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Visual prostheses for the blind

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Abstract

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

Keywords: Neural prosthesis; Electrical stimulation; Electrodes; Blindness, Bionic vision

Introduction:

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

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

It is estimated that 285 million people are visually impaired worldwide; 39 million of whom are blind [2]. While uncorrected refractive errors are the main cause of visual impairment, diseases associated with degeneration of the retina's photoreceptors result in severe vision loss with few or no therapeutic options for ongoing clinical management. Importantly, significant numbers of RGCs are spared following the

loss of photoreceptors. Although there are major alterations to the neural circuitry of these surviving neurons [3] their presence provides the potential to restore vision using electrical stimulation delivered by an electrode array located close to the retina (see Text Box 1. Electrical Stimulation of Neural Tissue). The clinical management of other forms of blindness, including glaucoma, diabetic retinopathy and trauma are also associated with limited therapeutic options and can result in a non-functional retina or optic nerve. While a retinal prosthesis is not suitable for these pathologies, electrical stimulation at other sites along the central visual pathway, particularly the visual cortex, has the potential to restore vision in these cases (Fig. 1).

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

Over the past two decades there has been increased interest in the development of visual prostheses. Much of this impetus stems from the success of cochlear

implants [9], advances in enabling technologies, and the lack of alternative therapeutic options for the treatment of these patients. There are at least 23 research groups developing visual prostheses [10], the majority of which are retinal prostheses.

<Fig 1 about here>

The normal and diseased retina

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

Viewing the retina through the pupil via an ophthalmoscope (a fundus image), the most notable feature is the surface vasculature, which originates from the pale circular region known as the optic disc, and provides nourishment to the inner retinal layers (Fig. 2b). The optic disc is the point where the axons of the RGCs form the optic nerve and exit the eye. Near the centre of the retina is an oval pigmented region known as the macula, which does not contain large blood vessels. This region

is specialized for central, high acuity vision, which is greatest at the fovea – a small depression in the centre of the macula containing almost exclusively cone photoreceptors (Fig 2b) [11].

Retinitis pigmentosa and age-related macular degeneration

Retinitis pigmentosa (RP) and age-related macular degeneration (AMD) are two degenerative diseases of the retina that result in blindness, secondary to photoreceptor loss (Fig 2d). RP is the collective term for a group of relatively rare hereditary deficits that lead to blindness in midlife, as a result of a gradual degeneration of photoreceptors. In typical rod-cone dystrophy, the lesion is initially restricted to the peripheral retina resulting in tunnel vision (Fig 2f), but over time the central macular region can also be affected. Importantly, there is currently no cure for RP. AMD is a leading cause of vision loss in older adults; in western countries it accounts for ~50% of all severe visual impairment and blindness [12]. It gradually destroys the high resolution macula region of the retina while typically leaving peripheral vision intact (Fig 2g). There are two forms of AMD. Dry AMD makes up the majority of cases (85-90%). With no effective treatment options the disease process ultimately leads to a severe loss of central visual field. Wet AMD makes up 10-15% of cases and is characterised by abnormal proliferation of blood vessels in the choroid. As the disease progresses this vascularization results in blood and fluid accumulation, damaging the photoreceptors of the macular region and resulting in severe loss of central vision (Fig. 2h). Wet AMD progresses rapidly and without intervention can cause severe damage within a few months. At present it is possible to use anti-vascular endothelial growth factor (anti-VEGF) drugs or retinal laser

treatment to reduce the formation of new blood vessels; however it is not possible to reverse the progression of the pathology.

Remodelling of the retina following loss of photoreceptors

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

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

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

<Fig 2 about here>

Design principles of visual prostheses

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

There are several design advantages to using a photodiode array, primarily the absence of wires, which simplifies the surgery. Additionally, because a photodiode array utilises existing ocular optics and eye position to localise the visual field, there is no need to take into account the subject's gaze. The major limiting factor associated with the use of photodiodes is their inability to provide sufficient energy necessary for retinal stimulation [21]. To overcome this limitation one photodiode based device includes an external power source and a leadwire assembly [16, 22], while a second design intends to use pulsed infrared light to provide both power and visual information directly to a photodiode array implanted in the retina [17].

The most common form of a visual prosthesis incorporates an electrode array located on or close to the retina. There are a number of anatomical sites where these electrodes can be placed including the inner surface of the retina (epiretinal),

between the retina and choroid (subretinal) or between the choroid and the sclera (suprachoroidal) (Fig 2i).

<Fig 3 about here>

Epiretinal:

Placing an electrode array on the inner surface of the retina ensures the electrodes stimulate the output of the retina - the axons of the RGCs. Such proximity to RGCs results in low thresholds for neural activation, minimizing the physical size required of individual electrodes and theoretically maximizing the resolution and acuity of prosthetic vision over electrodes positioned in other retinal locations. Surgically, the electrode array is fixed to the inner retinal surface using one or two retinal tacks. The devices make use of platinum, iridium oxide or conductive diamond electrodes coupled to stimulation electronics within a hermetic capsule that is contained entirely within the vitreous chamber. The implant housings are fixed in place of the lens or attached extraocularly to the sclera. The capsule is coupled to a receiving coil which is inductively linked to an external coil fitted to a pair of glasses that also houses the camera. There are several research groups and companies developing epiretinal device. [18, 23-25]. Second Sight Medical Product recently received regulatory approval in both Europe and the USA to treat late-stage RP with their 60 electrode Argus II device (Fig. 4a). Two technical challenges associated with the epiretinal approach are related to the significant constraints on device size with this surgical approach, and the fixation and long-term mechanical stability of the electrode array on the retinal surface using penetrating retinal tacks. Additional safety issues include the potential for mechanical damage to the retina and an increased risk of inflammation with devices that run leadwires from the vitreous through the sclera.

Subretinal:

Significant neural processing occurs within the outer and middle layers of the retina peripheral to the RGCs; epiretinal prostheses cannot take advantage of this processing. Subretinal electrode arrays are designed to be positioned at the level of the outer retina where, in a healthy eye, photoreceptors would be located [17, 22, 26, 27] (Fig 1i). While this is a logical choice for an implant whose function is to replace lost photoreceptors, it comes with its own challenges. The surgical approach is technically difficult and the electrode array and associated electronics must be extremely thin (<400 μm) to minimize retinal damage or detachment. In addition, there is the potential for a subretinal electrode array to impede blood supply from the choroid to the surviving retina. Finally, while at least some of the impetus for the development of a subretinal neural prosthesis is to take advantage of the normal processing that occurs in the outer and middle retina [22], this becomes a moot point after the remodelling that occurs following photoreceptor loss [3]. A number of groups are developing this approach, with the Alpha-IMS manufactured by Retina Implant AG being tested in multisite clinical trials [16, 22] (Fig. 4b). There are technical challenges with manufacturing a long term hermetic encapsulation with the thin profile of these implants. Some have chosen photodiodes as the sensing elements [16, 17]; while another group has developed an array of 256 electrodes driven by an implantable stimulator containing 256 current drivers [28]. Many of the safety concerns associated with epiretinal implants are also an issue for epiretinal devices.

Suprachoroidal:

While electrodes located in a tissue pocket between the choroid and sclera (the so-called suprachoroidal position) are some distance from their target neurons in the

inner retina, this approach has been adopted by a number of groups. This placement offers a safe and simple surgical approach and a mechanically stable location [29]. Clinical complications are minimized with the suprachoroidal approach, as multiple layers of the eye do not have to be breached in order to position the electrode array [19, 30-34]. A major limitation of this approach is an increase in stimulus thresholds as a result of the greater distance between the electrode array and the retina when compared with epi- and subretinal devices. Experimental studies have demonstrated that the retina can be effectively stimulated at safe levels using this electrode position [30, 35]. Moreover the choroid – which separates the electrode array from the retina in this approach – undergoes significant shrinkage in RP [36]. Recently, two groups have conducted successful clinical trials using this approach; both demonstrated that long-term severely blind patients can perceive discriminable percepts in response to electrical stimulation within safe limits [19, 37](Fig. 4c).

Visual prostheses based on stimulation of the central visual pathway:

Stimulation of the visual pathway at sites central to the retina has the potential to provide prosthetic vision for a wider range of pathologies, including those that result in damage to the optic nerve. Although clinical trials of cortical based devices were undertaken early in the development of visual prostheses [7, 38], there is currently no central visual prosthesis undergoing a clinical trial.

Optic Nerve:

Using a spiral cuff electrode the optic nerve has been targeted as an implant site for a clinical trial in a blind patient, which resulted in the generation of usable phosphenes [39]. More recently, there has been interest in targeting the optic nerve using an array of penetrating electrodes [40]. Highly focal excitation would be necessary in order to provide reliable retinotopic cues. Given this technological

challenge it is unclear how this approach would surpass the advantages of retinal implants.

<Fig 4 about here>

Lateral Geniculate Nucleus:

One group has proposed placing stimulating electrodes in the LGN of the thalamus [41]. The LGN is a well characterized retinotopic structure within the central visual pathway. This study showed that it was possible to elicit neural responses in the visual cortex from thalamic microstimulation, providing proof of concept for this stimulation site. Although there have been no clinical trials to date, the surgical approach would be similar to that used in deep brain stimulation to treat movement disorders associated with Parkinson's disease [42].

Visual Cortex:

Early clinical studies provided strong evidence that visual sensations could be readily evoked through stimulation of the cortical surface [7, 38] or via penetrating microelectrodes [43]. This research has recently been advanced by taking advantage of improved electrode technologies [20, 44-46]. Most groups propose placing individual modules or tiles each containing multiple stimulating electrodes along with associated stimulating circuitry within a hermetically sealed chamber. Multiple tiles can be inserted into the visual cortex to provide a large number of individually addressable electrodes.

The primary visual cortex is thought to be an ideal location for a visual prosthesis for several reasons; it is well organised retinotopically, it has adequate space for multiple implanted components and is known to have a large area devoted to central vision. However, it is unclear whether a prosthesis that bypasses all visual

processing occurring within the retina and LGN will contain sufficient information for higher order brain centres to accurately recognise percepts generated from electrical stimulation. As an example, there is a rich thalamocortical feedback loop that occurs in normal vision processing (the LGN receives the majority of its input from the visual cortex [41]); a cortical based prosthesis would bypass this processing stage. In addition, while the plastic brain plays an important role in improved clinical outcomes with sensory prostheses [47], it remains unclear whether direct stimulation of the visual cortex will recruit the same level of plastic reorganisation as stimulation arising from the retina.

Perceptual effects of visual prostheses

Phosphenes are visual sensations produced by stimuli other than light, including mechanical, magnetic or electrical stimulation of the retina or brain [4]. The phosphenes evoked by electrical stimuli have typically been described in the literature as flashes of light, often amorphous but sometimes with a clear well-defined shape. Studies have also reported complex phosphenes which can be darker than the patient's naturally perceived background, sometimes with both bright and dark areas in the same phosphene [25]. The brightness, shape, size, duration and location of a phosphene can be manipulated by varying the location and configuration of electrodes being stimulated and the electrical waveforms used [48-50].

Importantly, when stimulating multiple electrodes on an array, phosphenes can interact with one another to change the perceived image [51, 52]. Despite the complexities of phosphenes evoked through electrical stimulation, they form the basic building blocks of prosthetic vision. For example, psychophysical studies have

demonstrated that by stimulating appropriate electrodes on an array, it is possible to create the perception of retinotopically organized patterns and simple shapes such as lines of different orientations and geometric objects (e.g. triangle, square etc), regardless of whether the device is placed in the epiretinal [18], subretinal [50] or suprachoroidal [37, 53] space.

A camera and an image processing algorithm are required to provide a visual representation of the subjects' surroundings. Subjects implanted with the Argus II epiretinal system and using an external camera to source their visual field can perform object localisation, motion discrimination and discrimination of oriented gratings with a best visual acuity to date of 20/1260 [18, 54]. If a 16X zoom camera mode is enabled, then acuity measures increase to 20/200, but the field of view is correspondingly reduced from 20° down to a few degrees, making scanning of an image more time consuming [55]. The Alpha-IMS subretinal device with 25 times more electrodes than the Argus II has demonstrated best visual acuity of 20/546 [22], allowing patients implanted with this device to be able to detect and localize light and motion, identify, localize and discriminate high contrast objects and read large font letters [22]. Phosphenes generated by stimulation of the visual cortex are often described as more complex than those induced by retinal implants, although well-defined, localized and resolvable phosphenes are possible [7], and there are reports of blind subjects reading by incorporation of a camera with the device [56].

Head/Eye Movement Issues:

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

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

Role of plasticity and training

While the status of the visual cortex after long-term blindness is not well understood [14], it is clear from the existing clinical data that useful visual cues can be evoked via a visual prosthesis decades after the onset of blindness. Visual experience obtained through the use of a device is expected to result in improved performance as a result of plasticity within the central visual pathway. Strong support for the positive role of learning and plasticity comes from 30 years' experience of cochlear implant use in profoundly deaf adults. Studies examining factors that affect clinical performance consistently demonstrate that the duration of cochlear implant experience has a significant positive effect on speech understanding [57, 58]. These clinical results are supported by animal studies that show electrophysiological evidence of cortical reorganization in deafened animals reared using cochlear implants [59].

Careful device fitting and ongoing training are important for the clinical success of these devices. In order to maximize the benefits of plasticity, training using everyday tasks, not just object recognition, is required [60]. Device fitting can be a time

consuming procedure that will require ongoing monitoring. The threshold and dynamic range necessary to evoke a useable phosphene must be determined for each electrode on the array. This task becomes problematic with high density electrode arrays. Finally, the successful clinical application of visual prostheses must be a productive collaboration between the patient, their support family, researchers, clinicians and low vision rehabilitation specialists.

Future directions and concluding remarks

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

In the shorter term, there remain considerable technical challenges that must be addressed before visual prostheses receive widespread clinical acceptance. These include effective electrode fixation and long-term stability; a safe surgical technique that can be performed routinely by retinal surgeons; the maintenance of a healthy/undamaged electrode/neural interface; device miniaturization and hermetic sealing; MRI compatibility; suitable power consumption; safety of simultaneous electrical stimulation of multiple electrodes; eye tracking technology to account for eye movement; and the use of sophisticated image processing techniques such as feature extraction. However, the single most challenging issue will be associated with the fitting and patient training using devices with a large number of electrodes (>40). Despite these challenges, visual prostheses are destined to become a gold

standard in the clinical management of blind patients. Ultimately these devices will provide a level of prosthetic vision that will allow users to read large font print and recognise faces.

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Figure 1. Overview of the visual pathway from the retina to the primary visual cortex. Visual prostheses can potentially target several sites along this pathway including the retina, the optic nerve, lateral geniculate nucleus and the visual cortex. The majority of these structures have a well organised topographic map of the retina,

i.e. the spatial organisation of the retina is maintained throughout the visual pathway. This is referred to as retinotopic organization.

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

Figure 3. (a) Schematic diagram of a generic retinal prosthesis illustrating a receiver-stimulator unit implanted in the mastoid bone behind the ear (arrow), a leadwire assembly (arrowhead) connecting the output of the stimulator to an array of electrodes (e) implanted in the retina. The electrode array can be tacked in front of

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

Figure 4. Fundus images of three retinal prostheses in clinical use in late stage RP patients. (a) Epiretinal Argus II electrode array containing 60 platinum electrodes fixed to the inner retina via a retinal tack (arrow) (Image courtesy of Second Sight Medical Products Inc.). (b) Subretinal Alpha IMS retinal implant containing 1500 photodiode electrodes on a 3x3 mm matrix. A leadwire (arrow) delivers additional power to the electrodes to ensure that the stimulus levels are sufficient to excite retinal tissue. (Image courtesy of the Center for Ophthalmology, University of Tübingen, Germany). (c) Bionic Vision Australia's prototype suprachoroidal electrode array developed by the Bionics Institute containing 24 platinum electrodes. The edge of the array is illustrated by the dashed line (Image courtesy of the Centre for Eye Research Australia).

Text Box 1: Electrical stimulation of neural tissue

Generation of an action potential via an electrical stimulus:

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

Principles of safe electrical stimulation of neural tissue:

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

When a metal electrode is placed into an electrolyte, a layer of charge on the electrode surface will attract polarized water molecules, creating a capacitive layer at the electrode-tissue interface (Helmholtz double layer). At low charge densities (<20 micro-Coulomb per electrode surface area [$\mu C/cm^2$]) charge injection is dominated by this capacitance, no charge carrier crosses the electrode-tissue interface and no electrochemical reaction products are formed in the electrolyte [61, 62]. In practice, activation of neural tissue requires charge densities higher than can be achieved via purely capacitive means. As charge density is increased, reversible electrochemical Faradaic reactions begin to dominate the charge injection process, including oxide formation/reduction and hydrogen-atom plating (Table 1; [63]). Importantly, these reactions are localized to the electrode-tissue interface and can be readily reversed via the passage of an equal charge of opposite polarity - the charge-balanced biphasic pulse - ensuring that no new electrochemical species are released into the biological environment [61, 62]. Safe electrical stimulation is restricted to charge injection via these processes and is dependent on the use of a charge balanced stimulus waveform and the electrode material used. As an example, stainless steel electrodes are restricted to a maximum safe charge density of 40-50 $\mu C/cm^2$ geom. using these reversible processes compared with 210 $\mu C/cm^2$ geom. for Platinum (Pt) electrodes.

At higher stimulus intensities charge injection is achieved via several irreversible electrochemical reactions, including electrode corrosion products, electrolysis of water and oxidation of chloride ions (Table 1). These electrochemical reaction products diffuse away from the electrode-tissue interface resulting in tissue damage.

Platinum, Iridium (Ir) and their alloys are the most extensively used metal electrodes for large surface area electrodes while iridium oxide and titanium nitride are often used for micro-stimulation.

<Table 1 here>

Text Box 2: Building a neural prosthesis

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

A stimulating/recording electrode array must be developed for each application as its design features will be dependent on factors including the underlying anatomy and pathophysiology of the target site and surgical access. An electrode array designed for long-term use in humans must ensure: minimal insertion trauma; biocompatibility; that the electrical stimulus is localized to discrete groups of target neurons; mechanical and electrical stability; that it is designed to minimize the risks of infection (including smooth surfaces; the elimination of cavities; and careful selection of biomaterials); that the stimulus regime is non-damaging in the long-term; and that it is designed for safe removal and replacement [62].

The implanted electronics that make up the active components of a visual prosthesis must be protected from the corrosive biological environment by hermetically sealing them from body fluids. The long-term reliability of any prosthesis is associated with the efficacy of its hermetic seal. The gold standard sealing technique is to encase the electronics within a titanium capsule that is sealed using a laser welder [64, 65]. This hermetic sealing technique can be problematic for retinal prostheses where size restrictions are an important design constraint. The use of polymers for hermetic encapsulation is an attractive alternative because many have excellent biocompatibility, ease of fabrication, flexibility, electromagnetic transmission and cost compared with titanium. However, there remain technical challenges in obtaining long-term effective hermetic bonding using polymers [64] and this remains an important area of research.

In order for the hermetically sealed electronics to deliver electrical pulses to the electrode array and/or receive biological signals from the neural interface, the implant must also incorporate a feed-through assembly that allows the sealed electronics to make electrical connection to the electrodes without compromising the seal [65]. There are significant design pressures on manufactures to develop devices with large electrode counts; this places considerable pressure on the development of reliable high density feed-through assemblies and is an important limiting factor in developing high density electrode arrays.

Active implants such as visual prostheses require a power source to operate. There are two alternative power sources that are in common use. Many devices receive

their power via a battery located within the hermetically sealed capsule (e.g. a Deep Brain Stimulator). This approach presents surgical restrictions on the implant site as a result of its size. For devices such as retinal prostheses, power is typically provided via an external source whenever the implant is in use. An inductive link comprised of coils on each side of the skin coupled via a radio-frequency carrier signal (depicted in Fig. 3b).

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