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Restoring vision at the fovea

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In humans high quality, high acuity visual experience is mediated by the fovea, a tiny, specialized patch of retina containing the locus of fixation. Despite this, vision restoration strategies are typically developed in animal models without a fovea. While electrical prostheses have been approved by regulators, as yet they have failed to restore high quality, high acuity vision in patients. Approaches under pre-clinical development include regenerative cell therapies, optogenetics and chemical photosensitizers. All retinal vision restoration therapies require reactivation of inner retina that has lost photoreceptor input and that the restored signals can be interpreted at a behavioural level. A greater emphasis on tackling these challenges at the fovea may accelerate progress toward high quality vision restoration.

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Introduction

The human fovea is specialized for high acuity vision, contains the locus of fixation and mediates much of our conscious visual experience, yet it represents only a tiny patch of retina subtending less than the size of your thumbnail at arm's length. Age related macular degeneration (AMD), the leading cause of blindness in the developed world, begins with damage to the photoreceptors in this region and the loss of central vision. Vision restoration approaches which include the fovea have been shown to be more effective [1] perhaps because this tiny patch of retina provides input to a highly expanded representation within the visual brain [2]. Despite these compelling reasons to study it, much of the preclinical development is performed on animals without a fovea. In this review we consider how the vision restoration techniques currently being explored by the scientific community interact with the unique structure and physiology of the fovea and evaluate the prospects for restoring high quality foveal vision. We examine how functional outcomes at the fovea can be evaluated at preclinical and clinical stages and highlight key unanswered questions.

The structure of the fovea

The fovea has unique anatomical and physiological specializations [3] presenting both special challenges, and certain advantages for vision restoration. The fovea is avascular and foveal cones are slender and densely packed relative to their peripheral counterparts. This creates a high metabolic burden, which may make the fovea vulnerable to degeneration [4]. The inner retina, containing the neurons that perform the initial stages of visual processing are also specialised in this region. High acuity in the fovea is mediated by an expansion of the midget retinal ganglion cell (RGCs) class. Retinal physiology is reviewed in detail elsewhere [5], but here we note that unlike in the periphery where signals from large numbers of photoreceptors are pooled, each foveal midget RGC has a 'private line' through dedicated bipolar cell to an individual cone. This means the density of retinal ganglion cells at the fovea, and the area of visual cortex devoted to processing foveal signals, is increased relative to the periphery. While colour perception is a feature of foveal vision, from a restoration standpoint this is likely to be less important to quality of life than gains in acuity. From an evolutionary standpoint colour vision was a late addition to the fovea and that high acuity spatial vision brought about by high cone density and the specialized midget circuitry was the primary aim of the structure [5].

Directly above the region of high cone density, the inner retinal layers are thinned, creating perhaps the most distinctive anatomical feature of the fovea, the 'foveal pit'. The 200 μm floor of the pit, referred to as the 'foveola' is particularly thin and delicate. The foveal pit is formed during development where foveal RGCs are laterally displaced by hundreds of microns relative to the cones they are connected to. The radially displaced retinal ganglion cell somas pile up in a ring on the margins of the pit as shown in Figure 1. Recent experiments have shown that despite the huge distances moved by the ganglion cells relative to the cones they are connected to, the local spatial arrangement of retinal ganglion cell somas within the ring closely matches the relative arrangement of receptive field locations [6•]. This becomes important if we seek to bypass degenerated foveal cones and restore vision by directly stimulating the displaced ganglion cells. The thin inner limiting

Figure 1

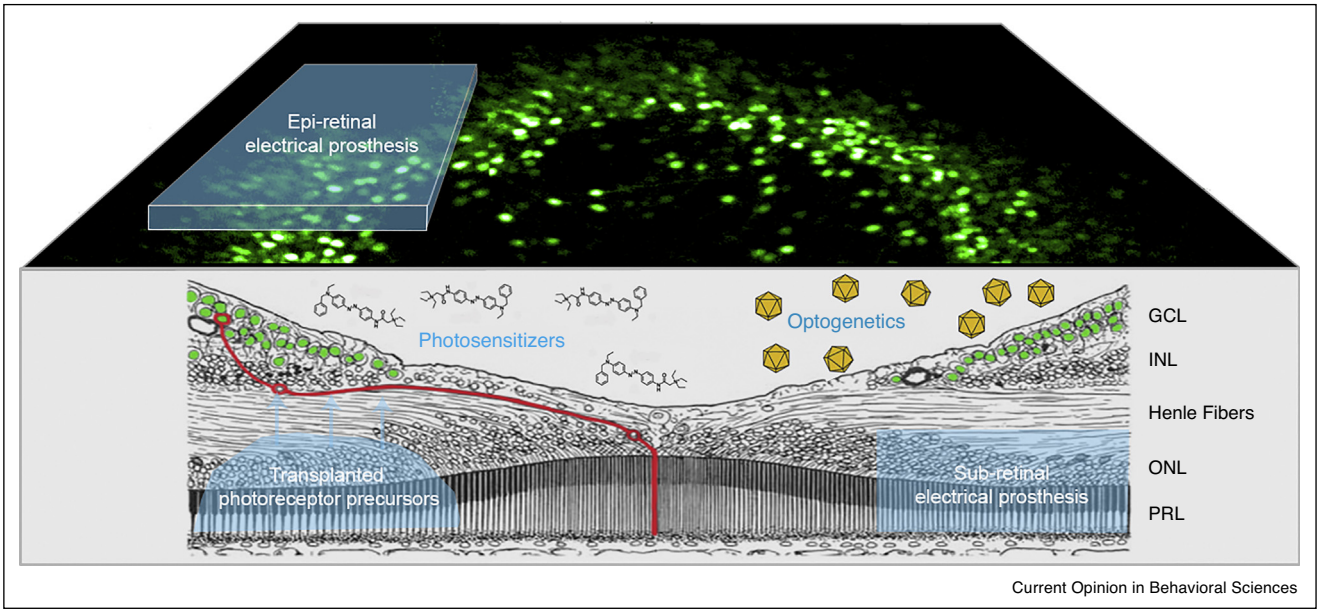

Illustration of vision restoration strategies at the fovea. Retinal ganglion cells are displaced from the foveal photoreceptors they serve (red line). This results in the formation of an RGC ring (green) around the foveal pit, the floor of which is referred to as the foveola. A selection of vision restoration strategies are shown: subretinal approaches (electrical prostheses, photoreceptor precursor transplantation), intravitreal (chemical photosensitizers and inner retina optogenetic) and the epi-retinal prosthesis. Abbreviations: GCL - Ganglion cell layer, INL - Inner nuclear layer, ONL - Outer nuclear layer, PRL – Photoreceptor layer.

membrane at the foveola is advantageous for restoration approaches that rely on intravitreal injections, allowing increased penetration of therapeutics into the retinal tissue at this location [7].

The current state of play

The only vision restoration therapy currently approved by regulators in the EU and the USA is the epiretinal Argus II electrical prosthesis. An electrode array is surgically implanted on the surface of the retina centred on the fovea but extending well beyond its margins. A head mounted camera converts the scene into patterns of electrical stimulation that are applied to RGCs [8]. One drawback of such prostheses is the sparsity of the stimulating electrodes and at present it is not possible to restore vision at acuities close to that of normal fovea [9]. Nevertheless, recipients of this device may see and interact with low spatial frequency, high contrast stimuli like a white ball rolling on a black table and show improvements in activities of daily living [10,11]. In Europe two sub retinal implants, the Alpha IMS and Alpha AMS (wireless version) are approved; in theory these offer an eightfold increase in resolution, however in practice, the achievable acuity is similar to the Argus II [12,13,14•,15]. A large range of electrical retinal prostheses are under development [16] and efforts are ongoing to develop higher resolution photovoltaic implants that are better able to confine the electric field and achieve closer contact with the target cells [17,18]. Higher acuity has been achieved in rodents [19] but these improvements have yet to be translated into primates and humans. Cortical magnification of the foveal region means that chip implantation directly in cortex may be a promising future direction [11,20] although magnification factor does vary significantly between individuals [21].

Hopes of high-quality vision restoration have long lain in regenerative therapies which offer the possibility of regrowing replacements for degenerated cones from transplanted stem cell derived photoreceptor precursor cells. This approach is currently in its early stages, with researchers actively working to establish photoreceptor precursor survival, maturation, synaptogenesis and integration with the host following cell delivery into the subretinal space [22–24]. Potential synaptic interactions between transplanted retinal sheets and the host have been observed in rodent models of retinal degeneration [25,26] and primate [27]. The fovea presents a challenge for transplantation because of tissue delicacy and the displacement of retinal ganglion cells relative to the native photoreceptors that drive them. During development RGC-photoreceptor connections are made before the lateral displacement occurs. Photoreceptors transplanted subretinally into the adult foveola would need to extend axons hundreds of microns laterally to connect with their target RGCs in the foveal ring. An alternative

approach would be to deliver cone precursors to the subretinal space directly under the ring of foveal RGCs to maximize the possibility of interaction. The impact of the degenerating environment on transplanted cells, particularly on cone function is still poorly understood [23,28,29]. *In vivo* retinal imaging of fluorescently labelled photoreceptor precursor cells has allowed longitudinal monitoring of transplant survival and remodelling in the intact non-human primate [30].

Instead of re-growing new photoreceptors, an alternative vision restoration approach involves repurposing the remaining architecture. Optogenetic vision restoration involves inserting light-sensitive ion channels directly into inner retinal neurons, making them intrinsically light sensitive and thus overcoming the loss of photoreceptor input. This is achieved by infecting inner retina with a virus that codes for the optogenetic actuator which is then synthesised by the infected cells themselves. Using custom promoters it is possible to target-specific cell classes like RGCs [31••] or bipolar cells [32,33]. The cell class chosen may affect the gain and the type of restored responses. The type of bipolar cells to which an RGC is connected, dictates whether it is an 'On center' RGC, increasing its activity in response to a light increment, or an 'off center' RGC, increasing its activity in response to a light decrement. Inserting channels into bipolar cells could potentially restore both 'on' and 'off' responses, whereas inserting the same channel directly into RGCs would turn every RGC into an 'on center' type. The psychophysical consequences of these choices are largely unexplored. Optogenetic actuators are currently relatively light insensitive as they are based on microbial opsins, but higher sensitivity actuators based on mammalian opsins and custom engineered G-protein coupled receptors are becoming available [34,35••,36,37].

Optogenetic vision restoration requires only a single injection and offers potentially high acuity, as rather than a sparse array of electrodes, every cell can be light sensitive. The drawbacks of using the foveal ring as a light sensor is that many cells are piled up on top of each other and the positions of the ganglion cells are dilated into a ring relative to the original positions of their foveal receptive fields [6•]. This may result in a perceived warping of the visual stimulus shape and size and a 'blind spot' in the foveal center. It may be possible to pre-distort the stimulus to compensate, or patients may adapt to this form of vision as they do to vision loss [38,39]. Head mounted optogenetic visual stimulators [40] are being developed, including versions with encoders that present the anticipated RGC firing pattern a scene would evoke, rather than the scene itself [41]. Optogenetic vision restoration has been demonstrated *ex-vivo* in foveal tissue [31••,42] and recently in the primate *in vivo* [43]. The perceptual and behavioural consequences of this unusual form of vision, remain unexplored.

As some photoreceptor inner segments are functionally preserved in degenerating retina [44], it may be possible to deliver optogenetic gene therapy directly to these cells, maintaining the spatial layout of the intact retina. This has been demonstrated *ex-vivo* in human retina [44] and offers the most straightforward route to naturalistic vision with the lightest requirement for adult plasticity. Recent efforts have focussed on the development of vector-promoter combinations that can produce expression in foveal cones via intravitreal rather than subretinal injection, avoiding detachment of the delicate foveola [45]. Viral transduction across the RPE may also be possible using ultrasonic techniques [46].

It is also possible to make the inner retina light sensitive using azobenzene-based photoswitches such as Benaq [47•]. This molecule can be delivered intravitreally and in mice preferentially targets retinal ganglion cells that have undergone physiological changes due to the loss of photoreceptor input, selectively restoring 'off responses' [48]. A major difference from optogenetic therapy, is that chemical photosensitizers are cleared from the retina in a month, necessitating repeated injections. This therapy has not yet been tested in a foveate animal and therefore whether sensitization is confined to the RGC ring or works pan-retinally is unknown.

All retinal vision restoration therapies rely on the functional preservation of retinal ganglion cells despite loss of photoreceptor input. Unfortunately, RGCs can undergo functional changes following photoreceptor loss including hyperactivity and remodelling [49,50–53] which may reduce the quality of the restored vision in the human [54]. It has been suggested that retinoic acid diffusing from RPE at the site of photoreceptor degeneration, into the ganglion cell layer, is the signal which triggers hyperpermeability of RGCs and this leads to hyperactivity [55•]. If this hypothesis is true, foveal RGCs may be less vulnerable to locally diffusing retinoic in the initial stages of macular degeneration than mouse models would suggest because foveal RGCs are displaced relative to region of degenerating photoreceptors. Regardless of the trigger, there is evidence that gap junction blockers like meclofenamic acid, can reduce hyperactivity and enhance visual performance in mice [56] but this solution has yet to be tested in large animal models or humans. As gap junctions create an electrical syncytium in the retina, disrupting these channels prevents waves of spontaneous activity spreading through the tissue.

Similar questions surround preventing or reversing pathological changes taking place to the retinal blood supply following photoreceptor degeneration [57,58]. Progressive changes in blood flow that have developed over many years of disease may result in a limited oxygen supply being available to 'restored' retinal ganglion cells, whose altered physiology may be more energy intensive.

There are many unanswered questions surrounding reintroducing function to a tissue that has been deprived of normal activity patterns for days, months or years. Functional and structural changes may be easier to combat if detected early clinical trials for vision restoration are typically performed in challenging end stage cases where little information can be gleaned. Little is currently known as to how to preserve or treat the retina to provide the biological infrastructure needed to achieve high quality vision restoration.

Toward high quality vision restoration at the fovea

To overcome the challenges of vision restoration at the fovea and accelerate progress toward successful phase III clinical trials, preclinical studies are necessary. Unfortunately, there is a paucity of animal models with human like-foveal specializations and within that group even fewer models of retinal degeneration. The mouse, the most commonly used laboratory animal [35••,59,60] has several genetic models of degeneration but no fovea-like specializations. In canine species several genetic degenerations have been discovered [61] and there is an 'area centralis' containing a small bouquet of cones at a density similar to that of the primate [62], however there is no foveal excavation or ganglion cell specialization. The ground squirrel has a cone dominated retina, with an 'area centralis' a larger area of densely packed cones [63] and an increased ganglion cell density but no foveal excavation or avascular zone [64]. This species has been used to explore circuit repair [49] due to the retinal changes that take place during hibernation. Other cone-dominant species continue to be explored as potential animal models for retinal disease [65,66].

Primates have the most similar foveal structure to humans, with macaque monkeys being the pre-clinical species of choice. Old world primates develop drusen [67] and an inherited form of achromatopsia was recently discovered in the rhesus macaque [68••], however at present, acute and inducible forms of vision loss, such as laser lesions [69] and cobalt chloride lesions [27] are more common. The marmoset, which is smaller and easier to breed has potential as another foveate model species [70,71]. Transgenic degeneration models in primate may soon be possible [72,73].

To evaluate the success of vision restoration therapies at the pre-clinical stage *in vivo*, it's possible to express the fluorescent calcium indicator GCaMP in foveal RGCs and use adaptive optics ophthalmoscopy to non-invasively read out cellular activity [74]. This method has demonstrated the restoration of pattern vision at the retinal level in the macaque [43]. In the future it may be possible to monitor restored activity using intrinsic signals [75,76] or voltage indicators [77]. The cortical magnification of foveal projections to the brain may allow recording of visually evoked potentials from primate fovea. This would allow us to assess if restoration at the retinal level translates to stimulation in higher nuclei. Ultimately psychophysics will provide the gold standard to evaluate how the brain is able to interpret the restored visual cues.

Currently all prospective vision restoration therapies can only 'restore' an impoverished form of vision, nevertheless patients are receiving electrical retinal prostheses, and optogenetic therapies are entering clinical trials. Amid the complexities of the diseased retina it can be difficult to distinguish cause and effect when studying vision restoration and testing is not yet fully standardized. In the clinic, Humphery visual field testing (perimetry) is common and at the fovea, higher density 'microperimetry' is used, however this is still very coarse compared to the grain of the photoreceptor mosaic. Adaptive optics ophthalmoscopy has been utilized to perform visual testing at high resolution [78] and this could be applied map foveal function before and after intervention. Visual field testing can be a problem for patients with foveal impairment if they are not able to fixate. In such cases tracking eye movements and the recovery of a stable fixation locus could be used to evaluate the success of an intervention.

Visual acuity is an appropriate metric to assess foveal vision and is pertinent to quality of life as the fovea mediates detailed spatial vision needed for reading, recognising faces and interpreting facial expressions. While valuable, acuity alone does not evaluate the richness of visual experience or usability of the restored function. Behavioural tests such as the multi-luminance mobility test have been developed [79] and for the fovea tests of contrast sensitivity [80], localization, shape and object perception are also informative. In ultra-low vision patient populations receiving the first generation of restorative therapies, acuity may not be measurable. Researchers have been working with patients to develop quality of life and visual function questionnaires capable of capturing a fuller picture of the impact of a therapy [81–83].

Lastly it should be noted that all efforts to restore vision at the retinal level are constrained by levels of plasticity in the adult brain which must interpret the restored signals. This is particularly relevant if the form of restored vision is very different from natural vision. Evidence from patients who have received retinal prostheses suggests that low resolution 'pixelated' scenes can be interpreted. Higher resolution forms of restored vision relying on direct activation of the RGC ring will require distortion of the stimulus or some degree of plasticity to achieve high acuity in practice. Visual rehabilitation training [84] is likely to be necessary for any form of vision restoration and whilst there is evidence of plasticity in the adult, it is limited [39]. In canine and murine pre-clinical studies

there is evidence that younger animals show a greater visual rescue following retinal gene therapy than older animals [85,86]. A similar age dependency has been reported in clinical trials [87] suggesting that once degeneration is too advanced rescue may be more limited. The increasing deployment of vision restoration therapies in preclinical models and patients may afford an opportunity to learn more about the fundamentals of both retinal rescue and visual plasticity of downstream nuclei. Primate psychophysics may help us to assess the bounds of usability of these forms of restored vision before they enter expensive clinical trials.

Conclusion

While current interventions cannot yet provide the high-quality vision that the term 'vision restoration' implies, a range of promising therapies are under development. Devising strategies which are cognisant of the unique feaures of the fovea may accelerate progress toward this goal. Access to new primate models of retinal degeneration and methods of evaluating function *in vivo* may make pre-clinical studies of foveal vision restoration more readily achievable, improving the quality of therapies entering clinical trials.

Conflict of interest statement

Nothing declared.

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