CLINICAL AND EXPERIMENTAL
OPTOMETRY

INVITED REVIEW

Prosthetic vision: devices, patient outcomes and retinal research

Clin Exp Optom 2015; 98: 395–410 DOI:10.1111/cxo.12342

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Submitted: 9 March 2015
Revised: 6 July 2015
Accepted for publication 4 August 2015

Retinal disease and its associated retinal degeneration can lead to the loss of photoreceptors and therefore, profound blindness. While retinal degeneration destroys the photoreceptors, the neural circuits that convey information from the eye to the brain are sufficiently preserved to make it possible to restore sight using prosthetic devices. Typically, these devices consist of a digital camera and an implantable neurostimulator. The image sensor in a digital camera has the same spatiotopic arrangement as the photoreceptors of the retina. Therefore, it is possible to extract meaningful spatial information from an image and deliver it via an array of stimulating electrodes directly to the surviving retinal circuits. Here, we review the structure and function of normal and degenerate retina. The different approaches to prosthetic implant design are described in the context of human and preclinical trials. In the last section, we review studies of electrical properties of the retina and its response to electrical stimulation. These types of investigation are currently assessing a number of key challenges identified in human trials, including stimulation efficacy, spatial localisation, desensitisation to repetitive stimulation and selective activation of retinal cell populations.

Key words: human implant, retinal degeneration, retinal prosthesis, vision loss, vision prosthesis

Visual perception involves the translation of light from the outside world into meaningful information about the visual scene. The loss of this sense is associated with restricted mobility and independence, which can have a significant impact on health and emotional wellbeing. Visual impairment represents a significant health problem with more than 285 million people experiencing visual impairment, of which 39 million are blind.[1] Readily treatable ocular conditions involve refractive error, where the optics of the eye do not focus light onto the retina. Placing spectacles or contact lenses in front of the eyes can usually solve these problems. Ocular conditions such as macular degeneration and retinitis pigmentosa (RP) are more serious because they destroy the photoreceptors of the retina that detect light, thus removing the essential first step in vision.

The function of damaged neural systems can be restored with neural prostheses - medical devices that electrically, chemically or otherwise stimulate excitable neural tissue.[2] A well-known example is the cochlear implant, which bypasses damaged hair cells of the inner ear and stimulates the auditory nerve inside the cochlea to provide a sense of hearing to the deaf. Similarly, the elements of the visual system that are left intact after degenerative retinal disease can be stimulated to restore visual perception in patients with loss of vision. This is referred to as prosthetic vision.

Prosthetic vision received attention from as early as 1929, when Foerster investigated the effects of electrical stimulation on the human visual cortex,[3] which led to a subject perceiving a spot of light. Brindley and Lewin[3] referred to this sensation as a 'phosphene' and confirmed the phenomenon by implanting an electrode array in another blind patient (for a qualitative description of a blind patient drawing a phosphene evoked by electrical stimulation of the retina) (Figure 1). The development of visual prostheses is being pursued by several groups worldwide. The question of where to stimulate the visual system has led to different approaches. In addition to visual cortical stimulation, research groups have stimulated the retina, optic nerve and lateral geniculate nucleus.[4–6] Visual prostheses that target higher stages of the visual system, such as the lateral geniculate nucleus or the visual cortex, do not need surviving retinal cells to function. Nonetheless, the brain surgery required for such prostheses is more invasive than the ocular surgery required for devices that target the retina. The focus of this review is microelectronic retinal prostheses that aim to restore visual perception through electrical stimulation of the surviving retina.

More than 95 per cent of photoreceptors are lost in cases of severe retinitis pigmentosa but 30 per cent of retinal ganglion cells (RGCs), forming the output of the retina, are preserved.[7] Similarly promising findings have been reported for disciform age-related macular degeneration, that is, a 70 per cent reduction in photoreceptors but no significant changes to retinal ganglion cell counts.[8] These findings suggest that for patients with these two ocular diseases and their variants, the restoration of sight through replacement of photoreceptor function is feasible.

OVERVIEW OF THE RETINA

The retina is a layer of tissue lining the inner wall at the back of the eye (Figure 2A) and contains three broad classes of neurons[9] organised into three nuclear layers separated

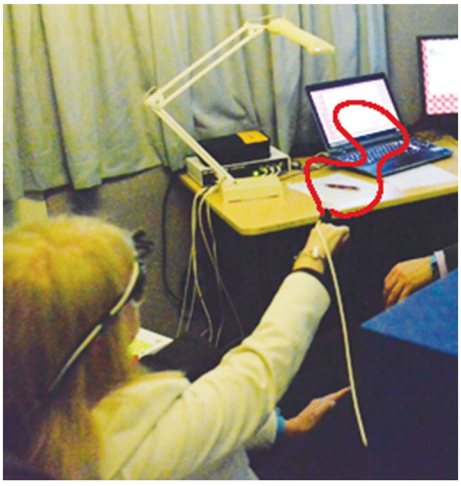

Figure 1. Patient implanted with a device developed by Bionic Vision Australia pointing in the direction and drawing the shape of a perceived phosphene. The implanted device is shown in Figure 4C. Reproduced with permission from the patient and Bionic Vision Australia.

by two synaptic (plexiform) layers (Figure 2B). Photoreceptors are located in the outer nuclear layer (ONL) and serve to detect light. Horizontal, bipolar and amacrine cells, situated in the inner nuclear layer (INL), comprise the interneurons of the retina and are responsible for maintaining the visual system's sensitivity to visual contrast, among other things. The ganglion cell layer contains the retinal ganglion cells that form the output of the retina, transmitting information from the retina to the brain via the optic nerve. The primate retina contains multiple subtypes of each class of these neurons: at least two types of horizontal cell, 12 bipolar cell types, 29 amacrine cell types and 10 to 15 retinal ganglion cell types.[10,11] The retinae of human and non-human primates share much in common, including the morphology and organisation of retinal circuitry and the same parallel pathways.[10–12]

Photoreceptors

In normal vision, incident light enters the eye via the cornea, traversing the aqueous humour, lens, vitreous humour and the full thickness of the neural retina before being absorbed by the photoreceptors (rods and cones) in the outermost retinal later (Figure 2A and 2B).[9] Rods are highly sensitive to light intensity and mediate vision in dim light but saturate at regular daylight intensities. Cones are responsible for colour vision and operate over a wide range of light intensities, functioning poorly in dim light. At higher light levels, cones respond preferentially to light of either long (red), medium (green) or short (blue) wavelength, with the difference between signals from each of these three cone types permitting the perception of colours in the visual spectrum. The density of cones is highest in the fovea, the central region of the macula (a small pigmented area around the centre of the retina). The fovea has a densely-packed cone arrangement and few rods. Only cones populate the very centre of the fovea (the foveola). There, the centre-to-centre spacing of cones is smallest. Together with the focal length of the eye, the cone spacing determines the anatomical limit of acuity.[13,14] Outside of the fovea cone photoreceptor density falls sharply, from ~200,000 cones/mm^2 in the fovea to less than 16,000 cones/mm^2 in the periphery.[13]

Midget and parasol pathways

Within the outer plexiform layer (OPL), photoreceptors synapse with bipolar cells and receive inhibitory input from horizontal cells. Bipolar cells are classified as either rod or cone bipolar cells corresponding to the type of photoreceptor that supplies their input. Most cone bipolar cells of the primate retina receive input from between two and ten cones.[11] Bipolar cells synapse with retinal ganglion cells and are laterally inhibited by amacrine cells within the inner plexiform layer (IPL). Signals generated by a given photoreceptor can traverse the neural network and reach the retinal ganglion cells in many ways.

Retinal ganglion cells outside the fovea synapse with large numbers of cells in the INL, which receive input from many photoreceptors. Such cells are said to have large 'receptive fields'.[15] Towards the fovea, cell density increases and receptive field size decreases. One particular type of foveal retinal ganglion cells, the midget ganglion cells, each receive input from a single (midget) bipolar cell, which receives its input from a single cone. Since the receptive field size of midget cells is particularly dependent on eccentricity, their density too varies significantly, from 45 per cent in the periphery to 95 per cent in the central retina.[12] The midget pathway enables the transmission of fine spatial detail and is thought to underlie high acuity vision.[12,16] Eight per cent of retinal ganglion cells are parasol cells in primate[10] and convey achromatic information concerning movement and luminance.[16] The midget and parasol retinal ganglion cells of the primate together account for most visual information leaving the retina. Certain neural properties allow each class to handle different aspects of visual processing.[17–19] Parasol retinal ganglion cells have extensive dendritic fields integrating input over large areas of the retina and therefore, have large receptive fields. In contrast, midget retinal ganglion cells have relatively small dendritic fields leading to small receptive fields well suited for discrimination of fine spatial detail.[12,20,21]

ON and OFF pathways

Generally, retinal ganglion cells can be grouped into two categories according to their functional and morphological properties.[22] Kuffler[23] discovered that receptive fields of ganglion cells have a central region that responds to either luminance increments (ON cells) or decrements (OFF cells) and an antagonistic surround that suppresses their response, when stimulated by the centre's preferred luminance polarity (Figure 2C). These properties are associated with different stratification patterns in the IPL: OFF and ON retinal ganglion cells synapse with OFF and ON bipolar cells in sublaminas a and b of the IPL, respectively.[21,24] The flow of neural activity through the ON and OFF pathways underlies feature detection by extracting the boundaries between objects formed by the contrast between neighbouring bright and dark regions in visual scenes.[25] The centre-surround receptive field structure of bipolar and ganglion cells arises from lateral interactions with horizontal cells. These cells

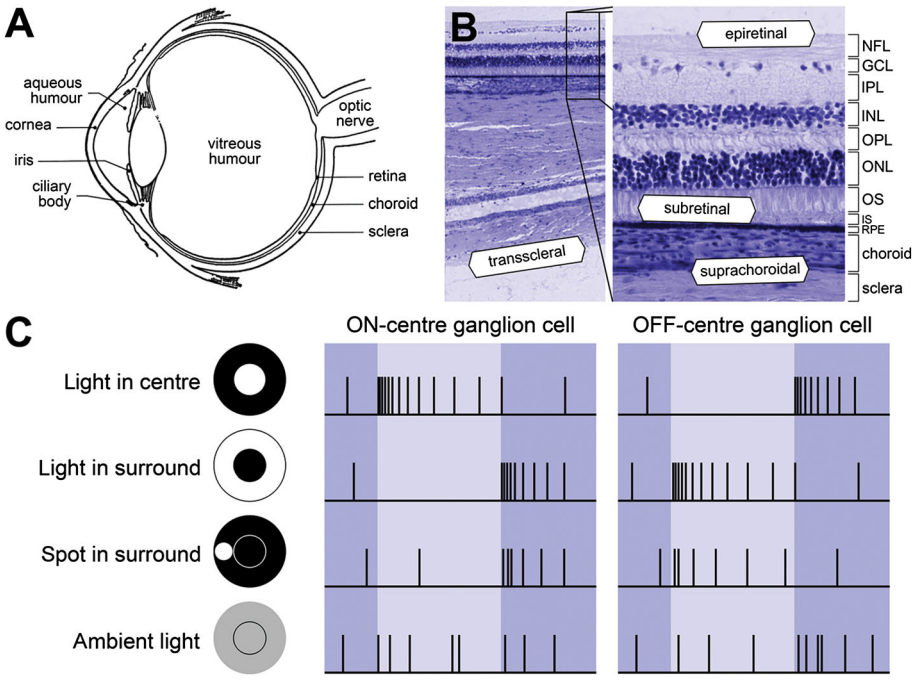

Figure 2. (A) Schematic illustration showing the gross anatomy of the human eye in cross-section. (B) Laminar organisation of the retina showing the possible sites of implantation for different retinal prostheses. Hereafter, the different approaches to retinal prostheses are referred to by the site of implantation of their stimulating electrode array, either epiretinal, subretinal, suprachoroidal or transscleral. Histological image from Histology and Virtual Microscopy Learning Resources, University of Michigan Medical School. Copyright © 2010 Regents of the University of Michigan under the Creative Commons Attribution-Non-commercial-Share Alike 3.0 License (http://creativecommons.org/licenses/by-nc-sa/3.0/). (C) Functional classification of retinal ganglion cells according to the polarity of the local luminance change that evokes an increase in firing rate. The centre-surround structure of retinal ganglion cell receptive fields is shown on the left. ON-centre retinal ganglion cells increase their firing rate in response to a local increase in luminance within the centre of their receptive field but are inhibited by local increases in luminance in the receptive field surround. OFF-centre retinal ganglion cells respond in a complementary fashion, increasing their firing rate in response to a local decrease in luminance within the centre of their receptive field and silencing their output to local luminance decrements in the receptive field surround. NFL: nerve fibre layer, GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, OPL: outer plexiform layer, ONL: outer nuclear layer, IS: photoreceptor inner segment, OS: photoreceptor outer segment, RPE: retinal pigment epithelium.

integrate input from multiple photoreceptors and respond to excitation of a central photoreceptor by inhibiting neural activity in all photoreceptors that synapse with the horizontal cell. The functional coupling of an excitatory photoreceptor response with this concentric, inhibitory horizontal cell network grants centre-surround antagonism to the bipolar cells.[26,27] The function of horizontal cells is to measure ambient light intensity and subtract it from localised neural activity, thus contributing to contrast coding.

Intrinsic properties of RGCs

Responses in retinal ganglion cells are partly modulated by intrinsic differences in the electrical properties of ON and OFF cells.[28,29] OFF cells generate spontaneous activity without synaptic input, have a resting potential closer to their activation threshold and show differences in voltage dependent Ca^{2+} and Na^{+} conductances, compared to ON cells. Henderson and Miller[30] demonstrated that the low voltage activated Ca^{2+} current was present in 70 per cent of retinal ganglion cells. This current generates rebound excitation, a feature attributed to post-inhibitory synaptic input that generates a high frequency burst of spikes.[31] Margolis and Detwiler[29] demonstrated that only OFF cells can generate rebound excitation, suggesting that the low voltage activated Ca^{2+} current might only be present in OFF cells. Additionally, differences in passive and active intrinsic properties have been found between different retinal ganglion cells in cat[32] and rat[33] and are well preserved after the loss of photoreceptors.[34,35] Intrinsic properties may contribute to the differential RGC responses to extracellular electrical stimulation[36–39] and might be exploited to optimise prosthetic stimulation strategies for specific cell types.

The degenerate retina

The retina undergoes extensive reorganisation during the progression of degenerative disorders, such as retinitis pigmentosa (RP).[40] Therefore, the structure and function of the RP-afflicted retina is different from the healthy retina (Figure 3). Retinal degeneration commonly begins when rods stop regenerating their outer segments. As the rods deteriorate, their neurites sprout and enter the inner layer. The loss of rod outer segments collapses the subretinal space and cones begin a similar deterioration of their outer segments. A dense layer of Müller cell processes forms over a substantial area of the retina, forming a 'glial seal'. At this point, the rate of rod death has significantly increased, many cells have died and the reorganisation of neural circuitry has begun. Rod and cone bipolar cells retract their dendrites, while cone-synapsing horizontal cell bodies expand and extend neurites into the IPL. After the complete loss of photoreceptors, the glial seal becomes compacted and Müller cell hypertrophy results in the formation of columnar structures that segment the retina. Neurons of the IPL produce dendrites, the foci of which form in the residual OPL. Neuronal cell death is now indiscriminate. A number of physiological processes take place alongside neuronal death during the advanced stages of neural remodelling, including cell migration, excessive neurite growth and formation of microneuromas, with horizontal and amacrine neurites forming abnormal connections within the neural network.[41]

Since they are no longer driven by the photoreceptors, surviving cells extend their neurites to derive input from residual visual pathways.[40] The formation of microneuromas demonstrates that retinal neurons are not

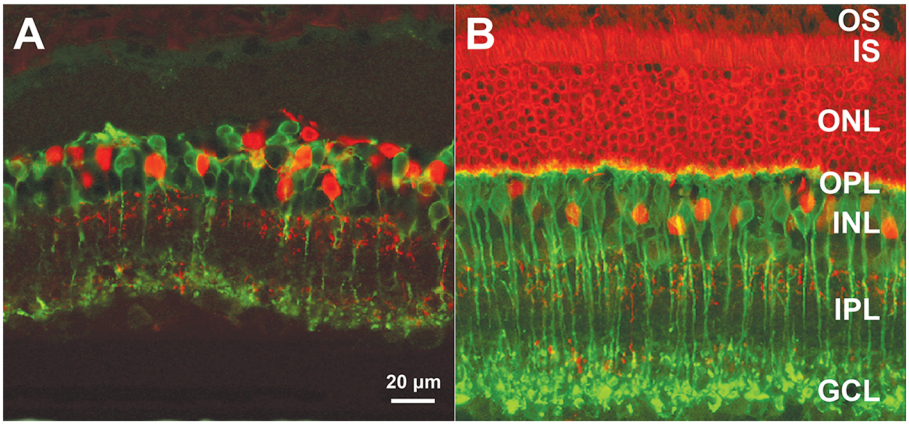

Figure 3. (A) The degenerate P23H rat retina is markedly different to its healthy counterpart (B). Abbreviations are as defined in Figure 2. Recoverin was used to label photoreceptors (red) and alpha-PCK stained rod bipolar cells (green). Images made by Nicolás Cuenca, www.retinalmicroscopy.com, University of Alicante, reproduced here with permission.

programmed to restore their original circuitry – the degenerate retina exhibits many different abnormal synaptic structures, which disrupt visual processing and introduce sporadic spiking behaviour. Some evidence for this stems from the intermittent perception of flashes of light known as photopsias commonly reported by patients with retinitis pigmentosa. Photopsias are thought to originate in the retina because not only do they eventually disappear (suggestive of retinal ganglion cell death) but they have also been temporarily induced through electrical stimulation of the retina in long-term RP patients.[40,42]The significant changes in retinal structure and function suggests that generating visual percepts through electrical stimulation may be more difficult in the degenerate retina than in the healthy retina.

Animals with degenerative retinal diseases that are pathologically equivalent to those found in humans provide a means for investigating human retinopathy and potential treatment.[43–47] One of the earliest animal models studied is the retinal degenerate (rd) mouse. Originally discovered in 1923 by Keeler (Hafezi et al.[48]), the rd mouse has a genetic mutation resulting in the rapid degeneration of the outer retina after the first postnatal week. The photoreceptor population is eliminated by one to three months. This mutation has been observed in human sufferers of the autosomal recessive form of retinitis pigmentosa,[49] which accounts for around 20 per cent of retinitis pigmentosa patients.[50] Autosomal dominant retinitis pigmentosa is another major type with 30 per cent prevalence among sufferers. An alternative animal model, the transgenically engineered P23H rat, is a model of the most prevalent genotype for this type of retinitis pigmentosa.[51,52] The identification of genetic sequences, which give rise to retinitis pigmentosa has clearly demonstrated that it is a group of diseases characterised by varying point mutations within the human genome. As the nature of disease varies across different animal models, their selection for study warrants careful consideration. For example, the slow progression of degeneration in the P23H rat leads to a comparatively late onset of retinal remodelling.[40] This may limit the animal's use in studying forms of human retinitis pigmentosa, where patients have lost their photoreceptors decades earlier. Alternatively, the Royal College of Surgeons (RCS) rat may prove to be a more useful model as degeneration in this model progresses quickly and retinal rewiring takes place sooner.[40]

RETINAL PROSTHESES

Retinal prostheses operate by injecting charge into excitable tissue to stimulate retinal neurons, such as retinal ganglion cells. An electrode array placed close to the retina forms an electrochemical system, in which the physiological medium is the electrolyte. At least two electrodes are needed to complete the circuit and permit stimulation: one to inject current into the electrolyte, the other to provide the current's return path. Electrical stimulation can potentially cause damage, which may be electrical, chemical or mechanical. A current waveform with non-zero direct current (DC) leads to a net charge transfer into the electrolyte and results in the increased production of chemical species at the electrode-tissue interface that may harm the retina or damage the electrode.[53] The use of short duration biphasic waveforms of the order of tens of microseconds in duration mitigate the production of such species with the second phase acting to reverse the offending electrochemical reactions.[53] Chemical and physiological damage can also result, if the electrode material is not biocompatible, in which case a toxic, necrotic or otherwise adverse response occurs. Other sources of tissue damage result from overstimulation: for example, oxygen and glucose depletion, changes in concentrations of extracellular potassium and release of neurotransmitters.[53]

A fundamental consideration for a retinal prosthesis is the selection of suitable electrode materials. Charge injection can take place through either capacitive reactions (that is, charging and discharging of the electrode-tissue interface) or faradaic reactions, where chemical species close to the electrode undergo oxidation or reduction through electron transfer.[53,54] Any faradaic reactions should be reversible to avoid corrosion of the electrode. The underlying mechanism is determined by the choice of electrode material, which should exhibit biocompatibility, be able to deliver sufficient charge to evoke responses within safe limits and be electrochemically stable. Platinum (Pt) and platinum-iridium (PtIr) alloys are widely employed for stimulation and support both capacitive and faradaic charge injection. However, the long-term usage of platinum has been associated with electrode dissolution.[55] Electrodes coated with iridium oxide have greater charge injection capabilities than Pt and PtIr alloys,[54] although some forms of the material have been shown to degrade and/or delaminate with repetitive stimulation.[56] Diamond is an alternative electrode material that does not exhibit the aforementioned problems but its hardness and lack of ductility have limited its use. Recent techniques have been developed that allow the fabrication of retinal prostheses from electrically insulating polycrystalline diamond and electrically conducting nitrogen-doped ultra-nanocrystalline diamond (N-UNCD).[57] Electrical stimulation via diamond electrodes has been shown to excite retinal ganglion cells in rat retina,[58] thus demonstrating their viability as a material for retinal prostheses.

Electrical stimulation has been associated with retinal damage in a number of *in vivo* animal studies. Butterwick et al.[59] investigated the dependence of damage thresholds on electrode size, pulse duration and number of pulses for a charge-balanced biphasic waveform. They found damage thresholds decreased with the number of pulses and observed the threshold current density to be independent of electrode surface area for diameters greater than 300 µm (scaling by $1/d^2$ for diameters less than 200 µm). The relationship between threshold current density, J, and pulse width, t, was deduced roughly as $J/t^{0.5}$. This scaling suggests that charge per phase and charge density are not the only factors that determine the tissue damage threshold. Another study investigated the pathology of electrically induced retinal damage in the rat[60]: damage was greatest when retinal contact and electrical stimulation were coupled.

Having discussed the general properties and problems associated with retinal prostheses, the following sections outline specific details of electrode placement.

Epiretinal prostheses

Epiretinal prostheses stimulate surviving retinal ganglion cells by injecting charge through an array of electrodes implanted at the boundary between the retina and the vitreous cavity (Figures 2B and 4A). One such device, the Argus I[4] consists of a miniature head-mounted camera that captures an image of the visual scene and converts it into a command sequence, which is then transmitted wirelessly to an implanted unit used to drive the electrode array. Notably, eye movements are not coupled to image motion, as they are in the healthy eye. With the exception of the electrode array, all of the device electronics are kept away from the retinal surface. The architecture of these devices allows visual processing adjustments and hardware upgrades by interfacing with the external components of the device, with no need for additional surgery. Some epiretinal prototypes (for example, Liu et al.[61]) position the electronics within the vitreous cavity, which acts as a heatsink and allows the device to dissipate a significant amount of power.[62,63]

In epiretinal prostheses, electrical stimulation likely activates not only the retinal ganglion cell somas but also their axons in the nerve fibre layer in direct contact with the electrode array. Schiefer and Grill[64] identified this problem using computational models of retinal ganglion cells and it was experimentally confirmed by Fried et al.,[65] who found that the region resulting in the lowest stimulation threshold was the axonal high density sodium-channel band. This is hypothesised to be the cause of distorted and/or displaced phosphenes observed in clinical trials of epiretinal prostheses.[66,67]

Subretinal prostheses

Zrenner et al.[68] developed a subretinal prosthesis (the Alpha IMS) that aims to replace photoreceptor function using an array of photodiodes implanted between the outer retina and the retinal pigment epithelium (Figure 2B). The bipolar cells, rather than the ganglion cells, are the targets of this prosthesis. In this approach, the retinal network in the INL is potentially better used to process electrical signals and elicit visual percepts. The device works by detecting incident light using a photodiode array and generating electrical pulses on a corresponding array of electrodes. Recent advances in the technology have lead to a wireless device that is powered by radio frequency[69] or via an inductive coil.[70] An advantage of this approach over epiretinal placement relates to device implantation. Long-term electrode attachment to the epiretinal surface gives rise to an assortment of complications including retinal detachment,[71,72] vitreous haemorrhaging[73] and cataract development.[74] Electrodes placed subretinally are supported by the strong natural adherence between the retinal pigment epithelium and sensory retina leading to fewer surgical problems. Lorach et al.[75] recently reported the successful use of passive photodiodes implanted in the subretinal space of healthy and RCS-degenerate rats, with no need for an extraocular power supply. The illumination of a few photovoltaic pixels in this prosthesis was able to elicit a detectable cortical response *in vivo*.

In contrast to epiretinal devices, the Alpha IMS device electronics are in direct contact with the retina, increasing the likelihood of thermal injury and placing further constraints on the output power of the device. The limited space available for device electronics represents an additional challenge. The subretinal study of Lorach et al.,[75]

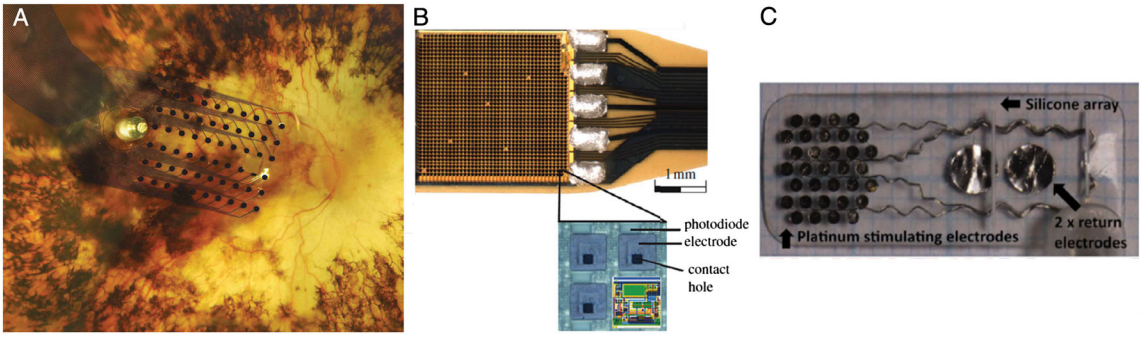

Figure 4. (A) The Argus II epiretinal implant with 60 stimulating electrodes of 200 µm diameter arranged in a rectangular grid. Image reproduced with permission. Copyright © 2015 Second Sight Medical Products, Inc. (B) A subretinal implant consisting of a microphotodiode array with 1,500 electrodes. Each electrode is driven by a photodiode with an amplifier circuit (inset). Figure adapted from Zrenner et al.[91] under the Creative Commons Attribution Licence (http://creativecommons.org/licenses/by/4.0/). (C) A suprachoroidal electrode array developed by Bionic Vision Australia. The 20 stimulating electrodes are 400 µm or 600 µm in diameter, arranged in a hexagonal grid bordered by a ring of electrodes that are ganged together. Figure adapted from Ayton et al.[95] under the Creative Commons Attribution Licence (http://creativecommons.org/licenses/by/4.0/).

discussed above, also found that the presence of an implant in the subretinal space resulted in the further loss of photoreceptors. This was attributed to the separation of the retina from the retinal pigment epithelium.[75] This may have implications for the efficacy of electrical stimulation, as the presence of photoreceptors is thought to lower thresholds for synaptic activation of retinal ganglion cells.[76] The state of degeneration in human patients will further complicate efforts to leverage the processing capabilities of the surviving INL, as the function of interneural circuitry may be compromised by neural remodelling.[40]

Suprachoroidal prostheses

Suprachoroidal electrode placement is between the choroid and sclera (Figure 2B).[77–80] As the electrodes are not in direct contact with the retina, suprachoroidal placement reduces the risks of incurring retinal damage by surgical implantation and device operation. Yamauchi et al.[81] compared suprachoroidal and subretinal implantation in the rabbit and observed histological evidence of ONL retinal damage following subretinal array placement. No such damage was found after suprachoroidal implantation. Heat on the choroidal surface also drives increases in choroidal blood flow in monkeys and humans,[82] which should act to dissipate heat and minimise the incidence of thermal trauma. Additional benefits include a relatively simple surgical procedure, reduced risk of choroidal haemorrhaging and good long-term implant stability[83]; however, the distance between the electrode array and the retina is of concern, as is the disadvantage of having to stimulate through the high-resistance retinal pigment epithelium.[84] Also, suprachoroidal electrical stimulation will likely activate a broader area of the retina, limiting spatial resolution.

Suprachoroidal-transretinal prostheses

A suprachoroidal-transretinal (or transscleral) implant refers to a retinal prosthesis that is placed in a scleral pocket behind the retina (Figure 2B), with return electrodes in the vitreous body to generate focal stimulation of retinal ganglion cells. In contrast to the suprachoroidal device, the transsceleral implant stimulates through an additional scleral layer. The surgical procedure is simple and less invasive than epiretinal and subretinal implants. The feasibility of the technique has been shown in rat,[85] rabbit,[86] cat[87] and dog[88] and has shown that activation can be achieved within safe limits. The main disadvantage of this device is the distance between the electrodes and target neurons, which limits the spatial resolution and requires higher current levels.

HUMAN TRIALS

Since their inception, clinical trials of the aforementioned retinal implants have revealed a range of issues that are directing further research in animal models. We now broadly review the performance and clinical outcomes of these devices, with detail of ongoing animal studies outlined later in the review.

Perceptual results from clinical trials

There have been ten clinical trials of retinal implants, each with a different device and varying in other factors, such as duration, number of participants, implant location and number of electrodes (Table 1). In this review we focus on the perceptual and psychophysical outcomes of these studies. Readers interested in the clinical outcomes or the engineering aspects are referred to other reviews.[89,90]

Under electrical stimulation with the implant, patients describe perception of phosphenes. These are often white to yellow, and localised to a region of the visual field[4,91]; however, other colours and 'dark' phosphenes have been reported, as well as poorly localised phosphenes.[92] The shape and size varies, from small and round, to oval, to lines or more complex shapes (Figure 1). These attributes can vary over time even though the stimulus remains unchanged. Variability of phosphene appearance within and across patients is large and poses a significant challenge for prosthetic vision.

Only a subset of studies has been of sufficient duration to investigate patient perception in greater detail than the basic perception of phosphenes (Table 2). These studies have focussed on assessing participants' performance in a number of functional tasks of daily living and characterising the basic psychophysics of prosthetic vision. While tests and methods have varied, it is possible to draw some general conclusions. It is generally the case that protocols have avoided spatio-temporal interactions between electrodes (except in the study of Horsager, Greenberg and Fine[93]).

Functional tasks and activities of daily living

ORIENTATION AND MOBILITY

Improving the ease and safety with which patients can move about in daily life is one the most important and perhaps most readily achievable goals for a retinal prosthesis. Compared to other functional tasks, the acuity required is relatively low; however, a wide field of view is beneficial.[94] Assessment of mobility has been restricted to longer duration trials, such as the Argus II, the Alpha IMS and that by Bionic Vision Australia (BVA; Ayton et al.[95]). Generally patients report some benefit in mobility from using their device. For example, many Argus II patients showed a two to three fold improvement in their ability to locate a door-like object or follow a white line in a high contrast environment[96]; however in some other studies subjects do not appear to benefit from their device in navigational tasks.[97]

OBJECT DETECTION AND RECOGNITION

Patients using a subretinal photodiode device (Retina Implant AG) were able to locate and recognise objects in a standardised dining table setting, consisting of a closed set of white objects on a black background.[70,91] The best performing patients could locate and identify spoons, forks and cups, while the worst performing patients could distinguish only larger objects, such as a plate from a saucer. Performance was significantly better with the system on compared to off.

LETTER READING

Twenty one Argus II patients (epiretinal) were tested for their ability to read letters spanning 41° of visual field.[98] The mean accuracy was 60 per cent but varied greatly between patients and also with letter complexity. A small subset of these patients were able to recognise letters spanning less than 10°, which is similar to results from studies with Retina Implant AG devices.[70,91] These results indicate that letter reading is of limited functional benefit to retinal prostheses patients with current devices.

Psychophysics

SPATIAL LOCALISATION AND ACUITY

The spatial resolution provided by retinal prostheses is low. A basic test asks subjects to

Device	Group	Duration of implantation	# Subjects	Implant position	Electrode count; Pitch (μm)	Ref.
Argus I	Second Sight	ongoing in 2/6	6	Epiretinal	16; 720	4
Argus II	Second Sight	ongoing	30	Epiretinal	60; 575	96
Retina implant device	Retina Implant AG	1-5 months	12	Subretinal	1500+16; ~72+280	91
Alpha IMS	Retina Implant	ongoing	9	Subretinal	1500; 72	70
EPIRET3	Epi-Ret	4 weeks	6	Epiretinal	25; ~250	160
IMI retinal implant system	IMI (GmbH)	months	20	Epiretinal	49; n.a.	161
IRIS (based on IMI retinal implant system)	Pixium Vision	18 months	n.a.	Epiretinal	n.a.	162
Japanese STS Device	Osaka Retinal Prosthesis Group	n.a.	2	Suprachoroidal-transscleral	9; 1000	101
Japanese STS Device	Osaka Retinal Prosthesis Group	5-7 weeks	2	Suprachoroidal-transscleral	49 (9 active electrodes); n.a.	100
BVA suprachoroidal implant	Bionic Vision Australia	2.5 years	3	Suprachoroidal	22; 1000	95,119

Table 1. Summary of clinical trials of retinal prostheses

Study	Phosphene perception	Spatial localisation	Spatial acuity	Temporal fading	Field of view (approx.)
Argus I	6/6[4]	3/3[163]	-	-	$10^o \times 10^o$
Argus II	32/32[96]	26/27[99] 27/28[96]	7/30: 20/1,260 -20/16,000, Grating[96]	8/9[92]	$17^o \times 10^o$
Retina Implant Device	11/11[91]	1/3[91]	1/3: 20/1,000, Landolt C[91]	3/3 direct stim. 0/3 photodiode[91]	$11^o \times 11^o$
Alpha IMS	8/9[70]	7/9[70]	2/9: 20/546- 20/2,000, Landolt C[70]	2/9 photodiode[70]	$11^o \times 10^o$
Japanese STS Device	2/2[100]	2/2[100]	-	-	$20^o \times 16^o$
Bionic Vision Australia	3/3[95]	3/3[95]	1/3: 20/4,451-20/21,059, Landolt C[95]	-	$12^o \times 12^o$

Table 2. Summary for available psychophysical results from clinical trials of retinal prostheses. For Phosphene Perception and Spatial Localisation, the entries *x*/*y* indicate the number of subjects performing better with the device on than off (*x*) over the total number of subjects performing the test or participating in the study (*y*). For 'spatial acuity' the range of spatial acuities measured for subjects performing better with device on than off is also given. The type of test used, either Grating or Landolt C, is also indicated. Where appropriate, for 'temporal fading', the table notes whether stimulation occurred via the photodiode array or via direct stimulation on one of 16 electrodes controlled externally by the experimenter. The 'field of view' is an approximation based on the size of the device and the visual angle it subtends on the retina.

locate a high contrast image on a screen, for example, in one of four locations.[70,91,99,100] Across studies, most subjects perform this kind of task above chance with their device on but perform more poorly or at chance with the device off (Spatial Localisation column of Table 2). Many patients perform spatial localisation tasks using head movements to scan the screen with the external camera, taking many seconds or minutes. Using this approach, objects can be localised even with one phosphene, as fine adjustments in head position can be used to discern when the object lies within the part of the camera's field of view that activates that phosphene. Studies using a subretinal implant with a photodiode array allow patients to use eye scanning and Zrenner et al.[91] have suggested that this may be the reason that one subject reported an image to 'appear clearly in its natural form and [be] visible as a complete entity'.

Horsager, Greenberg and Fine[93] reported that two subjects experienced phosphenes in response to stimulation via an epiretinal array with circular electrodes (260 μm or 520 μm diameter). The phosphenes had diameters of 1° to 3° of visual angle. Concurrent stimulation of four electrodes (2 by 2) did not generate discrete phosphenes: subjects reported only a single phosphene of 3 to 6°. In a larger study of 30 subjects implanted with an epiretinal device consisting of 60 electrodes (200 μm diameter, Figure 4A), Humayun et al.[96] reported that all subjects reported visual percepts, when the device was active and 96 per cent of subjects were able to perform significantly better in spatial localisation tasks. Seven subjects

scored reliably on visual acuity tests using gratings of oriented light and dark stripes, with the best subject scoring 6/378 (Table 2).

The Alpha IMS device was implanted in three subjects (Figure 4B).[91] Each electrode on the device included a light-sensitive diode connected to a differential amplifier, the output of which was connected to a square 50 by 50 μm electrode. All three subjects were able to perceive light mediated by the photodiodes. Spatial resolution was investigated in the best performing subject using a Landolt C test (best visual acuity, 6/300).

In a human study using a trans-scleral array with nine electrodes arranged in a grid, subjects reported seeing localised phosphenes.[101] The electrodes were 200 μm in diameter and were separated by 1.0 mm. Although visual acuity was not tested, subjects reported seeing phosphenes the size of small coins at arms length. Dumbbell-shaped phosphenes were reported when two adjacent electrodes were activated. Fujikado et al.[100] further showed that subjects implanted with a similar device with 500 μm electrodes performed significantly better than chance in an object discrimination task where two bars spanning 1.4° by 37° and 4.3° by 37° of visual angle were presented.

Most recently, a suprachoroidal device consisting of 20 stimulating electrodes 600 μm and 400 μm in diameter arranged in a hexagonal mosaic (Figure 4C) was trialled in three human subjects.[95] All three subjects reliably reported phosphenes, which were found to be variable but controllable in terms of their perceived brightness and complexity. Visual acuity using the Landolt C test was only reported in one subject, whose performance ranged from 6/1,335 to 6/6,312 (average 6/2,519)(Table 2).

TEMPORAL FIDELITY

Many subjects report that phosphene brightness fades over time with stimulation at constant pulse rates.[70,91,92] The time course varies from an almost immediate fading, to up to 15 seconds. This leads to the perception of a 'blinking' phosphene. Anecdotally, this effect is more common with epiretinal compared to subretinal stimulation (Table 2). The only studies that have quantified the time course of brightness have used epiretinal implants[92] and have shown that the time course of fading varies greatly between subjects and changes with pulse rate and stimulation duration. Lower pulse rates cause less fading. They also found persistence of the phosphene after stimulation, an increase in brightness at stimulus offset and changes in colour and size during the latter stage of stimulation.

BRIGHTNESS AND CONTRAST SENSITIVITY

The subjective brightness of phosphenes tends to change with both amplitude and frequency of pulsed stimulation but this varies between electrodes and across subjects. Increasing amplitude tends to increase brightness,[91,100,102] but the effect of stimulus frequency is less consistent across patients. Fujikado et al.[100] reported that a frequency of 20 Hz produced brighter phosphenes than either 10 Hz or 50 Hz in one suprachoroidal patient. Nanduri et al.[103] reported that in one epiretinial patient, increasing the frequency of stimulation increased phosphene brightness. Further frequency increases affected brightness far more than the size of phosphenes in this patient, whereas larger amplitudes tend to increase both equally. The ability to discriminate brightness between image regions (contrast) is important for the recognition of objects and form. While there are reports of subjects being able to distinguish up to 10 different brightness levels sequentially,[4] we are not aware of any studies examining spatial contrast.

FIELD OF VIEW

The field of view is important for carrying out a number of functional tasks such as locating an object, orientation and mobility and reading. For retinal implants the field of view is largely determined by the angle subtended by the electrode array. The size of the electrode array is limited by the surgical location of the implant and is currently greatest for suprachoroidal placement, intermediate for epiretinal placement and smallest for subretinal placement (Table 2).

THE RESPONSE OF THE RETINA TO ELECTRICAL STIMULATION

Ultimately, it is hoped that retinal prostheses will use electrical stimulation to replicate light-evoked activity. There are 10 to 15 different retinal ganglion cell types and 12 bipolar cell types in the primate.[10,11] Given the multiple types of bipolar and retinal ganglion cells, with each type exhibiting its own characteristic spatiotemporal response pattern,[104] replicating light responses is a challenging task. High-resolution vision requires a high degree of spatial specificity. This is a challenge for existing retinal prostheses due in part to the large number of retinal cells activated by electrical stimulation. It follows that electrical stimulation likely recruits multiple populations of neurons, resulting in responses bearing little resemblance to natural vision.

The responses of retinal ganglion cells to epiretinal electrical stimulation consist of two components:

1. A short-latency component with a single, time-locked action potential evoked less than 5 ms after stimulation and
2. Several bursts of action potentials appearing more than 9 ms after stimulation.[105]

These long-latency responses are abolished by pharmacologically blocking synaptic input to the retinal ganglion cells, suggesting that these responses arise from 'indirect' activation of retinal ganglion cells by way of photoreceptors and retinal interneurons. In contrast, the short-latency responses may be attributed to 'direct' activation of retinal ganglion cells. These temporally distinct responses to electrical stimulation (Figure 5A) have since been observed in several species, namely, mouse,[76] rabbit[106,107] and monkey[108] and have likewise appeared in evoked potential recordings from visual cortex, where direct retinal ganglion cell activation is largely represented by short latency cortical activity and indirect retinal ganglion cells activation by long latency cortical activity.[109,110]

Stimulation efficacy

WAVEFORM AND STIMULATION SITE

In the case of electrodes located on the inner surface of the retina, cathodic-leading biphasic pulses have lower charge thresholds than anodic-first pulses in rat,[108,111] guinea pig and monkey[108] and rabbit.[107] Conversely, anodic-leading pulses are more effective for subretinal stimulation in chicken[112] and rabbit.[107] The duration of the stimulus is a particularly important factor as it can also be used to determine the mode of retinal ganglion cell activation. Brief electrical pulses (less than 200 μs) are known to activate retinal ganglion cells directly, whereas longer pulses are more likely to engage neurons of the inner retina.[113] Boinagrov et al.[114] used intracellular recordings in healthy rat retina to highlight the interplay between electrode location, polarity and stimulus duration, showing that the lowest thresholds for direct retinal ganglion cell activation were elicited by short-duration (500 μs) cathodic stimuli delivered on the epiretinal surface. Synaptically mediated retinal ganglion cell activity was preferentially elicited by long-duration (4 ms) anodic stimuli delivered within the

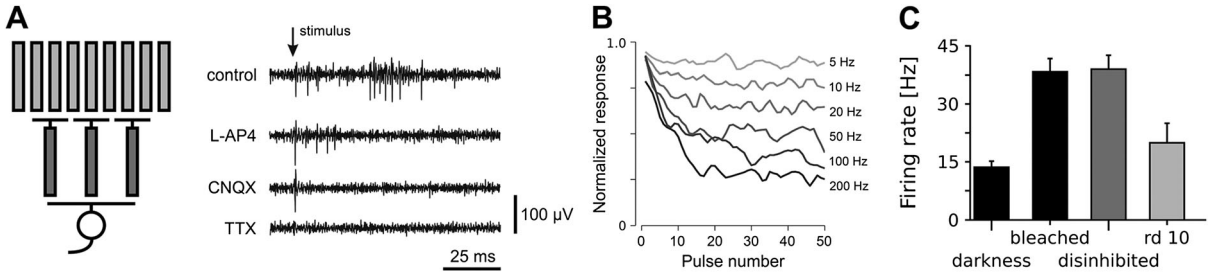

Figure 5. (A) Retinal ganglion cells are activated both directly and indirectly, via retinal interneurons, by electrical stimulation (control trace). The synaptic blocker L-AP4 blocks transmission between photoreceptors (light grey) and ON bipolar cells (dark grey), inhibiting long-latency ganglion cell responses. The glutamate receptor blocker CNQX blocks transmission between ON bipolar cells and ON ganglion cells (white), inhibiting medium-latency responses and leaving only short-latency responses arising from direct activation of retinal ganglion cells. Adapted from Eickenscheidt et al.,[107] with permission. (B) Retinal ganglion cell desensitisation is a function of both time and stimulus frequency (data from Hadjinicolaou et al.[111]). Here, the normalised response (ratio of spikes evoked by a given stimulus pulse, over the number of spikes evoked by the first pulse) is seen to plateau to a level dependent on stimulus frequency (indicated on the right). (C) Spontaneous hyperactivity is a notable physiological feature of the degenerate retina. Spontaneous firing rate of retinal ganglion cells in degenerate retina (rd10) is increased compared to that in normal retina (in darkness) (adapted from Menzler, Channappa and Zeck[140] under the Creative Commons Attribution Licence http://creativecommons.org/licenses/by/4.0/).

OPL. The same study demonstrated that with shallow (~30 µm) penetration of stimulating electrodes into the INL, activation thresholds for direct retinal ganglion cell activation were two-times lower than those obtained using electrodes placed on the epiretinal surface.

As it happens, cathodic-leading biphasic pulses are typically used in human clinical trials of epiretinal devices.[115–117] While Humayun et al.[118] reported that subjects did not experience notable differences between anodic or cathodic-leading monopolar stimulation, Horsager et al.[116] reported that cathodic-leading pulses resulted in lower thresholds in pilot studies. Anodic-leading pulses were also found to result in lower thresholds in clinical trials of a suprachoroidal implant.[119]

EXCITABILITY

To understand how stimulus duration can be manipulated to engage different retinal neurons, it is useful to consider the relationship between pulse duration and stimulus current threshold.[120] This relationship is quantified by two parameters that relate to cell excitability: the 'rheobase current' (the minimum current required to excite a cell, irrespective of pulse duration) and the 'chronaxie' (the minimum pulse duration required for activation using a current amplitude of twice the rheobase current). Compared with retinal ganglion cells, retinal interneurons have higher chronaxies[121,122] and require longer duration stimuli to reach threshold. The resulting synaptic activity is sustained by the relatively slow transmission of glutamate from bipolar cell to retinal ganglion cell, which takes place over the course of hundreds of milliseconds and likely contributes to the extended time-course of the indirect response.[113,123]

Cell excitability varies within individual neurons. Nowak and Bullier[124] recorded from cortical gray matter neurons and found that the chronaxie corresponding to axonal activation (~0.4 ms) was two orders of magnitude lower than that for direct, somatic activation (~15 ms). The chronaxie associated with post-synaptic responses to extracellular electrical stimulation was similar to that for axonal activation – suggesting that the axons are being activated. In the retina, it is presumed that the activation of passing retinal ganglion cell axons gives rise to the short latency retinal response.[110,122] The long latency response, on the other hand, has a more focal origin that corresponds well with the location of the stimulating electrode.[110]

The axons of neurons within the mammalian central nervous system feature a specialised membrane region, the axon initial segment (AIS), containing high-density clusters of voltage-gated ion channels. The AIS is the site of action potential initiation and supports many physiological roles.[125] Fried et al.[65] demonstrated in rabbit retina that the AIS is the site most sensitive to electrical stimulation. As well as finding differential sensitivity across different functional retinal ganglion cell types, the sodium channel bands in the AIS associated with brisk-transient and direction-selective cells were found to be distinct in length and proximity to the soma, suggesting that the bands are optimised to process information in specialised cell types. As the AISs of retinal ganglion cells have several different voltage-gated ion channel subtypes,[126,127] it seems likely that the collective expression of multiple subtypes will influence the response of retinal ganglion cells to electrical stimulation.

DESENSITISATION

The ability of retinal ganglion cells to respond to repetitive electrical stimulation progressively decreases with successive stimuli, and is dependent on the stimulus interval (Figure 5B).[111,128–130] This desensitisation of retinal ganglion cells has been observed in intracellular retinal ganglion cell recordings[111] and in extracellular recordings of retinal ganglion cell activity.[128,129,131] Freeman and Fried[132] found that desensitisation in rabbit retinal ganglion cells consists of two components: a fast-acting component (hundreds of milliseconds) associated with direct cell activation and a slow-acting, presynaptic component. While thresholds for direct retinal ganglion cell activation were resilient during repetitive stimulation, the synaptically-mediated response was suppressed after only a few successive pulses, indicating that desensitisation is largely mediated by retinal circuitry presynaptic to retinal ganglion cells. The time courses of these two desensitisation components matches reports from clinical trials of retinal prostheses, in which subjects report percepts that fade with two distinct phases of brightness.[92]

Is it possible to design a stimulation strategy that avoids retinal ganglion cell desensitization? If the fading of percepts observed in clinical trials arises from fatigue of retinal interneurons,[92,133] it may be possible to mitigate this effect using direct activation of retinal ganglion cells. Freeman and Fried[132] proposed a stimulation strategy that uses bursts of pulses to encode luminance and a train of pulses, the temporal characteristics of which match the spontaneous firing of a typical retinal ganglion cell. It is probable that discrete bursts of activity are used to encode the visual information leaving the retina.[134] The second component may desensitise the synaptically-mediated response, so as to elicit a robust direct retinal ganglion cell response to the first component. Tsai et al.[130] directly compensated for retinal ganglion cell desensitisation in rabbit retina by modulating the amplitude of delivered stimuli as a function of time and stimulus frequency. The fall in efficacy with successive pulses in response to high frequency (50 to 200 Hz) subretinal stimulation was attributed to a frequency-dependent decline in voltage-gated sodium current (I_{Na}), which plateaued in much the same way as retinal ganglion cell responsiveness in other studies[111] (Figure 5B). Accordingly, stimulus pulses were delivered at progressively larger amplitudes to increase the evoked I_{Na} and thus maintain the spike rate.

The efficacy of constant-frequency stimuli can also be improved by varying the pulse waveform. The efficacy of random pulse trains has also been compared for epiretinal stimulation by recording in rat superior colliculus.[135] The stimulus consisted of a 20 Hz pulse train (phase duration randomly selected: 0.1 to 20 ms), with corresponding pulse amplitudes set to elicit identical neural activity, compared to a constant frequency (20 Hz) pulse train. The early response component (latency of 3 to 12 ms) was more resilient when evoked by the time-varying stimulus. It is difficult to determine whether the improvement in early-phase signal strength was due to increased recruitment of presynaptic neurons, which would have the effect of desensitising the retinal network, to improve the efficacy of direct stimulation (for example, Freeman and Fried[132]).

DEGENERATION

A significant factor influencing stimulation efficacy is the state of degeneration in the diseased retina. The substantial anatomical reorganisation that takes place over the course of degeneration is accompanied by extensive physiological changes, which have been investigated in several different animal models.[34,136–138] Compared with the healthy retina, ganglion cells of the rd1 and rd10 mouse retina exhibit an elevated level of spontaneous activity that increases with photoreceptor degeneration (Figure 5C).[34,136,139,140] A particularly striking feature of the degenerate retina in these animals is the presence of oscillatory 'waves' of ganglion cell activity that fire at either ~5 Hz (rd10) or ~10 Hz (rd1).[136,137,139,140] Spontaneous oscillations have also been observed in neurons of the inner nuclear layer in degenerate mouse retina.[141] These waves of rhythmic activity may give rise to the photopsia observed by patients with retinitis pigmentosa, who report the perception of random flashes of light despite the absence of visual stimulation.[34]

The physiology of the degenerate retina depends on the particular type of disease. In degenerate mouse models, the characteristic physiological response properties of ON and OFF ganglion cells have been found to persist in at least a subset of cells in rd10 mice[34,137] but were absent beyond early-stage degeneration in the rd1 mouse.[136] The rd1 mouse also suffers a disproportionate loss of ON responses,[136] while ON and OFF responses in the rd10 mouse are similarly affected.[137] It seems likely that the response of the retina to electrical stimulation will also depend on the nature of disease and the choice of animal model for studying the degenerate condition requires careful consideration. In the case of rd10 mice, photoreceptor degeneration does not coincide with early development of the retina, while these two processes occur simultaneously in the rd1 mouse.[142,143] Further, light responses in the rd10 mouse last for several weeks more than those of the rd1 mouse.[136,137] As the pathology of the rd10 mouse more closely follows that of human retinitis pigmentosa, it may prove to be a more suitable animal model.[140,142,143]

Despite severe photoreceptor degeneration and a complete absence of any light response, the responses of RGCs in P23H rats to electrical stimulation were similar to normal rat retina.[144] Others have shown that the diseased retina requires more charge to activate[85,145] and that functional thresholds appear to increase as the degeneration progresses.[43,145,146]

Encouragingly, responses in visual brain areas to electrical stimulation of the diseased retina are readily achieved. Kanda et al.[87] evoked localised activity in the superior colliculus of visually deprived rats through transscleral stimulation, finding stimulation thresholds in the degenerate retina to be higher (mean: 12.9 nC versus 7.2 nC) and more variable (standard deviation: 7.7 nC versus 2.8 nC) than those of the healthy retina. Another study found that cortical responses could be evoked from stimulation of the degenerate retina in the mouse, dog and human.[109]

Encoding visual information

SELECTIVE ACTIVATION OF RETINAL CELL TYPES

It is unclear whether electrical stimulation can selectively activate particular retinal ganglion cell types. Retinal ganglion cells favour short duration pulses, while inner retinal neurons prefer longer pulse durations.[113] Freeman et al.[147] showed that retinal ganglion cells were best activated by high frequency (100 Hz) stimulation, with lower frequencies activating bipolar cells (25 Hz) and photoreceptors (5 Hz). Fried et al.[65] found that lowest thresholds for activation occurred when the stimulating electrode was placed directly above the proximal axon. They also showed that the spatial properties of the sodium channel bands differed among cell types, leading to the possibility of selective activation.

Sekirnjak et al.[108] demonstrated that focal activation of retinal ganglion cells could be achieved using high density electrodes with diameters comparable to that of single cells. Retinal ganglion cell activation was confined to small regions and short-latency responses achieved in single cells. Sekirnjak et al.[148] showed that single ON or OFF parasol cells could be selectively activated by short-duration biphasic pulses with little or no activation of neighbouring cells. Using a similar array, Jepson et al.[37] attempted to selectively stimulate ON and OFF midget, ON and OFF parasol and small bistratified retinal ganglion cells. They reported that selective activation of target cells was possible in some cases but not in others, with activation of axons accounting for approximately half the cases, where activation of non-target cells was observed.

Studies using large diameter electrodes to stimulate retinal ganglion cells have not been successful in demonstrating selective activation. When stimulating from an epiretinal location, retinal ganglion cells favour cathodic first biphasic pulses[108,149]; however, Sekirnjak

et al.[148] found that ON and OFF parasol cells had comparable thresholds, when using cathodic first stimulation. A similar finding was seen when comparing thresholds among other retinal ganglion cell types,[37] suggesting that stimulus amplitude alone cannot be used to selectively activate cell types; however, it is possible that variation in the relative position of the stimulating electrodes and the target cells in the study by Jepson et al.[37] resulted in increased variability of the estimated thresholds, obscuring small differences between cell types. Alternatively, it is possible that stimulus polarity and the site of stimulation play a crucial role. Using subretinal stimulation, Jensen and Rizzo[36] found that thresholds for OFF retinal ganglion cells were lower for anodic first current pulses, whereas for ON cells, thresholds for anodic and cathodic first stimuli were similar.

Twyford, Cai and Fried[39] is the only study to show a differential response between two retinal ganglion cell types in response to the same stimulus. Stimulus trains of biphasic pulses were applied at high frequency (2000 Hz) with a conical electrode placed directly above the AIS. When the amplitude of the pulses was ramped from 40 μA to 60 μA, ON 'brisk transient' cells exhibited an increase in activity, while OFF brisk 'transient cells' exhibited a decrease. For a stimulus where the pulses were ramped from 60 μA to 40 μA, the opposite was true. The mechanism for the differential response is unclear but it might be linked to differences in ionic channel expression among the cell types.

The indiscriminate activation of multiple retinal pathways by means of electrical stimuli represents a profound issue that will hinder the creation of meaningful prosthetic vision. A stimulation strategy that is able to selectively activate ON and OFF pathways may allow the perception of fundamental spatial patterns in patients. Selective activation of neural populations remains a key challenge to be addressed by all vision prostheses.

TEMPORAL RESOLUTION

A natural approach to prosthetic vision is to elicit spiking patterns in retinal ganglion cells that match those of their corresponding light responses. For epiretinal stimulation (that is, where the target neuron is the retinal ganglion cell), this can be done most easily through direct ganglion cell activation. Fried, Hsueh and Werblin[106] reported that electrical stimulation was able to evoke spike trains from retinal ganglion cells that precisely match those evoked by presentation of a simple visual stimulus. More recently, Wong et al.[150] recorded the spiking responses of single retinal ganglion cells in cat retina presented with short sequences of natural images. They then showed that among the functional class of retinal ganglion cells they recorded, cells responded reliably and robustly to epiretinal electrical stimulation with pulse trains that had similar temporal statistics to the responses evoked by the visual stimuli. A similar approach was taken by Jepson et al.,[38] who recorded spiking responses from small populations of retinal ganglion cells in macaque retina evoked by a simple moving visual stimulus. They showed that the evoked spatio-temporal pattern of retinal activity could be replicated with high spatial and temporal precision using appropriate patterns of electrical stimulation.

Although ganglion cells can be engaged in this way to reproduce naturalistic spike trains, it is difficult to activate the retinal network at high stimulation frequencies. While the threshold for direct ganglion cell activation changes little in response to high-frequency (16 Hz or more) stimulation, the synaptically-mediated retinal ganglion cell response is significantly suppressed.[132] This implies that a different stimulation strategy is required for prostheses that operate by engaging the retinal network. An interesting hypothesis proposed by Lorach et al.[151] is that the retina adapts to constant patterns of subretinal electrical stimulation in much the same way that the normal retina adapts to constant patterns of visual stimulation, that is, the retina is better suited to detecting 'changes' in subretinal stimulation, as opposed to responding to each consecutive pulse. It follows that a subretinal stimulation strategy that elicits naturalistic spike trains will be fundamentally different to its epiretinal counterpart.

SPATIAL RESOLUTION

There is considerable variation in the devices used in human studies and in the measurement and reporting of the achieved spatial resolution. Based on *in vitro* and *in vivo* studies, several factors are likely to play a role in determining the resolution of vision afforded by retinal prostheses. For example, electrode size, implant placement and electrode arrangement all potentially influence achievable spatial resolution. An epiretinal prosthesis with small enough electrodes should be able to activate single retinal ganglion cells,[37,108,148] whereas the achievable resolution of subretinal stimulation will be limited by the inherent lateral spread of neuronal activation within the retinal network.[129] Importantly, measures of spatial resolution obtained from animal studies will depend on the particular animal model used, each with their own complement of retinal ganglion cells and their respective dendritic field sizes.

Activation of single retinal ganglion cells has been reported using stimuli within safe charge limits delivered via high density epiretinal arrays of small (10 to 15 μm diameter) electrodes.[37,108,148] In contrast, Behrend et al.[152] found no benefit in using electrodes with diameters smaller than 60 μm – the smallest response area produced was around 150 μm, suggesting that this is the maximum resolution achievable. This apparent discrepancy might be attributable to the stimulus used. Stett et al.[153] reported that subretinal stimulation using electrodes of only 10 μm diameter evoked activity localised to an area within 100 to 200 μm of the electrode. Moreover, while direct activation of retinal ganglion cells is possible using subretinal stimulation, Tsai et al.[129] found that it is generally accompanied by activity arising from activation of the retinal network.

The influence of electrode size is likely also dependent on electrode placement. Shyu et al.[154] found that for stimuli delivered subretinaly, small electrodes (25 μm diameter) required significantly more current to generate a response in retinal ganglion cells than large electrodes (125 μm diameter); however, thresholds for activation using either small or large diameter epiretinal electrodes were similar and comparable to the lower thresholds for the large diameter subretinal electrodes.

Confining the extent of spatial activation with a view towards improving spatial resolution, has also been investigated *in vitro*. Habib et al.[155] investigated so-called 'hexapolar stimulation' in which electrodes were arranged in a hexagonal grid. Stimuli were delivered via the central electrode, while using the surrounding six electrodes as the return or 'guard'. Activation thresholds of cells located outside the guard were more than two-fold higher than cells inside the guard, with many cells outside the guard not activated even at maximal stimulus amplitude. Although these results demonstrate that electrode layout can improve spatial localisation of evoked activity and presumably improve spatial resolution, this improvement comes at the price of increased threshold current amplitudes compared to monopolar stimulation.[155]

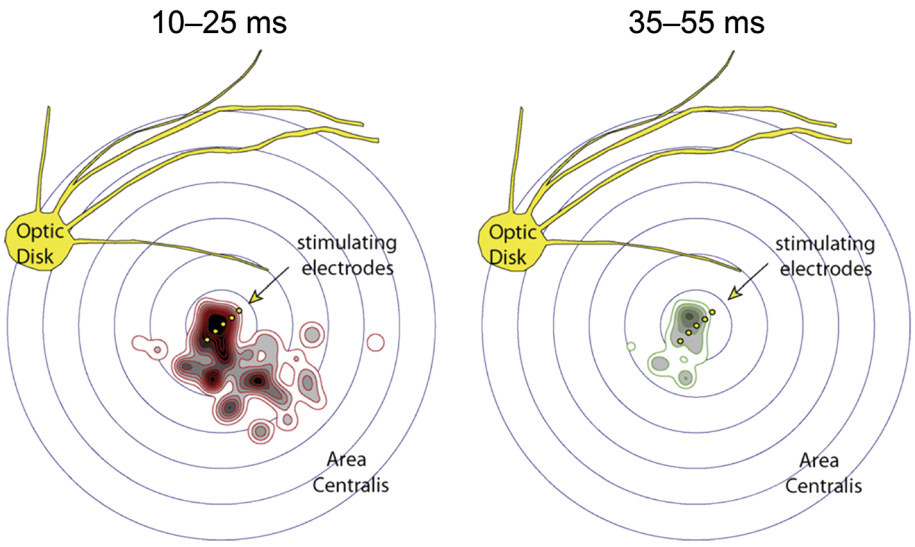

Figure 6. Spatial resolution depends on the mode (that is, direct or indirect) of retinal ganglion cell activation. Contour plots show the strength and extent of local field potentials recorded in primary visual cortex for early (direct activation; left) and late (indirect activation; right) LFP components. Adapted from Elfar et al.,[110] with permission.

Spatial resolution has also been investigated using acute *in vivo* recordings in cat visual cortex to measure the retino-cortical spread of activation during electrical stimulation of the retina.[78,110,156–158] Eckhorn et al.[156] investigated the role of electrode placement, comparing epi- and subretinal stimulation using 100 µm thin-film electrodes. The retino-cortical point spread function was converted into degrees of visual angle to determine the achievable resolution. They estimated the achievable spatial resolution to be comparable for epi- and subretinal stimulation (1.2° of visual angle for epiretinal stimulation and 0.9 to 1.3° for subretinal stimulation). They also estimated spatial resolution for epiretinal stimulation via smaller 20 µm diameter fibre electrodes. They found that the smaller electrodes resulted in higher estimated spatial resolution (0.68° of visual angle as opposed to 1.2° for the larger thin-film electrodes).

Stimulation in cat retina with suprachoroidal platinum electrodes has proven effective in evoking focal activation in primary visual cortex.[78] For suprachoroidal stimulation, the effect of electrode size has been assessed in chronic implantation studies in cats using arrays with 125 µm, 160 µm and 395 µm diameter electrodes.[157] Reliable responses could only be obtained with the larger electrodes. In a subsequent study using 400 µm diameter suprachoroidal electrodes, cortical response profiles were reportedly consistent with the electrical stimulation patterns, suggesting retinotopy was maintained.[158] Although the degree of localisation was not quantified, the authors report that cortical threshold increased 3 to 5 dB when stimulating the electrode immediately adjacent to the best (that is, lowest threshold) electrode.

Kanda et al.[85] demonstrated that transscleral stimulation could produce localised responses in the rat superior colliculus and estimated the achievable spatial resolution. They reported that two-point discrimination was possible for stimulation sites separated by 700 µm, comparable to 2.4° of visual angle in humans.

There is some evidence to suggest that the mechanism of retinal ganglion cell activation, either direct or indirect, may also influence achievable spatial resolution: specifically, that indirect activation is more spatially localised. Elfar et al.[110] recorded responses in cat cortex evoked by epiretinal stimulation. They reported that long latency responses, nominally attributed to indirect activation of retinal ganglion cells, were well localised and followed the retinotopic location of the electrical stimulus, while the cortical loci of short latency responses (attributed to direct activation of retinal ganglion cells) were diffuse and often shifted towards the area centralis - possibly indicative of activation of overlying retinal ganglion cell axons (Figure 6). These observations suggest that stimulating retinal ganglion cells indirectly via the retinal network, avoiding activation of passing axons, may offer better spatial resolution.

Sim et al.[159] explored this idea using the concept of an electrical receptive field (ERF), defined as the retinal region, over which electrical stimuli can evoke a response in an retinal ganglion cells. Mouse retinae were stimulated using a 3,200-element multi-electrode array developed for the Naval Research Laboratory retinal prosthesis and extracellular ganglion cell responses were measured using a 16-electrode recording array to construct the electrical receptive fields. It was found that the electrical receptive fields for subretinal stimulation were smaller than those of epiretinal stimulation and that charge thresholds were positively correlated with electrical receptive field area for both modes of stimulation. Further, in cells that expressed both direct and indirect retinal ganglion cell response components, the electrical receptive fields corresponding to each component differed in shape and size, consistent with the notion that direct and indirect retinal ganglion cellsresponses are governed by different retinal circuitry.[132]

Using their subretinal photovoltaic implant consisting of a 512-element multi-electrode array, Lorach et al.[151] measured electrical receptive fields in RCS-degenerate rats and found that they were similar in size to the visual receptive fields of normal rats. The degenerate retina was stimulated using patterns of alternating gratings of various spatial frequencies. Visual evoked potentials, measured in

primary visual cortex, were assessed together with their corresponding retinal responses to determine that the degenerate system could extract features smaller than the ganglion cell receptive fields, as in the healthy visual system. The authors conclude that such stimulation should be able to achieve a visual acuity of 6/75 in the human (approximately 0.2° of visual angle) and that further improvements to spatial resolution may be achieved with smaller photovoltaic electrodes.

CONCLUSION

The restoration of sight to those suffering from degenerative visual loss is challenging. Through the work of those pursuing the development of microelectronic retinal prostheses, prosthetic vision has progressed well beyond the rudimentary stages fathered by Brindley and Lewin[3] in the late 1960s. Clinical evaluation in blind human subjects has demonstrated improvements in spatial localisation, object or character recognition, motion detection and mobility. Even so, the vision afforded by those devices available today is rudimentary at best and there is much that needs to be done. With the continuing increase in our knowledge and understanding of the retina, its diseases and its response to electrical stimulation, improvements in the quality of prosthetic vision and thus, the quality of life of implant recipients, looks set to continue.

ACKNOWLEDGEMENTS

This work 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 and through the Centre of Excellence for Integrative Brain Function (CE140100007).

REFERENCES

1. World Health Organization. Universal eye health: a global action plan 2014–2019. 2013.
2. Ibbotson MR. Bionic eyes: where are we and what does the future hold? *Clin Exp Optom* 2012; 95: 471–472.
3. Brindley GS, Lewin WS. The sensations produced by electrical stimulation of the visual cortex. *J Physiol* 1968; 196: 479–493.
4. Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J et al. Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. *Vision Res* 2003; 43: 2573–2581.
5. Brelen ME, Duret F, Gerard B, Delbeke J, Veraart C. Creating a meaningful visual perception in blind volunteers by optic nerve stimulation. *J Neural Eng* 2005; 2: S22–S28.
6. Pezaris JS, Reid RC. Demonstration of artificial visual percepts generated through thalamic microstimulation. *Proc Natl Acad Sci U S A* 2007; 104: 7670–7675.
7. Santos A, Humayun MS, de Juan E Jr, Greenburg RJ, Marsh MJ, Klock IB et al. Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. *Arch Ophthalmol* 1997; 115: 511–515.
8. Kim SY, Sadda S, Pearlman J, Humayun MS, de Juan E Jr, Melia BM et al. Morphometric analysis of the macula in eyes with disciform age-related macular degeneration. *Retina* 2002; 22: 471–477.
9. Kolb H. How the retina works. *Am Sci* 2003; 91: 28–35.
10. Masland RH. The fundamental plan of the retina. *Nat Neurosci* 2001; 4: 877–886.
11. Wassle H. Parallel processing in the mammalian retina. *Nat Rev Neurosci* 2004; 5: 747–757.
12. Dacey DM. The mosaic of midget ganglion cells in the human retina. *J Neurosci* 1993; 13: 5334–5355.
13. Curcio CA, Sloan KR, Kalina RE, Hendrickson AE. Human photoreceptor topography. *J Comp Neurol* 1990; 292: 497–523.
14. Mather G. *The Physics of Vision - Light and the Eye. Foundations of Sensation and Perception.* London: Psychology Press Ltd, 2009. p. 145–177.
15. Hartline HK. The response of single optic nerve fibers of the vertebrate eye to illumination of the retina. *Am J Physiol* 1938; 121: 400–415.
16. Dacey DM, Petersen MR. Dendritic field size and morphology of midget and parasol ganglion cells of the human retina. *Proc Natl Acad Sci U S A* 1992; 89: 9666–9670.
17. Schiller PH, Logothetis NK. The color-opponent and broad-band channels of the primate visual system. *Trends Neurosci* 1990; 13: 392–398.
18. Schiller PH, Logothetis NK, Charles ER. Functions of the colour-opponent and broad-band channels of the visual system. *Nature* 1990; 343: 68–70.
19. Merigan WH, Byrne CE, Maunsell JH. Does primate motion perception depend on the magnocellular pathway? *J Neurosci* 1991; 11: 3422–3429.
20. Field GD, Chichilnisky EJ. Information processing in the primate retina: circuitry and coding. *Annu Rev Neurosci* 2007; 30: 1–30.
21. Field GD, Gauthier JL, Sher A, Greschner M, Machado TA, Jepson LH et al. Functional connectivity in the retina at the resolution of photoreceptors. *Nature* 2010; 467: 673–677.
22. Wassle H, Boycott BB. Functional architecture of the mammalian retina. *Physiol Rev* 1991; 71: 447–480.
23. Kuffler SW. Discharge patterns and functional organization of mammalian retina. *J Neurophysiol* 1953; 16: 37–68.
24. Nelson R, Famiglietti EV Jr, Kolb H. Intracellular staining reveals different levels of stratification for on- and off-center ganglion cells in cat retina. *J Neurophysiol* 1978; 41: 472–483.
25. Nelson R, Kolb H. ON and OFF pathways in the vertebrate retina and visual system. In: Chalupa LM, Werner JS, eds. *The visual neurosciences.* Cambridge, Massachusetts: MIT Press, 2003. p. 260–278.
26. Werblin FS, Dowling JE. Organization of the retina of the mudpuppy, Necturus maculosus. II. Intracellular recording. *J Neurophysiol* 1969; 32: 339–355.
27. Verweij J, Hornstein EP, Schnapf JL. Surround antagonism in macaque cone photoreceptors. *J Neurosci* 2003; 23: 10249–10257.
28. Myhr KL, Lukasiewicz PD, Wong RO. Mechanisms underlying developmental changes in the firing patterns of ON and OFF retinal ganglion cells during refinement of their central projections. *J Neurosci* 2001; 21: 8664–8671.
29. Margolis DJ, Detwiler PB. Different mechanisms generate maintained activity in ON and OFF retinal ganglion cells. *J Neurosci* 2007; 27: 5994–6005.
30. Henderson D, Miller RF. Low-voltage activated calcium currents in ganglion cells of the tiger salamander retina: experiment and simulation. *Vis Neurosci* 2007; 24: 37–51.
31. Mitra P, Miller RF. Mechanism underlying rebound excitation in retinal ganglion cells. *Vis Neurosci* 2007; 24: 709–731.
32. O'Brien BJ, Isayama T, Richardson R, Berson DM. Intrinsic physiological properties of cat retinal ganglion cells. *J Physiol* 2002; 538: 787–802.
33. Wong RC, Cloherty SL, Ibbotson MR, O'Brien BJ. Intrinsic physiological properties of rat retinal ganglion cells with a comparative analysis. *J Neurophysiol* 2012; 108: 2008–2023.
34. Margolis DJ, Newkirk G, Euler T, Detwiler PB. Functional stability of retinal ganglion cells after degeneration-induced changes in synaptic input. *J Neurosci* 2008; 28: 6526–6536.
35. Mazzoni F, Novelli E, Strettoi E. Retinal ganglion cells survive and maintain normal dendritic morphology in a mouse model of inherited photoreceptor degeneration. *J Neurosci* 2008; 28: 14282–14292.
36. Jensen RJ, Rizzo JF 3rd. Thresholds for activation of rabbit retinal ganglion cells with a subretinal electrode. *Exp Eye Res* 2006; 83: 367–373.
37. Jepson LH, Hottowy P, Mathieson K, Gunning DE, Dabrowski W, Litke AM et al. Focal electrical stimulation of major ganglion cell types in the primate retina for the design of visual prostheses. *J Neurosci* 2013; 33: 7194–7205.
38. Jepson LH, Hottowy P, Mathieson K, Gunning DE, Dabrowski W, Litke AM et al. Spatially patterned electrical stimulation to enhance resolution of retinal prostheses. *J Neurosci* 2014; 34: 4871–4881.
39. Twyford P, Cai C, Fried S. Differential responses to high-frequency electrical stimulation in ON and OFF retinal ganglion cells. *J Neural Eng* 2014; 11: 025001.
40. Marc RE, Jones BW, Watt CB, Strettoi E. Neural remodeling in retinal degeneration. *Prog Retin Eye Res* 2003; 22: 607–655.
41. Fariss RN, Li ZY, Milam AH. Abnormalities in rod photoreceptors, amacrine cells, and horizontal cells in human retinas with retinitis pigmentosa. *Am J Ophthalmol* 2000; 129: 215–223.
42. Delbeke J, Pins D, Michaux G, Wanet-Defalque MC, Parrini S, Veraart C. Electrical stimulation of anterior visual pathways in retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 2001; 42: 291–297.
43. Suzuki S, Humayun MS, Weiland JD, Chen SJ, Margalit E, Piyathaisere DV et al. Comparison of electrical stimulation thresholds in normal and retinal degenerated mouse retina. *Jpn J Ophthalmol* 2004; 48: 345–349.
44. O'Hearn TM, Sadda SR, Weiland JD, Maia M, Margalit E, Humayun MS. Electrical stimulation in normal and retinal degeneration (rd1) isolated mouse retina. *Vision Res* 2006; 46: 3198–3204.
45. Cho AK, Sampath AP, Weiland JD. Physiological response of mouse retinal ganglion cells to electrical stimulation: effect of soma size. *Conf Proc IEEE Eng Med Biol Soc* 2011; 2011: 1081–1084.

46. Weitz AC, Behrend MR, Humayun MS, Chow RH, Weiland JD. Interphase gap decreases electrical stimulation threshold of retinal ganglion cells. *Conf Proc IEEE Eng Med Biol Soc* 2011; 2011: 6725–6728.
47. Cho AK, Sampath AP, Weiland JD. Physiological response of normal and RD mouse retinal ganglion cells to electrical stimulation. *Conf Proc IEEE Eng Med Biol Soc* 2012; 2012: 2985–2988.
48. Hafezi F, Grimm C, Simmen BC, Wenzel A, Reme CE. Molecular ophthalmology: an update on animal models for retinal degenerations and dystrophies. *Br J Ophthalmol* 2000; 84: 922–927.
49. Takahashi M, Miyoshi H, Verma IM, Gage FH. Rescue from photoreceptor degeneration in the rd mouse by human immunodeficiency virus vector-mediated gene transfer. *J Virol* 1999; 73: 7812–7816.
50. Daiger SP, Bowne SJ, Sullivan LS. Perspective on genes and mutations causing retinitis pigmentosa. *Arch Ophthalmol* 2007; 125: 151–158.
51. Dryja TP, McGee TL, Reichel E, Hahn LB, Cowley GS, Yandell DW et al. A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. *Nature* 1990; 343: 364–366.
52. Olsson JE, Gordon JW, Pawlyk BS, Roof D, Hayes A, Molday RS et al. Transgenic mice with a rhodopsin mutation (Pro23His): a mouse model of autosomal dominant retinitis pigmentosa. *Neuron* 1992; 9: 815–830.
53. Merrill DR, Bikson M, Jefferys JG. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *J Neurosci Methods* 2005; 141: 171–198.
54. Cogan SF. Neural stimulation and recording electrodes. *Annu Rev Biomed Eng* 2008; 10: 275–309.
55. McHardy J, Robblee LS, Marston JM, Brummer SB. Electrical stimulation with pt electrodes. IV. Factors influencing Pt dissolution in inorganic saline. *Biomaterials* 1980; 1: 129–134.
56. Cogan SF, Guzelian AA, Agnew WF, Yuen TG, McCreery DB. Over-pulsing degrades activated iridium oxide films used for intracortical neural stimulation. *J Neurosci Methods* 2004; 137: 141–150.
57. Ganesan K, Stacey A, Meffin H, Lichter S, Greferath U, Fletcher EL et al. Diamond penetrating electrode array for epi-retinal prosthesis. *Conf Proc IEEE Eng Med Biol Soc* 2010; 2010: 6757–6760.
58. Hadjinicolaou AE, Leung RT, Garrett DJ, Ganesan K, Fox K, Nayagam DA et al. Electrical stimulation of retinal ganglion cells with diamond and the development of an all diamond retinal prosthesis. *Biomaterials* 2012; 33: 5812–5820.
59. Butterwick A, Vankov A, Huie P, Freyvert Y, Palanker D. Tissue damage by pulsed electrical stimulation. *IEEE Trans Biomed Eng* 2007; 54: 2261–2267.
60. Colodetti L, Weiland JD, Colodetti S, Ray A, Seiler MJ, Hinton DR et al. Pathology of damaging electrical stimulation in the retina. *Exp Eye Res* 2007; 85: 23–33.
61. Liu WT, Vichienchom K, Clements M, DeMarco SC, Hughes C, McGucken E et al. A neuro-stimulus chip with telemetry unit for retinal prosthetic device. *IEEE J Solid-State Circuits* 2000; 35: 1487–1497.
62. Piyathaisere DV, Margalit E, Chen SJ, Shyu JS, D'Anna SA, Weiland JD et al. Heat effects on the retina. *Ophthalmic Surg Lasers Imaging* 2003; 34: 114–120.
63. Gosalia K, Weiland J, Humayun M, Lazzi G. Thermal elevation in the human eye and head due to the operation of a retinal prosthesis. *IEEE Trans Biomed Eng* 2004; 51: 1469–1477.
64. Schiefer MA, Grill WM. Sites of neuronal excitation by epiretinal electrical stimulation. *IEEE Trans Neural Syst Rehabil Eng* 2006; 14: 5–13.
65. Fried SI, Lasker AC, Desai NJ, Eddington DK, Rizzo JF 3rd. Axonal sodium-channel bands shape the response to electric stimulation in retinal ganglion cells. *J Neurophysiol* 2009; 101: 1972–1987.
66. Rizzo JF 3rd, Wyatt J, Loewenstein J, Kelly S, Shire D. Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials. *Invest Ophthalmol Vis Sci* 2003; 44: 5362–5369.
67. Wilms M, Eckhorn R. Spatiotemporal receptive field properties of epiretinally recorded spikes and local electroretinograms in cats. *BMC Neurosci* 2005; 6: 50.
68. Zrenner E, Stett A, Weiss S, Aramant RB, Guenther E, Kohler K et al. Can subretinal microphotodiodes successfully replace degenerated photoreceptors? *Vision Res* 1999; 39: 2555–2567.
69. Wang L, Mathieson K, Kamins TI, Loudin JD, Galambos L, Goetz G et al. Photovoltaic retinal prosthesis: implant fabrication and performance. *J Neural Eng* 2012; 9: 046014.
70. Stingl K, Bartz-Schmidt KU, Besch D, Braun A, Bruckmann A, Gekeler F et al. Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS. *Proc Biol Sci* 2013; 280: 20130077.
71. Guven D, Weiland JD, Fujii G, Mech BV, Mahadevappa M, Greenberg R et al. Long-term stimulation by active epiretinal implants in normal and RCD1 dogs. *J Neural Eng* 2005; 2: S65–S73.
72. Walter P, Kisvarday ZF, Gortz M, Alteheld N, Rossler G, Stieglitz T et al. Cortical activation via an implanted wireless retinal prosthesis. *Invest Ophthalmol Vis Sci* 2005; 46: 1780–1785.
73. Majji AB, Humayun MS, Weiland JD, Suzuki S, D'Anna SA, de Juan E Jr. Long-term histological and electrophysiological results of an inactive epiretinal electrode array implantation in dogs. *Invest Ophthalmol Vis Sci* 1999; 40: 2073–2081.
74. Gerding H, Benner FP, Taneri S. Experimental implantation of epiretinal retina implants (EPI-RET) with an IOL-type receiver unit. *J Neural Eng* 2007; 4: S38–S49.
75. Lorach H, Goetz G, Mandel Y, Lei X, Kamins TI, Mathieson K et al. Performance of photovoltaic arrays in-vivo and characteristics of prosthetic vision in animals with retinal degeneration. *Vision Res* 2015; 111: 142–148.
76. Jensen RJ, Rizzo JF 3rd. Activation of retinal ganglion cells in wild-type and rd1 mice through electrical stimulation of the retinal neural network. *Vision Res* 2008; 48: 1562–1568.
77. Wong YT, Chen SC, Seo JM, Morley JW, Lovell NH, Suaning GJ. Focal activation of the feline retina via a suprachoroidal electrode array. *Vision Res* 2009; 49: 825–833.
78. Cloherty SL, Hietanen MA, Suaning GJ, Ibbotson MR. Focal activation of primary visual cortex following supra-choroidal electrical stimulation of the retina: Intrinsic signal imaging and linear model analysis. *Conf Proc IEEE Eng Med Biol Soc* 2010: 6765–6768.
79. Villalobos J, Nayagam DA, Allen PJ, McKelvie P, Luu CD, Ayton LN et al. A wide-field suprachoroidal retinal prosthesis is stable and well tolerated following chronic implantation. *Invest Ophthalmol Vis Sci* 2013; 54: 3751–3762.
80. Nayagam DA, Williams RA, Allen PJ, Shivdasani MN, Luu CD, Salinas-LaRosa CM et al. Chronic electrical stimulation with a suprachoroidal retinal prosthesis: a preclinical safety and efficacy study. *PLoS One* 2014; 9: e97182.
81. Yamauchi Y, Franco LM, Jackson DJ, Naber JF, Ziv RO, Rizzo JF et al. Comparison of electrically evoked cortical potential thresholds generated with subretinal or suprachoroidal placement of a microelectrode array in the rabbit. *J Neural Eng* 2005; 2: S48–S56.
82. Parver LM, Auker CR, Carpenter DO. Choroidal blood flow. III. Reflexive control in human eyes. *Arch Ophthalmol* 1983; 101: 1604–1606.
83. Zhou JA, Woo SJ, Park SI, Kim ET, Seo JM, Chung H et al. 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; 2008: 547428.
84. Heynen H, van Norren D. Origin of the electroretinogram in the intact macaque eye - II. Current source-density analysis. *Vision Res* 1985; 25: 709–715.
85. Kanda H, Morimoto T, Fujikado T, Tano Y, Fukuda Y, Sawai H. Electrophysiological studies of the feasibility of suprachoroidal-transretinal stimulation for artificial vision in normal and RCS rats. *Invest Ophthalmol Vis Sci* 2004; 45: 560–566.
86. Nakauchi K, Fujikado T, Kanda H, Morimoto T, Choi JS, Ikuno Y et al. Transretinal electrical stimulation by an intrascleral multichannel electrode array in rabbit eyes. *Graefes Arch Clin Exp Ophthalmol* 2005; 243: 169–174.
87. Kanda H, Mihashi T, Miyoshi T, Hirohara Y, Morimoto T, Terasawa Y et al. Evaluation of electrochemically treated bulk electrodes for a retinal prosthesis by examination of retinal intrinsic signals in cats. *Jpn J Ophthalmol* 2014; 58: 309–319.
88. Morimoto T, Kamei M, Nishida K, Sakaguchi H, Kanda H, Ikuno Y et al. Chronic implantation of newly developed suprachoroidal-transretinal stimulation prosthesis in dogs. *Invest Ophthalmol Vis Sci* 2011; 52: 6785–6792.
89. Weiland JD, Cho AK, Humayun MS. Retinal prostheses: current clinical results and future needs. *Ophthalmology* 2011; 118: 2227–2237.
90. Shepherd RK, Shivdasani MN, Nayagam DA, Williams CE, Blamey PJ. Visual prostheses for the blind. *Trends Biotechnol* 2013; 31: 562–571.
91. Zrenner E, Bartz-Schmidt KU, Benav H, Besch D, Bruckmann A, Gabel VP et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. *Proc Biol Sci* 2011; 278: 1489–1497.
92. Perez Fornos A, Sommerhalder J, da Cruz L, Sahel JA, Mohand-Said S, Hafezi F et al. Temporal properties of visual perception on electrical stimulation of the retina. *Invest Ophthalmol Vis Sci* 2012; 53: 2720–2731.
93. Horsager A, Greenberg RJ, Fine I. Spatiotemporal interactions in retinal prosthesis subjects. *Invest Ophthalmol Vis Sci* 2010; 51: 1223–1233.
94. Dagnelie G, Keane P, Narla V, Yang L, Weiland J, Humayun M. Real and virtual mobility performance in simulated prosthetic vision. *J Neural Eng* 2007; 4: S92–S101.
95. Ayton LN, Blamey PJ, Guymer RH, Luu CD, Nayagam DA, Sinclair NC et al. First-in-human trial of a novel suprachoroidal retinal prosthesis. *PLoS One* 2014; 9: e115239.
96. Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Sahel JA, Stanga PE et al. Interim results from the international trial of Second Sight's visual prosthesis. *Ophthalmology* 2012; 119: 779–788.

97. Garcia S, Petrini K, Lyndon DC, Rubin G, Nardini M. Assessing improvements in perception afforded by retinal prostheses in multisensory tasks. ARVO Annual Meeting Abstracts, 2014.
98. da Cruz L, Coley BF, Dorn J, Merlini F, Filley E, Christopher P et al. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. *Br J Ophthalmol* 2013; 97: 632–636.
99. Ahuja AK, Dorn JD, Caspi A, McMahon MJ, Dagnelie G, Dacruz L et al. Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. *Br J Ophthalmol* 2011; 95: 539–543.
100. Fujikado T, Kamei M, Sakaguchi H, Kanda H, Morimoto T, Ikuno Y et al. Clinical trial of chronic implantation of suprachoroidal-transretinal stimulation system for retinal prosthesis. *Sens Mater* 2012; 24: 181–187.
101. Fujikado T, Morimoto T, Kanda H, Kusaka S, Nakauchi K, Ozawa M et al. Evaluation of phosphenes elicited by extraocular stimulation in normals and by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa. *Graefes Arch Clin Exp Ophthalmol* 2007; 245: 1411–1419.
102. Greenwald SH, Horsager A, Humayun MS, Greenberg RJ, McMahon MJ, Fine I. Brightness as a function of current amplitude in human retinal electrical stimulation. *Invest Ophthalmol Vis Sci* 2009; 50: 5017–5025.
103. Nanduri D, Fine I, Horsager A, Boynton GM, Humayun MS, Greenberg RJ et al. Frequency and amplitude modulation have different effects on the percepts elicited by retinal stimulation. *Invest Ophthalmol Vis Sci* 2012; 53: 205–214.
104. Roska B, Werblin F. Vertical interactions across ten parallel, stacked representations in the mammalian retina. *Nature* 2001; 410: 583–587.
105. Jensen RJ, Ziv OR, Rizzo JF. Responses of rabbit retinal ganglion cells to electrical stimulation with an epiretinal electrode. *J Neural Eng* 2005; 2: S16–S21.
106. Fried SI, Hsueh HA, Werblin FS. A method for generating precise temporal patterns of retinal spiking using prosthetic stimulation. *J Neurophysiol* 2006; 95: 970–978.
107. Eickenscheidt M, Jenkner M, Thewes R, Fromherz P, Zeck G. Electrical stimulation of retinal neurons in epiretinal and subretinal configuration using a multicapacitor array. *J Neurophysiol* 2012; 107: 2742–2755.
108. Sekirnjak C, Hottowy P, Sher A, Dabrowski W, Litke AM, Chichilnisky EJ. Electrical stimulation of mammalian retinal ganglion cells with multielectrode arrays. *J Neurophysiol* 2006; 95: 3311–3327.
109. Chen SJ, Mahadevappa M, Roizenblatt R, Weiland J, Humayun M. Neural responses elicited by electrical stimulation of the retina. *Trans Am Ophthalmol Soc* 2006; 104: 252–259.
110. Elfar SD, Cottaris NP, Iezzi R, Abrams GW. A cortical (V1) neurophysiological recording model for assessing the efficacy of retinal visual prostheses. *J Neurosci Methods* 2009; 180: 195–207.
111. Hadjinicolaou AE, Savage CO, Apollo NV, Garrett DJ, Cloherty SL, Ibbotson MR et al. Optimizing the electrical stimulation of retinal ganglion cells. *IEEE Trans Neural Syst Rehabil Eng* 2015; 23: 169–178.
112. Stett A, Mai A, Herrmann T. Retinal charge sensitivity and spatial discrimination obtainable by subretinal implants: key lessons learned from isolated chicken retina. *J Neural Eng* 2007; 4: S7–S16.
113. Margalit E, Thoreson WB. Inner retinal mechanisms engaged by retinal electrical stimulation. *Invest Ophthalmol Vis Sci* 2006; 47: 2606–2612.
114. Boinagrov D, Pangratz-Fuehrer S, Goetz G, Palanker D. Selectivity of direct and network-mediated stimulation of the retinal ganglion cells with epi-, sub- and intraretinal electrodes. *J Neural Eng* 2014; 11: 026008.
115. Humayun MS, de Juan E Jr, Weiland JD, Dagnelie G, Katona S, Greenberg R et al. Pattern electrical stimulation of the human retina. *Vision Res* 1999; 39: 2569–2576.
116. Horsager A, Greenwald SH, Weiland JD, Humayun MS, Greenberg RJ, McMahon MJ et al. Predicting visual sensitivity in retinal prosthesis patients. *Invest Ophthalmol Vis Sci* 2009; 50: 1483–1491.
117. Dorn JD, Ahuja AK, Caspi A, da Cruz L, Dagnelie G, Sahel JA et al. The detection of motion by blind subjects with the epiretinal 60-electrode (Argus II) retinal prosthesis. *JAMA Ophthalmol* 2013; 131: 183–189.
118. Humayun MS, de Juan E Jr, Dagnelie G, Greenberg RJ, Propst RH, Phillips DH. Visual perception elicited by electrical stimulation of retina in blind humans. *Arch Ophthalmol* 1996; 114: 40–46.
119. Shivdasani MN, Sinclair NC, Dimitrov PN, Varsamidis M, Ayton LN, Luu CD et al. Factors affecting perceptual thresholds in a suprachoroidal retinal prosthesis. *Invest Ophthalmol Vis Sci* 2014; 55: 6467–6481.
120. Geddes LA. Accuracy limitations of chronaxie values. *IEEE Trans Biomed Eng* 2004; 51: 176–181.
121. Greenberg RJ. *Analysis of Electrical Stimulation of the Vertebrate Retina - Work towards a Retinal Prosthesis.* Baltimore: Johns Hopkins University, 1998.
122. Jensen RJ, Ziv OR, Rizzo JF 3rd. Thresholds for activation of rabbit retinal ganglion cells with relatively large, extracellular microelectrodes. *Invest Ophthalmol Vis Sci* 2005; 46: 1486–1496.
123. Lukasiewicz PD. Synaptic mechanisms that shape visual signaling at the inner retina. *Prog Brain Res* 2005; 147: 205–218.
124. Nowak LG, Bullier J. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter. *Exp Brain Res* 1998; 118: 477–488.
125. Kole MH, Stuart GJ. Signal processing in the axon initial segment. *Neuron* 2012; 73: 235–247.
126. Van Wart A, Matthews G. Impaired firing and cell-specific compensation in neurons lacking nav1.6 sodium channels. *J Neurosci* 2006; 26: 7172–7180.
127. Van Wart A, Trimmer JS, Matthews G. Polarized distribution of ion channels within microdomains of the axon initial segment. *J Comp Neurol* 2007; 500: 339–352.
128. Jensen RJ, Rizzo JF 3rd. Responses of ganglion cells to repetitive electrical stimulation of the retina. *J Neural Eng* 2007; 4: S1–S6.
129. Tsai D, Morley JW, Suaning GJ, Lovell NH. Direct activation and temporal response properties of rabbit retinal ganglion cells following subretinal stimulation. *J Neurophysiol* 2009; 102: 2982–2993.
130. Tsai D, Morley JW, Suaning GJ, Lovell NH. Frequency-dependent reduction of voltage-gated sodium current modulates retinal ganglion cell response rate to electrical stimulation. *J Neural Eng* 2011; 8: 066007.
131. Ahuja AK, Behrend MR, Kuroda M, Humayun MS, Weiland JD. An in vitro model of a retinal prosthesis. *IEEE Trans Biomed Eng* 2008; 55: 1744–1753.
132. Freeman DK, Fried SI. Multiple components of ganglion cell desensitization in response to prosthetic stimulation. *J Neural Eng* 2011; 8: 016008.
133. Zrenner E. Will retinal implants restore vision? *Science* 2002; 295: 1022–1025.
134. Berry MJ, Warland DK, Meister M. The structure and precision of retinal spike trains. *Proc Natl Acad Sci U S A* 1997; 94: 5411–5416.
135. Davuluri NS, Weiland JD. Time-varying pulse trains limit retinal desensitization caused by continuous electrical stimulation. *Conf Proc IEEE Eng Med Biol Soc* 2014; 2014: 414–417.
136. Stasheff SF. Emergence of sustained spontaneous hyperactivity and temporary preservation of OFF responses in ganglion cells of the retinal degeneration (rd1) mouse. *J Neurophysiol* 2008; 99: 1408–1421.
137. Stasheff SF, Shankar M, Andrews MP. Developmental time course distinguishes changes in spontaneous and light-evoked retinal ganglion cell activity in rd1 and rd10 mice. *J Neurophysiol* 2011; 105: 3002–3009.
138. Yee CW, Toychiev AH, Ivanova E, Sagdullaev BT. Aberrant synaptic input to retinal ganglion cells varies with morphology in a mouse model of retinal degeneration. *J Comp Neurol* 2014; 522: 4085–4099.
139. Goo YS, Ahn KN, Song YJ, Ahn SH, Han SK, Ryu SB et al. Spontaneous oscillatory rhythm in retinal activities of two retinal degeneration (rd1 and rd10) mice. *Korean J Physiol Pharmacol* 2011; 15: 415–422.
140. Menzler J, Channappa L, Zeck G. Rhythmic ganglion cell activity in bleached and blind adult mouse retinas. *PLoS One* 2014; 9: e106047.
141. Cameron MA, Suaning GJ, Lovell NH, Morley JW. Electrical stimulation of inner retinal neurons in wild-type and retinally degenerate (rd/rd) mice. *PLoS One* 2013; 8: e68882.
142. Chang B, Hawes NL, Hurd RE, Davisson MT, Nusinowitz S, Heckenlively JR. Retinal degeneration mutants in the mouse. *Vision Res* 2002; 42: 517–525.
143. Gargini C, Terzibasi E, Mazzoni F, Strettoi E. Retinal organization in the retinal degeneration 10 (rd10) mutant mouse: a morphological and ERG study. *J Comp Neurol* 2007; 500: 222–238.
144. Sekirnjak C, Hulse C, Jepson LH, Hottowy P, Sher A, Dabrowski W et al. Loss of responses to visual but not electrical stimulation in ganglion cells of rats with severe photoreceptor degeneration. *J Neurophysiol* 2009; 102: 3260–3269.
145. Siu TL, Morley JW. Visual cortical potentials of the mouse evoked by electrical stimulation of the retina. *Brain Res Bull* 2008; 75: 115–118.
146. Chan LH, Ray A, Thomas BB, Humayun MS, Weiland JD. In vivo study of response threshold in retinal degenerate model at different degenerate stages. *Conf Proc IEEE Eng Med Biol Soc* 2008; 2008: 1781–1784.
147. Freeman DK, Eddington DK, Rizzo JF 3rd, Fried SI. Selective activation of neuronal targets with sinusoidal electric stimulation. *J Neurophysiol* 2010; 104: 2778–2791.
148. Sekirnjak C, Hottowy P, Sher A, Dabrowski W, Litke AM, Chichilnisky EJ. High-resolution electrical stimulation of primate retina for epiretinal implant design. *J Neurosci* 2008; 28: 4446–4456.
149. Abramian M, Lovell NH, Morley JW, Suaning GJ, Dokos S. Activation of retinal ganglion cells following epiretinal electrical stimulation with hexagonally arranged bipolar electrodes. *J Neural Eng* 2011; 8: 035004.

150. Wong RC, Garrett DJ, Grayden DB, Ibbotson MR, Cloherty SL. Efficacy of electrical stimulation of retinal ganglion cells with temporal patterns resembling light-evoked spike trains. *Conf Proc IEEE Eng Med Biol Soc* 2014; 2014: 1707–1710.
151. Lorach H, Goetz G, Smith R, Lei X, Mandel Y, Kamins T et al. Photovoltaic restoration of sight with high visual acuity. *Nat Med* 2015; 21: 476–482.
152. Behrend MR, Ahuja AK, Humayun MS, Chow RH, Weiland JD. Resolution of the epiretinal prosthesis is not limited by electrode size. *IEEE Trans Neural Syst Rehabil Eng* 2011; 19: 436–442.
153. Stett A, Barth W, Weiss S, Haemmerle H, Zrenner E. Electrical multisite stimulation of the isolated chicken retina. *Vision Res* 2000; 40: 1785–1795.
154. Shyu JS, Maia M, Weiland JD, Ohearn T, Chen SJ, Margalit E et al. Electrical stimulation in isolated rabbit retina. *IEEE Trans Neural Syst Rehabil Eng* 2006; 14: 290–298.
155. Habib AG, Cameron MA, Suaning GJ, Lovell NH, Morley JW. Spatially restricted electrical activation of retinal ganglion cells in the rabbit retina by hexapolar electrode return configuration. *J Neural Eng* 2013; 10: 036013.
156. Eckhorn R, Wilms M, Schanze T, Eger M, Hesse L, Eysel UT et al. Visual resolution with retinal implants estimated from recordings in cat visual cortex. *Vision Res* 2006; 46: 2675–2690.
157. Shivdasani MN, Luu CD, Cicione R, Fallon JB, Allen PJ, Leuenberger J et al. Evaluation of stimulus parameters and electrode geometry for an effective suprachoroidal retinal prosthesis. *J Neural Eng* 2010; 7: 036008.
158. Shivdasani MN, Fallon JB, Luu CD, Cicione R, Allen PJ, Morley JW et al. Visual cortex responses to single- and simultaneous multiple-electrode stimulation of the retina: implications for retinal prostheses. *Invest Ophthalmol Vis Sci* 2012; 53: 6291–6300.
159. Sim SL, Szalewski RJ, Johnson LJ, Akah LE, Shoemaker LE, Thoreson WB et al. Simultaneous recording of mouse retinal ganglion cells during epiretinal or subretinal stimulation. *Vision Res* 2014; 101: 41–50.
160. Roessler G, Laube T, Brockmann C, Kirschkamp T, Mazinani B, Goertz M et al. Implantation and explantation of a wireless epiretinal retina implant device: observations during the EPIRET3 prospective clinical trial. *Invest Ophthalmol Vis Sci* 2009; 50: 3003–3008.
161. Hornig R, Zehnder T, Velikay-Parel M, Laube T, Feucht M, Richard G. *The IMI Retinal Implant System*. Artificial Sight: Springer, 2007. p. 111–128.
162. Pixium Vision. 2015 Available at: http://www.pixium-vision.com/en. [Accessed 4/7/2015].
163. Yanai D, Weiland JD, Mahadevappa M, Greenberg RJ, Fine I, Humayun MS. Visual performance using a retinal prosthesis in three subjects with retinitis pigmentosa. *Am J Ophthalmol* 2007; 143: 820–827.