Review

# Visual prostheses for the blind

Robert K. Shepherd[1,2], Mohit N. Shivdasani[1,2], David A.X. Nayagam[1,2,3], Christopher E. Williams[1,2], and Peter J. Blamey[1,2]

[1] Bionics Institute, 384-388 Albert St East Melbourne, 3002, Victoria, Australia
[2] Medical Bionics Department, University of Melbourne, 384-388 Albert St East Melbourne, 3002, Victoria, Australia
[3] Department of Pathology, University of Melbourne, Parkville, 3010, Victoria, Australia

**After more than 40 years of research, visual prostheses are moving from the laboratory into the clinic. These devices are designed to provide prosthetic vision to the blind by stimulating localized neural populations in one of the retinotopically organized structures of the visual pathway – typically the retina or visual cortex. The long gestation of this research reflects the many significant technical challenges encountered including surgical access, mechanical stability, hardware miniaturization, hermetic encapsulation, high-density electrode arrays, and signal processing. This review provides an introduction to the pathophysiology of blindness; an overview of existing visual prostheses, their advantages and drawbacks; the perceptual effects evoked by electrical stimulation; as well as the role played by plasticity and training in clinical outcomes.**

## Introduction

Neural prostheses restore or modulate neural activity in patients suffering from a variety of sensory or neurological disorders. Since the appearance of the first commercial devices in the 1970s, the field has grown to a $4.7 billion industry in 2012 with an annual growth rate of 20% [1]. Prominent innovations include neuromodulation devices to treat chronic refractory pain, cochlear implants that provide auditory cues for the profoundly deaf, and deep brain stimulators that reduce motor disorders in Parkinson's disease. Among the most exciting developments are visual prostheses, devices designed to provide artificial visual for the blind, resulting in increased independent living and quality of life. Here, we review the current status of both retinal and cortical based visual prostheses.

The retina is a highly specialized structure located at the back of the eye that converts light into nerve impulses. The outer retina contains ~150 million photoreceptors (see Glossary) that make excitatory and inhibitory connections with the first of a series of specialized cells that form the middle and inner layers of the retina. These cells in turn make synaptic connections to the ~1 million retinal ganglion cells (RGCs) that form the output of the retina, conducting action potentials via the optic nerve to the central visual pathway.

It is estimated that 285 million people are visually impaired worldwide; 39 million of whom are blind [2]. Although uncorrected refractive errors are the main cause of visual impairment, diseases associated with degeneration of the retinal photoreceptors result in severe visual loss with few or no therapeutic options for ongoing clinical management. Importantly, significant numbers of RGCs are spared following the loss of photoreceptors. Although there are major alterations to the neural circuitry of these surviving neurons [3], their presence provides the potential to restore vision using electrical stimulation delivered by an electrode array located close to the retina (Box 1). The clinical management of other forms of blindness, including

## Glossary

**Age-related macular degeneration (AMD)**: damage to the photoreceptors of the macula region of the retina leading to central blindness.
**Choroid**: located between the retina and the sclera, the choroid contains a rich network of blood vessels and connective tissue and is responsible for providing oxygen and nutrients to the outer layers of the retina.
**Cones**: a subtype of photoreceptor cell located in the outer retina responsible for color vision. They are optimized for performing in bright environments. Cones are densely packed in the central part of the visual field (the macula), but are relatively sparse in the peripheral retina. The human eye has approximately 6 million cone cells.
**Fovea**: a region of the macula responsible for sharp central vision.
**Lateral geniculate nucleus (LGN)**: the main relay center in the brain of visual information coming from the retina. The axons of the LGN project directly to the visual cortex.
**Macula**: an oval-shaped region of the central retina that contains a high concentration of cone cells and is responsible for central vision.
**Ophthalmoscope**: or fundoscope is an optical instrument used to examine the inside surface (fundus) of the eye opposite the lens.
**Optic nerve**: The second cranial nerve consists of the processes of RGCs. It transmits visual information from the retina to the brain and is part of the central nervous system.
**Phosphenes**: artificial visual percepts not produced by light. Phosphenes can be evoked by electrical, mechanical, or magnetic stimulation of the retina or visual cortex.
**Photoreceptor cells**: A neuron specialized for transducing energy in the form of light to neural signals in the form of action potentials. In vertebrates, the two classic types of photoreceptor cells are rods and cones.
**Retinal ganglion cells (RGCs)**: nerve cells whose axons connect the retina to the brain via the optic nerve. There are approximately 1 million RGCs in a normal human retina.
**Retinitis pigmentosa (RP)**: an inherited, degenerative eye disease caused by an abnormality of photoreceptors leading to peripheral blindness.
**Retinotopic**: an orderly map of the retina reproduced in structures of the central visual system including the LGN and the visual cortex.
**Rods**: a subtype of photoreceptor cells that are sensitive to low light intensities. These cells are optimized for night vision and are concentrated in the peripheral retina. Rods are not sensitive to color. The human retina has approximately 100 million rod cells.
**Visual cortex**: Located at the back of the brain in the occipital cortex and receiving most of its input from the LGN, the primary visual cortex is a key site for vision processing.
**Visual prostheses**: devices designed to provide artificial vision for the blind.

*Corresponding author:* Shepherd, R.K. (rshepherd@bionicsinstitute.org).
*Keywords:* neural prosthesis; electrical stimulation; electrodes; blindness; bionic vision.

0167-7799/$ – see front matter
 http://dx.doi.org/10.1016/j.tibtech.2013.07.001

**Box 1. Electrical stimulation of neural tissue**

*Generation of an action potential via an electrical stimulus*

Neurons exhibit a resting membrane potential of typically –70 to –80 mV – the intracellular environment is maintained at a negative potential relative to the extracellular environment. As a negatively charged electrode (*cathode*) is positioned close to a neuron the potential difference across the neural membrane is artificially lowered – the neuron will become depolarized at that point. As the amount of charge delivered to the cathode increases, the depolarization of the neural membrane increases until it reaches a threshold potential. At this point, transmembrane voltage-sensitive $Na^+$ channels open and allow extracellular $Na^+$ into the intracellular environment, thus initiating an action potential. The propagation of the action potential along the axon is achieved via normal physiological processes independent of whether or not the activity is generated using natural or artificial means.

*Principles of safe electrical stimulation of neural tissue*

Stimulating electrodes must inject charge into the biological environment without damaging the surrounding tissue. Electrical stimulation is achieved via a series of electrochemical reactions that convert the charge carriers from electrons (in the electrode) to ions (in the electrolyte) and must be performed using specific electrode materials in combination with brief reversible stimulus waveforms to ensure that no toxic electrochemical products are introduced into the biological environment.

When a metal electrode is placed into an electrolyte, a layer of charge on the electrode surface will attract polarized water molecules, creating a capacitive layer at the electrode-tissue interface (Helmholtz double layer). At low charge densities ($<20\ \mu C/cm^2$) charge injection is dominated by this capacitance, no charge carrier crosses the electrode–tissue interface and no electrochemical reaction products are formed in the electrolyte [67,68]. In practice, activation of neural tissue requires charge densities higher than can be achieved via purely capacitive means. As charge density is increased, reversible electrochemical Faradaic reactions begin to dominate the charge injection process, including oxide formation/reduction and hydrogen-atom plating (Table I; [69]). Importantly, these reactions are localized to the electrode–tissue interface and can be readily reversed via the passage of an equal charge of opposite polarity – the charge-balanced biphasic pulse – ensuring that no new electrochemical species are released into the biological environment [67,68]. Safe electrical stimulation is restricted to charge injection via these processes and is dependent on the use of a charge-balanced stimulus waveform and the electrode material used. As an example, stainless steel electrodes are restricted to a maximum safe charge density of 40–50 $\mu C/cm^2$ geom. using these reversible processes compared with 210 $\mu C/cm^2$ geom. for platinum electrodes.

At higher stimulus intensities, charge injection is achieved via several irreversible electrochemical reactions, including electrode corrosion products, electrolysis of water, and oxidation of chloride ions (Table I). These electrochemical reaction products diffuse away from the electrode–tissue interface, resulting in tissue damage.

Platinum, iridium, and their alloys are the most extensively used metal electrodes for large surface area electrodes, whereas iridium oxide and titanium nitride are often used for microstimulation.

**Table I. Reversible and irreversible electrochemical reactions associated with electrical stimulation using platinum electrodes**

| | |
|---|---|
| Oxide formation and reduction | $Pt + H_2O \leftrightarrow PtO + 2H^+ 2e^-$ |
| H-atom plating | $Pt + H_2O + e^- \leftrightarrow Pt\text{-}H + OH^-$ |
| Corrosion of the electrode | $Pt + 4Cl \rightarrow [PtCl_4]^{-2} + 2e^-$ |
| Hydrogen generation | $2H_2O + 2e^- \rightarrow H_2\uparrow + 2OH^-$ |
| Oxygen generation | $2H_2O \rightarrow O_2\uparrow + 4H^+ + 4e^-$ |
| Oxidation of chloride ion | $2Cl^- \rightarrow Cl_2\uparrow + 2e^-$ |

glaucoma, diabetic retinopathy, and trauma is also associated with limited therapeutic options and can result in a nonfunctional retina or optic nerve. Although a retinal prosthesis is not suitable for these pathologies, electrical stimulation at other sites along the central visual pathway, particularly the visual cortex, has the potential to restore vision in these cases (Figure 1).

Attempts to stimulate the visual pathway electrically in order to evoke artificial visual percepts or 'phosphenes', are not new. In 1755 Charles LeRoy delivered current to a metal coil wrapped around the head of a blind man producing a flame-like phosphene that unfortunately also evoked terrible cries from the subject [4]. From the 1930s, exploratory procedures, performed by neurologists during neurosurgical procedures in awake patients, consistently demonstrated that phosphenes could be evoked by the application of localized electrical stimulation to specific regions of the cerebral cortex [5]. Brindley and colleagues pioneered the first clinical trial of a visual prosthesis in the late 1960s by implanting 80 electrodes over the visual cortex [6,7]. Although their subjects perceived reproducible phosphenes that looked like points, spots, or bars, the devices were limited by the technology available. Although a proposal for a retinal visual prosthesis was first described in the 1950s [8], the technical complexity of this approach delayed its development until the 1990s.

Over the past two decades there has been increased interest in the development of visual prostheses. Much of this impetus stems from the success of cochlear implants [9], advances in enabling technologies, and the lack of alternative therapeutic options for the treatment of these patients. There are at least 23 research groups developing visual prostheses [10]; the majority of which are retinal prostheses.

## The normal and diseased retina

The human retina is a delicate and intricate network of photic-sensitive tissue lining the back of the eye. It transduces incident visible light, focused by the optics of the eye, into neural impulses, which form the perception of vision in the brain. The retina is comprised of an outer layer of photoreceptors, several specialist neural layers, and supporting architecture. Humans have two primary photoreceptors: rods and cones. The rods are optimized for low-light monochrome vision, whereas the cones are specialized for color vision in brighter environments. The photoreceptors are highly metabolically active and are supplied by the rich network of blood vessels in the adjacent layer of the eye, known as the choroid (Figure 2A). The light-sensing photoreceptor cells initiate a cascade of neural activity that propagates via a convergent retinal network to the RGCs whose axons form the optic nerve (Figure 2A).

Viewing the retina through the pupil via an ophthalmoscope (a fundus image), the most notable feature is the surface vasculature, which originates from the pale circular region known as the optic disc, and provides nourishment to the inner retinal layers (Figure 2B). The optic disc is the point where the axons of the RGCs form the optic nerve and exit the eye. Near the centre of the retina is an oval pigmented region known as the macula, which does

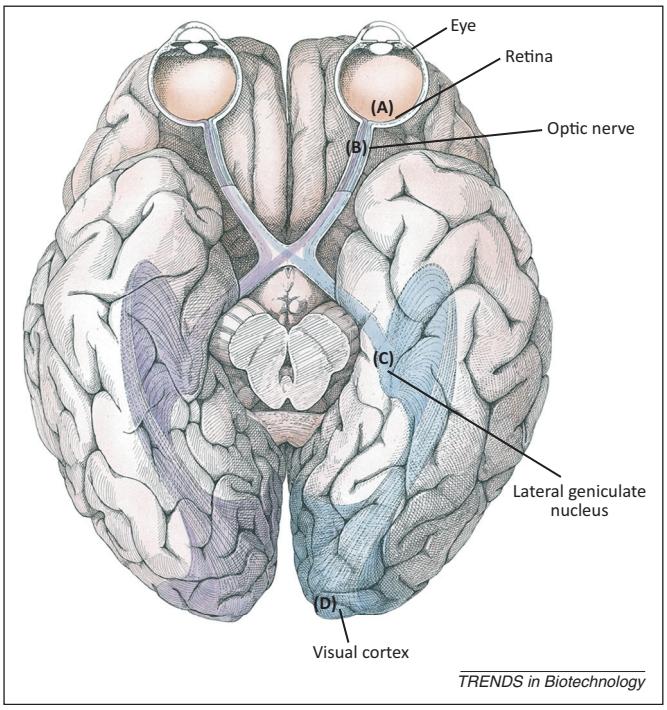


**Figure 1**. Overview of the visual pathway from the retina to the primary visual cortex. Visual prostheses can potentially target several sites along this pathway including: **(A)** planar electrode arrays placed at the epiretinal, subretinal, or suprachoroidal locations adjacent to the retina; **(B)** cuff electrodes around or penetrating electrodes into the optic nerve; **(C)** penetrating electrodes into the lateral geniculate nucleus; and **(D)** surface or penetrating electrodes over the visual cortex. These structures have a well-organized topographic map of the retina, that is, the spatial organization of the retina is maintained throughout the visual pathway. This is referred to as retinotopic organization. Adapted from [70].

not contain large blood vessels. This region is specialized for central, high-acuity vision, which is greatest at the fovea – a small depression in the centre of the macula containing almost exclusively cone photoreceptors (Figure 2B) [11].

### *Retinitis pigmentosa and age-related macular degeneration*

Retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are two degenerative diseases of the retina that result in blindness, secondary to photoreceptor loss (Figure 2D). RP is the collective term for a group of relatively rare hereditary deficits that lead to blindness in midlife, as a result of a gradual degeneration of photoreceptors. In typical rod–cone dystrophy, the lesion is initially restricted to the peripheral retina, resulting in tunnel vision (Figure 2F), but over time the central macular region can also be affected. Importantly, there is currently no cure for RP. AMD is a leading cause of vision loss in older adults; in western countries it accounts for ~50% of all severe visual impairment and blindness [12]. It gradually destroys the high-resolution macula region of the retina while typically leaving peripheral vision intact (Figure 2G). There are two forms of AMD. Dry AMD makes up the majority of cases (85–90%). With no effective treatment options, the disease process ultimately leads to a severe loss of central visual field. Wet AMD makes up 10–15% of cases and is characterized by abnormal proliferation of blood vessels in the choroid. As the disease progresses, this vascularization results in blood and fluid accumulation, damaging the photoreceptors of the macular region and resulting in severe loss of central vision (Figure 2H). Wet AMD progresses rapidly, and without intervention can cause severe damage within a few months. At present it is possible to use anti-vascular endothelial growth factor (anti-VEGF) drugs or retinal laser treatment to reduce the formation of new blood vessels; however, it is not possible to reverse the progression of the pathology.

### *Remodeling of the retina following loss of photoreceptors*

Although significant populations of RGCs survive following photoreceptor degeneration, the loss of afferent input produces major changes in both the structure and function of the remaining neural retina [3]. The extent of retinal remodeling can vary substantially, but is ubiquitous following loss of photoreceptors. A cascade of early neurochemical changes precede structural and functional revisions including the migration and rewiring of retinal circuitry, gliosis, ectopic neurite outgrowth, and RGC degeneration [3,13]. These alterations influence the sensitivity of RGCs to electrical stimulation as well as the neural processing through the retinal network [3]. Importantly, electrical stimulation of the long-term blind retina evokes stable, retinotopically organized visual precepts [14].

### *Other potential forms of blindness that could be treated with visual prostheses*

Other causes of incurable blindness include glaucoma, diabetic retinopathy, traumatic eye injury, peripheral visual pathway, or retinofugal lesions (such as optic nerve tumors), and central disorders [15]. Retinal prostheses are not suitable for these conditions because the injury foci are central to the RGCs, however, electrode arrays that directly stimulate more central structures within the visual pathway (Figure 1) provide viable alternatives.

## Design principles of visual prostheses

Visual prostheses can be broadly categorized into groups based on their underlying technology or the anatomical location in which the electrode array is implanted. From a technological perspective there are two basic designs. (i) Optical sensors such as an array of photodiodes that are implanted close to the retina. The normal optical properties of the eye focus light onto the photodiodes, which convert this energy into electrical pulses designed to depolarize proximal RGCs [16,17]. (ii) A classic sensory prosthesis that includes an external video camera, vision processor, and power supply, a transcutaneous telemetry link, an implantable stimulator connected to a leadwire, and electrode array located at the level of the retina or central visual pathway [18–20] (Figure 3; Box 2).

There are several design advantages to using a photodiode array; primarily the absence of wires, which simplifies the surgery. Additionally, because a photodiode array utilizes existing ocular optics and eye position to localize the visual field, there is no need to take into account the subject's gaze. The major limiting factor associated with the use of photodiodes is their inability to provide sufficient

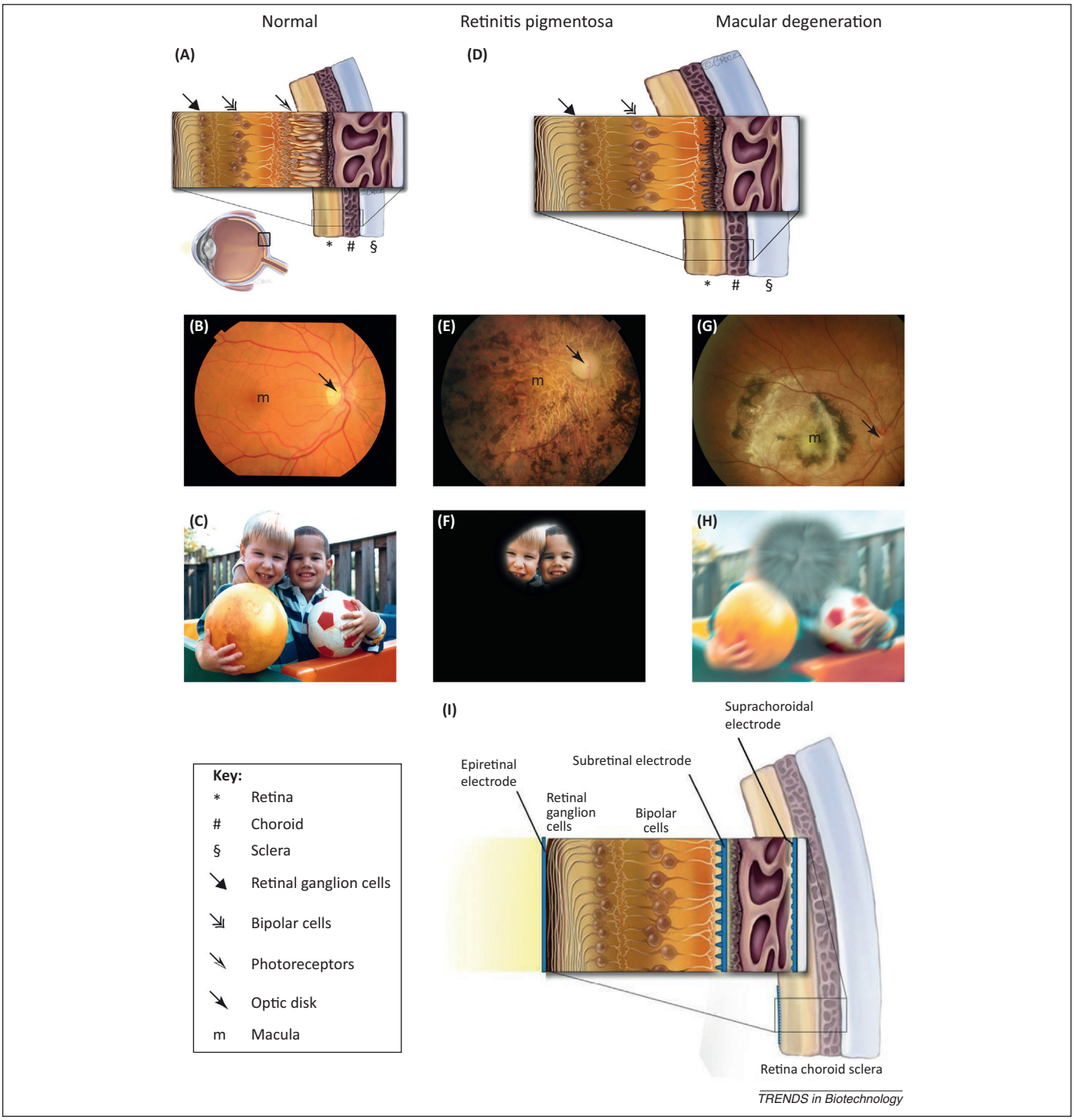


**Figure 2**. The anatomy of the eye in normal vision and following loss of photoreceptors. **(A)** Schematic of a normal retina, choroid, and sclera. The retina consists of several processing layers extending from the rods and cones of the outer retina through bipolar cells of the middle retina to the retinal ganglion cells (RGCs) that make up the inner retina. Axons of the RGCs project via the optic disc to form the optic nerve. Inset: horizontal section through the eye with the boxed region illustrating the location of the magnified schematics in panels A and D. **(B)** Color fundus image of a normal retina illustrating the optic disk (arrow) and macula region (m). **(C)** Simulated normal visual field. **(D)** Schematic of a retina with widespread photoreceptor degeneration. **(E)** Fundus image of a retina with retinitis pigmentosa (RP). **(F)** Simulated tunnel vision of a patient with RP. **(G)** Fundus image of a retina with age-related macular degeneration (AMD). **(H)** Simulated visual field of a patient with AMD, showing loss of central vision. **(I)** Potential sites to place an electrode array close to the retina including epiretinal, subretinal, and suprachoroidal positions. Panels A, D and I: courtesy of Bionic Vision Australia (Image by C. Roce). Panels B, E and G: courtesy of the Centre for Eye Research Australia. Panels C, F and H: courtesy of the National Institutes of Health National Eye Institute.

energy necessary for retinal stimulation [21]. To overcome this limitation one photodiode based device includes an external power source and a leadwire assembly [16,22], and a second design intends to use pulsed infrared light to provide both power and visual information directly to a photodiode array implanted in the retina [17].

The most common form of a visual prosthesis incorporates an electrode array located on or close to the retina. There are several anatomical sites where these electrodes

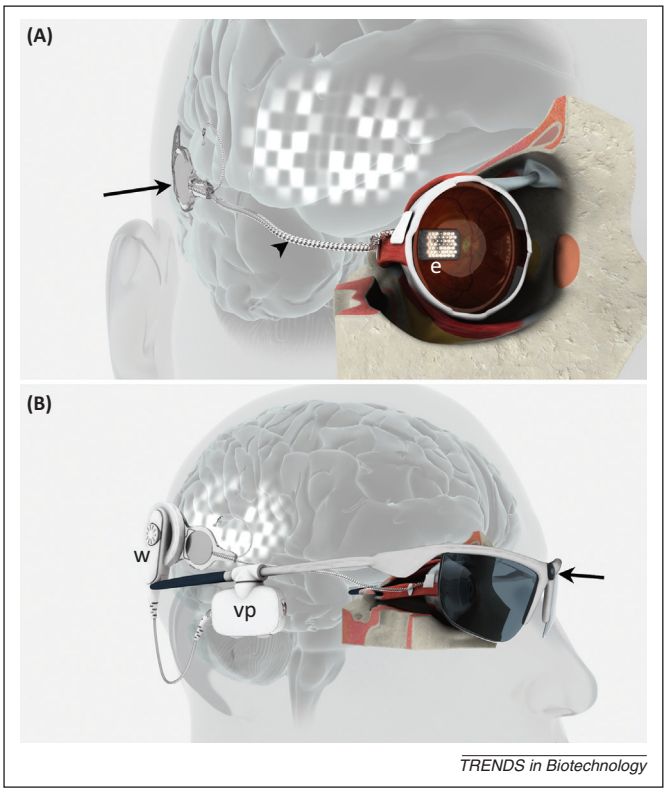


**Figure 3.** **(A)** Schematic diagram of a generic retinal prosthesis illustrating a receiver–stimulator unit implanted in the mastoid bone behind the ear (arrow), a leadwire assembly (arrowhead) connecting the output of the stimulator to an array of electrodes (e) implanted in the retina. The electrode array can be tacked in front of the retina (epiretinal); inserted between the choroid and the retina (subretinal); or inserted between the sclera and the choroid (suprachoroidal). A similar architecture would be suitable for a visual prosthesis based on stimulation of the visual cortex. **(B)** Overall schema of a retinal prosthesis that includes a video camera incorporated onto glasses (arrow), an external vision processor (vp) that provides both data and power across the skin via a wireless link (w) to the implanted receiver-stimulator, leadwire and electrode array illustrated in (A). The camera continuously feeds video signals to the vision processor that contains the patient's phosphene map, visual processing algorithms, and stimulation strategies. Each frame of the input video generates a sequence of commands at the vision processor that defines the electrodes and stimulus parameters required to generate a prosthetic image of the scene. (Images by Jack Parry; courtesy of the Bionics Institute).

can be placed, including the inner surface of the retina (epiretinal), between the retina and choroid (subretinal), or between the choroid and the sclera (suprachoroidal) (Figure 2I). Potential complications associated with a retinal prosthesis include mechanical stability of the implant in a location subject to extensive movement in the form of micro- and macrosaccades. An intended recipient of a visual prosthesis with vision impairment is expected to have a similar number of saccades as a normally sighted person; between 100 000 and 150 000 eye movements per day [23]. Mechanical stability can be a particular issue for epiretinal devices where the implant must be fixed to the inner retina. Heat generation using high-density electrode arrays and neural stimulating circuitry located within the eye is also a potential safety issue for retinal prostheses. International standards require that no outer surface of an active implant be 2 °C above body temperature (ISO 14708-1). Power dissipation levels <19 mW/mm$^2$ at the retinal surface are considered to operate within this safe range [24].

### *Epiretinal*

Placing an electrode array on the inner surface of the retina ensures the electrodes stimulate the output of the retina – the axons of the RGCs. Such proximity to RGCs results in low thresholds for neural activation, minimizing the physical size required of individual electrodes, and theoretically maximizing the resolution and acuity of prosthetic vision over electrodes positioned in other retinal locations. Surgically, the electrode array is fixed to the inner retinal surface using one or two retinal tacks. The devices make use of platinum, iridium oxide, or conductive diamond electrodes coupled to stimulation electronics within a hermetic capsule that is contained entirely within the vitreous chamber. The implant housings are fixed in place of the lens or attached extraocularly to the sclera. The capsule is coupled to a receiving coil that is inductively linked to an external coil fitted to a pair of glasses that also houses the camera. There are several research groups and companies developing epiretinal devices. [18,25–27]. Second Sight Medical Products recently received regulatory approval in both Europe and the USA to treat late-stage RP with

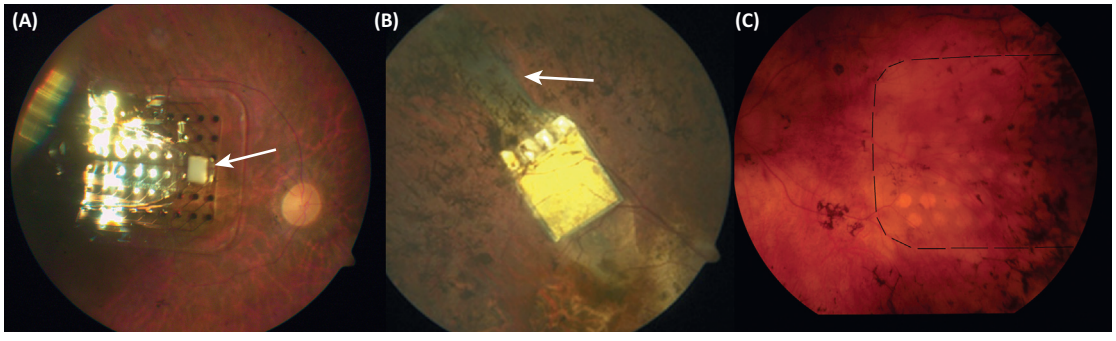


**Figure 4.** Fundus images of three retinal prostheses in clinical use in late stage RP patients. **(A)** Epiretinal Argus II electrode array containing 60 platinum electrodes fixed to the inner retina via a retinal tack (arrow) (Image courtesy of Second Sight Medical Products Inc.). **(B)** Subretinal Alpha IMS retinal implant containing 1500 photodiode electrodes on a 3 × 3 mm matrix. A leadwire (arrow) delivers additional power to the electrodes to ensure that the stimulus levels are sufficient to excite retinal tissue. (Image courtesy of the Center for Ophthalmology, University of Tübingen, Germany). **(C)** Bionic Vision Australia's prototype suprachoroidal electrode array developed by the Bionics Institute containing 24 platinum electrodes. The edge of the array is illustrated by the broken line (Image courtesy of the Centre for Eye Research Australia).

**Box 2. Building a neural prosthesis**

Apart from the photodiode technology being developed by some visual prosthesis groups, the majority of modern commercial neural prostheses consist of several essential components including an electrode array for stimulation and/or recording from neural tissue; a leadwire assembly connecting the electrode array to implanted stimulation and/or recording circuitry; a power source; and a transcutaneous wireless link to an external controller that provides data defining the stimulation parameters to be delivered to the electrode array (e.g., a visual processor, see Figure 3 in main text).

A stimulating/recording electrode array must be developed for each application because its design features will be dependent on factors including the underlying anatomy and pathophysiology of the target site and surgical access. An electrode array designed for long-term use in humans must ensure: minimal insertion trauma; biocompatibility; that the electrical stimulus is localized to discrete groups of target neurons; mechanical and electrical stability; that it is designed to minimize the risks of infection (including smooth surfaces, elimination of cavities, and careful selection of bio materials); that the stimulus regime is not damaging in the long-term; and that it is designed for safe removal and replacement [68].

The implanted electronics that make up the active components of a visual prosthesis must be protected from the corrosive biological environment by hermetically sealing them from body fluids. The long-term reliability of any prosthesis is associated with the efficacy of its hermetic seal. The gold standard sealing technique is to encase the electronics within a titanium capsule that is sealed using a laser welder [71,72]. This hermetic sealing technique can be problematic for retinal prostheses where size restrictions are an important design constraint. The use of polymers for hermetic encapsulation is an attractive alternative because many have excellent biocompatibility, ease of fabrication, flexibility, electromagnetic transmission, and cost compared with titanium. However, there remain technical challenges in obtaining long-term effective hermetic bonding using polymers [71] and this remains an important area of research.

In order for the hermetically sealed electronics to deliver electrical pulses to the electrode array and/or receive biological signals from the neural interface, the implant must also incorporate a feed-through assembly that allows the sealed electronics to make electrical connection to the electrodes without compromising the seal [72]. There are significant design pressures on manufactures to develop devices with a large electrode count. This places considerable pressure on the development of reliable high density feed-through assemblies and is an important limiting factor in developing high-density electrode arrays.

Active implants such as visual prostheses require a power source to operate. There are two alternative power sources that are in common use. Many devices receive their power via a battery located within the hermetically sealed capsule (e.g., a deep brain stimulator). This approach presents surgical restrictions on the implant site as a result of its size. For devices such as retinal prostheses, power is typically provided via an external source whenever the implant is in use. An inductive link comprised of coils on each side of the skin coupled via a radiofrequency carrier signal (see Figure 3B in main text).

their 60 electrode Argus II device (Figure 4A). Two technical challenges associated with the epiretinal approach are related to the significant constraints on device size with this surgical approach, and the fixation and long-term mechanical stability of the electrode array on the retinal surface using penetrating retinal tacks. Additional safety issues include the potential for mechanical damage to the retina and an increased risk of inflammation with devices that run leadwires from the vitreous through the sclera.

### *Subretinal*

Significant neural processing occurs within the outer and middle layers of the retina peripheral to the RGCs; epiretinal prostheses cannot take advantage of this processing. Subretinal electrode arrays are designed to be positioned at the level of the outer retina where, in a healthy eye, photoreceptors would be located [16,17,22,28,29] (Figure 2I). Although this is a logical choice for an implant whose function is to replace lost photoreceptors, it comes with its own challenges. The surgical approach is technically difficult and the electrode array and associated electronics must be extremely thin (<400 μm) to minimize retinal damage or detachment. In addition, there is the potential for a subretinal electrode array to impede blood supply from the choroid to the surviving retina. Finally, although at least some of the impetus for the development of a subretinal neural prosthesis is to take advantage of the normal processing that occurs in the outer and middle retina [22], this becomes a moot point after the remodeling that occurs following photoreceptor loss [3]. Several groups are developing this approach, with the Alpha-IMS manufactured by Retina Implant AG recently gaining European regulatory approval for the treatment of late stage RP [16,22] (Figure 4B). There are technical challenges with manufacturing a long-term hermetic encapsulation with the thin profile of these implants. Some have chosen photodiodes as the sensing elements [16,17]; whereas another group has developed an array of 256 electrodes driven by an implantable stimulator containing 256 current drivers [30]. Many of the safety concerns associated with epiretinal implants are also an issue for epiretinal devices.

### *Suprachoroidal*

Although electrodes located in a tissue pocket between the choroid and sclera (the so-called suprachoroidal position) are some distance from their target neurons in the inner retina, this approach has been adopted by several groups. This placement offers a safe and simple surgical approach and a mechanically stable location [31]. Clinical complications are minimized with the suprachoroidal approach, because multiple layers of the eye do not have to be breached in order to position the electrode array [19,32–36]. A major limitation of this approach is an increase in stimulus thresholds as a result of the greater distance between the electrode array and the retina when compared with epi- and subretinal devices. Experimental studies have demonstrated that the retina can be effectively stimulated at safe levels using this electrode position [32,37]. Moreover the choroid – which separates the electrode array from the retina in this approach – undergoes significant shrinkage in RP [38]. Recently, two groups have conducted successful clinical trials using this approach; both demonstrated that long-term severely blind patients can perceive discriminable percepts in response to electrical stimulation within safe limits of charge injection [19,39] (Figure 4C).

### *Visual prostheses based on stimulation of the central visual pathway*

Stimulation of the visual pathway at sites central to the retina has the potential to provide prosthetic vision for a

wider range of pathologies, including those that result in damage to the optic nerve. Although clinical trials of cortical-based devices were undertaken early in the development of visual prostheses [7,40], there is currently no central visual prosthesis undergoing a clinical trial.

### *Optic nerve*

Using a spiral cuff electrode, the optic nerve has been targeted as an implant site for a clinical trial in two blind patients, which resulted in the generation of usable phosphenes [41] and the ability to record electrically evoked potentials [42]. More recently, there has been interest in targeting the optic nerve using an array of penetrating electrodes [43]. Highly focal excitation would be necessary in order to provide reliable retinotopic cues. Given this technological challenge, it is unclear how this approach would surpass the advantages of retinal based implants.

### *Lateral geniculate nucleus*

One group has proposed placing stimulating electrodes in the LGN of the thalamus [44]. The LGN is a well characterized retinotopic structure within the central visual pathway. This study showed that it was possible to elicit neural responses in the visual cortex from thalamic microstimulation, providing proof of concept for this stimulation site. Although there have been no clinical trials to date, the surgical approach would be similar to that used in deep brain stimulation to treat movement disorders associated with Parkinson's disease [45].

### *Visual cortex*

Early clinical studies provided strong evidence that visual sensations could be readily evoked through stimulation of the cortical surface [7,40] or via penetrating microelectrodes [46]. This research has recently been advanced by taking advantage of improved electrode technologies [20,47–49]. Most groups propose placing individual modules or tiles, each containing multiple stimulating electrodes, along with associated stimulating circuitry within a hermetically sealed chamber. Multiple tiles can be inserted into the visual cortex to provide many individually addressable electrodes.

The primary visual cortex is thought to be an ideal location for a visual prosthesis for several reasons; it is well organized retinotopically, it has adequate space for multiple implanted components, and is known to have a large area devoted to central vision. However, it is unclear whether a prosthesis that bypasses all visual processing occurring within the retina and LGN will contain sufficient information for higher-order brain centers to recognize accurately percepts generated from electrical stimulation. As an example, there is a rich descending corticothalamic modulation feedback loop that occurs in normal vision processing (the LGN receives the majority of its input from the visual cortex [44]); a cortical based prosthesis would bypass this processing stage. In addition, although the plastic brain plays an important role in improved clinical outcomes with sensory prostheses [50], it remains unclear whether direct stimulation of the visual cortex will recruit the same level of plastic reorganization as stimulation arising from the retina. In this context, it should be noted that stimulation delivered to the RGCs via a retinal prosthesis is already several neural processing stages beyond the photoreceptors, and this may also result in a level of perceptual complexity.

## Perceptual effects of visual prostheses

Phosphenes are visual sensations produced by stimuli other than light, including mechanical, magnetic, or electrical stimulation of the retina or brain [4]. The phosphenes evoked by electrical stimuli have typically been described in the literature as flashes of light, often amorphous but sometimes with a clear well-defined shape. Studies have also reported complex phosphenes which can be darker than the patient's naturally perceived background, sometimes with both bright and dark areas in the same phosphene [27]. The brightness, shape, size, duration and location of a phosphene can be manipulated by varying the location and configuration of electrodes being stimulated and the electrical waveforms used [51–53].

Importantly, when stimulating multiple electrodes on an array, phosphenes can interact with one another to change the perceived image [54,55]. Despite the complexities of phosphenes evoked through electrical stimulation, they form the basic building blocks of prosthetic vision. For example, psychophysical studies have demonstrated that by stimulating appropriate electrodes on an array, it is possible to create the perception of retinotopically organized patterns and simple shapes such as lines of different orientations and geometric objects (e.g., triangle or square), regardless of whether the device is placed in the epiretinal [18], subretinal [53], or suprachoroidal [39,19] space.

A camera and an image processing algorithm are required to provide a visual representation of the subjects' surroundings. Subjects implanted with the Argus II epiretinal system and using an external camera to source their visual field can perform object localization, motion discrimination, and discrimination of oriented gratings with a best visual acuity to date of 20/1260 [18,56]. If a 16X zoom camera mode is enabled, then acuity measures increase to 20/200, but the field of view is correspondingly reduced from 20° down to a few degrees, making scanning of an image more time consuming [57]. The Alpha-IMS subretinal device with 25 times more electrodes than the Argus II has demonstrated best visual acuity of 20/546 [22], allowing patients implanted with this device to be able to detect and localize light and motion, identify, localize and discriminate high contrast objects, and read large font letters [22]. Phosphenes generated by stimulation of the visual cortex are sometimes described as more complex than those induced by retinal implants, although well-defined, localized and resolvable phosphenes are possible [7], and there are reports of blind subjects reading by incorporation of a camera with the device [58].

### *Head/eye movement issues*

An important technical issue associated with camera-based visual prostheses is related to the change in the position of a phosphene within the subject's visual field with eye movement, but not with passive movement of the head while maintaining a fixed eye gaze [7]. As already noted, photovoltaic devices are not burdened with this

issue because the technology enables a natural refreshed image to be sampled by the device each time the eye makes a microsaccade [16,22]. This is a major advantage of photodiode-based devices because it eliminates the need to incorporate sophisticated eye tracking techniques to correct the image sampled by a camera for eye movement. However, the use of a camera enables the application of vision processing algorithms to pre-process the image, before applying stimulation to the electrodes, a feature that will become more powerful as implant groups gain clinical experience.

## Role of plasticity and training

The fundamental findings by Hubel and Wiesel and their colleagues the 1960s and 1970s highlighted the importance of visual experience during development on the normal establishment of retinotopic maps and ocular dominance column plasticity in the visual cortex. Importantly, in pathologies where the onset of blindness occurs after periods of normal development, as is the case in RP and AMD, the primary visual cortex does not exhibit extensive retinotopic remapping following prolonged periods of sensory deprivation [59,60]. Consistent with these observations, clinical data demonstrate that useful retinotopically organized visual cues can be evoked via a visual prosthesis decades after the onset of adult onset blindness [39].

Visual experience obtained through the use of a device is expected to result in improved performance as a result of plasticity within the central visual pathway. Strong support for the positive role of learning and plasticity comes from 30 years of experience of cochlear implant use in profoundly deaf adults. Studies examining factors that affect clinical performance consistently demonstrate that the duration of cochlear implant experience has a significant positive effect on speech understanding [61,62]. These clinical results are supported by animal studies that show electrophysiological evidence of cortical reorganization in deafened animals reared using cochlear implants [63], although the extent of plastic change in response to activation of a visual prosthesis in a long-term blind subject must be tempered given the relatively simple retino-geniculate-visual cortex pathway when compared to the complexity of the multiple pathways that occur between the eighth nerve and the auditory cortex.

Careful device fitting and ongoing training are important for the clinical success of these devices. In order to maximize the benefits of plasticity, training using everyday tasks, not just object recognition, is required [64]. Device fitting can be a time-consuming procedure that will require ongoing monitoring. The threshold and dynamic range necessary to evoke a useable phosphene must be determined for each electrode on the array. This task becomes problematic with high-density electrode arrays. Finally, the successful clinical application of visual prostheses must be a productive collaboration between the patients, their support family, researchers, clinicians, and low vision rehabilitation specialists.

## Future directions and concluding remarks

In the 1970s, cochlear implants were branded as 'an aid to lip reading'. Over the subsequent 30 years they significantly exceeded these expectations and expanded the patient base from profoundly deaf adults to now include both severely deaf adults and children. We can expect similar outcomes for visual prostheses over the following decades as both the technology and clinical experience in managing patients using these devices become more sophisticated.

In the shorter term, there remain considerable technical challenges that must be addressed before visual prostheses receive widespread clinical acceptance. The existing research and commercial device development cover a very broad range of options for each of the outstanding questions listed in Box 3.

The possible electrode locations include the epiretinal, subretinal, suprachoroidal, and visual cortex, each with its own strengths and weaknesses. Safety, stability, and effectiveness are likely to be different in each of these electrode locations and there are insufficient long-term data in humans to determine the likely range of performance for each location. In the future, we may see combinations of electrodes in different sites, such as a small high-resolution array with many electrodes in an epiretinal position close to the fovea in combination with an array of larger electrodes in the suprachoroidal location to provide peripheral vision across a much wider field of view.

There is presently a trend towards larger numbers of electrodes, but there is no clear evidence that more electrodes correspond to better performance on visual tasks. Performance will also depend on the proportion of electrodes that produce visual percepts, the spatial separation and size of electrodes, and the size of the perceptual space that corresponds to the whole array. For example, legal blindness is defined in the USA as an acuity of 20/200 and an angular field of view greater than 20°. A person who can correctly identify letters on the lowest line of the Snellen chart (i.e., a person with 20/20 vision) is able to discern individual lines that are separated by a visual angle of one arc minute. It would require 1200 electrodes over a 20° angle to achieve a resolution of one arc minute. This corresponds to 1.44 million electrodes within a 7-mm

**Box 3. Outstanding questions**

The following are key questions that remain to be answered in order to advance the field of visual prostheses.

- What is the most suitable location for the electrode array?
- What is the optimal number of electrodes for a visual prosthesis?
- What is the optimum field of view for a visual prosthesis?
- What is the most suitable method of powering a visual prosthesis?
- How will simultaneous stimulation of electrodes affect the visual percepts?
- Is the use of eye tracking technology necessary for visual prosthesis users?
- How should visual acuity be measured for a visual prosthesis?
- How should clinical performance be measured with a visual prosthesis?
- How best do we engage the plastic brain using visual prostheses?
- Can we selectively stimulate retinal neurons in order to take maximum advantage of the natural vision processing?
- Will electrical stimulation of the retina halt or slow down the retinal remodeling that occurs following photoreceptor loss?
- Is it possible to combine electrical stimulation of the retina with therapeutic drugs administration (e.g., neurotrophins) to slow/stop the retinal remodeling?
- Is it possible to provide color vision via a visual prosthesis?

square area of the retina. If an acuity of 20/200 is acceptable, then 15 000 electrodes within a 7-$mm^2$ area would suffice. These electrodes may be too small to produce reliable phosphenes within the safe limits of electrical charge injection, and the phosphenes may overlap too much to provide the required acuity. The optimal number and spacing of electrodes in the visual cortex is likely to be different as the cortical retinotopic map of the macula is expanded relative to the macula itself. As more is learned about the psychophysics of artificial vision, a clearer notion of the optimum number of electrodes will emerge from the data.

The size constraints, energy dissipation capacity, and mobility of the eye are likely to lead to retinal prostheses with a power and wireless data module mounted on the skull, connected via a small number of very flexible wires to a stimulator situated in or on the eyeball. Stimulation of a large number of electrodes at reasonably high pulse rates is also likely to require stimulation of several electrodes in parallel rather than one electrode at a time. Understanding how to control the percepts produced by simultaneous stimulation and ensuring that the total stimulation is at a safe level are nontrivial problems for the future.

Stimulation of electrodes at fixed positions on the retina produces phosphenes that appear to move through space as the eye moves relative to the head. In devices with an external camera, eye tracking technology will be used to account for eye movements, also resulting in a more natural scanning of objects using the eyes, instead of using head movements to direct the camera. The devices that use light-sensitive devices on the retina avoid the need for eye tracking, and it is not yet clear whether eye tracking will be required for cortical stimulation devices. Sophisticated image processing techniques such as feature extraction, edge detection, depth mapping, face and letter recognition, may also be useful for performing particular tasks. Access to different zoom factors in the external vision processor may also be useful for tasks such as reading. This would be analogous to wearing reading glasses, for example.

Another very challenging issue may be the fitting and training of patients using devices with a large number of electrodes. The fitting and optimization methods that are currently used with small numbers of electrodes, such as measurement of thresholds and dynamic ranges for individual electrodes, will most likely need to be replaced with procedures for adjusting more global parameters for groups of electrodes, or for interpolating values between a sparse set of electrodes that are measured individually. The ultimate goal of visual prostheses is to provide improvement in the quality of life of blind patients by improving their performance on real-world tasks. The acuity measures that have been proposed for evaluation of prostheses will need to be augmented by measures of performance that are sufficiently difficult to allow significant improvement, and sufficiently useful to indicate an improved quality of life. The collection of these data in a way that allows comparative performance measures of various devices will require alignment of regulators, researchers, and commercial interests.

Finally, stimulation of fibers of passage is a potential issue for retinal implants, particularly for the epiretinal approach, and can also be an issue with the LGN and cortical approaches [65]. A clinical study using epiretinal stimulation where the electrode array is lying adjacent to the RGC axons, showed that patients reported arc-like or banana-like phosphenes, and these shapes were consistent with the modeled trajectory of the RGC axons travelling towards the optic nerve in each patient [66].

Despite these challenges, visual prostheses are destined to enable major advances in the clinical management of blind patients. Ultimately these devices will provide a level of prosthetic vision that will allow users to read large font print and recognize faces.

**Acknowledgments**

We thank our colleagues in Bionic Vision Australia (BVA) for their contributions to the BVA research effort. Fundus images were generously provided by Drs Lauren Ayton, Peter Dimitrov, and Penny Allen from CERA (suprachoroidal electrode array), Brian Mech from Second Sight Medical Products Inc. (the Argus II device), and Dr Katarina Stingl and Prof Eberhart Zrenner from the Center for Ophthalmology, University of Tuebingen, Germany (Alpha IMS subretinal implant). Dr Lauren Ayton, Dr Paige Shaklee, and two anonymous reviewers gave helpful comments on an earlier version of this manuscript. The Bionics Institute acknowledges the support it receives from the Victorian Government through its Operational Infrastructure Support Program. This research was supported by the Australian Research Council (ARC) through its Special Research Initiative (SRI) in Bionic Vision Science and Technology grant to Bionic Vision Australia. The Bionics Institute would also like to acknowledge support from the Potter Foundation and the Bertalli Family Trust.

**References**

1 Cavuoto, J. *et al.* (2011) *The Market for Neurotechnology: 2012–2016*. pp. 1–345, Neurotech Reports
2 World Health Organization (2012) *Visual Impairment and Blindness*. World Health Organization
3 Jones, B.W. *et al.* (2012) Retinal remodeling. *Jpn. J. Ophthalmol.* 56, 289–306
4 Marg, E. (1991) Magnetostimulation of vision: direct noninvasive stimulation of the retina and the visual brain. *Optom. Vis. Sci.* 68, 427–440
5 Penfield, W. and Perot, P. (1963) The brain's record of auditory and visual experience. *Brain* 86, 595–696
6 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. Engl.* 47, 106–108
7 Brindley, G.S. and Lewin, W.S. (1968) The sensations produced by electrical stimulation of the visual cortex. *J. Physiol.* 196, 479–493
8 Tassicker, G.E. (1956) Preliminary report on a retinal stimulator. *Br. J. Physiol. Opt.* 13, 102–105
9 Clark, G.M. (2003) *Cochlear Implants: Fundamentals and Applications*. Springer-Verlag
10 Cohen, E.D. (2007) Safety and effectiveness considerations for clinical studies of visual prosthetic devices. *J. Neural Eng.* 4, S124–S129
11 Batterbury, M. and Bowling, B. (2005) *Ophthalmology: An Illustrated Color Text*. Elservier Churchill Livingstone
12 Finger, R.P. *et al.* (2011) Incidence of blindness and severe visual impairment in Germany: projections for 2030. *Invest. Ophthalmol. Vis. Sci.* 52, 4381–4389
13 Chua, J. *et al.* (2009) Functional remodeling of glutamate receptors by inner retinal neurons occurs from an early stage of retinal degeneration. *J. Comp. Neurol.* 514, 473–491
14 Weiland, J.D. *et al.* (2011) Retinal prostheses: current clinical results and future needs. *Ophthalmology* 118, 2227–2237
15 Pascolini, D. and Mariotti, S.P. (2012) Global estimates of visual impairment: 2010. *Br. J. Ophthalmol.* 96, 614–618

16 Zrenner, E. *et al.* (2011) Subretinal electronic chips allow blind patients to read letters and combine them to words. *Proc. R. Soc. B* 278, 1489–1497
17 Mathieson, K. *et al.* (2012) Photovoltaic retinal prosthesis with high pixel density. *Nat. Photonics* 6, 391–397
18 Humayun, M.S. *et al.* (2012) Interim results from the international trial of Second Sight's visual prosthesis. *Ophthalmology* 119, 779–788
19 Fujikado, T. *et al.* (2011) Testing of semichronically implanted retinal prosthesis by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa. *Invest. Ophthalmol. Vis. Sci.* 52, 4726–4733
20 Normann, R.A. *et al.* (2009) Toward the development of a cortically based visual neuroprosthesis. *J. Neural Eng.* 6, 035001
21 Fernandes, R.A. *et al.* (2012) Artificial vision through neuronal stimulation. *Neurosci. Lett.* 519, 122–128
22 Stingl, K. *et al.* (2013) Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS. *Proc. Biol. Sci.* 280, 20130077
23 Yarbus, A.L. (1967) *Eye Movements and Vision*. Plenum Press
24 Opie, N.L. *et al.* (2012) Retinal prosthesis safety: alterations in microglia morphology due to thermal damage and retinal implant contact. *Invest. Ophthalmol. Vis. Sci.* 53, 7802–7812
25 Hadjinicolaou, A.E. *et al.* (2012) Electrical stimulation of retinal ganglion cells with diamond and the development of an all diamond retinal prosthesis. *Biomaterials* 33, 5812–5820
26 Klauke, S. *et al.* (2011) Stimulation with a wireless intraocular epiretinal implant elicits visual percepts in blind human. *Invest. Ophthalmol. Vis. Sci.* 52, 449–455
27 Keseru, M. *et al.* (2012) Acute electrical stimulation of the human retina with an epiretinal electrode array. *Acta Ophthalmol.* 90, e1–e8
28 Rizzo, J.F., III (2011) Update on retinal prosthetic research: the Boston Retinal Implant Project. *J. Neuroophthalmol.* 31, 160–168
29 Stingl, K. *et al.* (2013) Safety and efficacy of subretinal visual implants in humans: methodological aspects. *Clin. Exp. Optom.* 96, 4–13
30 Rizzo, J.F., III *et al.* (2011) Development of the Boston retinal prosthesis. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2011, 3135–3138
31 Villalobos, J. *et al.* (2013) A wide-field suprachoroidal retinal prosthesis is stable and well tolerated following chronic implantation. *Invest. Ophthalmol. Vis. Sci.* 54, 3751–3762
32 Shivdasani, M.N. *et al.* (2010) Evaluation of stimulus parameters and electrode geometry for an effective suprachoroidal retinal prosthesis. *J. Neural Eng.* 7, 036008
33 Morimoto, T. *et al.* (2011) Chronic implantation of newly developed suprachoroidal-transretinal stimulation prosthesis in dogs. *Invest. Ophthalmol. Vis. Sci.* 52, 6785–6792
34 Villalobos, J. *et al.* (2012) Development of a surgical approach for a wide-view suprachoroidal retinal prosthesis: evaluation of implantation trauma. *Graefes Arch. Clin. Exp. Ophthalmol.* 250, 399–407
35 Zhou, J.A. *et al.* (2008) A suprachoroidal electrical retinal stimulator design for long-term animal experiments and in vivo assessment of its feasibility and biocompatibility in rabbits. *J. Biomed. Biotechnol.* 2008, 547428
36 Suaning, G.J. *et al.* (2010) Discrete cortical responses from multi-site supra-choroidal electrical stimulation in the feline retina. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2010, 5879–5882
37 Cicione, R. *et al.* (2012) Visual cortex responses to suprachoroidal electrical stimulation of the retina: effects of electrode return configuration. *J. Neural Eng.* 9, 036009
38 Ayton, L.N. *et al.* (2012) Choroidal thickness profiles in retinitis pigmentosa. *Clin. Exp. Ophthalmol.* 41, 396–403
39 Blamey, P.H. *et al.* (2013) Psychophysics of a suprachoroidal retinal prosthesis. In *ARVO 2013 Annual Meeting*. pp. 1044
40 Dobelle, W.H. *et al.* (1974) Artifical vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis. *Science* 183, 440–444
41 Veraart, C. *et al.* (2004) Vision rehabilitation with the optic nerve visual prosthesis. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 6, 4163–4164
42 Brelen, M.E. *et al.* (2010) Measurement of evoked potentials after electrical stimulation of the human optic nerve. *Invest. Ophthalmol. Vis. Sci.* 51, 5351–5355
43 Sun, J. *et al.* (2011) Spatiotemporal properties of multipeaked electrically evoked potentials elicited by penetrative optic nerve stimulation in rabbits. *Invest. Ophthalmol. Vis. Sci.* 52, 146–154
44 Panetsos, F. *et al.* (2011) Consistent phosphenes generated by electrical microstimulation of the visual thalamus. An experimental approach for thalamic visual neuroprostheses. *Front. Neurosci.* 5, 1–12
45 Lozano, A.M. and Lipsman, N. (2013) Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron* 77, 406–424
46 Schmidt, E.M. *et al.* (1996) Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. *Brain* 119, 507–522
47 Schiller, P.H. *et al.* (2011) New methods devised specify the size and color of the spots monkeys see when striate cortex (area V1) is electrically stimulated. *Proc. Natl. Acad. Sci. U.S.A.* 108, 17809–17814
48 Troyk, P. *et al.* (2003) A model for intracortical visual prosthesis research. *Artif. Organs* 27, 1005–1015
49 Brunton, E. *et al.* (2012) A comparison of microelectrodes for a visual cortical prosthesis using finite element analysis. *Front. Neuroeng.* 5, 23
50 Fallon, J.B. *et al.* (2008) Cochlear implants and brain plasticity. *Hear. Res.* 238, 110–117
51 Perez Fornos, A. *et al.* (2012) Temporal properties of visual perception on electrical stimulation of the retina. *Invest. Ophthalmol. Vis. Sci.* 53, 2720–2731
52 Nanduri, D. *et al.* (2012) Frequency and amplitude modulation have different effects on the percepts elicited by retinal stimulation. *Invest. Ophthalmol. Vis. Sci.* 53, 205–214
53 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. *Invest. Ophthalmol. Vis. Sci.* 52, 5995–6003
54 Horsager, A. *et al.* (2010) Spatiotemporal interactions in retinal prosthesis subjects. *Invest. Ophthalmol. Vis. Sci.* 51, 1223–1233
55 Horsager, A. *et al.* (2011) Temporal interactions during paired-electrode stimulation in two retinal prosthesis subjects. *Invest. Ophthalmol. Vis. Sci.* 52, 549–557
56 Dorn, J.D. *et al.* (2013) The detection of motion by blind subjects with the Epiretinal 60-Electrode (Argus II) retinal prosthesis. *JAMA Ophthalmol.* 131, 183–189
57 Shael, J.A. *et al.* (2013) Acuboost: enhancing the maximum acuity of the Argus II Retinal Prosthesis System. In *ARVO 2013 Annual Meeting*. pp. 1389
58 Dobelle, W.H. *et al.* (1976) "Braille" reading by a blind volunteer by visual cortex stimulation. *Nature* 259, 111–112
59 Xie, J. *et al.* (2012) Preservation of retinotopic map in retinal degeneration. *Exp. Eye Res.* 98, 88–96
60 Baseler, H.A. *et al.* (2011) Large-scale remapping of visual cortex is absent in adult humans with macular degeneration. *Nat. Neurosci.* 14, 649–655
61 Blamey, P. *et al.* (2013) Factors affecting auditory performance of postlinguistically deaf adults using cochlear implants: an update with 2251 patients. *Audiol. Neurootol.* 18, 36–47
62 Lazard, D.S. *et al.* (2012) Pre-, per- and postoperative factors affecting performance of postlinguistically deaf adults using cochlear implants: a new conceptual model over time. *PLoS ONE* 7, e48739
63 Fallon, J.B. *et al.* (2009) Cochlear implant use following neonatal deafness influences the cochleotopic organization of the primary auditory cortex in cats. *J. Comp. Neurol.* 512, 101–114
64 Dagnelie, G. (2012) Retinal implants: emergence of a multidisciplinary field. *Curr. Opin. Neurol.* 25, 67–75
65 Histed, M.H. *et al.* (2009) Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. *Neuron* 63, 508–522
66 Nanduri, D. *et al.* (2011) Percept properties of single electrode stimulation in retinal prosthesis subjects. *ARVO Meet. Abstr.* 52, 442
67 Cogan, S.F. (2008) Neural stimulation and recording electrodes. *Annu. Rev. Biomed. Eng.* 10, 275–309
68 Shepherd, R.K. *et al.* (in press) Medical bionics. In *Comprehensive Biomedical Physics* (Zhou, S-A. and Zhou, L., eds), Elsevier
69 Huang, C.Q. *et al.* (2001) Stimulus induced pH changes in cochlear implants: an in vitro and in vivo study. *Ann. Biomed. Eng.* 29, 791–802
70 Hubel, D.H. (1988) *Eye, Brain and Vision*. Scientific Amercian Library
71 Amanat, N. *et al.* (2010) Welding methods for joining thermoplastic polymers for the hermetic enclosure of medical devices. *Med. Eng. Phys.* 32, 690–699
72 Guenther, T. *et al.* (2012) Bionic vision: system architectures: a review. *Expert Rev. Med. Devices* 9, 33–48