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Review article

Bionic eye review – An update

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ABSTRACT

Purpose: To date, reviews of bionic eye have concentrated on implants which were used in human trials in the developed countries. This is the main restriction of this systematic review examines, however this review discusses worldwide advances in retinal prosthetic research, assesses engineering features and clinical progress of recent implant trials, and identifies potential future research areas in the field of bionic implants.

Methods: A literature review searching PubMed, Google Scholar, and IEEExplore was performed using the PRISMA Guidelines for Systematic Review. We included peer-reviewed papers in the review which demonstrated progress in human or animal trials and papers with described innovative bionic eye engineering design. For each trial, a characteristic of the device, engineering solution, and latest clinical outcomes were presented.

Results: Eleven prosthetic projects fulfilled met our inclusion criteria and were ordered by stimulation location. Four have recently finished human trials, three are having conducted multi- or singlecenter human trials, and three are in preclinical animal testing stage. FDA has approved Argus II (FDA 2013, CE 2011); the Alpha-IMS (CE 2013) has been approved and obtained BCVA with Landolt-C test has taken into a multicenter clinical research. New approaches will be presented using alternating magnetic fields, low-intensity focused ultrasounds, optogenetics, implementing ionic gradients across neural cell membranes or influencing neurotransmitter levels will be presented in the review.

Conclusion: Several bionic eye have successfully achieved visual perception in animals and/or humans. However, many things need to be improved and engineering difficulties are to be resolved before bionic eye will be capable of fully and safely bring back vision functions. New approaches could improve medical outcome of future bionic eye.

1. Introduction

According to the WHO, it is estimated that globally about 253 million people live with vision impairment, including about 36 million of those who are reported to be amaurotic and 217 million with various vision impairments [1]. Most of those suffering from blindness suffer from moderate to severe vision impairments and are over 50 years old [1]. Chronic eye disorders are the predominant cause of vision loss. Only less than 20% of all visual impairments cannot be prevented or cured, which is why doctors and scientists have been working on the development of a bionic eye. Retinitis pigmentosa, cone dystrophies, choroideremia, wet AMD with a scar in the macula or geographic atrophy, Stargardt disease [2–4] constitute particular fields of interest of scientists working on the bionic eye. The present review will cover the history and current status of bionic eye development and the results of this modality for patients and ophthalmologists. Available reviews discussed the state of bionic eye research, but numerous blanks in the characteristics, description and presentation of this issue are still present [5,6]. In particular, knowledge is still incomplete about (a) other bionic eyes in early stages, (b) scientific progress and innovation in other countries including Japan, Korea, and Taiwan, and (c) material usage, engineering solutions and problems to be solved [2,7] (Fig. 1).

This systematic review examines the latest innovations in bionic eye research worldwide, assesses the technological solutions and technical specifications of 11 major bionic eye preclinical and clinical trials. The clinical trials of a few devices, for example Optobionics and Intelligent Medical Implants, are finished, but they are currently not in use. However, they have been presented

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and provided relevant viewpoints for current advanced solutions in bionic eye development. This review provides recent information on the clinical stage of every device and presents it from the historical view, focusing on problems which remain and difficulties in receiving, transducing and encoding through the visual pathway determining possible directions for the development of the bionic eye.

A literature review was performed using PubMed, Google Scholar, and IEEExplore through January-December 2019 with the keywords "bionic eye", "retinal prosthesis", "retinal implant", "epiretinal stimulation", "subretinal stimulation", "suprachoroidal stimulation", "optic nerve stimulation", "optic nerve prostheses", "occipital lobe prostheses", "occipital lobe stimulation" using the PRISMA guidelines for writing a systematic review [7,8]. Peer review articles were found with the use of references and keywords using basic literature and also systematic review articles [7].

2. System view

In terms of electrically stimulated visual prostheses, some similarities occur between retinal and cortical prostheses [9,10,12,13] with common features, such as digital imaging. It is important to both simplify images and highlight objects before creating electrical impulses which may be transmitted from electrode arrays to the optic pathway. Both wired and wireless connections may be used for such transmissions, and an integrated circuit, which

Visual Prostheses	Argus II	Alpha-IMS	IMI, IRIS	EPI-RET 3	OPTIVE NERVE STIMULATION	CORTICAL : NeuroPace, CORTIVIS, Orion
Image acquisition	External camera	Internal optical acquisition system	External camera	External camera	External camera	External camera
Light signal transfer into electrical signal	External modification by a microprocessor to accelerate machine vision tasks	Internal modification by the conversion of light into electric current by photodiodes	External modification by a microprocessor to accelerate machine vision tasks	External modification by a microprocessor to accelerate machine vision tasks	External modification by a microprocessor to accelerate machine vision tasks	External modification by a microprocessor to accelerate machine vision tasks
Electrode quantity	60	All 1500 microphotodiodes are connected to an amplifying device and electrode	61	25	16	Dobelle: 64 Normann: 100
Perimetry (maximal	Maximum 20^0	11^0 x11^0	Maximum 40^0	Data unavailable	14^0 x41^0	Data unavailable

Fig. 1. Table showing the characteristics of bionic eye solutions.

angle)						
Stimulation point	Epiretinal stimulation	Subretinal stimulation	Epiretinal stimulation	Epiretinal stimulation	Optic nerve stimulation	Occipital lobe stimulation
Visual analysing	Extrinsic computer analyses	Intrinsic processing	Extrinsic computer analyses	Extrinsic computer analyses	Extrinsic computer analyses	Extrinsic computer analyses
Clinical status	Commercially available (Europe - March 2011) (USA FDA approval February 2013). Trial identifiers: NCT01490827, NCT00407602, NCT01490827, NCT01860092, NCT01999049, NCT02227498, NCT02303288, NCT034181	Commercially (available in Europe CE marking July 2013). Trial identifiers: NCT01024803, NCT03561922	Phase II clinical trial January 2007. Clinical trial identifiers: NCT00427180, NCT02670980, NCT03629899	Completed acute clinical study	Experimental stage on humans	NCT02747589, NCT02983370, NCT03344848

Fig. 1 (*continued*)

	16, NCT03510234, NCT03635645					

Visual Prostheses	ASR MICROCHIP	STS Microchip	BVA 24 Chanel Device	AV-DONE	Prima	BVA
Image acquisition	Optical sensor	External camera	External camera	External camera	External camera	External camera
Light signal transfer into electrical signal	External modification by a microprocessor to accelerate machine vision tasks	Internal modification by conversion of light into electrical signal by photodiodes	-	-		External modification by a microprocessor to accelerate machine vision tasks
Electrode quantity	5000	49	24	7		44
Perimetry (maximal	Data unavailable	Data unavailable	Data unavailable	Data unavailable		Data unavailable

Fig. 1 (*continued*)

angle)						
Stimulation point	Subretinal stimulation	Intrascrelal stimulation	Suprachoroidal stimulation	Epiretinal stimulation		Suprachoroidal stimulation
Visual analysing	Extrinsic computer analyses	Intrinsic processing	Extrinsic computer analyses	Extrinsic computer analyses		Extrinsic computer analyses
Clinical status	Clinical trials 2000	Clinical trials 2012	Clinical trials 2012, NCT03406416	Completed acute clinical study.	NCT03333954, NCT03392324	Clinical trials 2016

Fig. 1 (*continued*)

stimulates the electrodes with pulses, may be installed either directly into the electrode array or in a separate package, which is then connected to the electrodes [9–15]. The most complicated signal pathway requires the following stages:

1. Modifying video images into digital data.
2. Converting digital data into the stimulation of a particular region of the retina taking into account the brightness of the background.
3. Converting stimulation from the electrodes into a stream of data.
4. Generating a signal to the retinal prostheses which transmits both power and data stream.
5. Sending radio frequency energy from one external coil to an inner one.
6. Subsequently, radio frequency signal energy recovery and data interpretation occurs.
7. Stimulation is induced depending on images from a camera.

Points 1–4 take place in external devices, 6–7 in an internal implant, and 5 both in external and internal devices. The pathway may have a reduced number of steps with a photodiode placed inside the eye. It would eliminate some points above, but would make the inner device more complicated and more difficult to implant. Such a device would have to detect a photon and generate energy. A high grade of miniaturization would make it possible for such a device to work effectively. The wireless transmission of power and visual details is present in most bionic eye systems.

This approach requires a device which is able to convert light into an electrical current (e.g. a photodiode) to be installed into the implant, where it may then be connected to an electrode. One of the potential approaches is to transfer images to the mixed photodiode-electrode array using a scaled down projector, which would generate light that could then be transformed into electrical energy and, subsequently, it would power the electrodes. Alternatively, the photoelectric impulses which are created, may be intensified by the surrounding light on a light-sensitive element. However, this array would require a separate power source. The second approach offers the benefit of allowing normal gaze fixation and, additionally, reduces head movements while watching one's surroundings. The wireless transmission of electric energy and information data triggers a conflict in radio frequency, not only between 2 modules but also other devices, e.g. Wifi routers. Modern retinal prostheses should have data transmission at the speed of megabit/second and the frequency carrier should be about 10 MHz [16], preferably below 10 MHz because of signal depletion in the human body and internal AC-DC transformation [17]. RF power transmission requires low frequency and large coils to be effective, whereas opposite values are needed for data transmission [18]. Such a solution will increase the efficacy of the whole system, but it requires careful engineering to avoid frequency interference between modalities. According to the literature a 256-channel retinal enhancing device with double band telemetry is the most effective for clinical purposes [18]. One of the first optical transmission applications was presented by Gross who used infrared optical and inductive power connection [16]. Optical transmission was also investigated to provide data and power transfer. However, power supply provided by a photodiode is insufficient to stimulate optical neurons [16]. The optical connection may reach data transfer speed of up to 200 Kb/s.

An integrated circuit is usually a part of retinal prostheses and has to perform numerous functions:

AC/DC adaptation, data modulation, digital data control, voltage or electrical current stimulation, and feedback from the implant to external modalities on the functioning of the implant.

The miniaturization and reduction of power intake are other challenges of the stimulation by the chip. One of latest inventions of the group is a complete installation of data filtering and modulating, good efficacy of AC-DC transformation, digital supervision, and 256-channel stimulation into a compact system [19]. A timing-controlled rectifier eliminates a great amount of power loss when compared to a typical diode-based rectifier, during alternating current into direct current transformation.

In CMOS fabrication a 232-channel stimulator chip was made. It was smaller than 5 × 5 mm in size, with the stimulation through small electrodes being possible thanks to high-voltage current [19]. The chip was equipped with voltage stabilizer circuit to stabilize electric sources making it unnecessary to generate large power on every output, reducing the risk of neuronal injury and making it possible to minimize the implant size. The basic impulse is generated when reported electrode voltages between pulses exceed ±50 mV.

In 0.18 μm CMOS fabrication a 256-channel chip was invented and operated as a part of the bionic eye [19]. The chip was equipped with power/data telemetry function and electrode voltage monitoring [19]. The chip was not designed to be implanted under the retina. It uses microelectrodes as a retina network. The software is planned to cooperate with high-voltage modalities allowing a variety of stimulation possibilities and may be set up as sources or sinks for current controlling [19].

A 512-channel retinal stimulator is another option for improving retinal prostheses [20]. A new function of this chip is the automatic calibration of integrated circuits on the output, which may improve the accuracy of the stimulus and decrease the impact of charge aggregation. 65 nm transistors enable the increase of the number of output channels and reduction of the chip size to 4.5 × 3.1 mm2 [20]. When implanted, such a size would fit entirely inside the eye unless improper installation techniques are used [21]. The chip uses ±2.5 V to minimize power consumption [20]. However, the chip offers low-voltage supply, so the current range is restricted [20].

Electrode technology in the Argus II and Alpha-IMS fabrication has developed significantly in comparison with other bionic modalities. Currently used implants, such as a neurosurgical stimulator, or cochlear implants need simple electrodes equipped with a few platinum electrode terminals enhanced with a polymer substrate. Retinal prostheses require a lot of densely packed terminals to stimulate the retina. In the Argus II the electrodes are composed of gray platinum and in the Alpha IMS – titanium nitride electrodes. Two kinds of electrodes are superior to bulk platinum, which is usually applied in neurostimulation. Platinum electrodes have charge capability of 0.1–0.35 mC/cm2 [21], gray platinum and titanium nitride ones have charge capability of 1 and 0.9 mC/cm2, respectively [22,23]. The electrodes are placed with the electrode array and must be delicate in design to prevent damage to the retina. Most retinal prostheses use polymers that have a wire connection cable and connect the electronic device with the electrode cluster. However, in the Alpha-IMS the electrodes are placed directly on the silicon IC, which helps to avoid a complex pathway to make a connection between electronic devices and the array. However, silicon IC is more hard-line in comparison with polymer. Therefore, there is a high risk of injuring the retina.

Visual field and acuity are other fundamental issues which have to be considered. The human retina is a hemisphere with the radius of about 1.25 cm. It is in the back of the eye, covering about 60° of the nasal and superior field, about 70° of the inferior field, as well as 90° of the temporal field [24]. In order to spread through the entire retina, electrode surface of almost 5 cm^2 is necessary. Epiretinal prostheses require the size of the device to be below 5 mm to provide safe surgery, though a foldable array may be implanted through a 5 mm eye incision [25,26]. The surgeon may use glide sheets to make it less traumatic [56]. This approach may potentially provide a visual field of 34° once it expands in the eye, compared with 19° for the Argus II and 11° for the Alpha-IMS. Based on this concept, subsequent development was tested through a long-term implantation in animal eyes to validate its feasibility [25]. Conversely, subretinal implant size is mainly limited by the risk of retinal detachment attributed to the insertion of an array under the retina [26]. With the increase of subretinal array size, a higher risk of detaching the entire retina may be expected. Retinal detachment has disastrous and irreversible consequences for retinal health, so the surgical process of subretinal Alpha-IMS implantation involves silicone oil injection to mitigate the likelihood of retinal detachment [27].

3. Electrode placement possibilities and stimulation strategies

The first retinal prosthesis was invented by Tassicker in 1956 [10,28], while the first cortical stimulator device was developed by Button in 1958 [28,29].

Visual percepts are obtained through direct signal transmission using inner retinal cells (bipolar and ganglion cells). Ganglion cells concentrate their axons on the optic disc to create the optic nerve, which then transmits electrical signals [14]. One benefit of using the retinal part of the optic tract is being able to use the inner retina in order to improve the perception of surroundings. Regrettably, the requirement of the high quality of inner retinal neurons renders a retinal prosthesis unattainable for many blind people who suffer from glaucoma or experienced a substantial ocular injury where the ganglion cells were damaged and other globe structures destroyed. Until now, most retinal bionic eyes have been used for RP patients.

There are two potential strategies for stimulating the visual cortex - stimulation may either be obtained by stimulating the surface of the visual cortex, or through the use of deeper electrodes. While the stimulation of the primary visual cortex (V1, V2, V3) may result in eliciting smaller central phosphenes, subsequently leading to better central vision, affecting the visual cortex (V1, V2, V3) may also lead to an over-stimulation of the central visual field on the visual cortex. Regrettably, in practice, the majority of the V1 area is not available for the implantation of deeper electrodes. Therefore, recent cortical prosthesis models only target the occipital pole and its superficial surroundings [7].

Another problem associated with cortical prostheses is the surgical access to the occipital pole. Although this surgical access is relatively uncomplicated, the performance of neurosurgical operations for non-life-saving reasons is questionable from the ethical and procedural point of view. It raises additional issues of their questionable necessity [10,11], particularly if other procedures, with a lower risk of mortality and morbidity, are available, such as the implantation of a retinal or suprachoroidal prosthesis. It is essential that the risk versus benefit ratio is thoroughly analysed prior to the implantation of cortical electrode arrays in amaurotic patients. Any clinical trials have to be accepted by relevant regulatory institutions. Therefore, further research is required in this field. It should include simulated phosphene vision experiments, as well as psychological tests which could help clarify the potential functional benefits for operated patients [7,10,11].

Both retinal and cortical implants should help increase the resolution of central phosphenes through the implantation of miniaturized, densely installed electrodes, leading to better visual acuity. However, the potential maximum density is limited by factors such as the current running from adjacent electrodes being able to create an accumulation of phosphenes, affecting the charge that electrode surface area delivers, which may potentially damage the optic pathway or electrode [30–32]. Beyond the limitations of those factors, achieving improvements in visual acuity could be possible using alternative, more complicated stimulation strategies which are still being developed.

Retinal prostheses are electronic devices which should offer support to blind people by restoring their visual acuity either partially or fully. Potential candidates for such a retinal vision prosthesis are those who suffer from a retinal disease, such as age-related macular degeneration (AMD), glaucoma or inherited retinal dys-

trophies such as retinitis pigmentosa (RP). The part of their optic tract which is suitable for stimulation varies and depends on the location of their disease or the area where damage occurred. Areas which are suitable for stimulation are the retina, optic nerve, lateral geniculate nucleus and the visual cortex. All these locations offer various advantages and disadvantages which will be subsequently discussed in more detail. Distinctions in the neural structure and signalling, surgical access, as well as potential implantation are challenges associated with stimulating each of those anatomical targets. Damage incurred to the inner retina or the optic nerve generates the need for a bionic eye which stimulates the optic tract more distally.

The electrical stimulation of a targeted location should lead to certain responses from light percepts, called phosphenes. When subtle, they could, in an adequate quantity, provide a blind person with useful information about their environment and surroundings. This principal observation supports current efforts to invent and develop a bionic eye.

Globally, numerous research teams are working in hope of inventing and developing new visual prostheses, targeting each possible region of the visual pathway. 20 such teams are developing various forms of a bionic eye which could affect different locations of the visual system. The primary locations which have reported progress for this research are Australia, the USA, Germany, France and Japan. However, they are all in different stages within their processes ranging from the experimental through clinical domains and, finally, commercial availability. So far only two devices have reached the final stage – the Argus II device (Second Sight Medical Products, Inc., Sylmar, CA, USA) [32] received the regulatory approval for clinical use in the EU in 2011, while the Alpha IMS (Retina Implant AG, Reutlingen, Germany) [25] received it in 2013. In 2016 the IRIS II received CE for clinical trials. The FDA approved the Argus II in 2013. These devices have thus far shown improvements in patients' visual acuity and have aided the managing of their daily activities.

To date, two research groups have reported the invention of a bionic eye which directly stimulates the optic nerve, while another two have reported on the implantation of such a prosthesis into the lateral geniculate nucleus in animals, thereby aiming to develop a visual prosthesis which affects these regions [11,33,34]. While optic nerve prostheses offer some promising initial results, important issues remain. The first problem is associated with the interference between the electrodes and the optic nerve [11,33]. A large number of contacts is required with the nerve fibres, so the risk of damage to the optic nerve is relatively high [11,33]. Moreover, implanting into the optic nerve requires an incision into a piece of dura mater, which may trigger an infection of the central nervous system or disturb blood circulation in the optic nerve [13]. Furthermore, due to the small size of the axons and their dense packing, the precision of visual stimulation, at its current stage of technological development, is rather low. Intraoperative imaging of the optic disc nerve fibres could lead to a higher precision during electrode implantation.

4. Results of visual prostheses implanted in the retina

With retinal prostheses, the image is initially taken by a camera, then evaluated and transmitted using an image analysing unit.

4.1. Epiretinal prosthetics

An epiretinal prosthesis affects the ganglion cell layer which then engages the stimulation of the inner surface of the retina using microelectrodes. In order to place a microelectrode array in the epiretinal space one needs to perform a pars plana vitrectomy using a retinal tack. OCT performed during an operation is useful in intrasurgical visualisation of device positioning and placement [35]. It allows for the best approximation of an implant over the retina with the shortest array to inner retinal surface distance, which is important in the functionality of an implant. An epiretinal prosthesis enables heat distribution through the vitreous and removes *trans*-scleral cables. Another advantage of epiretinal prostheses is that they allow the implantation of very big electrode arrays. Conversely, the implantation of epiretinal prosthesis involves entering through the retina and choroid, which increases the risk of tissue damage or gliosis. It also increases electrical resistance. Epiretinal stimulation primarily targets the ganglion cell layer, but it may also affect bipolar neurons or axons, which form the optic nerve. The stimulation of many different cells may demand retinal algorithms in order to correctly affect bipolar/ganglion cell receptive fields (RF).

The analysed data are transferred to the bionic eye, which is composed of 16 microelectrodes, which in turn activate the inner retinal neurons. Following an animal trial, the Argus I was tried on humans, achieving some promising outcomes [11,33,36]. All the electrodes had various threshold currents validated, which enabled visual responses. When ten electrodes had their current thresholds held constant, the threshold of three other electrodes increased, while the thresholds of the remaining three electrodes diminished. It was also observed that the size of the phosphenes increased in line with the stimulation current. A low amplitude of the electrical current conserved the energy of the prosthesis, allowing it to work longer. With the use of the camera the patients were able to move around their surroundings and gaining an increased familiarity using the camera, they were able to tackle tasks of increasing complexity. Patients reported experiencing four different colours [6,16]. Moreover, after training for about two and a half months [6,16], the patients were able to differentiate the brightness and direction of some moving objects [6,16,36]. The next version of the device was called the Argus II and included 25 important changes in the equipment. The number of electrodes was increased to 60, and wireless data transfer was introduced. Microelectromechanical devices were used to improve the stability of the prosthesis in the eye. The Argus II allowed patients to distinguish principal forms of motion and notice light. The superior visual acuity with the Argus II was 1.8 logMAR (20/1262 Snellen equivalent) [23]. More effective usage of retinal prosthesis can be achieved using integration of visual stimuli and a divisional power supply scheme for retinal prosthesis [37]. While visual rehabilitation some aspects have to be taken into account. First of all optotypes recognition under positive contrast conditions is easier than under positive contrast conditions [37]. In other words positive contrast patterns will require a lower update frequency when divisional power supply scheme is implemented and slower temporal integration during perception in order to obtain the same recognition effect as the one achieved with a similar negative contrast pattern. Secondly, patients with eye movements (saccadic movements) during presentation of the optotypes (1 s) could use both peripheral and central vision in recognizing used optotypes (Chinese and pseudo Korean characters [37]. Both types of vision seemed to be useful for the patients to spatially and temporally integrate Chinese and Korean characters more accurately, despite different visual angles (8°, 2°, and 1°) during the presentation [37]. Nevertheless, everyday activities were done better with the device on rather than off. The observation period was 5 years [38,39]. In 2019 a 10-year follow-up finished. The next version of this prosthesis, the Argus III, is still in R&D. Its main improvement will include an even greater electrode density, which should restore the patient's vision better than the previous device. The Argus II phase II multicenter trial involved the implantation of 30 subjects to evaluate the safety and effects on functional visual

and real-world task performance. The Argus II was evaluated by NICE and it was stated that more data should be collected to prove benefits to a patient in the quality of life and improvement concerning daily life activities [40]. A Functional Low-Vision Observer Rating Assessment (FLORA) was used to evaluate functional vision, well-being following the implantation and use of the Argus II [40]. 18 patients with Argus II implants showed no device- or surgery-related significant adverse effects (SAE) [3]. Between the second and fifth year of follow-up, SAEs were stable at the same level and included: conjunctival erosion in 13% of patients, hypotony in 13% of patients, conjunctival dehiscence in 10% of patients, presumed endophthalmitis in 10% of patients, and need for retacking in 6.7% of patients [3]. The follow-up between years 3 and 5 revealed a new rhegmatogenous retinal detachment, which was effectively managed [3].

4.2. Intelligent medical implants learning device. Intelligent retinal implant system II

The Intelligent Medical Implants (IMI) Learning Device implantation helped to elicit phosphenes in the majority of cases (19of20-subjects) [41,42]. This retinal prosthesis is composed of a microfabricated polyimide array including 49 platinum microelectrodes with a diameter of 250 μm [42]. They are separated with a 120 μm space from one another [40]. IMI is connected directly to an electronic modality which is attached to an external camera. The whole set was effective in the clinical setting. After developing IMI in 2007, Pixium Vision S.A. improved the device, which is now available as the Intelligent Retinal Implant System (IRIS) II [40]. The IRIS II prosthesis consists of a visual interface which collects and transmits signal to a pocket-size adaptor. There, it creates stimulation signals which are conducted to an extra- and intraocular implanted component composed of a 150-microelectrode array [40] and carrying a CE mark [4]. The IRIS disposes of more ways of transmitting signal than the Argus II. Initially, a continuous visual input is detected and created by a neuromorphic image sensor, simultaneously providing information of changing pixels and their light intensities [40]. The visual information elicited at this stage may be split into transient and sustained components [40]. Sustained components may be subjected to analysis using algorithms to improve image quality and may emphasize the most important elements and reduce secondary, irrelevant ones [40]. This process imitates the temporal resolution of the retina [40]. Secondly, instructions are created by a pocket processor, transmitted to the visual interface and sent optically via an infrared array directly to the implant [43]. A high speed of data transfer is important for activating larger numbers of electrodes being able to accommodate to the high speed of changing environment ahead [43]. Power is provided in a similar way to that in the Argus II. Probably being the most uniquely designed solution, the IRIS has a learning retinal encoder, which allows for an individualized customization to allot areas as excitatory or inhibitory imitating the retinal ON/OFF pathways [40,43].

Since 2016 data had been collected for the initial 10 patients who had the IRIS II implanted as a part of a clinical trial [4]. The preliminary results were reported at the International Eye and Chip Conference in 2017. The improvements were noted in square localization, localization of motion, picture perception, and perimetry assessment [44]. The percentage of SAEs was at 0.4 per patient [44]. However, having accepted that the lifespan of the device was shorter than expected, Pixium have suspended the trial pending further development of the device and surgical method. The trial is to be conducted till 2022. Some concerns arose regarding the endurance of the device.

Another epiretinal prosthesis is available, which was developed by Joseph Rizzo and John Wyatt from Harvard Medical School [45]. This device includes both intraocular and extraocular parts. The extraocular part consists of a CCD camera placed on a pair of glasses equipped with a battery [16,45]. The intraocular part has an array of photodiodes and an impulse generating adaptor, which are both located on a changed lens [16,45]. This device utilizes impulses to transmit data from the camera to the impulse-generating adaptor instead of a wire, as was the case of the first intraocular prosthesis.

4.3. Suprachoroidal retinal prostheses

Trials have been performed on three types of electrode arrays, with retinal implants being subjected to the highest number of human clinical trials so far. In 2014, Bionic Vision Australia [46,47] successfully completed a clinical trial of a visual prosthesis for the suprachoroidal area with 3 participants. The first suprachoroidal retinal prostheses had a 24-channel system, composed of 20 stimulation electrodes and 4 return electrodes [46,47]. The application of BVA involves cutting the temporalis muscle in order to fix the percutaneous device to the skull [46,47]. This modality has no photovoltaic features. It receives phosphenes via a head-placed camera and image processor to produce electrical stimulation patterns. A motion tracker and eye-facing camera were used to assess phosphene location, shape, and size of the objects [46,47]. Phosphenes could be evoked, but they were variable, with different location and stimulation thresholds [46,47]. A dedicated camera was used for light localization, optotype recognition, visual acuity tests, and daily living activity performance [46]. The visual acuity task was completed by one participant, reaching the average of 20/8397. The task was performed significantly better with the device on than off [46]. During direct electrode stimulation, all patients revealed superior character recognition and localization of static objects [46]. A fibrous capsule had developed around the implant after some period of stimulation. However, the transmission of electrical signals was possible [47].

The BVA group is implementing a next-generation of 44-channel modality [47]. The subsequent project is a 99-channel device, called the Phoenix-99, which will use a dual monopolar and hexapolar ('quasi-monopolar') stimulation [47,48].

4.4. Subretinal implants

The Retina Implant Alpha IMS is composed of a subretinal part with a microphotodiode array placed on a polyimide material, and a wire for electrical power and controlling features [25,50]. It is combined with a solenoid device for receiving signal, which is contained in a small subcutaneous container placed behind the ear, similarly to the technology used in cochlear implants. A separate, short cable connects the return electrode to the subdermal case. The device is composed of 1500 independent photodiode-amplifier-electrode units, with every part transforming local light stimulation into an electrical impulse, which is then amplified for the stimulation [33,50]. Every stimulation photodiode-amplifier-electrode unit has a dimension of 70 × 70 μm and includes a photodiode, an amplifier, and a stimulation electrode [33,50]. The Retina Implant Alpha IMS includes a vision chip, which is connected to a receiver, enclosed in a ceramic case, via an electrical supply wire. An electrical image of photosensation is transferred from all the points through to bipolar cells which, in turn, relay it to the inner layers of the retina and then the visual tract. Every electrode of the device usually produces 1 ms pulses at a constant frequency, typically 5 Hz [25]. Although each photodiode-electrode connection should theoretically work independently of the accompanying ones, in vitro research revealed that some interference may occur in the electric field of a single unit. Due to this interference, the image described by patients is similar to a blurred screen

of a black and white television, allowing them to see shapes up to the theoretical two-point resolution of a 0.25 visual angle. The transmission of inductive energy is enabled as power is supplied from an external battery supplied with a transmitter. Subretinal implants work by stimulating retinal bipolar cells by converting light into electrical signals [25,34]. An option of the external part of the Retina Implant Alpha IMS involves the adjustment of settings for contrast and brightness to allow the defining of optimal contrast in various lighting conditions. The visual acuity outcome is rather low, but dealing with everyday activities may be assessed with tabletop object recognition tasks, a self-assessment mobility questionnaire, and screen-based tests including Basic Light and Motion (BaLM), grating acuity, greyscale contrast discrimination and a full-field stimulus test [51].

5. Optic nerve prostheses

The main benefit of optic nerve prostheses is the fact that the entire perimetry is then situated in one narrow space. An optic nerve implant is fitted with special spiral cuff electrodes to transmit signals from a camera through the optic nerve to create visual stimulations [13]. Veraart et al. developed this type of implant, testing it in blind patients and obtaining promising results [41]. Using such a wrap cuff allows the bionic eye to generate many phosphenes by setting impulse parameters and enabling cooperation with the optic nerve [53]. Patients who tested those prostheses were able to function in everyday life and demonstrated basic skills, such as distinguishing various shape and bar orientations, with some patients even being able to read large optotypes [41].

6. Visual cortex stimulation

In 1755 Le Roy described blind patients experiencing flashes following the electrical stimulation of their head [8,52]. In 1800, Alessandro Volta also noticed that the stimulation of the eye or the optic nerve could trigger a sensation of light [8,52]. However, the ability to stimulate the nerve was not associated with the occipital cortex until Galvani noted the association by experimenting on frog legs. Further work by scientists such as Fritsch and Hitzig, as well as later research by Ferrier, Luciani and Tamburini proved that apart from the cerebral cortex showing functional reactions it is also possible to accurately pinpoint which regions of the cerebral cortex reacted to electrical stimuli [8,9,52]. Lowenstein and Borchard experimented by stimulating the visual cortex in soldiers with occipital injuries [52]. In 1956, John Button, together with Putman, stimulated the cerebral cortex of blind patients in order to trigger the sensation of light in them [52]. The first eye prosthesis which was based on visual cortex stimulation appeared in 1968. It was created by Brindley and Lewin and consisted of a matrix of eighty 1 mm^2 electrodes, which was placed in the occipital cortex [52]. It was then connected to a set of implanted radio receivers, thereby forming an electrical circuit which allowed for the wireless stimulation of the system [9,52]. The participant began to have a sensation of light when 39/80 electrodes were stimulated. While the tested system had no practical implications for the user, it proved that stimulating the visual cortex through numerous electrodes could contribute to the reception of optical signals and initiated the concept that employing a greater number of electrodes could lead to obtaining operational visual acuity in the future. The Brindley experiments inspired further research conducted by numerous scientists following the approach they initiated to visual prostheses. Both Brindley and Dobelle developed their eye prostheses separately, beginning with achieving the sensation of light, moving to distinguishing simple patterns which enabled patients to read Braille [52]. Brindley established that approximately 50 stimulation areas were required in order for patients to be able to perfectly read printed letters. However, in order to read a handwritten letter, 600 areas would have to be stimulated [52]. Dobelle's focus was on patient mobility rather than reading, with plans to implant 512 electrodes. Brindley ceased experimentation in 1982, while Dobelle continued trying to minimize the system and in 2000 he discovered that 21 electrodes were sufficient for patients to be able to distinguish objects and move around [9,52]. However, his system had disadvantages such as: a limited area of stimulation for the visual cortex, an increased risk of seizures, and cabling protruding from the back of the head, which connected the electrodes with the device that was under the skin, the functioning of which stimulated astrocyte proliferation. An alternative to this method included a cross-microstimulation with miniature electrodes. Despite being limited in terms of information, the research by Brindley and Dobelle forms the basis of knowledge in the area of the successful stimulation of the visual cortex through bionic eye prostheses in humans. Brindley invented and used a prototype comprising wirelessly operated electrodes, which effectively evoked a lot of phosphenes. The cortical stimulating prosthesis consisted of arrays of platinum electrodes which were encased in silicone suitable for occipital poles. In Dobelle's prosthesis every electrode was linked by a separate, subdurally placed, Teflon-isolated cable which linked with the stimulating devices via a transcutaneous plug [52]. Regrettably, system breakdowns and the possibility of developing infections and convulsions are some of the disadvantages of Dobelle's prototype, which may disqualify this visual cortex stimulator from further clinical trials [44,52]. Improvements to the devices would need to be implemented in order to acquire regulatory permits for further trials. Despite significant progress achieved in cortical visual prosthesis research, regulatory approval has not been granted so far. Such prostheses are currently developed in Australia, the USA, Canada and Spain [1,14,44,52] with clinical trials planned for the following few years.

Research on human intracortical stimulation was also carried out at the US National Institute of Health in the 1990s. It revealed the possibility of achieving a highly focal stimulation using low voltage currents. The analysis demonstrated that deep cortical stimulation could evoke the response of light percepts in amaurotic patients who do not experience any light sensation from cortical surface stimulation. The study employed six electrodes, which stimulated the cortex together; however, it is believed that a prosthesis may only be functionally useful if it evokes many more phosphenes. A recent survey carried out amongst the recipients of cortical prostheses revealed that functional effectiveness is achieved through a wide variety of phosphene diagrams, ranging from 7 to 119 phosphenes [42]. Thoroughly planned training and visual rehabilitation programmes need to be implemented in order to make such procedures successful, and objective assessment tools also need to be developed in order to quantify the results [42,52]. The Low Vision Team has to help patients with learning proper techniques with getting problems solution in everyday situations to take advantage of the benefit of the bionic eye in the daily life [8,52].Visual cortex has some plasticity, so with training and visual rehabilitation patients outcome may be much better [10,52].

7. Other indications

In the past, patients suffering from low visual acuity associated with advanced RP and choroideremia diseases had retinal prostheses implanted. However, in 2015, ophthalmologists in Manchester first used an epiretinal implant (the Argus II) in patients suffering from AMD [48,53]. The results are still collected and analysed,

and will be published in the near future. If the outcome of this study is positive, it may enlarge the list of potential medical indications for prosthesis use and increase the number of patients who could benefit from bionic eye use. Conversely, AMD patients whose central vision is damaged, risk impacting their unaffected peripheral vision with a bionic eye implant.

8. Contraindications and complications

8.1. Contraindications

1. Patients with eye conditions that could prevent the Argus II System from working (e.g. optic nerve disease, central retinal artery or vein occlusion, a history of retinal detachment, trauma, severe strabismus) [52–55],
2. Ophthalmological conditions that could prevent the successful implantation of the Argus II Implant or adequate healing after surgery (e.g. extremely thin conjunctiva, axial length of <20.5 or >26 mm, corneal ulcers, choroidal neovascularization in the area of the intended tack location) [54–58],
3. No adequate visualization of the inner structures of the eye (e.g. corneal opacity) [51,55,54],
4. No possibility of administering general anesthesia or recommended antibiotic and steroid regimen [54,55,57,58],
5. Excessive eye rubbing [54–58],
6. low communication capability, no possibility of cooperation with care providers and optimal use of the VPU (mental retardation, Usher syndrome, deafness, etc.) [53–57].

Implants need to be improved to offer methods for implanting a bionic eye prosthesis are available, all differing in complexity and both intraoperative and postoperative complications [60]. The following complications may be found in the literature: conjunctival and patients visual acuity and everyday functioning. The currently available models do not offer a sufficient risk to benefit ratio to carry out the surgical procedure. Numerous surgical scleral erosions, retinal detachment, hypotony and endophthalmitis for epiretinal prosthesis placement, increased retinal microaneurysms following subretinal prosthesis implantation, and subretinal bleeding for suprachoroidal prosthesis placement [43,2]. At 5 years after the implantation of the Argus II a total of 24 serious adverse events were identified among 12 patients (40%), all of which were treatable with standard approaches [40]. After a 3-year observation period one case of rhegmatogenous retinal detachment was diagnosed [40]. Three devices were unloaded based on the patients' decision, because of recurrent conjunctival erosions. After 4 years of using, two retinal prostheses were reported to gradually fail [39,40]. The cause of device failure was not clear but the prostheses remained implanted to follow a long-term safety profile [40,58].

9. Results and assessment of particular bionic eyes

According to the literature suprachoroidal and intrascleral devices are surgically safer, more stable and pose a lower risk of intraoperative and postoperative complications [42]. The implantation of the prostheses does not require a penetrative incision, which results in fewer complications. Conversely, placing the stimulating device distally from the ganglion cells, increases the patients' perceptive thresholds for the electrical impulses compared to epiretinal or subretinal implants [29,49,59]. However, despite this difference suprachoroidal and intrascleral devices still offer benefits to treated patients.

Patients who were qualified for retinal prosthesis implantation initially had very low visual acuity, with the majority of them only experiencing light perception. Following the surgery, and having turned on the retinal prosthesis, the patients experienced better visual acuity, which was verified using specific tasks or Landolt C optotypes. Despite improvements, postoperative visual acuity was very low and inadequate for reading texts with normal size print or recognizing faces. Initially, the patients were unable to read any optotype. However, after some training, the volunteers were able to count fingers and distinguish six-inch square optotypes from the distance of five feet [34]. The patients' experience associated with using public transportation, such as the underground, also improved.

Some papers have shown that a few patients were able to achieve a level of visual acuity which enabled them to recognize large letters. Some camera functions (e.g. zoom, focus) could improve visual acuity results for patients with retinal prostheses, although it would limit their visual field. Visual field and the location of phosphenes are important for purposes such as the exploration of one's surroundings. If typical responses to light percepts are moved to the periphery, such approaches require adjusting head or changing gaze direction.

The functional vision results for everyday life are rather similar between different kinds of retinal prostheses, even though visual acuity differs between those retinal prostheses when measured during an ophthalmological examination. Bionic eyes tested so far improved the patients' ability to perceive objects on a table, and to move around high-contrast impediments during various tasks. Enabling patients to have independent mobility is the general target for current versions of the bionic eye, and apart from visual acuity will always be a crucial part of vision restoration.

10. New approaches

Some scientists use bionic-compound-eye structure (BCES), which operates as a microlens array, is to used to empower 3D display systems [57].

Other approaches to optic tract stimulation have also been explored. Using alternating magnetic fields, low-intensity focused ultrasounds, optogenetics, implementing ionic gradients across neural cell membranes or influencing neurotransmitter levels are all examples of such methods [18,60,61].

1T1M (one-transistor-one-memristor) vision sensors were used when building the artificial retina. They were composed of one memristor and one MOSFET to construct a photoreceptor cell and ganglion cell [57]. In the retina 1T1M artificial photoreceptors are a new type of structures which may integrate spike and analog signal at the same time. However, researchers noted a problem with conducting the signal further through the optic tract [57]. Optogenetics may be a tool to potentially bypass numerous limitations of electrical stimulation [60]. The technique was tested in blind animal models of RP [6,62]. Dedicated ion channels may be used as special devices that may be controlled using the endogenous receptors [6,62].

Those new methods, together with conventional electrode stimulation, may offer a synergistic effect. Yagi T. reported to have multiplied neurons directly onto a microelectromechanical array, which in turn impacted the central nervous system neurons (e.g. retinal ganglion cells) [60,59]. Using 3D printers to help restore damaged retinal cells is also a possible way to achieve better visual acuity.

The last solution which is worth mentioning is organic photodiodes (OPD) which can perceive the light and express it as photovoltaic pixels [6]. Such a feature may be implemented in retinal prostheses. Single OPD and double OPD may be used to deliver a proper charge to stimulate neurons under near infrared electromagnetic waves which are physiologically safe [63]. A single charge is estimated at 1.4 V, while the size of the electrode is about

35 μm [63]. Microelectrode and photovoltaic prostheses manufactured with inorganic technologies were considered and used in many RP patients [64]. Newly developed prosthetic devices may use organic molecules such as organic photoswitches and conjugated polymers because of their huge potential for visual recovery and special interactions with the adjacent cells [64].

A combination of these methods may lead to the development of better connections between the stimulating electrodes and the destination neurons.

11. Challenges and conclusions

In hope of restoring vision in amaurotic patients, numerous eye prostheses have been invented and examined. While several promising results have been obtained, the goal of offering patients full vision is yet to be achieved, with various problems still to be solved. Firstly, the knowledge of the retina is a relatively new field within medicine. Secondly, we are still restricted by hardware limitations, although these are expected to be resolved in the coming years, considering the pace of technological development. Finally, software is also an important component of a successful bionic eye system, meaning that research should focus on image and signal processing, compression, coding and information channels, in order to achieve the best possible results with the existing hardware.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.05.041.

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