Advances in visual prostheses: engineering and biological challenges

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TOPICAL REVIEW

Advances in visual prostheses: engineering and biological challenges

Eleonora Borda and Diego Ghezzi*

Medtronic Chair in Neuroengineering, Center for Neuroprosthetics and Institute of Bioengineering, School of Engineering, École Polytechnique Fédérale de Lausanne, Geneva 1202, Switzerland

* Author to whom any correspondence should be addressed.

E-mail: diego.ghezzi@epfl.ch

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Abstract

Vision is an extraordinary sense through which we can appreciate the beauty of the world we live in, gain invaluable knowledge and communicate with others using visual expression and arts. On the contrary, blindness is a threatening medical condition disrupting the life of affected people and their families. Therefore, restoring sight is one of the open challenges of our society. Today, the synergistic convergence of science and technology holds the potential to provide blind patients with artificial vision using visual prostheses: a type of implantable medical device able to reactivate visual neurons using electrical stimulation. Although clinical trials showed that vision restoration is still far away, significant technological advances make visual prostheses a valuable solution for blind patients. This review is not only a description of the state-of-the-art. Instead, it provides the reader with an update on recent developments, a critical discussion of the open challenges, and an overview of promising future directions.

1. Introduction

An estimated 596 million people suffered from distance vision impairment worldwide in 2020, of which 43 million being blind [1]. Moreover, due to an increase in life expectancy, the number of blind people will predictably increase to 61 million by 2050 [1, 2]. Blindness dramatically affects educational and employment opportunities [2], causing physical and mental comorbidities [3], especially in low- and middle-income settings where most essential services and specific government-supported aids may be lacking. In the case of older adults, vision impairment can also contribute to social isolation, difficulty in walking, higher risk of falls and injuries, and greater likelihood of early entry into nursing or care homes [4]. The high degree of disability that people with severe vision impairments encounter can as well directly impact family members, friends and other carers. Lastly, vision impairment poses an enormous global financial burden for society, with an estimated cost of productivity loss as high as 16.5 billion USD in the United States of America [4]. Given these reasons, the hope that neurotechnology will restore vision, at least partially, is stronger than ever.

In the visual system, information flows from the retina to the visual cortices. Damage anywhere along this pathway might result in an interruption of the signal flow, causing blindness. Today, different vision restoration strategies have been proposed and are currently under investigation. Prospective approaches, like gene and cell therapies or optogenetics, only focus on the retina [5, 6], and they are ineffective when pathologies irremediably damage the retina or the optic nerve [7, 8]. Visual prostheses bypass the damaged segment of the visual path and electrically stimulate the downstream surviving visual neurons to induce artificial vision. As such, there are compelling reasons to pursue the development of visual prostheses. With multiple devices granted Food and Drug Administration (FDA) approval and CE mark for clinical use and many others in preclinical and clinical validation, visual prostheses represent a viable therapeutic solution to improve mobility and daily-life activities in blind individuals.

This review describes advances and challenges in visual prostheses. We provide an overview of the visual system to help familiarise the reader with its complexity. Next, we describe different types of visual prostheses, highlighting their strengths and weaknesses and suitability for specific kinds of blindness. Afterwards, we identify the open challenges currently limiting the development of the field. We conclude with an outlook on the road to market and what has been learned from the first generation of clinically approved visual prostheses.

2. Vision, blindness and artificial vision

Visual information is first processed spatially, temporally and chromatically in the retina, the neural portion of the eye (figure 1(a)). There are five types of neurons in the retina spread across three layers: photoreceptors (rods and cones) in the outer nuclear layer (ONL), horizontal cells (HCs), bipolar cells (BCs) and amacrine cells (ACs) in the inner nuclear layer (INL), and retinal ganglion cells (RGCs) in the ganglionic layer (GL). A vertical neural circuit composed of photoreceptors, BCs and RGCs converts light into neural signals [9]. Synaptic connections between photoreceptors and BCs occur in the outer plexiform layer (OPL) and between BCs and RGCs in the inner plexiform layer (IPL). HCs and ACs laterally modulate the information process at the level of photoreceptors and RGCs, respectively. Cones are responsible for high acuity and colour vision, while rods allow us to see at low light. Then, the visual information travels to higher visual centres via the optic nerve, which is composed of the axons of RGCs (figure 1(b)). The optic nerve, like the retina, is part of the central nervous system. Axons are myelinated and three meningeal layers (pia mater, arachnoid and dura mater) cover the nerve. At the optic chiasm, axons from the nasal retina cross the medial plane and project to the contralateral hemisphere, while axons from the temporal retina project to the ipsilateral hemisphere. The partial decussation of the nerve fibres organises the visual representation of each hemifield in the contralateral brain hemisphere (figure 1(b)). After the optic chiasm, the axons of the same side form the optic tract and connect the retina to the various visual targets. Axons driving structured visual information reach the dorsal lateral geniculate nucleus (LGN) in the thalamus. Relay neurons in the LGN send their axons to the primary visual cortex (V1), located in the occipital pole. As the initial stage of cortical processing, V1 integrates information about rapidly changing stimuli, high acuity, and colour vision. Higher-level processing, such as object recognition and spatial relations between objects in the visual field, occurs in other visual areas via the ventral and dorsal streams.

Two metrics assess the quality of vision or the presence of visual impairment: visual acuity and visual field. Visual acuity determines the sharpness of vision. A healthy subject can recognise an octotype on a Snellen chart when it subtends 5 min of arc (figure 2(a)). This value corresponds to a minimum angle of resolution (MAR) of 1 min of arc or a 5 μm separation on the retina [10]. Cone density, which is not homogeneous across the visual field, is directly related to our visual acuity. The maximal visual acuity is in the centre of the fovea and drops rapidly with increased eccentricity (figure 2(b)). The other parameter used to define the quality of vision is the visual field size. A normal visual field for one eye spans approximately 60° nasally to 107° temporally and from 70° above the horizontal meridian to 80° below (figure 2(c)).

Vision loss generally occurs when the visual acuity or the visual field size decreases. The World Health Organisation defines blindness as a presenting visual acuity less than 3/60 (20/400) or a visual field size less than 20°. Although more than 50% of blindness cases worldwide can be prevented or treated, such as cataract (33.4%), uncorrected refractive error (20.9%) and trachoma (1.4%), others suffer from incurable pathologies such as macular degeneration (6.6%), glaucoma (6.6%) or diabetic retinopathy (2.6%) [13]. Overall, any type of disease occurring along the entire visual pathway due to genetic, degenerative, traumatic or environmental reasons can cause blindness.

Benjamin Franklin proposed in 1752 the idea of using electricity to restore sight [14]. A few years later, in 1755, Charles LeRoy evoked visual disturbances in a blind volunteer by delivering electric current pulses through a wire coiled around his head [15]. Despite this demonstration of electrical stimulation of the visual system, the systematic exploration of the occipital cortex via electrical stimulation started only after World War I. In 1918, Löwenstein and Borchardt induced flickering perception in the opposite half of the visual field by stimulation in one occipital pole [16]. Then, Krause and Foerster induced small evoked flickering visual percepts in different locations of the visual field by moving the stimulated point [17, 18]. These experiments demonstrated the possibility of electrically inducing the perception of bright white/yellow dots (called phosphenes). Phosphenes are the building blocks of artificial vision [19]. Blind people perceive the world by combining multiple phosphenes in a meaningful manner (figure 3(a)). Initially, phosphenes might be irregular and difficult to interpret, but it is assumed that neuroplasticity triggered by learning and rehabilitation will improve artificial vision over time (figure 3(b)) [20].

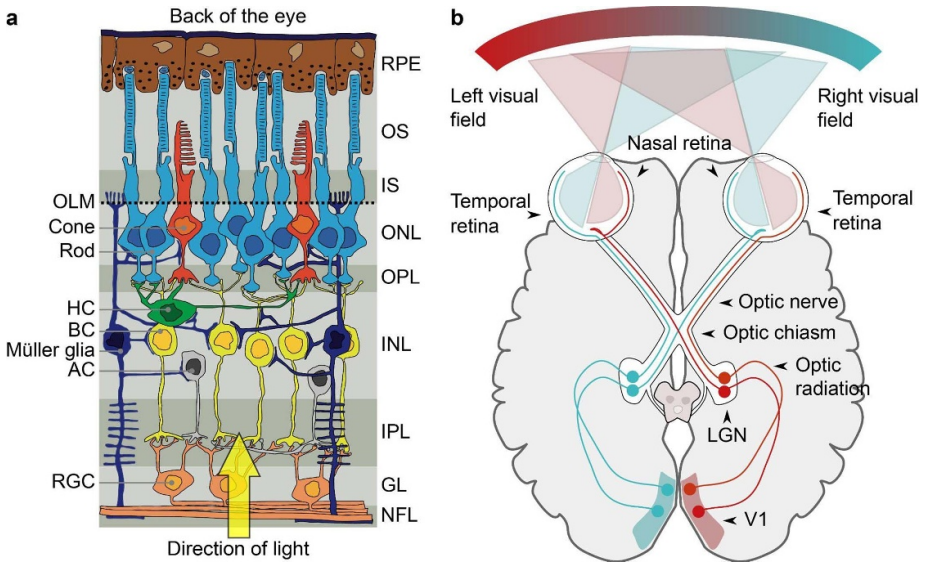

Figure 1. (a) Layered structure of the retina. RPE: retinal pigmented epithelium; OS: outer segment; IS: inner segment; ONL: outer nuclear layer; OPL: outer plexiform layer; INL: inner nuclear layer; IPL: inner plexiform layer; GL: ganglionic layer; NFL: nerve fibre layer; OLM: outer limiting membrane; HC: horizontal cell; BC: bipolar cell; AC: amacrine cell; RGC: retinal ganglion cell. The original image has been obtained by the authors from the Wikimedia website where it was made available by Ютатан under a CC BY-SA 3.0 licence. It is included and adapted within this article on that basis. It is attributed to Peter Hartmann. (https://commons.wikimedia.org/wiki/File:Retina_layers.svg). (b) Drawing of the visual system. LGN: lateral geniculate nucleus; V1: primary visual cortex. The original image has been obtained by the authors from the Wikimedia website where it was made available by Miquel Perello Nieto under a CC BY-SA 4.0 licence. It is included and adapted within this article on that basis. It is attributed to Miquel Perello Nieto. (https://commons.wikimedia.org/wiki/File:Human_visual_pathway.svg).

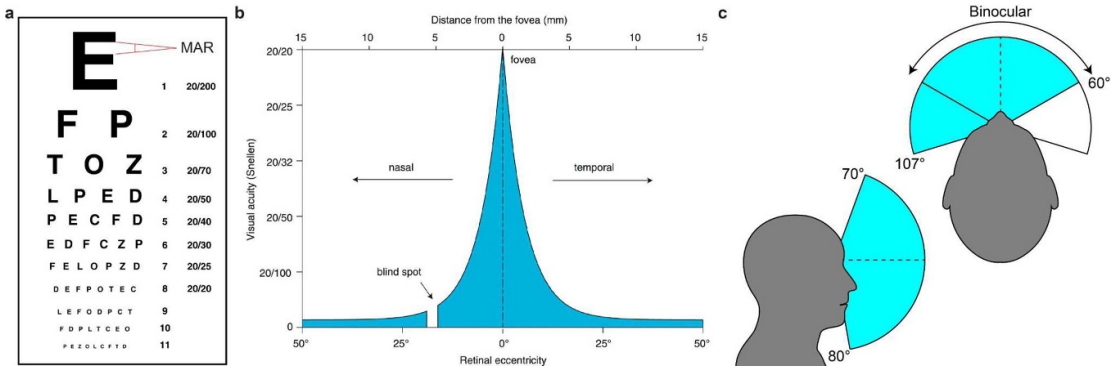

Figure 2. (a) Snellen chart to assess visual acuity. The MAR is the minimum angle of resolution corresponding to the smallest recognisable gap in the octotype. Reproduced from [11]. CC BY 4.0. (b) Quantification of the visual acuity as function of the retinal eccentricity (or distance from the fovea). Reproduced from [12]. CC BY 4.0. (c) Horizontal (top image) and vertical (bottom image) visual field size. For the horizontal size, the cyan area corresponds to the visual field of the left eye and the white area corresponds to the visual field of the right eye. The binocular area is indicated by the arrows. The dashed lines are the vertical and horizontal meridian respectively.

3. Neuroprostheses for artificial vision through electrical stimulation

Visual prostheses are classified into four categories based on the location along the visual pathway (figure 4(a)). Accordingly, this section describes the current approaches to visual prostheses, organised by position following the natural flow of information: retina, optic nerve, LGN, and V1 (figure 4(b)). We will discuss each approach's main advantages, drawbacks, and clinical applications.

Most of the work to date has been focused on retinal stimulation, which quickly became the preferred strategy since it uses the downstream natural process of visual information. The optic nerve is also a target to elicit phosphenes and could have a broader range of applications than retinal prostheses. The LGN in the thalamus has potential for individuals with either retinal or optic nerve pathologies. Similarly, the visual cortex is a target for all blindness, but cortical injuries and stroke. The population of blind patients that could benefit from prostheses increases by moving the surgical placement from the retina to the cortex. However, at the same time, there is also an increase in surgical complexity and risks.

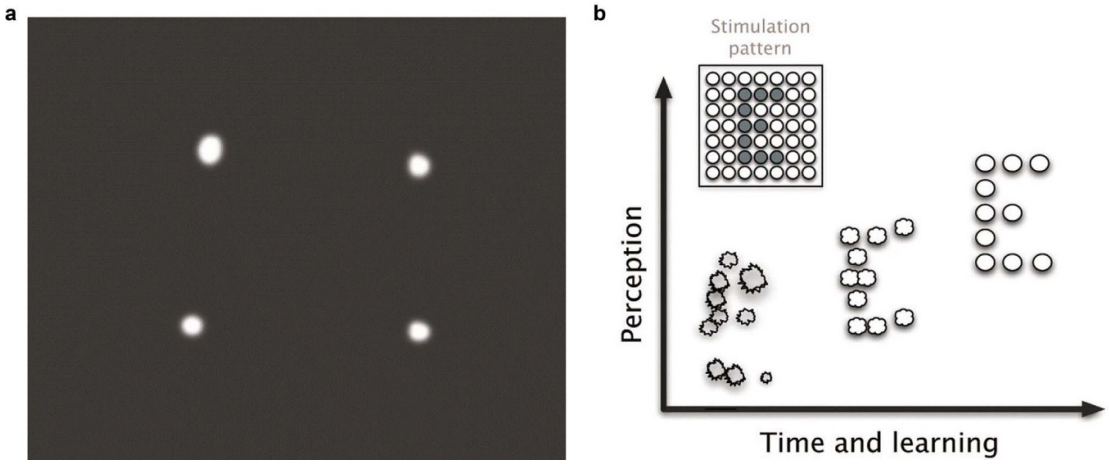

Figure 3. (a) Phosphenes arranged as a square generated by stimulating four electrodes simultaneously. (b) Neuroplasticity improves perception over time. (a), (b) Reproduced from [20]. CC BY 4.0.

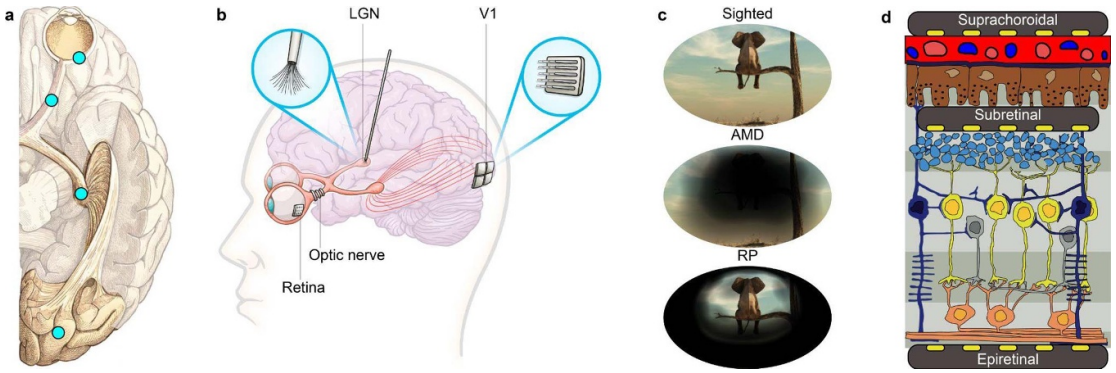

Figure 4. (a) The cyan circles show the possible locations for visual implants along the visual pathway: retina, optic nerve, LGN, and V1. (b) Illustration of the four categories of visual prostheses. Reprinted from [37], Copyright (2015), with permission from Elsevier. (c) Illustration of vision in a sighted (top), AMD (middle) and RP (bottom) subject. (d) Epiretinal, subretinal and suprachoroidal placement of retinal implants. Subretinal prostheses might be separated from target cells (BCs) by remaining debris following photoreceptor degeneration, represented by circles (in light blue). The original image has been obtained by the authors from the Wikimedia website where it was made available by Юкатан under a CC BY-SA 3.0 licence. It is included and adapted within this article on that basis. It is attributed to Peter Hartmann. (https://commons.wikimedia.org/wiki/File:Retina_layers.svg).

3.1. Retinal prostheses

Retinal prostheses aim to electrically stimulate the surviving retinal neurons. Therefore, they can offer artificial vision only to blind patients with outer retinal diseases, causing the progressive loss of retinal photoreceptors. These diseases are the major causes of incurable blindness in the western world [21]. They include retinitis pigmentosa (RP), macular dystrophies (e.g. Stargardt disease) and age-related macular degenerations (AMDs). Macular degeneration affects retinal cones and results in blurred or no vision in the centre of the visual field (figure 4(c)). In contrast, peripheral vision remains preserved in most cases. AMD is the most preeminent pathology amongst outer retinal diseases. Unlike AMD, RP is a set of rare inherited retinal rod-cone dystrophies, causing loss of night vision and the constriction of the visual field (tunnel vision), later followed by cone dysfunction and eventually total blindness (figure 4(c)) [5, 22].

Retinal prostheses have quickly become the leading device among visual prostheses. Several devices have been commercialised [23–25] thanks to their relative ease of implantation and lower surgical risks compared to other approaches. Besides the ease of surgical accessibility, they can also profit from the retinotopic organisation and early positioning in the visual pathway [26, 27].

Retinal prostheses can be implanted in three locations (figure 4(d)). Epiretinal prostheses are anchored to the retinal inner surface, subretinal prostheses are inserted between the retina and the RPE, and suprachoroidal prostheses are implanted between the choroid and the sclera. Consequently, the retina can be electrically stimulated either from the GL (as in epiretinal prostheses) or the INL (as in subretinal and suprachoroidal prostheses). The device position (epiretinal, subretinal or suprachoroidal) and the

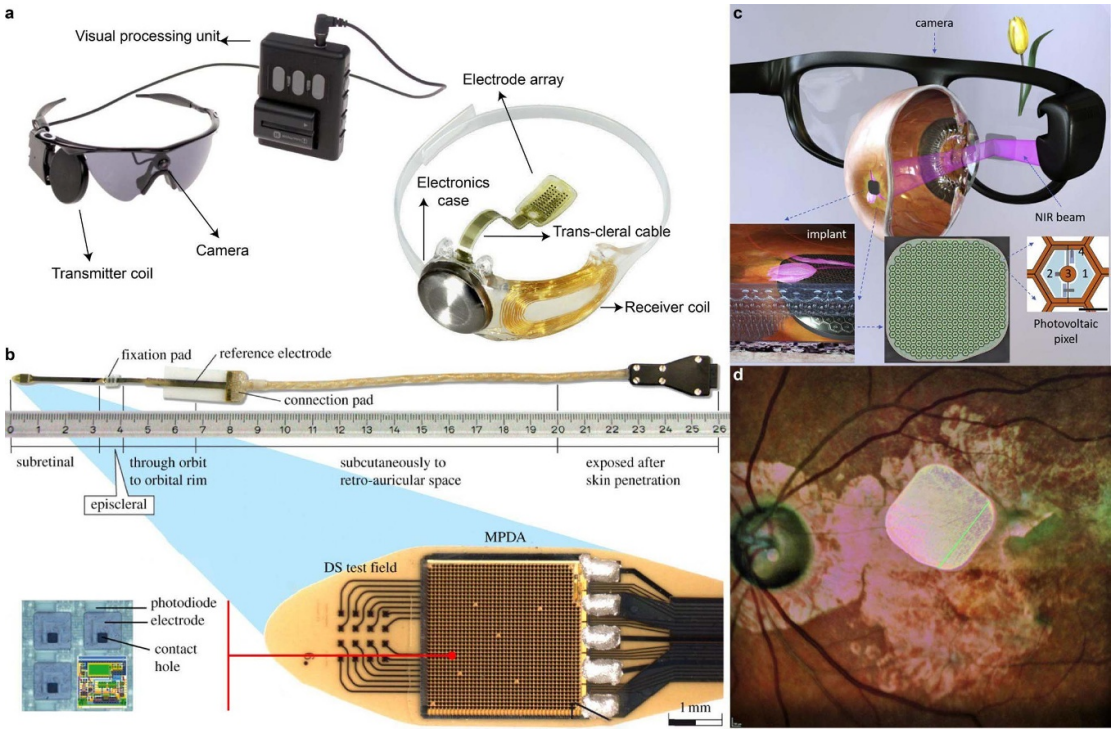

Figure 5. (a) The Argus® II system. Reproduced from [62]. CC BY 4.0. (b) The Alpha-IMS subretinal prosthesis. Reproduced from [52]. CC BY 4.0. (c) The PRIMA Bionic Vision System composed of the PRIMA photovoltaic retinal prosthesis and the wearable projecting glasses with camera. (d) Fundus image of the PRIMA implant placed below the macula of one patient with atrophic AMD. Reproduced from [48]. CC BY 4.0.

characteristics of the electrical pulses (such as duration and waveform) determine which cell population is predominantly activated [28, 29]. Subretinal and suprachoroidal prostheses primarily activate BCs, whose membrane depolarisation triggers synaptic release causing the glutamatergic excitation of RGCs. This mechanism is known as network-mediated stimulation since RGCs are indirectly stimulated via their presynaptic network. Epiretinal prostheses with short (e.g. less than 1 ms) and rectangular pulses directly activate RGCs. However, the network-mediated stimulation is also possible from an epiretinal device if long (more than 8 ms) or non-rectangular pulses are used [29–31].

For more extensive reading about retinal prostheses, we refer to previous articles [32–36].

3.1.1. Epiretinal prostheses

The implantation of epiretinal prostheses relies on a surgical approach familiar to vitreoretinal surgeons. Epiretinal surgery allows the placement of sizable devices for artificial vision in a large portion of the visual field [38–40]. Wide artificial vision is crucial for totally blind people to perform everyday visual tasks such as general orientation, safe ambulation, obstacle avoidance and object recognition [41]. Moreover, another advantage of epiretinal implants is the facilitation of heat dissipation via the vitreous [42]. The main surgical drawback is the requirement of one or more retinal tacks to anchor the prosthesis to the retina, which could cause retinal damage. Retinal tacks also lose mechanical stability over time, which can increase the distance between electrodes and the retina and, in consequence, increase the current required for retinal stimulation and reduce resolution [43–45].

Epiretinal stimulation remains an open challenge. Although the electrodes are close to RGCs, they are not directly in contact with their somas. In fact, the NFL composed by the axons converging to the optic disc is in between electrodes and cell bodies (figure 4(d)). Due to axonal activation, phosphenes often appear with an elongated shape distorting the image perceived by the patient [46]. A way to mitigate this phenomenon is to use long and non-rectangular pulses that will preferentially induce network-mediated stimulation, resulting in a more localised activation [29, 31].

So far, only two epiretinal implants have received commercialisation approval for RP patients: the Argus® II (Second Sight Medical Products Inc; CE mark and FDA approval) in figure 5(a) and the IRIS® II (Pixium Vision SA; CE mark) [34, 35]. Both devices are now out of production. A third device is currently under clinical evaluation (NR600, Nano Retina, Rainbow Medical Group). The implant is a wireless light-powered prosthesis with three-dimensional penetrating electrodes to stimulate BCs from the epiretinal side.

3.1.2. Subretinal prosthesis

Subretinal prostheses are inserted between the retina and the RPE (figure 4(d)). Therefore, they do not need fixation with retinal tacks and have greater mechanical stability. On the other hand, subretinal surgery is more delicate due to the adhesive junctions between the retina and the RPE [47]. Subretinal prostheses directly stimulate the remaining INL and use its processing capability. For this reason, these prostheses might provide higher visual acuity and more naturalistic perception [48, 49]. However, the presence of debris due to photoreceptor degeneration might increase the distance from the electrodes to BCs and reduce resolution and stimulation efficiency [50]. A major constraint in subretinal prostheses however is the maximum size of the implant, which is limited by the risk of retinal detachment. Devices have a size providing a maximum restored visual angle of about 10°, suitable only for applications where a small part of the visual field is lost, such as AMD [48, 49]. For totally blind patients, like in RP or severe forms of AMD, a much wider visual field would be required to allow the patient to perform everyday tasks [41].

Subretinal prostheses have been pioneered in the early 90s by the artificial silicon retina (ASR, Optobionics): an array of photovoltaic diodes coupled to capacitive electrodes. Six RP patients have been implanted with the ASR device [51]. However, visual improvements were likely due to a generalised neurotrophic effect rather than a direct effect from electrical stimulation. Today, only one subretinal prosthesis, the Alpha IMS implant (figure 5(b)) and its successor Alpha AMS (Retina Implant AG), have received marketing approval (CE mark) [52, 53]. Unfortunately, the company dissolved in 2019. The subretinal prosthesis PRIMA (Pixium Vision SA) is currently in clinical evaluation for AMD patients (figures 5(c) and (d)) [48, 49].

3.1.3. Suprachoroidal prosthesis

The third location is the suprachoroidal space, between the choroid and the sclera (figure 4(d)). This location reduces the risk of retinal damage compared to the other two approaches since it does not require intravitreal manipulation [54]. However, a high risk of subretinal and suprachoroidal haemorrhage has been reported during preclinical and clinical evaluation [55–57]. Like subretinal prostheses, they have good mechanical stability without fixation with retinal tacks [56, 58] and, like epiretinal prostheses, they have good heat dissipation capacity and allow the insertion of large arrays [57]. Suprachoroidal prostheses aim at the stimulation of BCs, but the considerable distance between the electrodes and the retina is a major issue. The presence of choroid, RPE, and debris of photoreceptors makes the selective stimulation of BCs extremely difficult, leading to poor spatial resolution [59, 60]. Due to the considerable distance from BCs, high current amplitudes are required for retinal stimulation, possibly leading to damage due to overstimulation [35, 61].

Two clinical trials are ongoing in RP patients, one in Australia (Bionic Vision Technologies) [57] and one in Japan (Osaka University) [58]. The results showed that implanted patients could localise static objects, light or trajectories, despite the poor visual acuity. In Australia, the second generation of the suprachoroidal prosthesis with more electrodes is currently under clinical assessment [55].

3.2. Optic nerve prostheses

When severe damage to the eye or the retina occurs (as traumatic eye injury or retinal detachment), or the lack of optical transparency prevents vitreoretinal surgery, retinal prostheses are no longer suitable [63]. Optic nerve prostheses are an attractive solution to overcome the exclusion criteria of retinal implants (figure 4(b)). Moreover, the relatively small diameter of the optic nerve facilitates the electrical stimulation of a wide visual field.

In 1998, a group in Leuven (Belgium) was the first to propose a prototype of optic nerve prosthesis in humans [64]. They implanted a self-sizing spiral cuff with four electrodes in the intracranial segment of a blind subject suffering from RP. The patient reported phosphenes and described them by their position, shape, number of dots, colour and dimension. The results showed excellent retinotopic correspondence between the quadrant of the visual field in which the phosphene appeared and the electrode used. After a few months of training, the patient distinguished line orientations and identified characters despite having only four electrodes [65–67]. The research proved that optic nerve stimulation elicits phosphenes in the entire visual field with some degree of selectivity. However, phosphenes were irregular in shape and not stable over time. The lack of stable phosphene could be attributed to the lack of mechanical stability of the cuff device [68].

The other challenge presented by existing cuff devices is to selectively activate specific fibres, including those in the central portion of the nerve, to improve the resolution of artificial vision [69]. Therefore, intraneural arrays were implemented to increase fibre selectivity (figure 6(a)). Three platinum wires were implanted in the optic disc of an RP patient eliciting phosphenes in three distinct positions for each electrode [70]. Unfortunately, functional vision tests were not performed. Recently, a few groups have developed optic nerve prostheses based on intraneural electrode arrays. The C-Sight project tested an optic nerve prosthesis

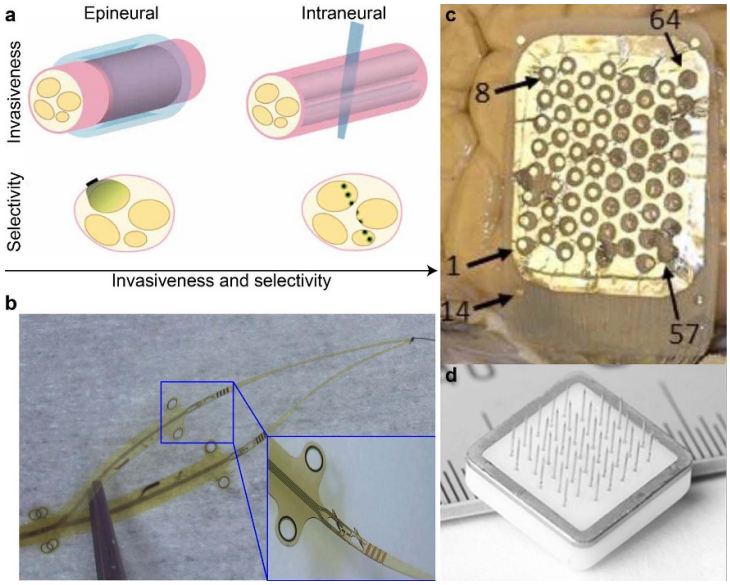

Figure 6. (a) Sketch of epineural and intraneural nerve prostheses. Epineural are less invasive than intraneural, but also less selective. Reproduced from [76]. © The Author(s). Published by IOP Publishing Ltd. CC BY 4.0. (b) Picture of the OpticSELINE. Adapted from [74], with permission from Springer Nature. (c) Picture of the epicortical array explanted after 36 years from one of Dobelle's patients. Reproduced from [77]. © The Author(s). Published by IOP Publishing Ltd. CC BY 4.0. (d) Picture of one module of the GENNARIS intracortical visual prostheses developed at the Monash Vision Group. Reproduced from [78]. CC BY 4.0.

based on four stiff electrodes to stimulate the intra-orbital segment of the nerve in rabbits and cats [71–73]. However, this implant is too rigid compared to the nerve tissue and is therefore unsuitable for chronic implantation. Another group has validated a thin and flexible intraneural electrode array called OpticSELINE (figure 6(b)). Results in rabbits showed that the selective activation of different portions of the optic nerve induced spatially organised cortical activation patterns in the rabbit's V1 [63, 74, 75]. These are promising steps towards developing a more focused optic nerve stimulation. However, the long-term functionality of the device and the biocompatibility should be tested before moving into human application [69].

3.3. Thalamic prostheses

The LGN is a stratified compact structure in the thalamus receiving input from the optic nerve and relaying information to the primary visual cortex [7]. Given its deep location, only recently have visual prostheses targeting the LGN been investigated thanks to advances in deep brain stimulation (figure 4(b)). Three main advantages drive the interest in the LGN. First, it can help patients who lost the optic nerve, for example, due to glaucoma or ocular trauma. Second, it is possible to cover a wide visual field with an overrepresentation of the foveal region, thus restoring possibly high-acuity artificial vision [79]. However, since the LGN is located after the optic chiasm, a bilateral implant is required to cover both hemifields. Third, LGN presents retinotopic organisation and well-defined physical separation of the parvocellular and magnocellular pathways, respectively relaying information about small, slow, colourful things (parvocellular; high spatial frequency information; low temporal frequency information) and large, fast, and colourless things (magnocellular; low spatial frequency; high temporal frequency) [37, 80]. Therefore, it might encode a more naturalistic perception.

In animals, LGN microstimulation produced simple discrete visual percepts [81] and visual cortical responses similar to those elicited by natural vision [82]. So far, there have been very few preclinical studies in animals conducted to test the stimulation efficacy [81, 83, 84]. With future advancements from the technological point of view, LGN visual prostheses could start to carve their way into a feasible solution for patients [85].

3.4. Cortical prostheses

After the pioneering experiments of Löwenstein and Borchardt [16], Krause [17] and Foerster [18], cortical prostheses were the first ones to be developed among visual implants.

The first cortical prosthesis had only four intracortical electrodes [86, 87] but was able to evoke some visual percepts in the subject [88]. In 1968, Brindley and Lewin proposed the first permanently implanted cortical prosthesis, consisting of an epineural array of 80 electrodes implanted over the occipital cortex

[89, 90]. The volunteer, a blind subject with glaucoma, perceived phosphenes and recognised simple patterns. A second subject was implanted a few years later with a bilateral device. He recognised patterns induced by sequential activation of electrodes corresponding to the Braille alphabet [91]. At the same time, Dobelle started a long-term project to develop a portable cortical visual prosthesis. Initial results in the first set of subjects were promising [92–94], but the project suddenly closed after the bilateral implantation of 16 blind volunteers between 2002 and 2004.

A cortical prosthesis offers the advantage of artificial vision in most conditions of blindness, excluding traumatic brain injuries and stroke [7]. On the other hand, the complexity of the visual cortex with neurons specifically tuned for specific cues [95] could hinder the ability to evoke simple uniformly shaped phosphenes. Stimulation paradigms adapted explicitly for each patient might also be required [96]. This aspect becomes even more critical when considering the effect of neuroplasticity, which is the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganising its structure, functions, or connections [97]. Indeed, researchers demonstrated that visual perception and performance in solving visual tasks could improve with learning and time [20, 98].

Cortical prostheses follow two main approaches: epicortical arrays placed on the cortical surface (figure 6(c)) or intracortical electrodes penetrating the cortical layers (figure 6(d)). Epicortical prostheses are less invasive since they do not penetrate the brain, as confirmed by a post-mortem study on a patient implanted by Dobelle, who retained the epicortical array for 36 years (figure 6(c)) [77]. However, the current amplitudes required to elicit a phosphene is much higher than with intracortical electrodes because of the distance between the electrodes and the neurons. This distance reduces the spatial resolution of artificial vision [99], and high currents might be unsafe due to the risk of seizures [88]. Intracortical prostheses are more invasive but take advantage of the close contact between the electrodes and the neurons to provide a more selective stimulation at much lower current amplitudes [100, 101]. Therefore, evoked phosphenes are smaller and closer. However, the implantation technique requires pneumatic insertion tools that limit the area reachable with the device to only the occipital pole. Contrary to epineural implants, intraneural electrodes cannot be placed in the interhemispheric fissure, where a large portion of the visual field is mapped [102]. In this case, phosphenes are evoked only in a few degrees of the visual field. Therefore, placing the electrodes in higher visual areas where spatial representation is still preserved [26, 103] could be a possible solution to enlarge the visual field.

Four projects are currently in clinical evaluation. The Orion I (Second Sight Medical Products Inc.) is a flexible electrode array already implanted in six subjects. However, due to the high current intensities required to elicit phosphenes, this approach might induce seizures, as reported by one subject [104, 105]. The other three are intracortical prostheses. The GENNARIS (Monash Vision Group) consists of 11 modules with 43 electrodes each (figure 6(d)) [106]. The CORTIVIS (Miguel Hernández University of Elche) uses a Utah array with 100 electrodes [107]. The ICVP (Illinois University of Technology) is developing a wireless floating microelectrode array with 16 microelectrodes [108].

For more extensive reading about cortical prostheses, we refer the reader to previous review articles [37, 109, 110].

4. Current challenges and potential solutions

Visual prostheses have been an incredible breakthrough leading to artificial vision in several blind patients suffering from RP, AMD, glaucoma, or other traumatic injuries. So far, retinal prostheses have reached marketing approval [23, 53, 111], and other devices are in preclinical and clinical testing. However, artificial vision still does not offer the patient the possibility of regaining fully functional vision. Quantitative limitations in artificial vision are a product of both technological and biological challenges, which will be addressed in the following paragraphs, together with potential solutions.

4.1. Quantitative limitations

4.1.1. Visual field size

Everyday experience shows that the visual angle size has primary importance in mapping and interacting with the environment, consequently affecting one's understanding of layout space, walking distance evaluation, identify-and-reach tasks, spatial cognition, and attention. Many studies have highlighted that restoring a large visual field is necessary to make artificial vision helpful in everyday life [41, 112–116]. Studies under simulated prosthetic vision identified a visual angle of 30°–35° as the minimal requirement for mobility and daily tasks (figure 7) [41, 117–120]. However, this number might underestimate the real needs of implanted patients due to the perceptual and behavioural learning required to adapt to artificial vision [121, 122]. The entire visual field is mapped over the anatomical area in all the structures mentioned (retina,

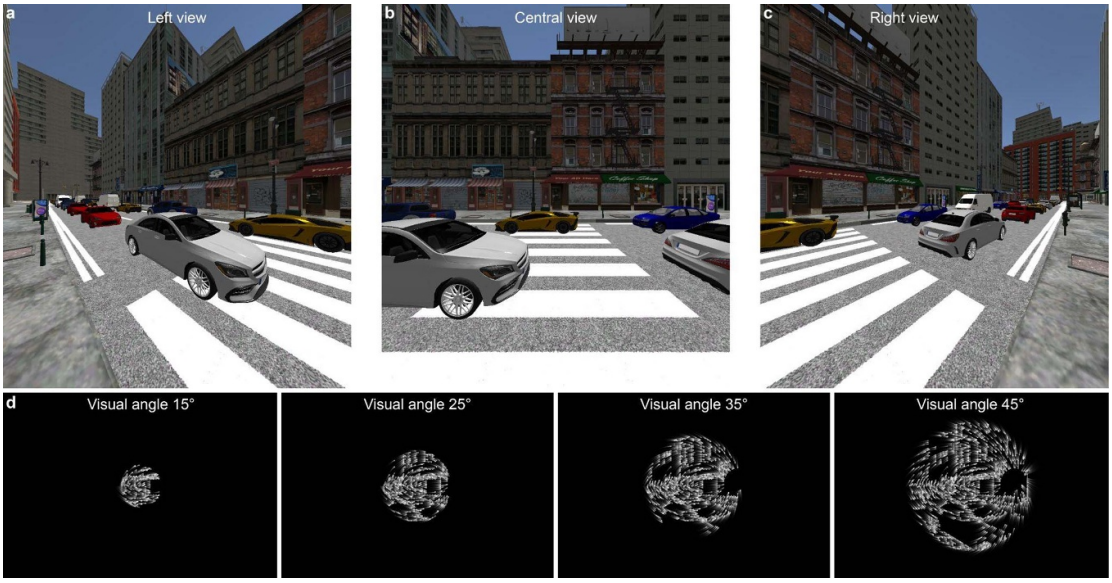

Figure 7. (a)–(c) Virtual reality views of a busy street with cars: left view (a), central view (b) and right view (c). (d) Image rendering is simulated prosthetic vision of the busy street with cars at increasing visual angles. Reproduced from [41].

optic nerve, LGN and V1). Therefore, as a rule of thumb, enlarging the visual field means having electrodes covering a wider tissue area.

In retinal prostheses, wide coverage of the retina remains an open challenge. Moreover, it is possible only for epiretinal and suprachoroidal implants. Subretinal prostheses are typically small in size, since large subretinal implants might encounter considerable difficulty in the surgical placement and represent a high risk of retinal detachment [32]. Multiple PRIMA devices have been placed in the rabbit eye to increase the visual angle [123]. However, it remains unclear if this tiling procedure will be feasible in patients. On the other hand, the surgical fixation to the retina is another open challenge for wide epiretinal implants [124].

Larger prostheses might also require larger and potentially riskier incisions to insert the device and from which the connection cable will have to exit the eye to connect with the stimulator. Nevertheless, the main issue with wider prostheses is the limited number of electrodes usually available in the array. In conventional visual prostheses, the electrode number and electrode density are limited by the implantable pulse generator, the cable from the pulse generator to the array, and the feedlines in the array. A fixed electrode number reduces the electrode density if electrodes are spread over a wider surface area, which might worsen visual resolution [125]. One way to overcome this problem in retinal prostheses is to use wireless photovoltaic technology where each pixel converts incident light into electrical stimulation [38, 39, 48, 49, 126–132]. In retinal stimulation, photovoltaic technology is intuitive since the retina is designed to absorb the light entering from the pupil. Photovoltaic retinal stimulation is achieved using artificial light projected into the eye (using a projection system as in augmented reality goggles) and absorbed by a semiconductor layer embedded into the stimulating electrodes. This wireless solution avoids a trans-scleral cable which are known to limit the maximum number and density of electrodes on the device and to induce post-operative complications such as eye inflammation or leakage through the incision. To this aim, POLYRETINA is a high-density wide-field epiretinal prosthesis containing 10 498 photovoltaic pixels distributed over an active area of approximately 43° [38, 39, 131, 132]. Yet, an open challenge for both subretinal (PRIMA) and epiretinal (POLYRETINA) photovoltaic implants is projecting wide-angle images through the pupil necessary to increase the visual field size.

Both the optic nerve and LGN are compact, making it easier to access the entire visual field of one eye (optic nerve) or a whole hemifield (LGN) with a single implant. However, their small size is a challenge for implant and electrode miniaturisation, particularly when targeting the optic nerve. An epiretinal implant like POLYRETINA on the other hand can have more than 10 000 electrodes over 43° (approximately 140 mm^2), that is an area ten times larger than the total cross-area of the optic nerve.

Most of the primary visual cortex surface lies in the interhemispheric area and the calcarine fissure [102], creating a hurdle for developing wide-angle cortical prostheses. Although placing the electrodes in higher visual areas [103] could be a possible solution to enlarge artificial vision.

4.1.2. Spatial resolution

The visual angle is certainly not the only barrier. Object identification and recognition require devices that are able to provide a high enough resolution during artificial vision. In other words, increasing spatial resolution means increasing the number of separable phosphenes per unit area evoked in the patient's visual field. Another challenge threatening artificial vision lies in the capability of the device to stimulate multiple independent phosphenes to create form perception.

So far, most studies regarding spatial resolution have been conducted with retinal implants. Clinical trials showed that the best visual resolution was achieved using subretinal prostheses. The highest visual acuities reported to date, as measured with the Landolt-C test, were 20/460 with the subretinal implant PRIMA (in AMD patients) [48] and 20/546 with the subretinal implant Alpha-AMS (in RP patients) [133]. Grating acuities reported in the literature range from 20/1260 with the epiretinal Argus® II implant to 20/364 with the subretinal Alpha-AMS implant [53]. This comparison shows that subretinal prostheses have so far provided better resolution than epiretinal prostheses. This result is primarily due to two factors. First, the Argus® II implant had a significant separation between electrodes (575 μm), about 5–8 times higher than PRIMA and Alpha-AMS. A larger electrode separation will inevitably lead to a lower resolution. Second, the Argus® II implant stimulates RGCs directly. Therefore, evoked phosphenes are distorted (resulting in an elongated shape) due to unwanted axonal stimulation in nerve fibre bundle trajectories [134–136]. Two approaches have been proposed to improve resolution in epiretinal stimulation. One solution would be to selectively activate individual RGCs by establishing a one-to-one connection between RGCs and electrodes [137]. Also, high stimulation frequency allows discrimination among RGC types [138]. Otherwise, increasing the pulse duration [31] or using non-rectangular pulses [29] facilitates network-mediated stimulation. Sinusoidal electrical stimuli in epiretinal configuration allowed the classification of overlapping but spatially displaced objects in explanted retinas [139]. Epiretinal prostheses with higher pixel density and targeting network-mediated stimulation might overcome these issues and provide high resolution. POLYRETINA reported *ex-vivo* a spatial resolution of 120 μm (or 20/480) equivalent to the electrode separation [132]. The two approaches to avoid axonal stimulation (selective direct stimulation and epiretinal network-mediated stimulation) point towards different directions, and today they seem mutually exclusive. However, this is an important research question that needs to be addressed in epiretinal stimulation.

Subretinal implants are further away from the GL, and usually induce circular phosphenes. However, patients might still experience arcuate and linear phosphenes when high current amplitudes are used [140], most probably due to direct RGC activation. A similar effect has also been observed with suprachoroidal implants, where the subjects described geometrically complex percepts [141].

Reducing the size of the electrode is necessary to increase electrode density. However, the electrode size is not the only limiting factor, and further reducing the electrode diameter might not correlate to better resolution [142]. On the other hand, the denser the electrodes, the higher is the risk of cross-talk between electrodes. Visual prostheses could benefit from current-steering approaches that would limit the extent of the activated tissue during stimulation, reducing the risk of cross-talk and increasing the spatial selectivity. A common approach is to use bipolar stimulation through two close electrodes, as shown in retinal [36, 143, 144], optic nerve [75], and thalamic prostheses [81]. Different groups demonstrated that spatially organised phosphenes are induced by applying current-steering or modulating current amplitudes during optic nerve stimulation [65, 73]. Despite these results, the selective activation of a few optic nerve fibres by each electrode remains an open challenge. Another example of nonspecific activation can also be found when stimulating the visual cortex. In animal studies, researchers have found that stimulation activates interconnected neurons distant from the electrode, even at low currents [145].

From the perceptual point of view, each electrode should evoke a reproducible phosphene located in a region of the visual field. The stimulation parameters play a crucial role in the characteristics of phosphenes, such as brightness, duration, size or colour. Generally, short trains of charge-balanced biphasic pulses evoke individual phosphenes [146]. Whether the stimulation through multiple electrodes is synchronous or sequential [91, 98, 147], each electrode should excite selectively only a specific subset of neurons, different from those stimulated by neighbouring electrodes. When the stimulation resolution is low, as it is for the Argus® II or epicortical visual prostheses, it has been shown that phosphenes might fuse into a blob during synchronous activation of multiple electrodes. The sequential activation of electrodes is an attractive strategy allowing form vision in patients [91, 98].

Future developments in field-steering technology will be beneficial to improve stimulation therapies not only for visual prostheses but in general for the neuroprosthetics field.

4.1.3. Temporal resolution

Artificial vision can also be hampered by poor temporal resolution. A significant limitation in artificial vision is phosphene fading [148–150], a perceptual phenomenon similar to the Troxler effect, which affects retinal

prostheses and makes continuous perception above flicker fusion nearly impossible. In sighted humans, the Troxler effect is prevented by various ocular micromovements (tremors, drifts and microsaccades) that refresh a static image and limit retinal adaptation [151, 152]. Retinal prostheses can avoid fading if three criteria are met [153]. First, natural or artificial light must activate the electrodes, so that eye micro movements can effectively shift the stimulated area of the retina, like for Alpha IMS/AMS [53], PRIMA [48] and POLYRETINA [132]. Second, high-density electrode arrays are required to ensure high-resolution stimulation to move the projected image by one or two electrodes over the prosthesis leading to stimulation of different retinal areas. Third, patients must have preserved their physiological ocular micromovements, such as for AMD patients. However, this ideal case is rarely reached and has only been reported for the PRIMA device [48] and some patients with Alpha IMS, most likely with preserved eye movements [154]. Contrarily, patients implanted with Argus® II, IRIS® II and EPI-RET 3 prostheses were instructed to perform large body and head movements to scan the visual scene and refresh the stimulation pattern on their retina. Such large movements made the experience of artificial vision physically and mentally tiring. Therefore, several groups have developed an interest in exploring compensatory stimulation strategies to reduce retinal desensitisation and avoid fading [155–157] and tested them with sighted subjects under simulated prosthetic vision [153].

Another limitation is the maximal frame frequency and the possibility of reaching flicker fusion (30 Hz or above). So far, flicker fusion has been achieved only for the PRIMA device in AMD patients [48]. Patients with other retinal prostheses were more comfortable with lower frame frequencies (between 1 and 20 Hz), most likely due to the process of perceptual fading. The retina has been widely studied, and much knowledge has also been gained thanks to the many patients who have been implanted. Meanwhile, little is known about other visual targets. Stimulation approaches, such as dynamic current steering, have been investigated and proved to be a helpful strategy for recognising shapes [91, 98] and while dynamic current steering combined with high-density electrode arrays holds promises of improvement in cortical prostheses [100], more needs to be known about safe stimulation frequency limits and the possibility of reproducing flicker fusion. As such, it is crucial to understand how to modulate spatiotemporal stimulations to generate individual phosphenes and combine them into perceived objects and visual scenes.

4.2. Technological challenges

4.2.1. Electrode–tissue interface

The electrode–tissue interface is one of the most critical elements of a neural interface from a mechanical, chemical and electrical point of view [158, 159].

Electrodes should be close to and have a comparable dimension of target neurons to achieve high-resolution stimulation, ideally down to a single neuron [20]. However, decreasing the electrode size imposes constraints on the electrode material to maintain low impedance and high charge injection capacity. Exceeding the charge injection limit of electrodes will cause irreversible damage to both electrodes and tissue. Since the charge injection limit is a property of a material, smaller electrodes can safely deliver less charge compared to larger electrodes. Smaller electrodes have higher charge density stimulation threshold and lower dynamic range, as shown in explanted ratinas [160, 161]. These results have important implications for high-density prostheses.

In the last 20 years, advances like carbon-based materials and nanomaterials have been explored to improve the performance at the electrode–tissue interface [162–165]. Conductive polymers have been widely used in implantable devices for research as they are considerably softer than metals, flexible and conformable, and have a high charge injection capacity [166–170]. The use of polymer-based coatings in visual prostheses could be beneficial to allow smaller and denser electrodes [33]. Among carbon-based materials, graphene-based materials emerge in neural interfaces, given their outstanding electrical and optical properties [171]. Recently, the safety and biocompatibility of graphene electrodes for retinal implants has been assessed [172]. Nanomaterials for neural stimulation have also been developed thanks to the latest advancement in nano-engineering [173]. In addition, these novel materials are compatible with flexible and stretchable substrates and cleanroom microfabrication processes. In conclusion, reducing the electrode size will allow visual prostheses to significantly increase the number of electrodes in the array, which might translate into higher visual acuity and improved visual function for the patients.

Another crucial element of the electrode–tissue interface is the biological response. It has been shown that all biocompatible materials used so far provoke an inflammatory response and some degree of foreign body reaction [174, 175]. For visual prostheses, regardless of whether they are epineural or intraneural, matching the neural tissue mechanical properties with the implanted ones would help in improving the long-term stability and efficacy of the stimulation. In particular, for epineural prostheses, when the target tissue covers a wide area (like in the retina or the visual cortex), the choice of the substrate plays an important role. Exploiting conformable or foldable substrates has two advantages: ease of insertion during

the surgical procedure and improved contact with the neural tissue [176]. Minimally invasive surgical insertion is crucial for epiretinal prostheses, where having a large implant in order to cover a greater visual field would mean having to create a wider incision with associated risks. To overcome this issue, POLYRETINA is a foldable and injectable photovoltaic epiretinal prosthesis that can be safely delivered with a 6 mm size cut through the sclera and conform better to the curvature of the eye [39, 38]. Accessibility is also an issue for cortical prostheses since most of the visual field is mapped in the interhemispheric area and the calcarine sulcus. The surgical procedure is just one aspect of the challenge. The prosthesis should conform to the shape and curvature of the cortical surface. Soft, flexible or conformable arrays like those developed for auditory brain stem stimulation could offer a potential solution to ensure better coverage of the target area [177]. An injectable ultra-thin electrode mesh could be a possibility to overcome the issue for both retinal and intracortical approaches [178, 179]. Besides, advancements from the material side should be followed by solutions for hermetic packaging to ensure robust isolation barriers over long periods [180].

4.2.2. Image processing and advanced encoding strategies

In general, a visual prosthesis is composed of a camera worn on glasses, capturing the visual information and sending it in real-time to a signal-processing unit that converts the image into a sequence of stimulation patterns. Visual information processing is a crucial step. However, traditional computer vision approaches, such as edge detection, contrast enhancement, and difference of Gaussians, have been tested in retinal prostheses and proved limited usefulness in daily life [181–183].

Recent studies in healthy subjects under simulated prosthetic vision have investigated other solutions such as saliency detection and object recognition [184]. Saliency detection extracts a region or object of interest by computing from image features, and it can be divided into three types: feature-based, region-based and object-based. This method works efficiently for image or static object recognition tasks. However, due to the complexity of saliency calculation, real-time performance is the limiting factor for visual prostheses [185–188]. Machine learning approaches, such as convolutional neural networks [189] and deep learning [190, 191], could recognise multiple objects in complex scenes, helping navigation, obstacle avoidance and target object finding. A drawback of these methods is the high training cost required for good accuracy. Once the visual information has been pre-processed and features have been extracted, a personalised spatiotemporal stimulation strategy should be generated. Such a customised approach is needed because phosphenes maps are specific to each patient and might change over time. Machine learning could also play a role in optimising stimulation parameters to create more naturalistic electrical stimulation patterns, as shown for optic nerve [192] and cortical [193] prostheses. Last, the conceptual idea of multi-area cortical stimulation has been recently proposed to help create high visual acuity, colour and motor perception to provide a more naturalistic perception [103]. Combining machine learning and multi-area stimulation will require further experimental investigation and both hardware and software advancements.

Similar to other neuromodulation therapies [194], researchers are also considering and exploring bi-directional and closed-loop feedback approaches for retinal [36, 195–198] and cortical [100, 199] prostheses. This combination would allow prostheses to automatically adjust the stimulation parameters and improve the performance over time. Most of the image processing algorithms and the closed-loop approaches have been tested so far *in-silico* or *in-vitro*. The challenge for the future will then be to determine their efficacy in real-world settings. One additional parameter to consider when designing closed-loop feedback is the presence of voluntary and involuntary eye movements. They affect the spatial localisation of the phosphene elicited by retinal [200] and cortical [101] stimulation, even after years of blindness.

4.2.3. Wireless power and data transmission

Neurostimulation has been routinely performed with electrodes wired to an electric pulse generator. Leads-wires breakage is common [35] and leads to malfunctioning or not functioning of the device. Moreover, cables and connectors apply mechanical forces on the implant and the tissue, causing long-term scarring [201]. New methodologies of wireless modulation of the nervous system have recently started to gain attention.

Photovoltaic technologies have emerged for wireless stimulation in retinal implants [49, 165]. In particular, new developments in organic bioelectronics and photovoltaics showed superior features in conformability, flexibility and stretchability [38, 39] compared to silicon-based technology. One important key factor to consider in organic photovoltaics technology is the light conversion efficiency of the materials. It is necessary to find efficient materials to reduce the electrode size and offer better resolution while maintaining a sufficient output current for stimulation [165]. While photovoltaic prostheses [38, 48] rely only on passive light-to-charge conversion from projected images, the NR600 implant (Nano Retina, Rainbow Medical Group) uses infra-red laser light projected onto photovoltaics elements to power an image

detector collecting natural light from the eye optics and a processing unit converting the image into patterned electrical stimulations.

While light-based technologies are convenient for retinal implants, they are not well suited for other visual prostheses which do not have a natural transparent window to light. Thus, other wireless data and power transfer solutions can be used [201]. Among the approaches under investigation, inductive power transfer seems to be the preferred solution for high-resolution intra-cortical stimulation [202] due to the small distance between the transmitter and the receiver. The GENNARIS system (Monash Vision Group) uses inductive power transfer from a single transmitter coil to transmit data and power to 11 implanted receiver with 43 electrodes each [106].

4.3. Biological challenges

Another significant limiting factor for better artificial vision is the insufficient understanding of the neural visual code in blind individuals and the effect of visual deprivation and plasticity [203].

In general, a prosthesis is validated for its efficacy in animal models. However, it remains unclear whether experimental animals are appropriate models to predict efficacy in humans. Preclinical trials are performed either on sighted [74, 100, 204–206] or blind [126, 132] animal models. Even when blind animal models are used, it is difficult to establish how well they reflect human diseases. For example, most of our knowledge comes from rodents with genetic mutations leading to an RP-like form of blindness. These rodents show a significant remodelling of the retinal circuits after photoreceptor degeneration [207]. Yet, there are divergent opinions about the integrity of retinal circuits in humans. While some studies reported their anatomical and functional preservation [208, 209], others highlighted the remodelling and reorganisation of the synapses, particularly in RP patients, but also in advanced dry forms of AMD [210–212]. In addition, remodelling might be extremely variable from patient to patient. Variability could also be found in the residual oculomotor behaviour, cellular preservation along the visual pathway, and remaining neuroplasticity. Last, motor strategies, mental representations and associative perceptions that can be affected by visual field loss are impacted by each patient's history of blindness [121, 213, 214]. For example, in patients affected by retinal degenerations, the synaptic reorganisation might reduce the efficacy of the electrical stimulation [207, 215, 216]. Given the unpredictable nature of these plastic events, if stimulation parameters are not adapted accordingly, they might distort evoked phosphenes. Therefore, candidates for visual prostheses must be carefully screened. Among other criteria, the selection for retinal prostheses is based on retinal imaging to verify structural integrity [217] and corneal stimulation with lens electrodes to verify the retinal excitability [217–219]. Additional criteria should be considered since these tests are not informative on the functional preservation of the retinal circuits.

The success of visual prostheses strongly depends on our understanding of the adaptive and compensatory changes occurring within the brain [220] and the role of perceptual learning. Psychophysical testing and personalised visual rehabilitation strategies should be challenged to improve the outcome of artificial vision. In addition to measures of quantitative visual function such as acuity, field size, motion detection and localisation, other measures of qualitative functional vision will also be required for a more accurate depiction of a person's abilities with a visual prosthesis. These are commonly described as orientation and mobility or activities of daily living [35]. The downside of these tests is the limited relevance out of a controlled laboratory environment. On the other hand, it is hard to evaluate real-world functional assessment and self-reports due to their highly subjective and non-standardised nature [221]. Virtual, mixed and augmented reality could help create virtually controlled but highly complex environments. These simulations can be helpful to gain an insight into what would be the real-world performance for an implanted subject. Augmented reality settings simulating prosthetic vision could help compare the accuracy of virtual reality prediction and patient performance. Additionally, the cognitive fatigue reported so far by users has discouraged them from using the implant long-term [221]. Hence, this mental effort should also be included in a standardised evaluation by mapping body movements, head scans [153], eye movements, decision time and pupillary measures [222].

Finally, designing a multisensory rehabilitation based on gamification in the short-term [121] and supported with a pharmacological enhancement of synaptic plasticity [223–225] could also improve the capacity of patients to make practical use of their devices in the long-term.

5. Road to market: what to learn from the first generation of clinically approved visual prostheses

In the last 30 years, significant efforts have been made to develop and commercialise visual prostheses. However, the only systems approved for clinical use target the retina and patients affected only by RP. These

are the Argus® II (Second Sight Medical Products Inc.), the IRIS® II (Pixium Vision SA) and the Alpha-IMS/AMS (Retinal Implant AG). None of them is still on the market.

The number of people affected by RP is estimated to be about 1.5–2 million [226], but only 12% of these have a visual acuity worse than counting fingers and 0.5% have no perception of light [227]. So far, retinal prostheses have been implanted in end-stage RP patients which are not enough to make a profitable market [228]. The potential market size is also drastically reduced considering that some of these patients might have other complications leading to exclusion according to criteria set for each device.

Companies have had to face economic problems related to limited market size, cost of research and development, regulatory approval, and low acceptance of the device by clinicians and patients [229]. Second Sight Medical Products leveraged the existing Argus® II technology and developed Orion I, a surface grid for subdural stimulation of the primary visual cortex. Orion I has been accepted as a breakthrough device by the FDA and has already been tested in six completely blind subjects for 19 months with positive outcomes. Pixium Vision focused on the PRIMA device to address geographic atrophy in AMD patients [48, 49]. Two early feasibility studies are active in Europe and the United States of America simultaneously. This double strategy must comply with two different regulatory approval procedures, one from the FDA and one for CE certification in Europe [229].

Medical device regulation is another crucial step for any kind of neuroprosthetic device. It has been implemented to protect patients' safety by using only sufficiently tested devices before entering the market. Currently, the FDA offers pre-submission processes that allow early dialogue with the assessment body and simplify the path for innovative devices. On the other hand, Europe has not yet defined streamlined processes to obtain the CE mark for complex devices such as visual prostheses, even though new regulations have been implemented since 2020 [229].

The device cost needs to be discussed to make visual prostheses available while keeping the company profitable. The Argus® II ranged from 115 000 EUR in Europe to 150 000 USD in the United States of America, excluding surgery, hospitalisation, and rehabilitation. A patient implanted with the Argus® II estimated that the total cost of device, surgery and rehabilitation was 497 000 USD [228]. Companies should therefore find agreements with insurances or governments to reimburse these costs, provided that the benefits for visual prosthesis recipients lead to a tangible reduction in health care costs [47].

Finally, Second Sight Medical Products and Retinal Implant AG discontinued their products. The Argus® II was approved for clinical use in many countries with more than 350 users worldwide. The device is now obsolete, and users declared not having technical support if their implant will stop working [228]. Despite being justified by financial elements, this outcome remains ethically unacceptable and solutions must be found to ensure clinical and technical support to existing patients. Nevertheless, several groups continue to run successful clinical trials and pursue commercial development. Despite the long, unpredictable and costly road to market, they could take advantage of this favourable moment in which neurotechnology is receiving great financial attention. Neurotechnology is a rapidly growing field, with several new companies entering the business. Unfortunately, not all these companies will succeed. Learning from previous experiences will help neurotech entrepreneurs to develop a sustainable business.

6. Conclusion

Restoring vision is the grand challenge that many research groups and companies are trying to solve. Although remarkable engineering progress has been made since the very first prototype of a visual prosthesis [87], results from the clinical use of commercially available retinal prostheses showed that for now, patients affected by retinal degeneration could only expect a form of vision substitution (artificial vision) rather than vision restoration [221].

Visual prostheses should provide higher resolution and wider angle to substantially help the patients to perform daily activities autonomously. This goal includes reducing the electrode size and finding biomimetic materials so that wireless electronics can be physically embedded within the neural tissue for a long-term period. Artificial intelligence can play a relevant role by advancing image processing and encoding steps to fine-tune the stimulation parameters towards a more naturalistic perception. Moreover, prostheses might learn to adapt in a contextually dependent manner and provide the patient information in the most helpful and accurate way possible. The ability to artificially produce a visual perception in blind individuals lies in the present understanding of the visual system, its processing units, and how electrical stimulation along the visual pathways can elicit visual sensations. Undoubtedly, a deeper understanding of the functioning of the visual system in blindness is crucial knowledge to design better visual prostheses. Fundamental neuroscience research in animal models and humans is necessary to close significant knowledge gaps, including understanding the role of visual plasticity and neurorehabilitation, determining the impact of retinal

remodelling and deciphering the neural code to restore vision in blind subjects. The combination of these elements will make artificial vision closer to vision.

To accomplish this mission, interdisciplinary teams of clinicians and healthcare providers, materials scientists, engineers, neuroscientists and artificial intelligence experts will have to work hand-in-hand towards the next generation of visual prostheses. Lastly, the joint effort of regulatory bodies in streamlining the approval processes for innovative technologies and investors helping to close the gap from research to market will be essential to make the artificial vision a sustainable solution for those patients still in the dark.

Artificial vision has always been a pioneering research activity in the medical field. Charles LeRoy performed his experiment three decades before Luigi Galvani reported about animal electricity. One of the first permanent cortical stimulators implanted in humans was a visual prosthesis [89]. The Argus® II [111] was among the first implantable microelectrode arrays manufactured with cleanroom processes to be approved by regulatory agencies. The subretinal visual implant Alpha IMS [150] was one of the first CE-approved implantable medical devices with a high-channel-count (1500 pixels) and implantable electronics in contact with the central nervous system. Photovoltaic retinal prostheses [48] were the first example of neurostimulation devices providing fully wireless electrical stimulation to the nervous system without the need for implantable batteries or active electronic units. Certainly, research in visual prostheses will push neurotechnology even further.

Data availability statement

No new data were created or analysed in this study.

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ORCID iD

Diego Ghezzi https://orcid.org/0000-0002-0554-7510

References

[1] Burton M J *et al* 2021 The lancet global health commission on global eye health: vision beyond 2020 *Lancet Glob. Health* **9** e489–551
[2] Bourne R *et al* 2021 Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the Global Burden of Disease Study *Lancet Glob. Health* **9** e130–43
[3] Court H, McLean G, Guthrie B, Mercer S W and Smith D J 2014 Visual impairment is associated with physical and mental comorbidities in older adults: a cross-sectional study *BMC Med.* **12** 181
[4] World Health Organization 2019 *World Report on Vision*
[5] Scholl H P, Strauss R W, Singh M S, Dalkara D, Roska B, Picaud S and Sahel J-A 2016 Emerging therapies for inherited retinal degeneration *Sci. Transl. Med.* **8** 368rv6
[6] Xue K and MacLaren R E 2020 Correcting visual loss by genetics and prosthetics *Curr. Opin. Physiol.* **16** 1–7
[7] Mirochnik R M and Pezaris J S 2019 Contemporary approaches to visual prostheses *Mil. Med. Res.* **6** 19
[8] Cehajic-Kapetanovic J, Singh M S, Zrenner E and MacLaren R E 2022 Bioengineering strategies for restoring vision *Nat. Biomed. Eng.* 1–18
[9] Masland R H 2012 The neuronal organization of the retina *Neuron* **76** 266–80
[10] Goetz G and Palanker D 2016 Electronic approaches to restoration of sight *Rep. Prog. Phys.* **79** 096701
[11] Betts J G, Young K A, Wise J A, Johnson E, Poe B, Kruse D H, Korol O, Johnson J E, Womble M and DeSaix P 2013 *Anatomy and Physiology* (Houston, TX: OpenStax)
[12] Lambertus S, Bax N M, Fakin A, Groenewoud J M M, Klevering B J, Moore A T, Michaelides M, Webster A R, van der Wilt G J and Hoyng C B 2017 Highly sensitive measurements of disease progression in rare disorders: developing and validating a multimodal model of retinal degeneration in Stargardt disease *PLoS One* **12** e0174020
[13] Bourne R R A *et al* 2013 Causes of vision loss worldwide, 1990–2010: a systematic analysis *Lancet Glob. Health* **1** e339–49
[14] Watson W 1752 XXXI. An account of Mr Benjamin Franklin's treatise, lately published, intituled, experiments and observations on electricity, made at Philadelphia in America *Phil. Trans. R. Soc.* **47** 202–11

[15] LeRoy C 1755 Mémoire où l'on rend compte de quelques tentatives que l'on a faites pour guérir plusieurs maladies par l'électricité *Hist. Acad. R. Sci.* **60** 87–95
[16] Löwenstein K and Borchardt M 1918 Symptomatologie und elektrische Reizung bei einer Schußverletzung des Hinterhauptlappens *Deutsch. Z. Nervenheilkunde* **58** 264–92
[17] Krause F 1924 Die Sehbahn in Chirurgischer Beziehung und die Faradische Reizung des Sehzentrums *Klin. Wochenschr.* **3** 1260–5
[18] Foerster O 1929 Beitrage zur pathophysiologie der sehbahn und der spehsphare *J. Psychol. Neurol.* **39** 435–63
[19] Ghezzi D 2020 Translation of a photovoltaic retinal prosthesis *Nat. Biomed. Eng.* **4** 137–8
[20] Fernandez E 2018 Development of visual neuroprostheses: trends and challenges *Bioelectron. Med.* **4** 12
[21] Gregory-Evans K and Bhattacharya S S 1998 Genetic blindness: current concepts in the pathogenesis of human outer retinal dystrophies *Trends Genet.* **14** 103–8
[22] Hamel C 2006 Retinitis pigmentosa *Orphanet J. Rare Dis.* **1** 40
[23] Muqit M M K, Velikay-Parel M, Weber M, Dupeyron G, Audemard D, Corcostegui B, Sahel J and Mer Y L 2019 Six-month safety and efficacy of the intelligent retinal implant system II device in retinitis pigmentosa *Ophthalmology* **126** 637–9
[24] Humayun M S *et al* 2012 Interim results from the international trial of second sight's visual prosthesis *Ophthalmology* **119** 779–88
[25] Stingl K *et al* 2017 Interim results of a multicenter trial with the new electronic subretinal implant alpha AMS in 15 patients blind from inherited retinal degenerations *Front. Neurosci.* **11** 445
[26] Farnum A and Pelled G 2020 New vision for visual prostheses front neurosci-switz *Front. Neurosci.* **14** 36
[27] Ghezzi D 2015 Retinal prostheses: progress toward the next generation implants *Front. Neurosci.* **9** 290
[28] Boinagrov D, Pangratz-Fuehrer S, Goetz G and Palanker D 2014 Selectivity of direct and network-mediated stimulation of the retinal ganglion cells with epi-, sub- and intraretinal electrodes *J. Neural Eng.* **11** 026008
[29] Chenais N A L, Leccardi M J I A and Ghezzi D 2019 Capacitive-like photovoltaic epiretinal stimulation enhances and narrows the network-mediated activity of retinal ganglion cells by recruiting the lateral inhibitory network *J. Neural Eng.* **16** 066009
[30] Lee J I and Im M 2018 Non-rectangular waveforms are more charge-efficient than rectangular one in eliciting network-mediated responses of ON type retinal ganglion cells *J. Neural Eng.* **15** 055004
[31] Weitz A C, Nanduri D, Behrend M R, Gonzalez-Calle A, Greenberg R J, Humayun M S, Chow R H and Weiland J D 2015 Improving the spatial resolution of epiretinal implants by increasing stimulus pulse duration *Sci. Transl. Med.* **7** 318ra203
[32] Yue L, Weiland J D, Roska B and Humayun M S 2016 Retinal stimulation strategies to restore vision: fundamentals and systems *Prog. Retin. Eye Res.* **53** 21–47
[33] Barriga-Rivera A, Bareket L, Goding J, Aregueta-Robles U A and Suaning G J 2017 Visual prosthesis: interfacing stimulating electrodes with retinal neurons to restore vision *Front. Neurosci.* **11** 620
[34] Cheng D L, Greenberg P B and Borton D A 2017 Advances in retinal prosthetic research: a systematic review of engineering and clinical characteristics of current prosthetic initiatives *Curr. Eye Res.* **42** 334–47
[35] Ayton L N *et al* 2019 An update on retinal prostheses *Clin. Neurophysiol.* **131** 1383–98
[36] Tong W, Meffin H, Garrett D J and Ibbotson M R 2020 Stimulation strategies for improving the resolution of retinal prostheses *Front. Neurosci.* **14** 262
[37] Lewis P M, Ackland H M, Lowery A J and Rosenfeld J V 2015 Restoration of vision in blind individuals using bionic devices: a review with a focus on cortical visual prostheses *Brain Res.* **1595** 51–73
[38] Ferlauto L, Leccardi M, Chenais N, Gilliéron S, Vagni P, Bevilacqua M, Wolfensberger T J, Sivula K and Ghezzi D 2018 Design and validation of a foldable and photovoltaic wide-field epiretinal prosthesis *Nat. Commun.* **9** 992
[39] Vagni P, Airaghi Leccardi M Jole, Vila C, Zollinger E Geneviève, Sherafatipour G, Wolfensberger T J and Ghezzi D 2022 POLYRETINA restores light responses *in vivo* in blind Göttingen minipigs *Nat. Commun.* **13**
[40] Schaffrath K *et al* 2021 New epiretinal implant with integrated sensor chips for optical capturing shows a good biocompatibility profile *in vitro* and *in vivo Biomed. Eng.* **20** 102
[41] Thorn J T, Migliorini E and Ghezzi D 2020 Virtual reality simulation of epiretinal stimulation highlights the relevance of the visual angle in prosthetic vision *J. Neural Eng.* **17** 056019
[42] Opie N L, Burkitt A N, Meffin H and Grayden D B 2012 Heating of the eye by a retinal prosthesis: modeling, cadaver and *in vivo* study *IEEE Trans. Biomed. Eng.* **59** 339–45
[43] Ahuja A and Behrend M R 2013 The Argus™ II retinal prosthesis: factors affecting patient selection for implantation *Prog. Retin. Eye Res.* **36** 1–23
[44] Shepherd R K, Shivdasani M N, Nayagam D, Williams C E and Blamey P J 2013 Visual prostheses for the blind *Trends Biotechnol.* **31** 562–71
[45] Yue L, Falabella P, Christopher P, Wuyyuru V, Dorn J, Schor P, Greenberg R J, Weiland J D and Humayun M S 2015 Ten-year follow-up of a blind patient chronically implanted with epiretinal prosthesis Argus *Ophthalmology* **122** 2545–52
[46] Humayun M S *et al* 2003 Visual perception in a blind subject with a chronic microelectronic retinal prosthesis *Vis. Res.* **43** 2573–81
[47] Mills J O, Jalil A and Stanga P E 2017 Electronic retinal implants and artificial vision: journey and present *Eye* **31** 1383–98
[48] Palanker D, Mer Y L, Mohand-Said S, Muqit M and Sahel J A 2020 Photovoltaic restoration of central vision in atrophic age-related macular degeneration *Ophthalmology* **127** 1097–104
[49] Palanker D, Mer Y L, Mohand-Said S and Sahel J A 2022 Simultaneous perception of prosthetic and natural vision in AMD patients *Nat. Commun.* **13** 513
[50] Flores T, Lei X, Huang T, Lorach H, Dalal R, Galambos L, Kamins T, Mathieson K and Palanker D 2018 Optimization of pillar electrodes in subretinal prosthesis for enhanced proximity to target neurons *J. Neural Eng.* **15** 036011
[51] Chow A Y, Chow V Y, Packo K H, Pollack J S, Peyman G A and Schuchard R 2004 The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa *Arch. Ophthalmol.* **122** 460–9
[52] Zrenner E *et al* 2011 Subretinal electronic chips allow blind patients to read letters and combine them to words *Proc. R. Soc.* B **278** 1489–97
[53] Edwards T L, Cottriall C L, Xue K, Simunovic M P, Ramsden J D, Zrenner E and MacLaren R E 2018 Assessment of the electronic retinal implant alpha AMS in restoring vision to blind patients with end-stage retinitis pigmentosa *Ophthalmology* **125** 432–43
[54] Villalobos J *et al* 2013 A wide-field suprachoroidal retinal prosthesis is stable and well tolerated following chronic implantation *Investigative Ophthalmol. Vis. Sci.* **54** 3751–62
[55] Petoe M A *et al* 2021 A second-generation (44-channel) suprachoroidal retinal prosthesis: interim clinical trial results *Transl. Vis. Sci. Technol.* **10** 12
[56] Eggenberger S C *et al* 2021 Implantation and long-term assessment of the stability and biocompatibility of a novel 98 channel suprachoroidal visual prosthesis in sheep *Biomaterials* **279** 121191

[57] Ayton L N *et al* 2014 First-in-human trial of a novel suprachoroidal retinal prosthesis *PLoS One* **9** e115239
[58] Fujikado T *et al* 2016 One-year outcome of 49-channel suprachoroidal-transretinal stimulation prosthesis in patients with advanced retinitis pigmentosa *Investigative Ophthalmol. Vis. Sci.* **57** 6147–57
[59] Petoe M A *et al* 2017 Determining the contribution of retinotopic discrimination to localization performance with a suprachoroidal retinal prosthesis *Investigative Opthalmol. Vis. Sci.* **58** 3231
[60] Shivdasani M N *et al* 2017 Identification of characters and localization of images using direct multiple-electrode stimulation with a suprachoroidal retinal prosthesis *Investigative Ophthalmol. Vis. Sci.* **58** 3962–74
[61] Bloch E, Luo Y and da Cruz L 2019 Advances in retinal prosthesis systems *Ther. Adv. Ophthalmol.* **11** 2515841418817501
[62] Farvardin M, Afarid M, Attarzadeh A, Johari M K, Mehryar M, Nowroozzadeh M H, Rahat F, Peyvandi H, Farvardin R and Nami M 2018 The Argus-II retinal prosthesis implantation; from the global to local successful experience *Front. Neurosci.* **12** 584
[63] Gaillet V, Borda E, Zollinger E G and Ghezzi D 2021 A machine-learning algorithm correctly classifies cortical evoked potentials from both visual stimulation and electrical stimulation of the optic nerve *J. Neural Eng.* **18** 046031
[64] Veraart C, Raftopoulos C, Mortimer J T, Delbeke J, Pins D, Michaux G, Vanlierde A, Parrini S and Wanet-Defalque M-C 1998 Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode *Brain Res.* **813** 181–6
[65] Veraart C, Wanet-Defalque M, Gérard B, Vanlierde A and Delbeke J 2003 Pattern recognition with the optic nerve visual prosthesis *Artif. Organs* **27** 996–1004
[66] Delbeke J, Oozeer M and Veraart C 2003 Position, size and luminosity of phosphenes generated by direct optic nerve stimulation *Vis. Res.* **43** 1091–102
[67] Brelén M E, Duret F, Gérard B, Delbeke J and Veraart C 2005 Creating a meaningful visual perception in blind volunteers by optic nerve stimulation *J. Neural Eng.* **2** S22
[68] The Lasker/IRRF Initiative for Innovation in Vision Science 2014 Chapter 1—restoring vision to the blind: the new age of implanted visual prostheses *Transl. Vis. Sci. Technol.* **3** 3
[69] Fried S I and Shivdasani M N 2020 Selective activation of the visual cortex *Nat. Biomed. Eng.* **4** 139–41
[70] Sakaguchi H, Kamei M, Fujikado T, Yonezawa E, Ozawa M, Cecilia-Gonzalez C, Ustariz-Gonzalez O, Quiroz-Mercado H and Tano Y 2009 Artificial vision by direct optic nerve electrode (AV-DONE) implantation in a blind patient with retinitis pigmentosa *J. Artif. Organs* **12** 206–9
[71] Lu Y, Yan Y, Chai X, Ren Q, Chen Y and Li L 2013 Electrical stimulation with a penetrating optic nerve electrode array elicits visuotopic cortical responses in cats *J. Neural Eng.* **10** 036022
[72] Sun J, Chen Y, Chai X, Ren Q and Li L 2013 Penetrating electrode stimulation of the rabbit optic nerve: parameters and effects on evoked cortical potentials *Graefe's Arch. Clin. Exp. Ophthalmol.* **251** 2545–54
[73] Yan Y, Lu Y, Li M, Ma Z, Cao P, Chen Y, Sun X, Chai X, Ren Q and Li L 2016 Electrically evoked responses in the rabbit cortex induced by current steering with penetrating optic nerve electrodes *Investigative Ophthalmol. Vis. Sci.* **57** 6327–38
[74] Gaillet V, Cutrone A, Artoni F, Vagni P, Pratiwi A M, Romero S A, Paola D L D, Micera S and Ghezzi D 2020 Spatially selective activation of the visual cortex via intraneural stimulation of the optic nerve *Nat. Biomed. Eng.* **4** 181–94
[75] Borda E, Gaillet V, Leccardi M J I A, Zollinger E G, Moreira R C and Ghezzi D 2022 Three-dimensional multilayer concentric bipolar electrodes restrict spatial activation in optic nerve stimulation *J. Neural Eng.* **19** 036016
[76] Paggi V, Akouissi O, Micera S and Lacour S P 2021 Compliant peripheral nerve interfaces *J. Neural Eng.* **18** 031001
[77] Towle V L, Pytel P, Lane F, Plass J, Frim D M and Troyk P R 2020 Postmortem investigation of a human cortical visual prosthesis that was implanted for 36 years *J. Neural Eng.* **17** 045010
[78] Lewis P M, Ayton L N, Guymer R H, Lowery A J, Blamey P J, Allen P J, Luu C D and Rosenfeld J V 2016 Advances in implantable bionic devices for blindness: a review *ANZ J. Surg.* **86** 654–9
[79] Mullen K T, Dumoulin S O and Hess R F 2008 Color responses of the human lateral geniculate nucleus: selective amplification of S-cone signals between the lateral geniculate nucleno and primary visual cortex measured with high-field fMRI *Eur. J. Neurosci.* **28** 1911–23
[80] Abbasi B and Rizzo J F 2021 Advances in neuroscience, not devices, will determine the effectiveness of visual prostheses *Semin. Ophthalmol.* **36** 1–8
[81] Pezaris J S and Reid C R 2007 Demonstration of artificial visual percepts generated through thalamic microstimulation *Proc. Natl Acad. Sci.* **104** 7670–5
[82] Panetsos F, Sanchez-Jimenez A, Cerio E D, Diaz-Guemes I and Sanchez F M 2011 Consistent phosphenes generated by electrical microstimulation of the visual thalamus. An experimental approach for thalamic visual neuroprostheses *Front. Neurosci.* **5** 84
[83] Choi C, Kim P, Shin S, Yang J and Yang Y 2014 Lateral geniculate body evoked potentials elicited by visual and electrical stimulation *Korean J. Ophthalmol.* **28** 337–42
[84] Tangutooru S M, Yoon W J, Troy J B and Phil D 2014 Early design considerations for a thalamic visual prosthesis to treat blindness resulting from glaucoma *2nd Middle East Conf. Biomedical Engineering* pp 249–52 **This research was made possible by the NPRP grant #NPRP5-457-2-181 from the Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors
[85] Kyada M J, Killian N J and Pezaris J S 2017 *Artificial Vision, A Clinical Guide* (Cham: Springer International Publishing) pp 177–89
[86] JC B 1958 Electronics brings light to the blind *Radio Electron.* **29** 53–55
[87] Button J and Putnam T 1962 Visual responses to cortical stimulation in the blind *J. Iowa Med. Soc.* **52** 17–21
[88] Lewis P M and Rosenfeld J V 2016 Electrical stimulation of the brain and the development of cortical visual prostheses: an historical perspective *Brain Res.* **1630** 208–24
[89] Brindley G S and Lewin W S 1968 The sensations produced by electrical stimulation of the visual cortex *J. Physiol.* **196** 479–93
[90] Brindley G S 1970 Sensations produced by electrical stimulation of the occipital poles of the cerebral hemispheres, and their use in constructing visual prostheses *Ann. R. Coll. Surg.* **47** 106–8
[91] Donaldson P E K 1973 Experimental visual prosthesis *Proc. Inst. Electr. Eng.* **120** 281
[92] Dobelle W H, Stensaas S S, Mladejovsky M G and Smith J B 1973 A prosthesis for the deaf based on cortical stimulation *Ann. Otol. Rhinol. Laryngol.* **82** 445–63
[93] Dobelle W H, Mladejovsky M G and Girvin J P 1974 Artificial vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis *Science* **183** 440–4
[94] Dobelle W H, Mladejovsky M G, Evans J R, Roberts T S and Girvin J P 1976 'Braille' reading by a blind volunteer by visual cortex stimulation *Nature* **259** 111–2
[95] Fernandes R A B, Diniz B, Ribeiro R and Humayun M 2012 Artificial vision through neuronal stimulation *Neurosci. Lett.* **519** 122–8

[96] Maynard E M 2001 Visual prostheses *Annu. Rev. Biomed. Eng.* **3** 145–68
[97] Mateos-Aparicio P and Rodríguez-Moreno A 2019 The impact of studying brain plasticity *Front. Cell. Neurosci.* **13** 66
[98] Beauchamp M S, Oswalt D, Sun P, Foster B L, Magnotti J F, Niketeghad S, Pouratian N, Bosking W H and Yoshor D 2020 Dynamic stimulation of visual cortex produces form vision in sighted and blind humans *Cell* **181** 774–83
[99] Schmidt E, Bak M, Hambrecht F, Kufta C, O'Rourke D and Vallabhanath P 1996 Feasibility of a visual prosthesis for the blind based on intracortical micro stimulation of the visual cortex *Brain* **119** 507–22
[100] Chen X, Wang F, Fernandez E and Roelfsema P R 2020 Shape perception via a high-channel-count neuroprosthesis in monkey visual cortex *Science* **370** 1191–6
[101] Caspi A, Barry M P, Patel U K, Salas M A, Dorn J D, Roy A, Niketeghad S, Greenberg R J and Pouratian N 2021 Eye movements and the perceived location of phosphenes generated by intracranial primary visual cortex stimulation in the blind *Brain Stimul.* **14** 851–60
[102] Schira M M, Tyler C W and Rosa M G P 2012 Brain mapping: the (un)folding of striate cortex *Curr. Biol.* **22** R1051–3
[103] Meikle S J and Wong Y T 2022 Neurophysiological considerations for visual implants *Brain Struct. Funct.* **227** 1523–43
[104] Kosta P *et al* 2018 Electromagnetic safety assessment of a cortical implant for vision restoration *IEEE J. Electromagn. RF Microw. Med. Biol.* **2** 56–63
[105] Michael P B, Michelle A S, Uday P, Varalakshmi W, Soroush N, William H B, Daniel Y, Jessy D D and Nader P 2020 Video-mode percepts are smaller than sums of single-electrode phosphenes with the Orion® visual cortical prosthesis *Investigative Ophthalmol. Vis. Sci.* **61** 927
[106] Rosenfeld J V, Wong Y T, Yan E, Szlawski J, Mohan A, Clark J C, Rosa M and Lowery A 2020 Tissue response to a chronically implantable wireless intracortical visual prosthesis (Gennaris array) *J. Neural Eng.* **17** 046001
[107] Fernández E *et al* 2021 Visual percepts evoked with an intracortical 96-channel microelectrode array inserted in human occipital cortex *J. Clin. Invest.* **131**
[108] Troyk P R 2016 The Intracortical Visual Prosthesis Project *Artificial Vision, A Clinical Guide* (Cham: Springer) pp 203–14
[109] Niketeghad S and Pouratian N 2019 Brain machine interfaces for vision restoration: the current state of cortical visual prosthetics *Neurotherapeutics* **16** 134–43
[110] Pio-Lopez L, Poulkouras R and Depannemaecker D 2021 Visual cortical prosthesis: an electrical perspective *J. Med. Eng. Technol.* **45** 1–14
[111] Luo Y H L and da Cruz L 2016 The Argus® II retinal prosthesis system *Prog. Retin. Eye Res.* **50** 89–107
[112] Geruschat D R, Turano K A and Stahl J W 1998 Traditional measures of mobility performance and retinitis pigmentosa *Optom. Vis. Sci.* **75** 525–37
[113] Szlyk J P, Fishman G A, Alexander K R, Revelins B I, Derlacki D J and Anderson R J 1997 Relationship between difficulty in performing daily activities and clinical measures of visual function in patients with retinitis pigmentosa *Arch. Ophthalmol.* **115** 53–59
[114] Haymes S A, Johnston A W and Heyes A D 2002 Relationship between vision impairment and ability to perform activities of daily living *Ophthalmic Physiol. Opt.* **22** 79–91
[115] Sugawara T, Hagiwara A, Hiramatsu A, Ogata K, Mitamura Y and Yamamoto S 2010 Relationship between peripheral visual field loss and vision-related quality of life in patients with retinitis pigmentosa *Eye* **24** 535–9
[116] Subhi H, Latham K, Myint J and Crossland M D 2017 Functional visual fields: relationship of visual field areas to self-reported function *Ophthalmic Physiol. Opt.* **37** 399–408
[117] Fornos A P, Sommerhalder J, Pittard A, Safran A B and Pelizzone M 2008 Simulation of artificial vision: IV. Visual information required to achieve simple pointing and manipulation tasks *Vis. Res.* **48** 1705–18
[118] Sommerhalder J, Fornos A P and Gabel V P 2017 *Prospects and Limitations of Spatial Resolution Artificial Vision* (Cham: Springer International Publishing) pp 29–45
[119] Dagnelie G, Keane P, Narla V, Yang L, Weiland J and Humayun M 2007 Real and virtual mobility performance in simulated prosthetic vision *J. Neural Eng.* **4** S92–101
[120] Cha K, Horch K W and Normann R A 1992 Mobility performance with a pixelized vision system *Vis. Res.* **32** 1367–72
[121] Beyeler M, Rokem A, Boynton G M and Fine I 2017 Learning to see again: biological constraints on cortical plasticity and the implications for sight restoration technologies *J. Neural Eng.* **14** 051003
[122] Chen S C, Suaning G J, Morley J W and Lovell N H 2009 Simulating prosthetic vision: II. Measuring functional capacity *Vis. Res.* **49** 2329–43
[123] Lee D Y, Lorach H, Huie P and Palanker D 2016 Implantation of modular photovoltaic subretinal prosthesis *Ophthalmic Surg. Lasers Imaging Retin.* **47** 171–4
[124] Lohmann T K *et al* 2019 The very large electrode array for retinal stimulation (VLARS)—a concept study *J. Neural Eng.* **16** 066031
[125] Waschkowski F *et al* 2014 Development of very large electrode arrays for epiretinal stimulation (VLARS) *Biomed. Eng.* **13** 11
[126] Lorach H *et al* 2015 Photovoltaic restoration of sight with high visual acuity *Nat. Med.* **21** 476–82
[127] Ghezzi D *et al* 2013 A polymer optoelectronic interface restores light sensitivity in blind rat retinas *Nat. Photon.* **7** 400–6
[128] Maya-Vetencourt J F *et al* 2017 A fully organic retinal prosthesis restores vision in a rat model of degenerative blindness *Nat. Mater.* **16** 681–9
[129] Antognazza M Rosa *et al* 2016 Characterization of a Polymer-Based, Fully Organic Prosthesis for Implantation into the Subretinal Space of the Rat *Adv. Healthcare Mater.* **5** 2271–82
[130] Tang J, Qin N, Chong Y, Diao Y, Wang Z, Xue T, Jiang M, Zhang J and Zheng G 2018 Nanowire arrays restore vision in blind mice *Nat. Commun.* **9** 786
[131] Leccardi M J I A, Chenais N A L, Ferlauto L, Kawecki M, Zollinger E G and Ghezzi D 2020 Photovoltaic organic interface for neuronal stimulation in the near-infrared *Commun. Mater.* **1** 21
[132] Chenais N A L, Leccardi M J I A and Ghezzi D 2021 Photovoltaic retinal prosthesis restores high-resolution responses to single-pixel stimulation in blind retinas *Commun. Mater.* **2** 28
[133] Zrenner E, Bartz-Schmidt K U, Besch D, Gekeler F, Koitschev A, Sachs H G and Stingl K 2016 The Subretinal Implant ALPHA: Implantation and Functional Results *Artificial Vision, A Clinical Guide* (Cham: Springer) pp 65–83
[134] Nanduri D, Humayun M S, Greenberg R J, McMahon M J and Weiland J D 2008 Retinal prosthesis phosphene shape analysis *2008 30th Annual Int. Conf. IEEE Engineering in Medicine and Biology Society* vol 2008 pp 1785–8
[135] Luo Y H-L, Zhong J J, Clemo M and da Cruz L 2016 Long-term repeatability and reproducibility of phosphene characteristics in chronically implanted Argus II retinal prosthesis subjects *Am. J. Ophthalmol.* **170** 100–9

[136] Beyeler M, Nanduri D, Weiland J D, Rokem A, Boynton G M and Fine I 2019 A model of ganglion axon pathways accounts for percepts elicited by retinal implants *Sci. Rep.* **9** 9199
[137] Gogliettino A R *et al* 2022 High-fidelity restoration of visual signals by electrical stimulation in the central primate retina *bioRxiv Preprint* (https://doi.org/10.1101/2022.05.24.493162)
[138] Cai C, Twyford P and Fried S 2013 The response of retinal neurons to high-frequency stimulation *J. Neural Eng.* **10** 036009
[139] Corna A, Ramesh P, Jetter F, Lee M-J, Macke J H and Zeck G 2021 Discrimination of simple objects decoded from the output of retinal ganglion cells upon sinusoidal electrical stimulation *J. Neural Eng.* **18** 046086
[140] Wilke R *et al* 2011 Spatial resolution and perception of patterns mediated by a subretinal 16-electrode array in patients blinded by hereditary retinal dystrophies *Investigative Opthalmol. Vis. Sci.* **52** 5995
[141] Sinclair N C, Shivdasani M N, Perera T, Gillespie L N, McDermott H J, Ayton L N, Blamey P J and Consortium B V A 2016 The appearance of phosphenes elicited using a suprachoroidal retinal prosthesis phosphenes of a suprachoroidal retinal prosthesis *Investigative Ophthalmol. Vis. Sci.* **57** 4948–61
[142] Behrend M R, Ahuja A K, Humayun M S, Chow R H and Weiland J D 2011 Resolution of the epiretinal prosthesis is not limited by electrode size *IEEE Trans. Neural Syst. Rehabil. Eng.* **19** 436–42
[143] Ho E, Lei X, Flores T, Lorach H, Huang T, Galambos L, Kamins T, Harris J, Mathieson K and Palanker D 2019 Characteristics of prosthetic vision in rats with subretinal flat and pillar electrode arrays *J. Neural Eng.* **16** 066027
[144] Shivdasani M N, Sinclair N C, Dimitrov P N, Varsamidis M, Ayton L N, Luu C D, Perera T, McDermott H J, Blamey P J and Consortium B 2014 Factors affecting perceptual thresholds in a suprachoroidal retinal prosthesis factors affecting retinal prosthesis thresholds *Investigative Ophthalmol. Vis. Sci.* **55** 6467–81
[145] Histed M H, Bonin V and Reid C R 2009 Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation *Neuron* **63** 508–22
[146] Cicione R, Fallon J B, Rathbone G D, Williams C E and Shivdasani M N 2014 Spatiotemporal interactions in the visual cortex following paired electrical stimulation of the retina *Investigative Ophthalmol. Vis. Sci.* **55** 7726–38
[147] Moleirinho S, Whalen A J, Fried S I and Pezaris J S 2021 The impact of synchronous versus asynchronous electrical stimulation in artificial vision *J. Neural Eng.* **18** 051001
[148] Fornos A P, Sommerhalder J, da Cruz L, Sahel J A, Mohand-Said S, Hafezi F and Pelizzone M 2012 Temporal properties of visual perception on electrical stimulation of the retina *Investigative Opthalmol. Vis. Sci.* **53** 2720
[149] Stronks H C and Dagnelie G 2014 The functional performance of the Argus II retinal prosthesis *Expert Rev. Med. Device* **11** 23–30
[150] Stingl K *et al* 2013 Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS *Proc. R. Soc.* B **280** 20130077
[151] Greschner M, Bongard M, Rujan P and Ammermüller J 2002 Retinal ganglion cell synchronization by fixational eye movements improves feature estimation *Nat. Neurosci.* **5** 341–7
[152] Kagan I, Gur M and Snodderly D M 2008 Saccades and drifts differentially modulate neuronal activity in V1: effects of retinal image motion, position, and extraretinal influences *J. Vis.* **8** 19
[153] Thorn J T, Chenais N A L, Hinrichs S, Chatelain M and Ghezzi D 2022 Virtual reality validation of naturalistic modulation strategies to counteract fading in retinal stimulation *J. Neural Eng.* **19** 026016
[154] Hafed Z M, Stingl K, Bartz-Schmidt K-U, Gekeler F and Zrenner E 2016 Oculomotor behavior of blind patients seeing with a subretinal visual implant *Vis. Res.* **118** 119–31
[155] Chenais N A L, Leccardi M J I A and Ghezzi D 2021 Naturalistic spatiotemporal modulation of epiretinal stimulation increases the response persistence of retinal ganglion cell *J. Neural Eng.* **18** 016016
[156] Davuluri N S and Weiland J D 2014 Time-varying pulse trains limit retinal desensitization caused by continuous electrical stimulation *2014 36th Annual Int. Conf. IEEE Engineering in Medicine and Biology Society* vol 2014 pp 414–7
[157] Soto-Breceda A, Kameneva T, Meffin H, Maturana M and Ibbotson M R 2018 Irregularly timed electrical pulses reduce adaptation of retinal ganglion cells *J. Neural Eng.* **15** 056017
[158] Woeppel K, Yang Q and Cui X T 2017 Recent advances in neural electrode–tissue interfaces *Curr. Opin. Biomed. Eng.* **4** 21–31
[159] Leccardi M J I A and Ghezzi D 2020 Organic electronics for neuroprosthetics *Healthc. Technol. Lett.* **7** 52–57
[160] Damle S, Carleton M, Kapogianis T, Arya S, Cavichini-Corderio M, Freeman W R, Lo Y-H and Oesch N W 2021 Minimizing iridium oxide electrodes for high visual acuity subretinal stimulation *Eneuro* **8** ENEURO.0506-20.2021
[161] Corna A, Herrmann T and Zeck G 2018 Electrode-size dependent thresholds in subretinal neuroprosthetic stimulation *J. Neural Eng.* **15** 045003
[162] Wu N, Wan S, Su S, Huang H, Dou G and Sun L 2021 Electrode materials for brain–machine interface: a review *InfoMat* **3** 1174–94
[163] Song E, Li J, Won S M, Bai W and Rogers J A 2020 Materials for flexible bioelectronic systems as chronic neural interfaces *Nat. Mater.* **19** 590–603
[164] Fanelli A and Ghezzi D 2021 Transient electronics: new opportunities for implantable neurotechnology *Curr. Opin. Biotechnol.* **72** 22–28
[165] Medagoda D I and Ghezzi D 2021 Organic semiconductors for light-mediated neuromodulation *Commun. Mater.* **2** 111
[166] Hassarati R T, Goding J A, Baek S, Patton A J, Poole-Warren L A and Green R A 2014 Stiffness quantification of conductive polymers for bioelectrodes *J. Polym. Sci.* B **52** 666–75
[167] Ferlauto L, D'Angelo A N, Vagni P, Leccardi M J I A, Mor F M, Cuttaz E A, Heuschkel M O, Stoppini L and Ghezzi D 2018 Development and characterization of PEDOT:PSS/alginate soft microelectrodes for application in neuroprosthetics *Front. Neurosci.* **12** 648
[168] Fanelli A, Ferlauto L, Zollinger E G, Brina O, Reymond P, Machi P and Ghezzi D 2021 Transient neurovascular interface for minimally invasive neural recording and stimulation *Adv. Mater. Technol.* **7** 2100176
[169] Ferlauto L, Vagni P, Fanelli A, Zollinger E Geneviève, Monsorno K, Paolicelli R Chiara and Ghezzi D 2021 All-polymeric transient neural probe for prolonged in-vivo electrophysiological recordings Biomaterials **274** 120889
[170] Cuttaz E, Goding J, Vallejo-Giraldo C, Aregueta-Robles U, Lovell N, Ghezzi D and Green R A 2019 Conductive elastomer composites for fully polymeric, flexible bioelectronics *Biomater. Sci.* **7** 1372–85
[171] Kostarelos K, Vincent M, Hebert C and Garrido J A 2017 Graphene in the design and engineering of next-generation neural interfaces *Adv. Mater.* **29** 1700909
[172] Nguyen D *et al* 2021 Novel graphene electrode for retinal implants: an *in vivo* biocompatibility study *Front. Neurosci.* **15** 615256
[173] Zeng Q, Li X, Zhang S, Deng C and Wu T 2022 Think big, see small—a review of nanomaterials for neural interfaces *Nano Sel.* **3** 903–18
[174] Anderson J M, Rodriguez A and Chang D T 2008 Foreign body reaction to biomaterials *Semin. Immunol.* **20** 86–100

[175] Salatino J W, Ludwig K A, Kozai T D and Purcell E K 2017 Glial responses to implanted electrodes in the brain *Nat. Biomed. Eng.* **1** 862
[176] Fallegger F, Schiavone G and Lacour S P 2020 Conformable hybrid systems for implantable bioelectronic interfaces *Adv. Mater.* **32** e1903904
[177] Vachicouras N *et al* 2019 Microstructured thin-film electrode technology enables proof of concept of scalable, soft auditory brainstem implants *Sci. Transl. Med.* **11** eaax9487
[178] Hong G, Fu T-M, Qiao M, Viveros R D, Yang X, Zhou T, Lee J M, Park H-G, Sanes J R and Lieber C M 2018 A method for single-neuron chronic recording from the retina in awake mice *Science* **360** 1447–51
[179] Hong G, Yang X, Zhou T and Lieber C M 2017 Mesh electronics: a new paradigm for tissue-like brain probes *Curr. Opin. Neurobiol.* **50** 33–41
[180] Vanhoestenberghe A and Donaldson N 2013 Corrosion of silicon integrated circuits and lifetime predictions in implantable electronic devices *J. Neural Eng.* **10** 031002
[181] Humayun M S *et al* 2009 Preliminary 6 month results from the argustm ii epiretinal prosthesis feasibility study *2009 Annual Int. Conf. IEEE Engineering in Medicine and Biology Society* vol 2009 pp 4566–8
[182] Shire D B *et al* 2012 ASIC design and data communications for the Boston retinal prosthesis *2012 Annual Int. Conf. IEEE Engineering in Medicine and Biology Society* vol 2012 pp 292–5
[183] Barnes N *et al* 2016 Vision function testing for a suprachoroidal retinal prosthesis: effects of image filtering *J. Neural Eng.* **13** 036013
[184] Wang J, Zhu H, Liu J, Li H, Han Y, Zhou R and Zhang Y 2021 The application of computer vision to visual prosthesis *Artif. Organs* **45** 1141–54
[185] Li H, Su X, Wang J, Kan H, Han T, Zeng Y and Chai X 2018 Image processing strategies based on saliency segmentation for object recognition under simulated prosthetic vision *Artif. Intell. Med.* **84** 64–78
[186] Li H, Han T, Wang J, Lu Z, Cao X, Chen Y, Li L, Zhou C and Chai X 2017 A real-time image optimization strategy based on global saliency detection for artificial retinal prostheses *Inf. Sci.* **415** 1–18
[187] Guo F, Yang Y and Gao Y 2018 Optimization of visual information presentation for visual prosthesis *Int. J. Biomed. Imaging* **2018** 3198342
[188] GUO F, YANG Y, Xiao Y, GAO Y and YU N 2019 Recognition of moving object in high dynamic scene for visual prosthesis *IEICE Trans. Inf. Syst.* **102** 1321–31
[189] Sanchez-Garcia M, Martinez-Cantin R and Guerrero J 2019 Indoor scenes understanding for visual prosthesis with fully convolutional networks *Proc. 14th Int. Joint Conf. Computer Vision Imaging Computer Graphics Theory Applications* pp 218–25
[190] Lozano A, Suárez J S, Soto-Sánchez C, Garrigós J, Martínez-Alvarez J J, Ferrández J M and Fernández E 2020 Neurolight: a deep learning neural interface for cortical visual prostheses *Int. J. Neural Syst.* **30** 2050045
[191] van Steveninck J R, Güçlü U, van Wezel R and van Gerven M 2022 End-to-end optimization of prosthetic vision *J. Vis.* **22** 20
[192] Romeni S, Zoccolan D and Micera S 2021 A machine learning framework to optimize optic nerve electrical stimulation for vision restoration *Patterns* **2** 100286
[193] Lozano A, Suárez J S, Soto-Sánchez C, Garrigós J, Martínez J-J, Vicente J M F and Fernández-Jover E 2019 Understanding the brain function and emotions *8th Int. Work-Conf. Interplay between Natural and Artificial Computation, IWINAC 2019: Proc. Part I (Lecture Notes Computer Science)* (*Almería, Spain, 3–7 June 2019*) pp 108–19
[194] Krook-Magnuson E, Gelinas J N, Soltesz I and Buzsáki G 2015 Neuroelectronics and biooptics: closed-loop technologies in neurological disorders *JAMA Neurol.* **72** 823–9
[195] Shah N P and Chichilnisky E J 2020 Computational challenges and opportunities for a bi-directional artificial retina *J. Neural Eng.* **17** 055002
[196] Guo T, Yang C Y, Tsai D, Muralidharan M, Suaning G J, Morley J W, Dokos S and Lovell N H 2018 Closed-loop efficient searching of optimal electrical stimulation parameters for preferential excitation of retinal ganglion cells *Front. Neurosci.* **12** 168
[197] Montes V R, Gehlen J, Lück S, Mokwa W, Müller F, Walter P and Offenhäusser A 2019 Toward a bidirectional communication between retinal cells and a prosthetic device—a proof of concept *Front. Neurosci.* **13** 367
[198] Montes V R, Gehlen J, Ingebrandt S, Mokwa W, Walter P, Müller F and Offenhäusser A 2020 Development and *in vitro* validation of flexible intraretinal probes *Sci. Rep.* **10** 19836
[199] Rotermund D, Ernst U A and Pawelzik K R 2019 Open Hardware for neuro-prosthesis research: a study about a closed-loop multi-channel system for electrical surface stimulations and measurements *Hardwarex* **6** e00078
[200] Caspi A, Roy A, Dorn J D and Greenberg R J 2017 Retinotopic to spatiotopic mapping in blind patients implanted with the Argus II retinal prosthesis spatial mapping in a visual prosthesis *Investigative Ophthalmol. Vis. Sci.* **58** 119–27
[201] Barbruni G L, Ros P M, Demarchi D, Carrara S and Ghezzi D 2020 Miniaturised wireless power transfer systems for neurostimulation: a review *IEEE Trans. Biomed. Circuits Syst.* **14** 1160–78
[202] Wong Y T, Feleppa T, Mohan A, Browne D, Szlawski J, Rosenfeld J V and Lowery A 2019 CMOS stimulating chips capable of wirelessly driving 473 electrodes for a cortical vision prosthesis *J. Neural Eng.* **16** 026025
[203] Merabet L B, Rizzo J F, Amedi A, Somers D C and Pascual-Leone A 2005 What blindness can tell us about seeing again: merging neuroplasticity and neuroprostheses *Nat. Rev. Neurosci.* **6** 71–77
[204] Majji A B, Humayun M S, Weiland J D, Suzuki S, D'Anna S A and de Juan E 1999 Long-term histological and electrophysiological results of an inactive epiretinal electrode array implantation in dogs *Investigative Ophthalmol. Vis. Sci.* **40** 2073–81
[205] Sachs H G, Schanze T, Wilms M, Rentzos A, Brunner U, Gekeler F and Hesse L 2005 Subretinal implantation and testing of polyimide film electrodes in cats *Graefe's Arch. Clin. Exp. Ophthalmol.* **243** 464–8
[206] Schwahn H N, Gekeler F, Kohler K, Kobuch K, Sachs H G, Schulmeyer F, Jakob W, Gabel V-P and Zrenner E 2001 Studies on the feasibility of a subretinal visual prosthesis: data from Yucatan micropig and rabbit *Graefe's Arch. Clin. Exp. Ophthalmol.* **239** 961–7
[207] Jones B W, Watt C B, Frederick J M, Baehr W, Chen C, Levine E M, Milam A H, Lavail M M and Marc R E 2003 Retinal remodeling triggered by photoreceptor degenerations *J. Comp. Neurol.* **464** 1–16
[208] Santos A, Humayun M S, de Juan E, Greenburg R J, Marsh M J, Klock I B and Milam A H 1997 Preservation of the inner retina in retinitis pigmentosa: a morphometric analysis *Arch. Ophthalmol.* **115** 511–5
[209] Medeiros N E and Curcio C A 2001 Preservation of ganglion cell layer neurons in age-related macular degeneration *Investigative Ophthalmol. Vis. Sci.* **42** 795–803
[210] Jones B W, Pfeiffer R L, Ferrell W D, Watt C B, Marmor M and Marc R E 2016 Retinal remodeling in human retinitis pigmentosa *Exp. Eye Res.* **150** 149–65

[211] Jones B W, Pfeiffer R L, Ferrell W D, Watt C B, Tucker J and Marc R E 2016 Retinal remodeling and metabolic alterations in human AMD *Front. Cell Neurosci.* **10** 103
[212] Sullivan R K P, WoldeMussie E and Pow D V 2007 Dendritic and synaptic plasticity of neurons in the human age-related macular degeneration retina *Investigative Opthalmol. Vis. Sci.* **48** 2782
[213] Vargas-Martín F and Peli E 2006 Eye movements of patients with tunnel vision while walking *Investigative Ophthalmol. Vis. Sci.* **47** 5295–302
[214] Dulin D, Hatwell Y, Pylyshyn Z and Chokron S 2008 Effects of peripheral and central visual impairment on mental imagery capacity *Neurosci. Biobehav. Rev.* **32** 1396–408
[215] Marc R E and Jones B W 2003 Retinal remodeling in inherited photoreceptor degenerations *Mol. Neurobiol.* **28** 139–47
[216] Jones B W and Marc R E 2005 Retinal remodeling during retinal degeneration *Exp. Eye Res.* **81** 123–37
[217] Finn A P, Grewal D S and Vajzovic L 2018 Argus II retinal prosthesis system: a review of patient selection criteria, surgical considerations, and post-operative outcomes *Clin. Ophthalmol.* **12** 1089–97
[218] Yanai D, Lakhanpal R R, Weiland J D, Mahadevappa M, Boemel G V, Fujii G Y, Greenberg R, Caffey S, de Juan E and Humayun M S 2003 The value of preoperative tests in the selection of blind patients for a permanent microelectronic implant *Trans. Am. Ophthal. Soc.* **101** 223–30
[219] Naycheva L, Schatz A, Röck T, Willmann G, Messias A, Bartz-Schmidt K U, Zrenner E and Gekeler F 2012 Phosphene thresholds elicited by transcorneal electrical stimulation in healthy subjects and patients with retinal diseases *Investigative Opthalmol. Vis. Sci.* **53** 7440
[220] Merabet L B, Rizzo J F, Pascual-Leone A and Fernandez E 2007 'Who is the ideal candidate?': decisions and issues relating to visual neuroprosthesis development, patient testing and neuroplasticity *J. Neural Eng.* **4** S130
[221] Erickson-Davis C and Korzybska H 2021 What do blind people 'see' with retinal prostheses? Observations and qualitative reports of epiretinal implant users *PLoS One* **16** e0229189
[222] Cooper-Martin E 1994 Measures of cognitive effort *Mark. Lett.* **5** 43–56
[223] Rokem A and Silver M A 2013 The benefits of cholinergic enhancement during perceptual learning are long-lasting *Front. Comput. Neurosci.* **7** 66
[224] Chamoun M, Huppé-Gourgues F, Legault I, Rosa-Neto P, Dumbrava D, Faubert J and Vaucher E 2017 Cholinergic potentiation improves perceptual-cognitive training of healthy young adults in three dimensional multiple object tracking *Front. Hum. Neurosci.* **11** 128
[225] Vetencourt J F M, Sale A, Viegi A, Baroncelli L, Pasquale R D, O'Leary O F, Castrén E and Maffei L 2008 The antidepressant fluoxetine restores plasticity in the adult visual cortex *Science* **320** 385–8
[226] Allen P J 2021 Retinal prostheses: where to from here? *Clin. Exp. Ophthalmol.* **49** 418–29
[227] Grover S, Fishman G A, Anderson R J, Tozatti M S V, Heckenlively J R, Weleber R G, Edwards A O and Brown J 1999 Visual acuity impairment in patients with retinitis pigmentosa at age 45 years or older *Ophthalmology* **106** 1780–5
[228] Strickland E and Harris M 2022 What happens when a bionic body part becomes obsolete? *IEEE Spectr.* **59** 24–31
[229] Chevrie K 2020 Navigating the regulatory pathway for an innovative bionic vision system *Advanced Biomedical Clinical Diagnostic Surgical Guidance Systems XVIII* vol 11229 p 112290X