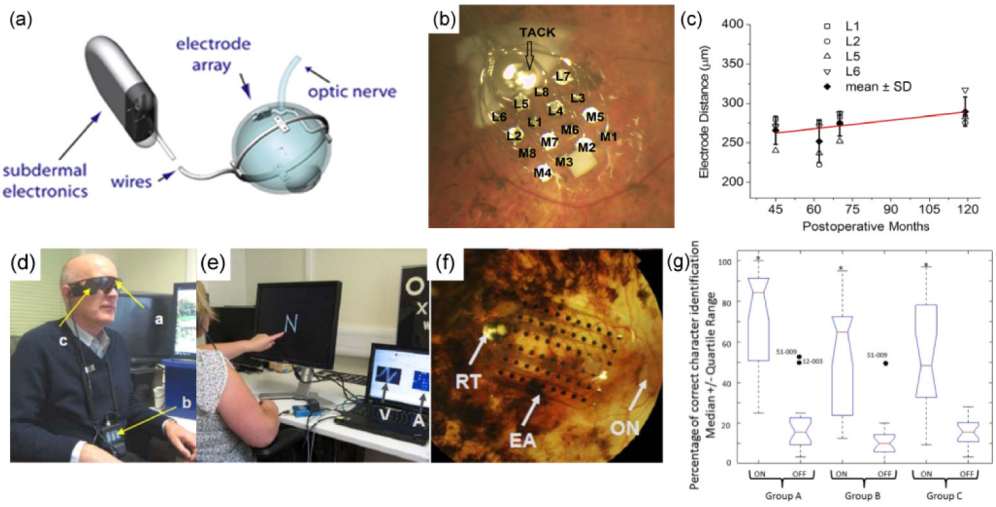

Fig. 4. Epiretinal prosthesis. (a) Diagrams showing the schematics of the Argus I implant and (b) the electrode array on the retina. (c) Graph showing the changes in the electrode–retina distance with the postoperative time. Electrodes L1, L2, L5, and L6 are electrodes on quadrant 4, and they represented by squares, circles, up triangles, and down triangles, respectively. Mean distance of all 4 electrodes are presented by filled diamonds. Red line = linear regression of the mean; SD = standard deviation. Reproduced with permission from Ref. [84], copyright Elsevier. d-f) Clinical trials of Argus II. d) Photograph of a subject with the Argus II system showing the video glasses (**a**), the Video processing unit (**b**) and the inductive coil (**c**). (e) Subject showing the format for the letter identification tasks with a letter displayed on a monitor in white on black, Century Gothic font. The monitor on the side shows the real time map of the electrodes being stimulated in the array (**A**) and the camera view (**V**); note that the actual test is carried out in the dark. (f) Fundus photograph of the retinal stimulating array in situ. The optic nerve is indicated and the retinal tack that secures the electrode array is clearly visible. (g) Box and whisker graphs illustrating the median percentage correct and quartiles for Test I letter Groups A, B and C comparing the device on and off. Group A represents easy letter group, B is medium, and C is complicated letter group. Reproduced with permission from Ref. [32], copyright BMJ Publishing group.

To overcome the low spatial resolution of the 16-electrode array identified by Argus I, the same industrial group developed the Argus II that had improved performance (Figs. 4(d) and 4(e)) [32].

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The Argus II consists of 60 electrode arrays (Fig. 4(f)). The basic configuration and principles are the same as Argus I, but the number of the electrodes was increased to improve resolution. As shown in Fig. 4 (g), the patient can identified English letters even the complex letters (Group C letters). With the help of Argus II, a subject can have a corrected vision of 20/1262.

4.3. Intelligent medical implants

Intelligent medical implants (IMI) are models developed by the Intelligent Implants GmbH company [19]. They particularly emphasized the precise implementation of image by processing iterations through a computer-aided leaning process. The image is trimmed by a signal processor and is then stimulated on an implanted device consisting of 49 electrode arrays. The device was implanted in a total of seven subjects, but performance was only confirmed in the clinical trial because there was no real-time image capture system for the commercialization such as a camera.

Although several epiretinal devices have been developed, the reduction of information occurs with this downstream stimulation since every stimulated ganglion cells has same polarity and waveform even though they have different functionality such as contrast, motion, and edge [75,85]. Furthermore, the mechanical fixation of the device for the adhesion between retina surface and the device, which is based on applying pressure on the retina, may cause implant dislocation, inflammation, cataract, haemorrhage, and corneal oedema [47,86]. In addition, the threshold current of the epiretinal device is relatively large compared to the subretinal device [87].

5. Subretinal device

5.1. Subretinal stimulation device

In the subretinal approach, photodiodes are implanted under the retina to generate a current that stimulates the retina (Fig. 5(a), 5(b)). Eberhart Zrenner's group in Germany is sponsored by the German government and research is ongoing [88]; additionally, research has also been conducted by Optobionics, USA [89]. Placing the device at the level of photoreceptors allows the signal processing of the retinal interneurons to be used to generate physiological vision, which reduces the demand for image processing. Another advantage is that only a relatively simple, low current microphotodiode-based device is required [23,57,90].

The optoelectronic subretinal implant converts light coming through the photodiodes into an electrical signal. (Figure 5(e)) However, current photodiodes do not produce enough charge to stimulate the retinal cells. In fact, there are studies showing that pure photovoltaic currents do not provide enough charge to stimulate bipolar cells [91]. Therefore, most of subretinal implants require additional power supplies, such as near-infrared radiation or RF (radio frequency) power transmission, and a connection unit for data transmission [92]. In addition, it is important to place visual stimulation electrodes close to the target neuron cell to achieve low threshold current and high resolution, which is typically done using protruding electrodes or penetrating electrodes [2]. From a surgical perspective, subretinal implant placement is technically challenging because of the high surgical difficulty and adhesion between retinal pigment epithelium (RPE) cells as a result of degeneration (Fig. 5(f)) [77].

5.2. Subretinal device (ASR)

The artificial silicon retina (ASR) microchip device is a silicon-based device with a diameter of 2-mm, contains approximately 5,000 microelectrode tip microphotodiodes and is powered by incoming light. IrOx electrodes were electrochemically deposited for each 20 μm × 20 μm square pixel [57]. The device has a pixel current of approximately 10 nA. In a clinical trial reported in 2004, ASR microchips were implanted in the right eye of six RP patients. All ARS devices functioned electrically during the 6- to 18-month period.

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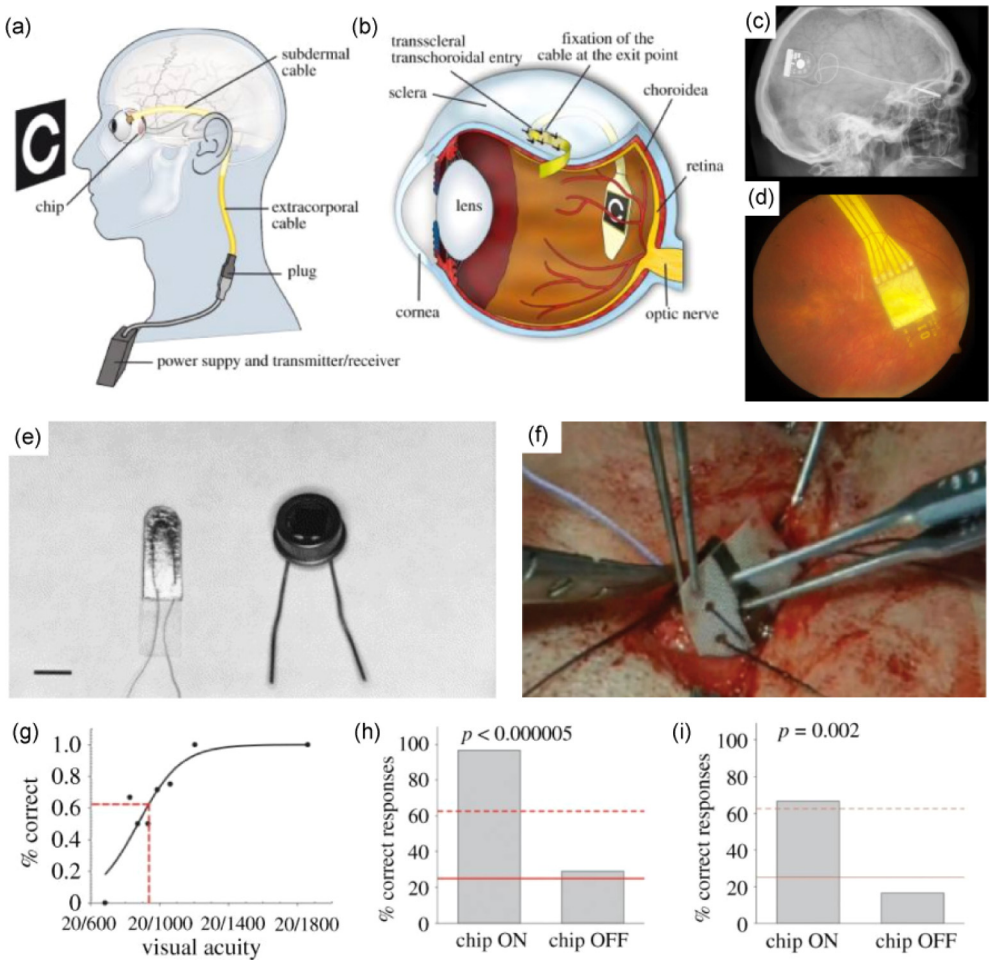

Fig. 5. Subretinal prosthesis. (a) The cable from the implanted chip in the eye leads under the temporal muscle to the exit behind the ear and connects with a wirelessly operated power control unit. (b) Position of the implant under the transparent retina [54]. (c) Retina Implant Alpha IMS: clinical setting. Illustration of the placement of the receiver coil and the power supply cable in an X-ray image. (d) Image of the Retina Implant Alpha IMS on the eye fundus [55]. (e) Photograph of a large external photodiode and the connected bipolar strip electrode. Bar, 5 mm [89]. (f) Photographs of the decisive surgical step for implantation ; Fixation of the silicone patch by sutures to the lateral orbital rim [34]. (g) Landolt 'C' ring used in clinical tests of visual acuity. (h) Letters (8.5 cm high, 1.7 cm line width). (i) Random dot pattern moving in four different directions to assess spatio-temporal resolution. The inserts under each panel show the best results of patient 2 with the chip turned on and chip turned off. Solid line, chance rate; dashed line, psychometrically accepted recognition threshold; probability p as estimated from the binomial function [54]. Reproduced with permission from Ref. [54], copyright 2010 The Royal Society and [55], copyright 2013 The Royal Society and [89], copyright 1997 Elsevier Science Ireland Ltd and [34], copyright 2008 BMJ Publishing Group Ltd.

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All subjects displayed visual improvement and no subjects showed symptoms of infection, inflammation, erosion, retinal detachment, or migration. At the retina site far from the implant, an unexpected improvement in visual function occurred. The need for further research was raised to validate results of these studies. However, the final conclusion of this company's efforts – before going out of business – was that ambient light alone could not stimulate a significant number of neurons [57,89].

5.3. Subretinal device (Alpha IMS)

Retina Implant AG (Reutlingen, Germany) and Zrenner's team developed a hybrid device consisting of microphotodiodes and a microelectrode array [22,93]. The device is composed of an active chip with 1,500 independent microphotodiode arrays (MPDA) and 16 titanium nitride electrode arrays for direct stimulation to retina using external power. (Figures 5(c), 5(d)) The MPDA consists of 1,500 independent photodiode-amplifier-electrode units, each of which transforms the local luminance information into an amplified electrical current that stimulates adjacent bipolar cells [87]. Thus the luminance-based electrical image is sent to bipolar cells and is processed inside the retina and in the visual pathway. Each electrode of the chip typically emits a pulse of 5 Hz for 1 ms to create a flickering perception that can be divided into up to nine levels [22]. Alpha IMS is distinguished from ARS in that it is an active device that uses external power for signal amplification. A 15 cm cable is connected to the external plug at the back of the ear and is responsible for signal control, power, and external stimuli. Clinical trials of RP patients with more than seven patients that lasted for four weeks have been successfully performed [34]. The majority of these subjects (86%) were aware of light as a result of clinical trials conducted from 2010 to 2014. Phosphenes were generated when stimulation was applied by electrodes at intervals of approximately 1 degree; subjects recognized figure patterns such as a point, line, and rectangle (Figs. 5(g)-5(I)) [54]. The highest recorded visual acuity was 20/546, but its durability and lifetime were not optimized.

Alpha AMS (Retina Implant AG, Reutlingen, Germany) is an improved version of Alpha IMS and has greatly enhanced its durability. Subretinal implant Alpha AMS consists of a metal-oxide-semiconductor (CMOS) chip attached to a polyimide (PI) foil that contains 1,600 pixels on the 4.0 mm × 3.2 mm × 70 µm chip. Each pixel has a size of 70 µm × 70 µm and includes photodiode, amplifier, and stimulation electrode as well as Alpha IMS devices. Alpha AMS results for 15 patients were reported in 2017. Based on clinical trial, the average lifetime of Alpha AMS is estimated to be 3.3 years [79]. Two of 15 patients were able to distinguish the Landolt C-ring up to visual acuity values of 20/1111 and 20/546. Consistent with patient results using the previous Alpha IMS device, one patient had a maximum visual acuity of 20/546. Both Alpha AMS and Alpha IMS was able to reproduce vision. AMS was stable over a period of 12 observations. AMS showed improved durability and observational safety as compared to previous versions of IMS [46].

6. Suprachoroidal device

6.1. Suprachoroidal stimulation

Placing protheses in the suprachoroidal space does not require transvitreal surgery, is potentially less invasive, and it is easy to repair or replace the device (Figs. 6(a) and 6(b)). However, there is a significant risk of hemorrhage and fibrosis in the suprachoroidal space after surgery because of the large number of vessels. Also, because of the distance from the neurosensory retina, a larger stimulus is needed to achieve visual perception, and spatial resolution is reduced because of spread of the current [77].

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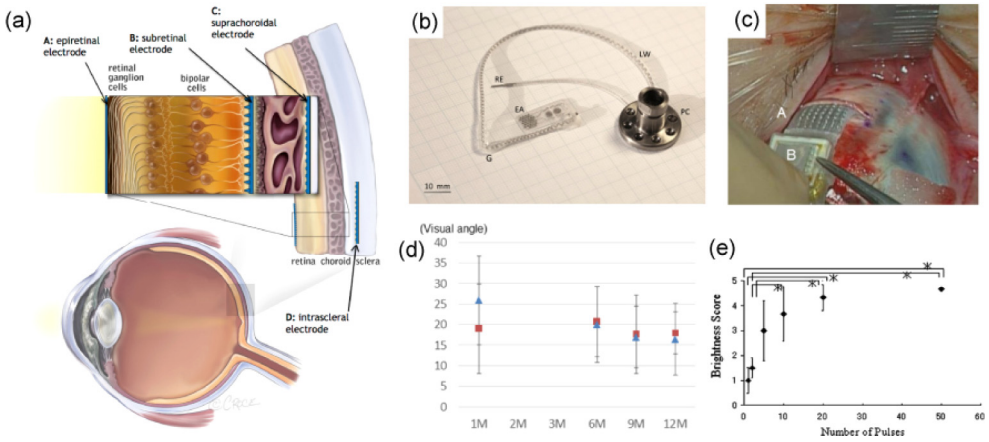

Fig. 6. Suprachoroidal device. (a) Potential anatomical locations for retinal prosthesis implantation [20]. (b) Implantable array and orbital lead wire assembly on the left with percutaneous pedestal on the right. Each abbreviation is as follows: (EA) electrode array, (LW) lead wire, (PC) percutaneous connector, (RE) return electrode and (G) grommet [94]. (c) Photographs of the surgical procedures during the insertion of the electrode array (A) connected with a multiplexer integrated circuit (B) [97]. (d) Results of the localization test in patient during follow-up period. Red square represent the average deviation of the touched point from the center of square with the system turned on, and blue triangle represent that with the system turned off [97]. (e) The relationship between the brightness of the phosphenes and the number of pulse. With the increase of pulse number, the brightness increased up to 20 pulse and saturated. Bar represents standard error. $P < 0.05$ [98] Reproduced with permission from Ref. [20], copyright 2007 Springer and [94], copyright 2013 Wiley Publishing Group and [97], copyright 2015 Springer.

6.2. *Suprachoroidal device*

The Bionic Vision Australia (BVA) team developed a suprachoroidal device, which is a 24-channel system consisting of 20 stimulation channels and four return electrodes. Dissection of the temporalis muscle is required to attach the transdermal connector to the bone [77,94]. Three RP patients had an implanted device for two years, which allowed the location, shape, and size of the phosphenes to be mapped. Reliable phosphenes were confirmed by all patients. Phosphene shapes ranged from simple to complex shapes that included various elements of space and time. The position of phosphene in the field of view roughly coincided with the position of the stimulation electrode. Overlap of phosphenes induced in adjacent electrodes was observed in one patient, which decreased with increasing distance between electrodes. An average 20/8397 visual acuity value was reported for one subject. The BVA team is developing a fully implantable device with 44 channels and is the solving the problem of high stimulation thresholds [95,96].

The suprachoroidal-transretinal stimulation (STS) system is being developed by NIDEK and Japan's Artificial Project. Like the BVA system, the STS system uses a temporal incision and requires a tunneled connection between the decoder, the internal coil, the stimulating array, and the return electrode (Figs. 6(c) and 6(d)). When a camera with glasses is used to detect light above the threshold and the light is processed by a computer in the arm of the eyeglasses, the external coil relays the signal to the decoder through the secondary coil, which generates a biphasic pulse that stimulates individual electrodes in turn (Fig. 6(e)). The STS system consists of a 3D 49 microelectrode array with penetrating electrodes inserted into the sclera pocket, unlike other systems [63]. Clinical trials with two RP patients were conducted to verify the biocompatibility. Surgical implantation of a retinal implant in the scleral pocket of one eye was completed without

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retinal detachment or retinal/vitreal hemorrhage. The implanted STS maintained its function during the 4-week experimental period. In this clinical trial, only nine of 49 electrodes were used for the functional test, and phosphenes were induced by a current that was delivered via six and four electrodes to two patients, respectively. Clinical results showed that phosphenes in the field of view corresponded to the implants during direct stimulation [99]. However, the functionality test results did not show any consistency in respect to the on/off state of the device (Fig. 6(d)) [97]. More research is needed to make conclusions regarding suprachoroidal implants.

7. Summary

In summary, we have investigated electronic vision-restoring devices that are implanted in various anatomical locations. Ever since it was discovered that electrical signals have a significant effect by generating phosphenes, electronic devices have evolved to capable of doing this at a very rapid pace. Such devices have been implanted in humans and have made it possible to recognize the contours and movements of objects. However, there are challenges that need to be solved in the future. First, retinal prosthesis should be accompanied by an increase in spatial resolution. As the dimensions of the stimulating electrode become smaller, it is difficult to apply a high-resolution electrode array in a commercial setting, because sufficient impedance of the electrode required for stimulation is not guaranteed. Second, device miniaturization is necessary. All of today's devices require a camera, a signal processing device, implantation of the electronic device behind the ear, and other requirements, which limit the motion of the user. Finally, long-term stability must be ensured. Based on 10-year transplantation results, it is suggested that the training effect is rarely appeared which improve the ability to recognize the signal compared to right after implantation, and the distance between the device and the retina surface became distant which resulting in the increase of the current threshold [84]. Therefore, a system must be developed in which the device conformally attaches to the retina and remains stuck on the retina for long periods of time and effectively deliver current signals. Development of such a system will provide an efficient means of restoring sight to future blind patients.

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