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Editorial

Vision research special issue: Sight restoration: Prosthetics, optogenetics and gene therapy

1. Introduction

As a species that cherishes the sense of vision, we fear blindness more than any infirmity, other than cancer (National Alliance For Eye and Vision Research & Alliance For Eye and Vision Research, 2014). Although blind individuals now have more tools and opportunities than ever before (see Fig. 1), learning the skills required to be a functional blind individual, especially late in life, remains a daunting task.

This special issue is inspired by the wide variety of innovative approaches that are currently being developed to prolong or partially restore vision. Our primary goal was to provide an integrated discussion of these various approaches in a single volume. Current sight restoration research involves a wide range of technologies that vary greatly both in their underlying scientific methodologies and in the challenges that they face. As a result, different approaches have rarely been discussed within an integrated literature, making it difficult to compare their relative opportunities and challenges in this rapidly developing field. This is a particularly timely moment for such a special issue. An extraordinary variety of potential therapies have begun, or are about to begin clinical trials, and one variant of retinal prosthesis is on the market in both Europe and America.

This editorial review is heavily inspired by the many contributors to the US National Eye Institute's Audacious Goals meeting of 2013, in which leaders in the field were given the opportunity to discuss the opportunities and challenges offered by current sight restoration technologies. Probably all of the interesting ideas of this editorial should be attributed to one of the many attendees who contributed to the discussion. Any incorrect or foolish ideas are of course entirely our own.

A wide variety of approaches towards sight restoration are currently being actively researched (e.g. Mellough et al., 2014; Nagel-Wolfrum et al., 2014; Pearson et al., 2014). This special issue focusses on three main approaches that primarily focus on alleviating the effects of photoreceptor diseases and are currently in, or are approaching, clinical trial status. Gene therapies use the delivery of genes to directly compensate for the loss of function of a disease gene, or, alternatively, use genes such as growth factors to generically prolong the life and functioning of photoreceptors. Optogenetics and small molecule photoswitches endow retinal cells with the ability to sense light by creating novel (or modulating existing) light-sensitive ion channels or pumps. Finally retinal and cortical prostheses use electrical stimulation to directly elicit neural responses.

2. Photoreceptor disease

Currently well over 200 different gene mutations result in irreversible vision loss, which collectively have the potential to affect over 20 million individuals (Retnet, 2014). Among the more common of these genetic retinal diseases are age-related macular degeneration (AMD) and retinitis pigmentosa (RP) (Resnikoff et al., 2004). Both RP and AMD involve loss of photoreceptors, but the pattern of loss is very different across the two diseases.

RP is caused by a wide variety of genetic deficits that usually directly affect photoreceptor cells (Daiger, Sullivan, & Bowne, 2013). Typically showing a simple Mendelian inheritance pattern (Daiger, Sullivan, & Bowne, 2013), RP generally (though not always) shows onset in middle age or later life (Hartong, Berson, & Dryja, 2006). RP most often initiates with death of the rods, leaving behind cones, which gradually lose function and die. The first sign of disease is poor or no night vision, due to rod dysfunction. Loss of cone-mediated vision progresses from the mid-periphery to the fovea (Fig. 2A). Thus, in later stages of the disease, the relatively high acuity afforded by remaining foveal photoreceptors creates 'tunnel' vision: reading is still possible but driving and self-navigation become increasingly difficult.

AMD and related diseases have the genetic architecture of complex traits, with environmental factors and risk alleles contributing to its incidence (Seddon, 2013). Like RP, AMD onset occurs in middle age or later, with prevalence increasing dramatically with age (Friedman et al., 2004). Early stages of age-related macular degeneration, which involve a relatively small degree of vision loss, are characterized by accumulations of extracellular material between the innermost layer of the choroid and the retinal pigment epithelium and changes in retinal pigment epithelium pigmentation. Later AMD is characterized by atrophy of the RPE with or without choroidal neovascularization, and the degeneration, dysfunction and death of macular rods and cones, eventually resulting in complete loss of foveal vision (Fig. 2B) (Curcio, Medeiros, & Millican, 1996; Medeiros & Curcio, 2001).

In later stages, both RP and AMD result in decreased cell counts across the layers of the neural retina, including ganglion, bipolar, and amacrine cells, as well as significant disorganization of connectivity (Marc & Jones, 2003; Marc et al., 2008).

3. From the real-world to the retinal response

Most of the sight restoration technologies considered in this volume (optogenetics, small molecule photoswitches and prosthetics) need to dynamically capture the visual scene using a

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Fig. 1. Brazil vs. Argentina in the Final of the Football for 5 at the 2007 Parapan American Games in Rio de Janeiro. (Copyright: 3.0 Br, Attribution: Marcello Casal Jr/ABr, Agência Brasil).

camera, and then recode the camera input into a form suitable for stimulation of the diseased retina (or cortex) (Fig. 3). The exception are forms of gene therapy, where a disease gene is compensated for by delivery of a normal allele of a disease gene.

The use of a camera poses two major challenges. The first is compensating for eye-movements. Unless the camera is implanted within the eye, any eye-movements will result in the visual image appearing to 'jump' in the world. One possible solution is gaze-contingent updating of visual stimulation. Reasonable approximations of this technology are already available in the laboratory (e.g. Richlan et al., 2013; Saunders & Woods, 2014), and spectacle mounted eye-tracking systems currently exist. However, developing a robust miniature device with sufficient temporal resolution will be a significant technical challenge. The second possibility is implanting the camera in the eye (Monge et al., 2013), but this will require significant advances in miniaturization, will need to be demonstrated to be biocompatible, and will likely have to meet significant aesthetic challenges.

The second challenge involves recoding the camera input into a form suitable for stimulation of the diseased retina. Early stages of recoding include enhancing and simplifying the video image via image processing. In their paper in this special issue, *Active confocal imaging for visual prostheses*, Peli and colleagues take this a step further by providing an example of an algorithm that actively emphasizes objects of interest in the scene and reduces background clutter.

Later stages of this recoding require finding the stimulation protocol that best replicates that enhanced image, given the nonlinear neural processing between stimulation and percept – 'hacking the circuits for seeing'. Here, sight restoration technologies are likely to rely heavily on basic science examining both the anatomical structure and the information processing functions of the retinal circuitry (Gollisch & Meister, 2010). It will also be important to understand how the information transformations carried out by retinal circuits are altered by disease. This is likely to be an iterative process, as people begin to be treated with prosthetics, gene therapy, optogenetics and small molecule photoswitches, we will learn our "unknown unknowns" in the retina.

Currently there are two main approaches to mimicking the retinal circuitry. The first is based on measuring (Jensen et al., 2003; Jensen, Ziv, & Rizzo, 2005a,b; Sekirnjak, et al., 2006, 2009) and modeling (e.g. Nirenberg & Pandarinath, 2012) the neural code of individual retinal cells to novel forms of stimulation. In this issue, Rattay and colleagues, in their article, *Modeling the response of ON and OFF retinal bipolar cells during electric stimulation*, provide an elegant example of this approach, using computational modeling to suggest that for retinal prostheses, it might be possible to bias the relative activation of ON vs. OFF bipolar cells using cathodic vs. anodic stimulation.

However, even if the response of individual retinal cells to stimulation, whether electrical, optogenetic or via small molecule photoswitches, were fully understood, further challenges remain. As

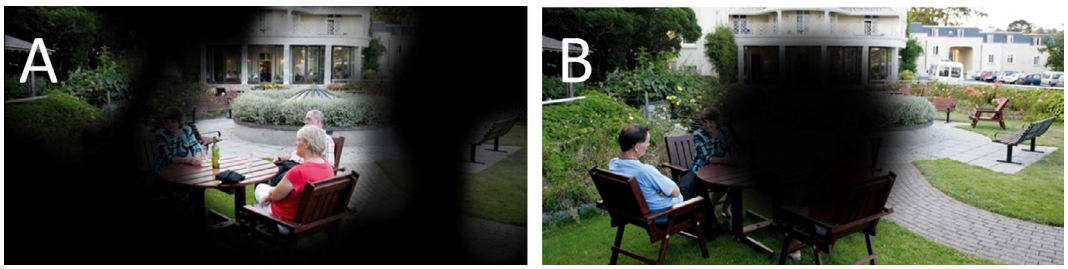

Fig. 2. Visual loss typical of later stages of retinitis pigmentosa (A) and macular degeneration (B). Permission to use these images kindly granted by Action for Blind People (www.actionforblindpeople.org.uk).

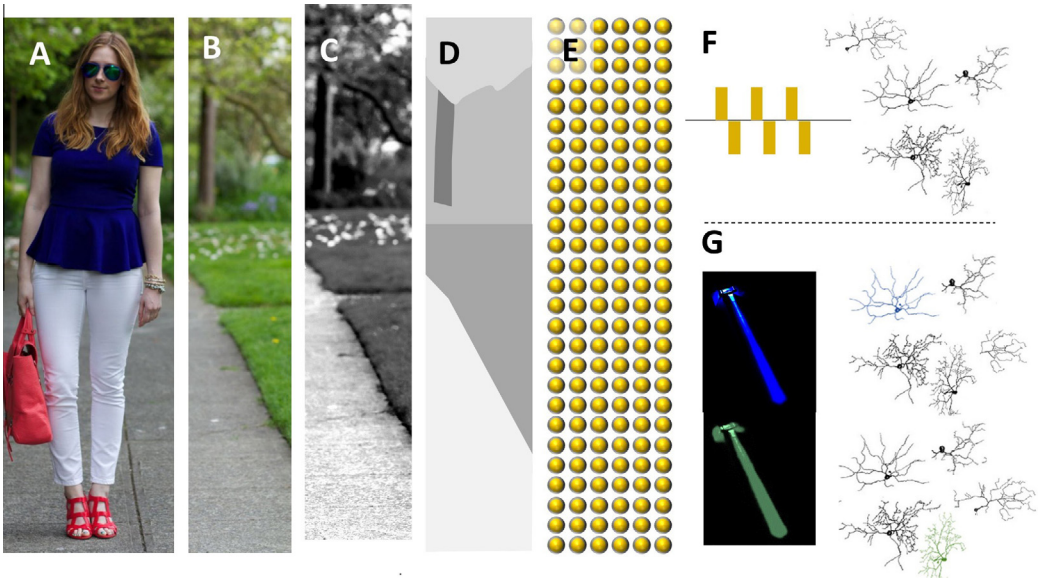

Fig. 3. The visual scene is captured by a camera, likely hidden in a pair of glasses (A). The captured image (B) is converted to grayscale and basic (C) or more sophisticated (D) image processing occurs. The resulting image is sent to an array in the eye (E) that converts the processed image into a stimulation protocol. In the case of electrical stimulation (F) although current devices try to selectively stimulate ganglion cells, it is likely that a wide range of cell types (including bipolar and amacrine) and sub-types (ON- and OFF-, midget and parasol) are stimulated. In the case of optogenetic or photoswitch stimulation it is likely that restricted sub-types of cells will be stimulated (G).

discussed by Rattay et al. in this special issue, any stimulation device implanted in patients is likely to stimulate 'clusters' within a network rather than individual cells. This significantly increases the complexity of the encoding problem. Indeed it is not entirely clear how well the ability to predict the response of individual cells will generalize to being able to predict the response when a cluster of (possibly diverse) cell types is stimulated. A second constraint is that the parameters of any encoding model must be estimated. In the case of Nirenberg and Pandarinath (2012) an input–output model designed to produce spike trains that best replicate natural responses to visual input was fitted by finding the parameters that best predicted experimentally observed ganglion cell spike trains for each individual ganglion cell. However, spike train data will not be available for patients, so models will either be based on psychophysical data (requiring a highly constrained model capable of being fitted with only a small number of parameters), or generalized from macaque (for which there are no RP or AMD disease models), or mouse retina.

Thus, at least in the foreseeable future, any encoding model for sight restoration technologies is likely to rely heavily on psychophysics, though these psychophysical models are likely to be heavily influenced by our knowledge of the retinal code. While models describing the percepts elicited by electrical stimulation based on behavioral performance have been developed (de Balthasar et al., 2008; Greenwald et al., 2009; Horsager et al., 2009, 2011; Horsager, Greenberg, & Fine, 2010; Nanduri et al., 2012), and it has been shown that these models show remarkable similarities to linear-nonlinear models of the retina (Horsager et al., 2009), this work has not yet been integrated into a single model capable of predicting the optimal stimulation sequence needed to replicate a desired visual percept.

Finally, encoding vision involves an understanding of how retinal pathways are decoded by the cortical circuitry that follows, including how this circuitry is affected by loss of visual input. Changes in cortical circuitry as a result of visual loss includes loss of visual processing abilities (Kalia et al., 2014; Ostrovsky, Andalman & Sinha, 2006; Ostrovsky et al., 2009), even when vision is lost after the critical period (Fine et al., 2003; Sikl et al., 2013), as well as the development of novel cross-modal responses to auditory and tactile stimulation within occipital cortex. It is not clear how these novel cross-modal responses will interact with restored vision (Dormal et al., 2014; Heimler, Weisz, & Collignon, 2014). Interestingly, although most individuals with RP or AMD retain vision in at least one region of their visual field, there is only a relatively small literature examining the cortical effects of blindness in individuals where some region of the visual field is spared (Cheung et al., 2009). In this special issue, Tjan and colleagues, in *Correlation of Vision Loss with Tactile-Evoked V1 Responses in Retinitis Pigmentosa*, show that in partially blind individuals the extent of tactile V1 responses is correlated with the extent of vision loss. It remains to be seen whether these cross-modal responses will affect the ability of individuals to make use of restored vision.

4. Gene therapy

With the enormous advances in human genetics brought about by "SNP chips", and inexpensive and rapid DNA sequencing, we are approaching a complete catalogue of mutations that lead to loss of vision. With this knowledge has come increasing interest in using gene therapy to directly compensate for the loss of function of a diseased gene.

The first disease to be successfully targeted with gene therapy was a specific form of Leber's congenital amaurosis (LCA), associated with a gene defect in RPE65, a recessive gene expressed only in the pigment epithelium that is characterized by low rod and cone vision from birth. Using AAV, it was possible to safely and effectively mediate the RPE65 gene defect in LCA by delivery of a normal copy of the gene (Bainbridge et al., 2008; Maguire et al., 2008).

Subsequently, humans with choroideremia, a recessive disease characterized by progressive atrophy of the choroid, RPE, and photoreceptors (Kalatzis, Hamel, & MacDonald, 2013), have been treated using a similar approach (MacLaren et al., 2014). These successes have opened the door for more than 30 clinical ocular gene therapy trials (Angeles et al., 2014). Current successes and future challenges are described in this special issue by Luk Vandenberghe and colleagues in *Promising and delivering gene therapies for vision loss*. One challenge of note is that AAV is unable to

accommodate some of the larger disease genes, e.g. ABCA4 for Stargardt's Disease. In such cases, viral vectors with larger capacity, such as lentiviral vectors (Kong et al., 2008) provide possible alternatives.

So far, the viral gene therapy approach has been limited to specific gene deficits. This is a serious limitation given that the number of genes associated with eye disease (currently almost 600, (OMIM, 2014)) in both syndromic and non-syndromic diseases, is larger than that of any other human organ. As a result, although collectively many millions of individuals suffer from RP and AMD, many individual forms of the disease are only carried within relatively small populations. For example approximately 70 genes are currently associated with RP alone (Retnet, 2014). Thus a gene-by-gene approach will make it logistically challenging and prohibitively expensive to individually target less common gene deficits. Despite this, animal models and clinical trials are now targeting more complex genetic deficiencies, including RP, AMD and glaucoma (Angeles et al., 2014).

In the meantime gene-independent approaches are being developed with the goal of providing a generic method (e.g. delivery of a growth factor or anti-oxidation genes) of keeping photoreceptors alive and functioning (e.g. Campochiaro et al., 2006; Sahel & Roska, 2013). Such approaches are likely to be particularly useful in diseases in which cell types not affected *directly* by the disease gene are nonetheless affected by the disease. For example, most genes associated with RP are expressed preferentially in rods, the cell type that is affected first in this disease. Cones typically do not express the disease gene, and their dysfunction and death seems to be due to non-autonomous causes that are unlikely to be gene-specific. In cases such as these it may be possible to preserve or prolong survival and function of photoreceptors using generic growth factors.

5. Optogenetics & small molecule photoswitches

Optogenetic proteins create light-sensitive ion channels or pumps that makes cells responsive to light (Bamann, Nagel, & Bamberg, 2010). In the context of sight recovery, these optogenetic proteins are delivered to a subset of the remaining retinal cells (Busskamp et al., 2012). Photoswitch compounds, a more recent approach described in more detail in this special issue by Van Gelder in his review, *Photochemical approaches to vision restoration*, elicit light sensitivity more directly, via small molecule photoswitches that directly modulate the activity of ion channels by reversibly activating and deactivating the channel with exposure to particular wavelengths of light (Polosukhina et al., 2012; Tochitsky et al., 2014). As described below, both optogenetics and photoswitches have proved capable of restoring behavioral light responses in animal models of genetic forms of blindness (Busskamp et al., 2010; Polosukhina et al., 2012; Tochitsky et al., 2014).

Optogenetic proteins have been used both to augment the light responses of photoreceptors and to create novel light sensitive responses within bipolar, amacrine or ganglion cells. One advantage to targeting photoreceptors with optogenetic proteins is that, in early to mid-states of the disease, the retinal circuitry remains reasonably intact, even after significant photoreceptor dysfunction and/or death. Any type of photoreceptor-initiated signal can tap into this circuitry, resulting in the delivery of information to the brain in a manner similar to that delivered by a healthy retina. In an early example of optogenetic therapy targeting photoreceptors, AAV vectors were used to deliver halorhodopsin, an optogenetic protein, to RP cones in mice, thereby augmenting their response to light and successfully producing light-driven behavior (Busskamp et al., 2010).

The obvious disadvantage to targeting photoreceptors is that, in later stages of the disease few photoreceptors may remain. One potential strategy is to target the photoreceptors with optogenetic proteins in conjunction with additional therapy to prolong photoreceptor survival. Alternatively, even once photoreceptors are gone, retinal neurons that are downstream of photoreceptors can be still be targeted with optogenetic proteins. Both channel rhodopsin and halorhodopsin have been delivered to retinal ganglion cells in mice and rats (Busskamp et al., 2012; Lagali et al., 2008; Mutter, Swietek, & Munch, 2014; Zhang et al., 2009), again resulting in visually guided behavior. Moreover, using transcription regulatory elements, it has proved possible to selectively target certain subtypes of retinal neurons. For example, channel rhodopsin has been selectively targeted to "ON" bipolar cells, using both an AAV vector and electroporation, and this selective targeting also elicited light-driven behavior (Doroudchi et al., 2011; Lagali et al., 2008).

Small molecule photoswitches, such as DENAQ, modulate the activity of voltage-gated ion channels (Tochitsky et al., 2014) rather than supplying a gene with an ion channel. For example, in RP mice, potassium channels are blocked by the *trans* form of DENAQ. When exposed to blue-green light, DENAQ isomerizes to the *cis* form and becomes inactive. In mice with retinal degeneration, but not wild type mice, DENAQ resulted in light-driven ganglion cell activity and light-dependent vision. Whereas these early studies used an endogenous ion channel as the target of the photoswitch molecule, a new study reports the use of a promising combination of a designer receptor and a photoswitch. Gaub et al. used a channel with an amino acid change that makes it uniquely susceptible to a photoswitch molecule (Caporale et al., 2011; Gaub et al., 2014). They then used AAV to deliver this photoswitch-sensitive channel to either ON bipolar cells or retinal ganglion cells, and later injected the eyes with the photoswitch. This approach proved successful in both mouse and dog models of RP (Gaub et al., 2014). There were interesting differences between targeting ganglion as compared to ON bipolar cells. Targeting ganglion cells resulted in a homogenous response across the ganglion cell population: Almost all cells fired in the presence of light, with similar temporal dynamics regardless of their original identity (e.g., ON vs. OFF, transient vs. sustained). In contrast, targeting ON bipolar cells resulted in a more diverse pattern of ganglion cell responses, likely due to the diversity of synaptic connectivity between ON bipolar cells and their downstream ganglion cells. It remains to be seen how similar ganglion cell responses produced by targeting a single bipolar type are to those elicited by light.

Despite these promising beginnings, major obstacles remain. As far as delivery is concerned, small molecule photoswitches and optogenetics face very different challenges. Small photoswitch molecules are highly diffusible, and even those that bind to a channel are likely lost during channel turnover (Gaub et al., 2014). Since frequent injections are not ideal over a time span of decades, photoswitches will need to be altered to have a longer half-life in the retina, and/or less invasive delivery methods will need to be developed. Progress in this direction has been made: The recently implemented photoswitch compounds (DENAQ and MAG) last for approximately one week after vitreal injection (Gaub et al., 2014; Tochitsky et al., 2014). Optogenetic proteins have the opposite issue – they can be delivered by AAV, but delivery is irreversible as AAV vectors cannot be removed. Regulation of transcription or protein stability are possible ways to reduce protein levels should toxicity or immunogenicity arise.

Both photoswitches and optogenetics must demonstrate safety as far as toxicity and immunogenicity are concerned. Even though the eye has historically been seen as an immune-privileged site, long-term exposure and alterations in the ocular environment due to disease may create a different landscape for immune

responses. Historically, demonstrating immunological safety tends to prove challenging because of the variable nature of the immune system. As far as small molecule photoswitches are concerned, those tested to date do not show short-term toxicity in mice or canines (Gaub et al., 2014; Tochitsky et al., 2014). However a lack of long-term toxicity has not been demonstrated in either mouse models or humans. While it is unlikely that small molecule photoswitches will elicit an immune response, there is the potential concern that these molecules may act as haptens if they become associated with larger molecules, such as proteins. Optogenetic proteins have elicited no toxic or immunological effects to date in mice out to one year (Busskamp et al., 2010), but the safety requirements for adding foreign genetic material to humans are likely to be extremely stringent, especially given that optogenetic proteins come from very divergent organisms–archaebacteria, algae, etc.

One limitation that will slow the development of safe and effective treatments of all kinds is a lack of a good primate model for photoreceptor diseases. Developing such a model, either through chemicals that damage photoreceptors in a way that mimics naturally occurring human diseases, or through genetic manipulations (Busskamp et al., 2014), would provide a powerful tool for testing the safety and efficacy of many sight-recovery approaches.

A second major challenge common to both optogenetics and photoswitches is that healthy photoreceptors (particularly rods) have a robust signal-transduction cascade that greatly amplifies the signals emanating from a small number of photons. Neither optogenetic proteins nor photoswitches have an amplification scheme, raising the concern that large amounts of light will be required for useful vision. Indeed, it is not clear whether or not there is a window in which one can deliver enough light to sufficiently activate these molecules without reaching levels that cause retinal damage over a long period of time. This is a particular issue because some photoswitches and optogenetic proteins are more sensitive to shorter wavelength light, which is more damaging to biological molecules than longer wavelengths. As a consequence, significant effort is being put into developing photoswitches and optogenetic proteins sensitive to longer wavelengths (Gaub et al., 2014) via combinations of genetic and chemical engineering, as well as searching far and wide through nature for long-wavelength-sensitive proteins (Aston-Jones & Deisseroth, 2013; Knopfel et al., 2010).

A similar concern is that healthy photoreceptors have shut-off mechanisms that quickly return cells to their ground state. Thus, although optogenetic proteins and photoswitches have a response to the onset of light that is faster than that of normal photoreceptors (likely due to the lack of phototransduction), the return to ground state tends to be slow, and it is not clear how this will affect visual processing. A high degree of temporal resolution is critical for a variety of environmentally important visual tasks, such as judging the motion of rapidly moving objects. As a consequence, significant effort is being made to develop photoswitches and optogenetic proteins with dynamics that reasonably match those of the normal visual system (Gaub et al., 2014).

Finally, one of the great advantages of small molecule photoswitches and optogenetics over electric prostheses is that these therapies are likely to be able to selectively stimulate different categories of cells (bipolar vs. ganglion) including selective subtypes (ON vs. OFF bipolar). Optogenetic proteins can be targeted to specific cell types using transcription regulatory elements, as has been done for ON bipolar cells (Doroudchi et al., 2011; Lagali et al., 2008), and/or specific capsid types that target viral delivery to specific cell types (Auricchio et al., 2001; Watanabe et al., 2013). One potential path forward is to make designer photoswitches selective for specific channels found within particular retinal cell types, as may be the case for DENAQ, which appears to selectively target mixed-cation (I_h) channels that are sensitized by loss of the photoreceptors (Tochitsky et al., 2014). As a result, non-degenerate retina is insensitive to DENAQ, suggesting that it may be possible to selectively target degenerate retina without interfering with normal phototransduction and visual processing in spared regions of the retina.

However, as described above, even once the capacity to target specific subtypes has been developed, making best use of this capacity will require hacking the circuit for seeing: knowing much more than we currently do about retinal circuitry and which combination of cell types will best produce useful vision. In this area, the progress made by basic scientists in molecularly identifying the ~60 cell types of the retina (e.g. Cherry et al., 2009; Helmstaedter et al., 2013; Sumbul et al., 2014), which can lead to specific and regulated gene expression (Kim et al., 2008), is likely to be of critical importance.

6. Retinal and cortical prosthetics

Retinal and cortical prostheses use electrical stimulation to directly elicit neural responses, analogous to a cochlear implant. Although the earliest attempts to develop a visual prosthesis focused on cortex (Brindley & Lewin, 1968; Dobelle, 2000), most current research efforts have focused on retinal prostheses (e.g. Chow et al., 2004; Humayun et al., 2012; Klauke et al., 2011; Palanker et al., 2005; Stingl et al., 2013). However there are many diseases that result in damage to the retina or atrophy of the optic nerve (including glaucoma) that preclude a retinal implant, motivating the development of devices implanted within the lateral geniculate (Pezaris & Reid, 2007) or cortex. Moreover, as discussed by Born and colleagues in *Cortical magnification plus cortical plasticity equals vision?,* given current electrode technology, the over-representation of the fovea within visual cortex provides a motivation for cortical implantation that should not be overlooked.

Retinal prosthetics can either be implanted epiretinally, between the ganglion cells and the vitreous humor, or subretinally, in the space of the missing or ailing photoreceptors, next to the choroid. These approaches differ substantially in the challenges that they face. In 2013 the FDA approved the sale of the Argus 60 epiretinal prosthesis to patients, with European approval following shortly afterwards. As described in this special issue by Zrenner et al. in *Subretinal Visual Implant Alpha IMS – Clinical Trial Interim Report*, a subretinal device, the Alpha IMS, is in the later stage of clinical trials. Moreover, a large number of groups worldwide working on both retinal and cortical devices are at the design or animal-model stage (e.g. Ghezzi et al., 2013; Palanker et al., 2005; Villalobos et al., 2014).

While devices that restore some functioning vision in humans are now being implanted in patients, large hurdles remain before it could reasonably be claimed that these devices genuinely 'restore sight'. One engineering issue is that devices that are near clinical-trials stage still have very low resolution, with 60–1000 electrodes and a limited number of discriminable gray levels (Greenwald et al., 2009). For comparison, a low-resolution monitor contains over 300,000 pixels. Although basic way-finding can be carried out at surprisingly low resolutions (Dagnelie et al., 2007) much higher resolution will be needed to recognize individuals or carry out activities of daily living based primarily on visual information, as can be seen in Fig. 4.

Creating higher resolution arrays will require solving a number of technical challenges. One challenge regards materials and manufacturing: it is difficult to build an array with a large number of very small electrodes, made of materials that can withstand the high current density levels necessary to elicit percepts with small electrodes (Aregueta-Robles et al., 2014). A related difficulty is that power and data demands increase substantially as a function of the size and the number of electrodes. Current prosthetic devices are

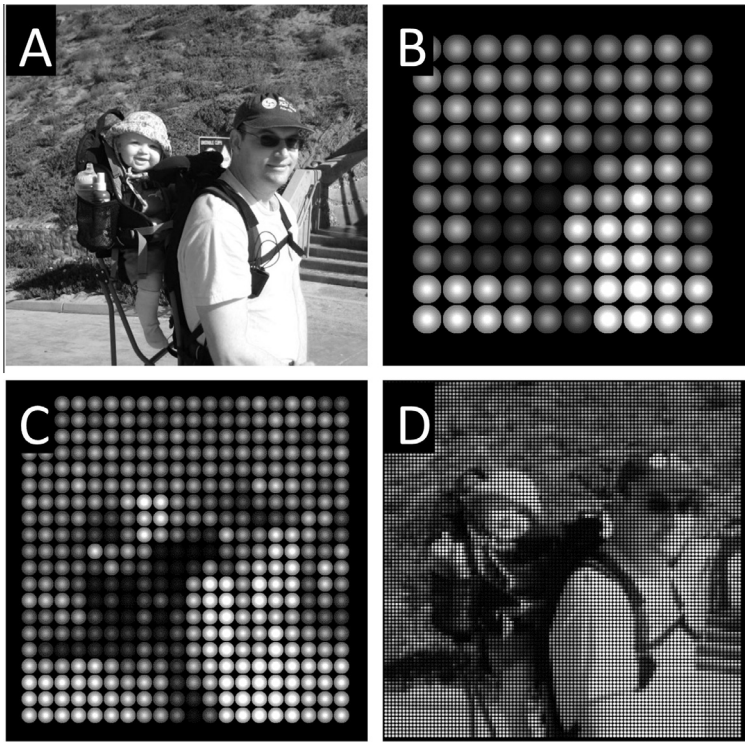

Fig. 4. Simulations of a picture of Geoffrey and Zachary Boynton (A) at multiple resolutions: 10 × 10 (B), 20 × 20 (C) and 100 × 100 (D).

powered and controlled by wireless induction, limiting both the power and data that can be received over time.

One approach currently being explored to alleviate the need for an external power supply is the development of photovoltaic arrays that directly convert light into current. Because the light level on the retina during normal vision is likely not adequate to power these arrays, these methods propose to project images from a camera onto the retina using higher intensity light. Lorach et al., in *Performance of photovoltaic arrays in vivo and characteristics of prosthetic vision in animals with retinal degeneration*, show that such a device can elicit percepts using near infra-red light levels that are below safety limits.

Another potential approach is to increase resolution using 'current steering'. When neighboring electrodes have overlapping current fields it is possible to 'shape' the current field so that the region of maximum current lies between two electrodes. The use of anodic currents can be further used to shape the current field. Thus, in theory, provided electrodes are close enough that their current fields overlap significantly, it may be possible to use a finite set of electrodes to produce intermediate 'virtual' electrodes. This approach has been used to enhance pitch perception in cochlear implant users (Bonham & Litvak, 2008; Donaldson, Kreft, & Litvak, 2005; Hughes & Goulson, 2011) but has not yet been demonstrated successfully in retinal prosthesis patients, although it has been shown that the current fields of 250–500 μm electrodes at 800 μm center-to-center resolution interact significantly, suggesting that such an approach is plausible (Horsager et al., 2010).

Keeping arrays in close proximity to the retina is also a significant technical challenge that has been described as attaching the array to a retina that resembles '1-ply wet tissue paper' (Robert Greenberg, Second Sight, personal communication) during eye-movements with acceleration speeds that can be greater than 2×10^4 deg/sec^2. What makes this a particular concern is that any 'lift-off' of the array from the retina results in an exponential increase in power requirements (de Balthasar et al., 2008).

Another issue that remains to be resolved is that targeting specific cell types with electrical stimulation is extremely difficult. Indeed, it is not clear whether it is possible to selectively stimulate ganglion cells vs. bipolar cells, let alone differentiate between different subtypes such as ON and OFF cells. One possible solution would be very high resolution arrays, with a resolution similar to that of the ganglion cells, so that a limited number of cells near the electrode are stimulated. While the feasibility of this approach has been demonstrated in the dish (Sekirnjak et al., 2009), achieving this *in vivo* would be an engineering marvel. Current research has focused on trying to design electrical time-courses that target specific cell types. For example, it has been demonstrated that bipolar cells are more sensitive to longer pulse widths than ganglion cells (Jensen, Ziv, & Rizzo, 2005b). As described above, in this special issue Rattay and colleagues present simulations suggesting it might be possible to selectively target either the ON or OFF pathway by using either anodic- or cathodic-first voltage pulses.

This lack of ability to selectively target particular cell types is related to one of the major issues in current prosthetic design: There seems to be significant axonal stimulation in current devices (Nanduri et al., 2011). Every ganglion cell has an axon that traverses the retinal surface *en route* to the optic nerve. If an electrode lies over axons that belong to distant ganglion cells whose axons happen to pass through that location, then any percepts elicited by electrical stimulation of that axon will produce phosphenes (the experience of seeing light without light actually entering the eye) that are elongated in shape and poorly localized. Unless this can be solved, this will greatly reduce the resolution and spatial specificity elicited by even high-resolution devices. Possible solutions include developing arrays in closer proximity to target cells, 'blocking' axonal stimulation using anodic stimulation and trying to compensate for these distortions in the stimulation protocol.

7. What is sight restoration and how should one measure it?

What is sight restoration? Certainly meaningless blobs of light should not be considered as such, but equally the ability to restore even relatively poor vision would be a triumph. Current ways of assessing vision use metrics and measures based on normal vision

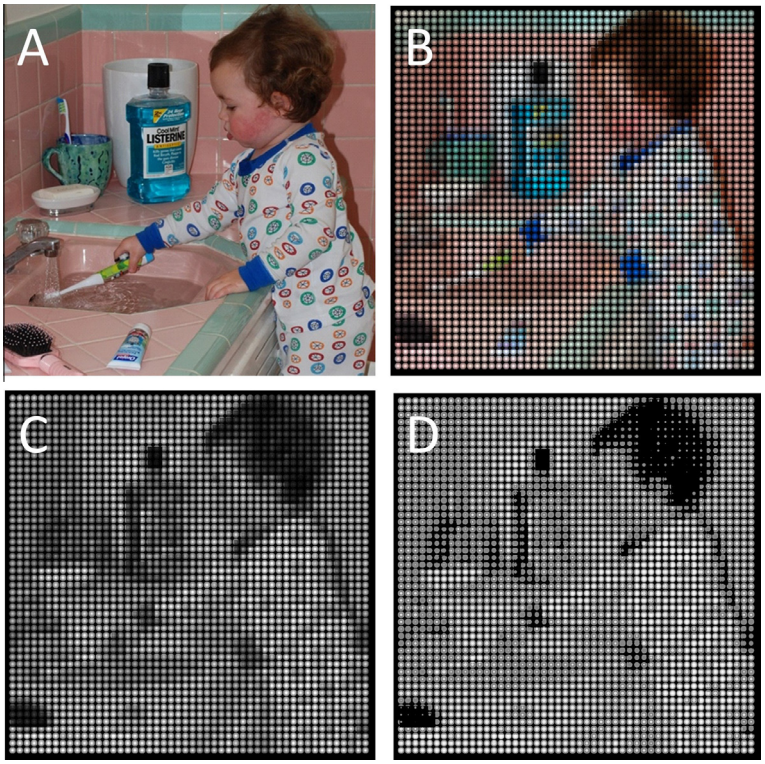

Fig. 5. Simulations of a picture of Theodore Fine (A) at 50 × 50 resolution with (B) and without color information. Grayscale images are simulated with 256 (C) and 5 (D) discriminable gray levels.

and visual loss, which are inappropriate for sight-restoration techniques in a number of ways. For example, current tests rely very heavily on acuity, and presume normal color vision and dynamic range. While color is relatively unimportant for visual comprehension for individuals with normal visual acuity – we have no difficulty watching black and white films – it is likely to play a much more critical role in individuals with low vision as illustrated in Fig. 5, especially for devices with a limited range of discriminable gray levels.

The metrics that will be required to evaluate these different therapies will need to be sensitive and reliable (like current tests), as well as being well-matched to important activities of daily life. These metrics also need to generalize across different therapeutic modalities. The vision provided by an electrical prosthetic is likely to be very different from that provided by optogenetics, not simply in terms of resolution, sensitivity and field of view, but also in terms of temporal dynamics and phosphene misalignment. Metrics that can characterize the relative strengths and weakness of different therapies, and how these correspond to different activities of daily living, will be required before patients can make an informed decision about which therapy, if any, is right for them.

8. The wish to fix things: A final note of caution

"The wish to fix people reflects pessimism about their condition and optimism about their method of repair" (Solomon, 2012).

Attempts to help those with a disability (e.g. Alexander Graham Bell and Thomas Edison promoting exclusive oralism in the case of deaf individuals) or who are different in some way (such as being transgender (Burke, 1996)) have on occasion promoted 'normality' at the cost of happiness, health and functionality.

Many of the ethical issues that face the field of sight restoration have close analogues in the cochlear implant. While cochlear implants are an extraordinary technology, they do not restore normal hearing. At the age of 5 the average cochlear implant user has the language abilities of a 2.5 year old, even if implanted before 18 months of age (Niparko et al., 2010; Tobey et al., 2013). Nonetheless parents who choose for their children to live as fully functioning members of the Deaf community rather than as an impoverished hearing person are likely to have their choices questioned. Sweden requires parents to meet with representatives of the Deaf community and learn about their lives before opting for cochlear implant surgery for their child.

One of the most difficult moments in my career (Ione Fine) was when a parent phoned me to ask about the Second Sight prosthetic implant. I explained that these were test devices, and that any device available in the next decade would likely offer very limited functionality. In the discussion that followed she told me her child was happy and active, played freely and had a full and functional life. Her main motivation for calling me was that she "couldn't stand the pity on people's faces when she had to explain that her daughter was blind".

It is fairly likely that in the near future this parent will be given the option of whether or not to choose a sight restoration procedure for their child. It's also likely that the 'restored sight' on offer will provide less functionality then fluent use of a cane, guide dog and the many other technologies available to blind individuals. Regardless of what this parent eventually decides to do for her child, we hope the decision can be made with the advice and support of members of the blind community whose lives have been shaped by their abilities, not their disability.

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