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TOPICAL REVIEW

Prosthetic interfaces with the visual system: biological issues

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Abstract

The design of effective visual prostheses for the blind represents a challenge for biomedical engineers and neuroscientists. Significant progress has been made in the miniaturization and processing power of prosthesis electronics; however development lags in the design and construction of effective machine–brain interfaces with visual system neurons. This review summarizes what has been learned about stimulating neurons in the human and primate retina, lateral geniculate nucleus and visual cortex. Each level of the visual system presents unique challenges for neural interface design. Blind patients with the retinal degenerative disease retinitis pigmentosa (RP) are a common population in clinical trials of visual prostheses. The visual performance abilities of normals and RP patients are compared. To generate pattern vision in blind patients, the visual prosthetic interface must effectively stimulate the retinotopically organized neurons in the central visual field to elicit patterned visual percepts. The development of more biologically compatible methods of stimulating visual system neurons is critical to the development of finer spatial percepts. Prosthesis electrode arrays need to adapt to different optimal stimulus locations, stimulus patterns, and patient disease states.

1. Introduction

The design of prostheses for the visual system presents a challenging problem for the biomedical engineer and neuroscientist. Great progress has been made in the miniaturization of prosthetic device electronics; however, development lags in the construction of practical stimulation interfaces with the visual system. The anatomy of the visual system is highly evolved and massively parallel in design. The optimization of neural interfaces to each level of the visual system presents different challenges and benefits. These problems cannot be solved by the methods of electronic circuit design or neuroscience alone, but by a hybrid of the two that adapts to the complex organization of natural neural systems. A variety of excellent reviews have appeared on visual prostheses (e.g. Margalit *et al* (2002, 2005), Hetling and Baig-Silva (2004), Tehovnik *et al* (2005), Weiland *et al* (2005)). This review departs from past neuroscience and engineering reviews of visual prostheses in that it deals primarily with actual problems encountered interfacing electronic devices to neurons of the visual system; encompassing anatomical, electrochemical, neuroethology, vascular, surgical, disease and physiological issues. References and documentation are supplied to the dimensions of human (or primate) visual system structures.

For prosthesis design, it is critically important to understand how natural vision operates in normal individuals and also in the severely visually impaired. This review covers what is known about the organization of the major target areas in the human brain for visual prostheses, the physiology and microanatomy of these areas from an engineering perspective, and issues involved in selectively stimulating neurons at each level of the visual system. Patients with a retinal disease called retinitis pigmentosa (RP) form a large portion of the prosthetic implant candidates currently undergoing clinical trials (Veraart *et al* 1998, Delbeke *et al* 2002, Humayun *et al* 2003, Chow

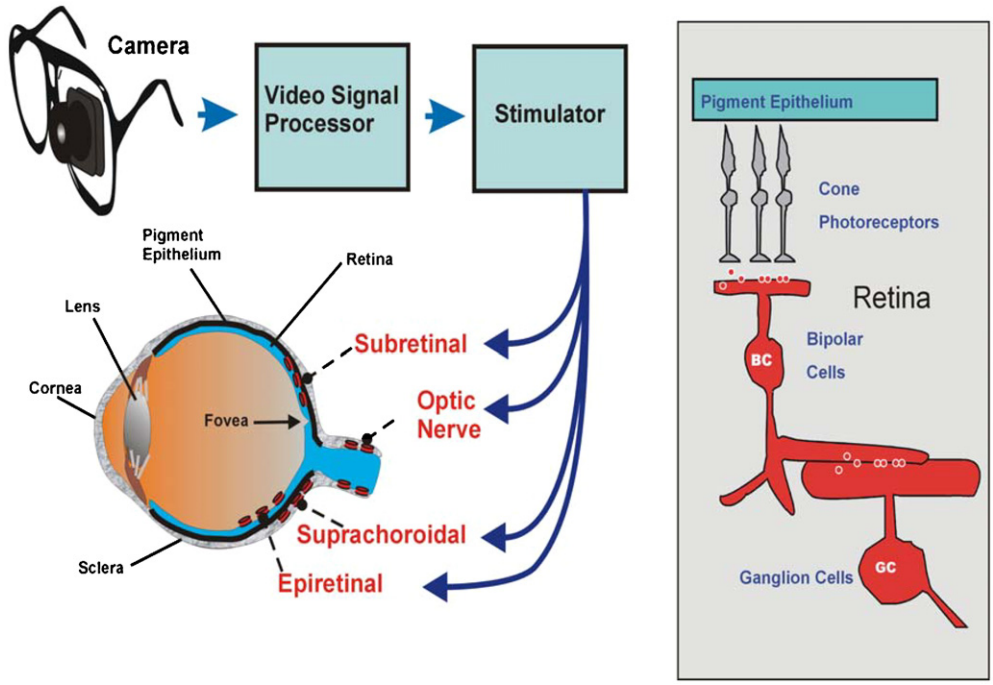

Figure 1. Schematic diagram of a typical retina-based visual prosthesis showing the different proposed locations for the stimulation electrodes (red discs). The retina and optic nerve are shown in blue. The electrodes of epiretinal prostheses lie closest to the retinal ganglion cells, while those of subretinal prostheses lie in the outer retina closest to the pigment epithelium. The electrodes of suprachoroidal or extraocular prostheses lie outside the retina behind the pigment epithelium. The stimulation electrodes of optic nerve prostheses are placed on the retinal optic nerve directly. Inset right: general structure of the retina showing the light-activated pathway from photoreceptors to ganglion cells. For more details see text.

et al 2004, Mahadevappa *et al* 2005). The review discusses how the visual areas are affected by RP and describes the visual behavior of end-stage RP patients in detail to assist in understanding their visual capabilities and needs.

2. Normal retinal function

In normal vision, light from the external visual environment enters the eye and is focused by the cornea and lens optics to form an image at the back of the eye on a sensory layer termed the 'retina' (figure 1). The retina is a thin layered network of neurons that contains light-sensitive cells called photoreceptors (figure 1 inset). Each point of light in visual space is focused by the eye's optics on a corresponding point on the retinal surface, whose local intensity is encoded by retinal photoreceptors (e.g. figure 2(b)). Each neuron in the retinal network receives input from retinal photoreceptors within a spatial region that defines its 'receptive field'.

Two photoreceptor types in the outer retina transduce the light signal: rods, whose high sensitivity to light aids in vision in the dark, and cones, which can adapt to higher diurnal light levels. The cones also encode human color vision, and three spectral subtypes are present in humans. In normal retinal function, light strikes the outer segments of photoreceptors and is absorbed by visual pigment proteins named opsins, resulting in the isomerization of their chromophore 11-cis-retinal. Through a complex biochemical process, opsin activation by light results in the closure of depolarizing ion channels normally open in the photoreceptor membrane, which causes the membrane potential to hyperpolarize and results in a reduction in synaptic neurotransmitter release. The neurotransmitter released at the photoreceptor synaptic terminal is the excitatory amino acid glutamate.

Rod and cone photoreceptors send the light signal through synapses in the outer retina onto two different classes of bipolar cells located in the inner retina. These two cell classes have synaptic receptors for glutamate that produce opposite responses to light. OFF-center bipolar cells hyperpolarize to light like their photoreceptor inputs, while ON-center bipolar cells depolarize to light. In primates, there are ten different bipolar cell types (Boycott and Wässle 1991), with the midget bipolar cells being the most common type involved in central vision. In lower vertebrates, different bipolar cell types respond to different ranges of contrast in the visual scene (Burkhardt and Fahey 1998) and this may partly account for the many primate bipolar cell types. The stimulated bipolar cells synaptically release glutamate, which depolarizes both ON- and OFF-center amacrine and ganglion cells in the inner retina.

On average, one million ganglion cells are found in the inner retina of humans, but this number varies up to two-fold between individuals (Curcio and Allen 1990). In primates and humans, the retinal ganglion cells are thought to comprise between 13 and 18 different types (Polyak 1941, Kolb *et al* 1992, Dacey and Packer 2003, Dacey *et al* 2005). Upon excitation by bipolar cells, retinal ganglion cells generate action potentials. These action potentials propagate down the ganglion cell axon, exit the eye at the optic disc, and

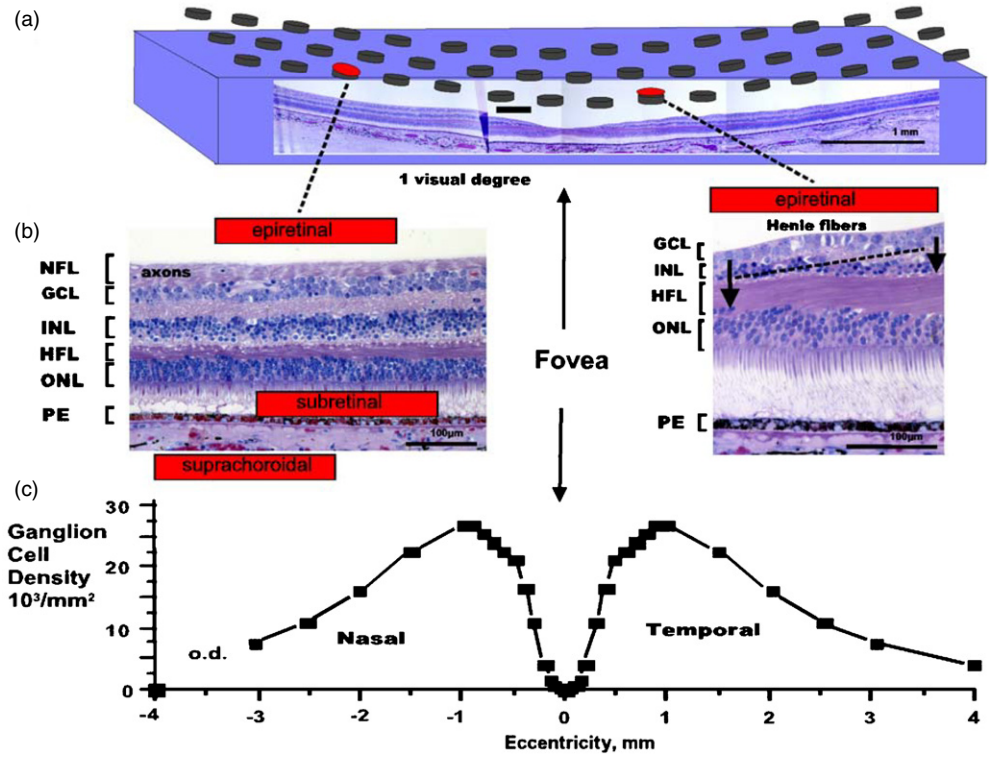

Figure 2. Model of a stimulating electrode array from a retina-based visual prosthesis placed over a cross section through the foveal retina of a 72 year old male. (a) A 15 × 3 array of epiretinal disc electrodes (250 μm diam.) is shown spanning the central retina along the nasal–temporal axis. Shrinkage is uncorrected. (b) Cross sections of foveal retina with different stimulus electrode configurations (red). The thickness of the nerve fiber layer (NFL), Henle fiber layer (HFL) and ganglion cell layer (GCL) can vary significantly with retinal eccentricity. Left: in the nasal retina, a thick nerve fiber layer of ganglion cell axons covers the local ganglion cell stimulation targets from an epiretinal stimulus electrode. A subretinal electrode could better stimulate local inner retinal neurons but may occlude oxygen diffusion by choroidal capillaries adjacent to the pigment epithelium (PE). A suprachoroidal stimulus electrode is less invasive to the retina, but is located behind the resistive barrier of the pigment epithelium. Right: on the slope of the foveal pit, the nerve fiber layer is thin and the cone photoreceptors are displaced from their postsynaptic bipolar cell targets in the inner nuclear layer (INL) by their long fibers of Henle (arrows). (c) Average density of ganglion cells across the nasal-temporal axis of the human fovea. Note the central fovea, a target of prosthesis stimulation, is devoid of ganglion cells. Ganglion cells receiving synaptic input from central foveal cone photoreceptors are displaced laterally from the fovea center, reaching a peak density at 1 mm retinal eccentricity. od: optic disc. (Adapted from Curcio and Allen 1990). ONL: outer nuclear layer (photoreceptors).

excite the visual areas of the brain through the optic nerve. The presence of functional ganglion cells is critical to the operation of all retina-based visual prostheses. In humans, about 90% of the ganglion cells in the central visual area are a single class of ganglion cell termed 'midget' or P-type and are thought to encode color and high spatial resolution vision. These cells form the 'parvocellular' pathway to the visual areas of the brain. A second sparser class of ganglion cells, termed 'parasol' or M-type, is sensitive to movement and low-contrast stimuli. These cells form the 'magnocellular' pathway. The innermost retinal layer is the 'nerve fiber layer' formed from the crossing fascicles of unmyelinated axons from more distal retinal ganglion cells converging on the optic disc (figure 2(b)).

3. Role of the fovea in visually guided behavior

In human and primate retinas, a small central area called the 'fovea' is specialized for high resolution vision. The fovea plays a key role in visually guided behavior. Through fixational eye movements, we constantly direct the fovea to analyze the fine details in a visual scene. A human fovea is shown in cross section in figure 2(a). The foveal pit subtends the central 3° of vision, and occupies a retinal surface area roughly 1 mm in diameter (1° of visual angle is equal to 275–300 μm at the retina (e.g. Drasdo and Fowler (1974) figure 4). Retinal thickness of the parafovea averages around 150 μm (Neubauer *et al* 2001); however, in the center of the foveal pit the retina becomes extremely thin as only cone photoreceptors are present. The density of cones is highest at the fovea: peaking at a density of 199 200 ± 87 200 mm^{-2} (Curcio *et al* 1990). In the fovea all second- and third-order retinal neurons are displaced centrifugally in an annular ring away from their foveal cones. This structural pattern is formed early in post-natal life (Hendrickson and Yuodelis 1984) making replacement by stem cells difficult. Cone photoreceptor cells synaptically contact bipolar and horizontal cells through elongated processes termed the 'fibers of Henle' which form laterally-displaced synaptic endings (figure 2(b)). It is the fovea and its surrounding region that most retinal prosthetic devices strive to stimulate. Stimulation of the peripheral retina may require patients to learn eccentric eye fixation techniques.

Like their photoreceptor inputs, roughly 50% of all ganglion cells in humans are localized within 4.5 mm of the fovea (Curcio and Allen 1990). However, since the fovea

contains only cone photoreceptors, ganglion cells receiving foveal cone connections are also displaced centrifugally toward the periphery, an average of 0.37 mm away from the center (figure 2(b)) (Sjostrand *et al* 1999). Single midget bipolar cells receive input from single foveal cones, which contact midget ganglion cells. At ∼1 mm from the fovea, the ganglion cell density peaks at 25–30 000 cells mm^{-2}. This density then slowly declines so that at 3 mm from the fovea, the ganglion cell density is less than 1/5 of the peak. How these displaced foveal ganglion cells are locally stimulated is critical to the generation of effective pattern vision by retinal prostheses.

4. The prosthetic candidate (visually-impaired patient)

An important issue in visual prosthesis design is understanding the nature and visual needs of the implant candidate population. The majority of these visually impaired patients suffer from diseases within the eye itself; particularly degenerative retinal diseases that effect central visual function. A large patient group currently involved in clinical trials of retinal prostheses have the end-stages of a progressive photoreceptor degeneration known as 'retinitis pigmentosa' or RP. A second potential patient pool have end-stages of the retinal disease 'macular degeneration' (Margalit and Sadda 2003). This is a disease in which abnormal blood vessels grow under the central retina, leak fluid and blood and eventually cause degeneration, and scarring. Finally, a small percentage of the severely impaired patients have strokes of the optic chiasm, optic nerve atrophy, or optic nerve neuritis. For these patients, the retina is non-functional and the only remaining option currently under study is a prosthesis that stimulates the visual cortex. To date at least 23 different groups are designing visual prostheses (Hessburg and Rizzo 2007, Wickelgren 2006).

RP is a genetically-based retinal disease that initially presents as a degeneration of rod photoreceptors which results in a loss of night vision. Pigmented lesions with the appearance of 'spicules' are seen in the retina upon ophthalmoscopic examination. RP patients often report shimmering or flashes of light in their visual fields. Peripheral vision is gradually lost resulting in a narrow central visual field some 3–10° in diameter. In its end-stage, RP can result in a near complete degeneration of the retinal photoreceptors. A few isolated islands of light sensitivity may remain in the peripheral retina. Disease progression is highly variable, and only RP patients who are severely visually impaired would potentially benefit from the current visual prostheses (e.g. Berson *et al* (2002), Grover *et al* (1998, 1999), Fishman (1978), Milam *et al* (1998)). These severely afflicted patients are at best only able to detect the presence of light or hand motion in a few isolated areas of the visual field (Grover *et al* 1998). The retinas of RP patients exhibit a foveal slope (Stone *et al* 1992), however their foveolae are abnormal. In cross section, they typically exhibit two *or fewer* rows of photoreceptor cell bodies unlike the five–eight rows normally present (table 2 in Stone *et al* (1992)).

End-stage RP, while ostensibly causing degeneration of foveal photoreceptors can also induce secondary degeneration of the foveal ganglion cells, a critical stimulation target of retinal prostheses (Stone *et al* 1992, Santos *et al* 1997, Humayun *et al* 1999a). Histological studies of the macula indicate that while 78% of the inner nuclear layer neurons survive, only 30% of the ganglion cells remain and in a few cases there can be a total loss (Santos *et al* 1997, Humayun *et al* 1999a). Although inner nuclear layer neurons and ganglion cells are reduced in RP patients, the retinal neurons remaining can elicit the sensation of light in patients when electrically stimulated (Humayun *et al* 1996, Rizzo *et al* 2003a, 2003b, Feucht *et al* 2005). In human retinitis pigmentosa, the normally layered retina tends to degenerate with the few surviving rods sprouting neurites that extend to the inner limiting membrane (Li *et al* 1995), and abnormal neural connections are formed by amacrine and horizontal cells (Fariss *et al* 2000). Thus a retinal prosthesis in an end-stage RP patient's eye may potentially stimulate a retina with unusual connections not seen in normal individuals. Animal models of RP, such as the RCS rat and the Rd mouse (Potts and Inoue 1969, Marc and Jones 2003) exhibit similar patterns of retinal neuron reorganization (Strettoi and Pignatelli 2000, Jones *et al* 2003, Marc *et al* 2003) and are actively being studied by prosthesis researchers (e.g. Suzuki *et al* (2004)).

Currently, mutations in over 30 different retinal genes have been implicated in RP making a simple genetic cure for the disease difficult to achieve (Wang *et al* 2005, Rivolta *et al* 2002, Milam *et al* 1998). The genetics of RP are complex, as the disease can be autosomal-dominant, autosomal-recessive, X-linked, or of non-familial etiology (simplex). About 60% of RP cases still have no known genetic cause (Wang *et al* 2005, Milam *et al* 1998). The degree of visual loss in RP is mildest in cases of autosomal-dominant disease and most severe in cases of X-linked disease (Fishman, 1978). Posterior subcapsular cataracts of the lens, commonly associated with late-stage RP, can confound assessment of patient visual performance. While it is likely that genetic vectors or stem cell technology may ultimately repair some forms of RP (Acland *et al* 2001), the sheer number of mutations involved precludes simple therapies and may require intact rod precursors (MacLaren *et al* 2006). However, visual cortex function is often unaffected in RP patients (e.g. Jacobson *et al* (1985)). Thus for these advanced patients, a visual prosthesis may be the only option.

5. Retinal visual prostheses

Retinal prostheses attempt to integrate into the diseased retinal network of the visually impaired patient's eye in order to create the percept of pattern vision. The typical prosthesis uses a camera, mounted either on glasses or in the eye to provide the visual input (figure 1). The camera output is sent through a video processor and neural stimulator to stimulus electrodes embedded in the patient's eye to create the sensation of vision. Unlike visual prostheses in the brain, retinal prostheses are readily accessible surgically and can be monitored through the eye. Currently, most prostheses types proposed use electrical current to depolarize neurons.

5.1. Retinal prostheses relying on electrical current stimulation

Electrical stimulation of the globe of the human eye has long been known to elicit an artificial sensation of light termed an electrophosphene (e.g. Purkinje (1823)). Further research showed the electrophosphenes were of ocular origin (e.g. Finklestein (1894)), and finally due to activation of the retina itself (Granit and Helme 1939, Brindley 1955). The first retinal prosthesis for the blind was proposed by Tassiker (1956). It consisted of a light-sensitive selenium photodiode cell placed behind the retina. There are three possible mechanisms by which electrical stimulation can activate retinal pathways to elicit electrophosphenes in blind patients. First, electrodes can depolarize and form action potentials in ganglion cell axons. Second, electrical currents can depolarize and form action potentials in local ganglion cells directly. Finally electrical currents can depolarize cells in the retinal network such as bipolar or amacrine cells which propagate the visual signal to ganglion cells. The electrochemical properties of stimulating electrodes containing Pt or Ir metal have been extensively studied (e.g. Brummer and Turner (1977), Rose and Robblee (1990), Robblee *et al* (1983)). As with most neural stimulation, stimulation protocols are limited to charge balanced biphasic current pulses of short duration (0.05–5 ms) to prevent metal electrode dissolution. Four different locations are currently being evaluated for the stimulus electrodes in retinal prostheses: epiretinal, subretinal, suprachoroidal and the optic nerve (figure 1).

5.2. Epiretinal stimulation electrodes

In the epiretinal configuration, the stimulation electrode array is placed in the vitreous cavity directly over the inner retinal surface in close proximity to the ganglion cell bodies. Advantages of this design include that it is less invasive to the retina, does not occlude the retinal vasculature, and can be monitored ophthalmoscopically. In acute clinical trials with an epiretinal electrode, several groups have shown that biphasic current pulse stimulation elicited an electrophosphene in blind volunteers (Humayun *et al* 1996, Rizzo *et al* 2003a, Feucht *et al* 2005). Higher frequency stimulation of 40–50 Hz gave non-flickering maintained percepts (Humayun *et al* 1999b, see also Brindley (1955)). Currently, clinical trials of a 4×4 array of silicon-insulated Pt disc epiretinal electrodes (250–500 μm diam.) are ongoing in RP patients (Mahadevappa *et al* 2005). The electrode array is held against the retinal surface with an implanted titanium tack. A camera and video processor connected to a modified cochlear implant pulse generator is used to provide visual stimulation (Humayun *et al* 2003). In the patients, biphasic stimulation of most electrodes elicited electrophosphenes (threshold 24–702 μA, 1 ms, cathodic first), and some were able to detect movement (Humayun *et al* 2003, Mahadevappa *et al* 2005). The electrophosphene 'visual field' map of one implanted individual has been reported (Humayun *et al* 2003); however it is unclear how well the map corresponds to the actual retinal electrode locations (see also Rizzo *et al* (2003b)). Currently, several epiretinal prostheses are under development incorporating 49–60 electrodes to improve spatial resolution (Hornig and Richard 2006, Javaheri *et al* 2006, Wickelgren 2006).

5.3. Subretinal stimulation electrodes

Stimulating electrode arrays are also being tested in the subretinal space of visually impaired patients. This space is located between the pigment epithelium and the photoreceptor layer of the retina. The advantage of the subretinal stimulation location is that it can depolarize the remaining bipolar cells in the retinal circuits of RP patients, which may produce a more natural excitation of the ganglion cells. The disadvantages of these arrays may stem from the barrier they form between the choriocapillaris vasculature and the retina, leaving the retinal artery vasculature as the sole retinal oxygen source (see section 10). To date, two main types of subretinal devices are being tested: passively and actively powered stimulation arrays.

Passively powered subretinal stimulation arrays are currently being tested in clinical trials in RP patients (Chow *et al* 2004). Chow and Chow (1997) fabricated an implantable circular microchip 2 mm in diameter and 25 μm thick containing an array of 5000 silicon microphotodiodes with IrOx electrodes termed an 'artificial silicon retina' or ASR. Light passively strikes photodiodes in the array, which generate local electrical currents that activate the inner retinal synaptic circuitry to elicit the sensation of vision. Preliminary experiments with implanted ASRs in rabbit eyes using IR LEDs as stimuli suggested it was possible to record photodiode-evoked cortical potentials thought to originate from the stimulated retina (e.g. Peyman *et al* (1998)). However when stimulating humans with IR light in the dark, it is important to control for the IR spectral sensitivity of rods and long wavelength cones (see Griffin *et al* (1947), Stockman and Sharpe (2000), Pardue *et al* (2001)). A second group headed by Eberhardt Zrenner fabricated a similar series of passively powered silicone photodiode chips that were tested in pigs, rats, and chicken retinas (Zrenner 2002b). In animal studies, both groups found that the implant was well tolerated by the adjoining retina. However, Zrenner's group has concluded that it is unlikely for single microphotodiodes to be able to generate sufficient current to activate local neurons in the retinal network using ambient light levels (Zrenner 2002a, Gekeler and Zrenner 2005). Their active microphotodiode implant incorporates adaptation circuits and external power sources (Gekeler and Zrenner 2005).

There are also problems in evaluating the effectiveness of the passive photodiode retinal implants. Unlike more complex prostheses, a passive photodiode array is chronically active and cannot be turned off, complicating metrics of clinical success due to lack of a non-functional control. Healing factors induced by the surgery could confound device effectiveness, as studies have shown that surgical wounds increase intrinsic retinal neurotrophins (Cao *et al* 1997, 2001, Sakai *et al* 1999). Healing factors appear to have a neuroprotective effect, slowing the natural photoreceptor degeneration in animal models of RP. Pardue *et al* (2005a, 2005b) have recently reported in an RP rat model that implantation of active or inactive ASR chips preserve photoreceptor nuclei equally.

The second type of subretinal stimulation electrode array under investigation is actively powered. This array design is currently in the prostheses under study by two groups; one headed in the US by Joseph Rizzo, and a second in Germany by Eberhard Zrenner. Both groups propose to provide power to their prostheses through telemetry coils typically mounted on eyeglasses (Gekeler and Zrenner 2005, Rizzo 2006). In the rabbit retina, stimulation with active subretinal electrode arrays is able to generate electrically evoked potentials in visual cortex with charge densities of as little as 10 μC cm^{-2} (Gekeler *et al* 2004), however higher stimulation thresholds have been found in pigs (100 μC cm^{-2}) (Sachs *et al* 2005, Schanze *et al* 2006). Subretinal electrode stimulation with cathodal pulses may also be able to selectively stimulate ON- versus OFF-center ganglion cells in the rabbit retina (Jensen and Rizzo 2006), a critical feature for evoking electrophosphenes more biologically relevant to normal retinal function. Preliminary tests in RP patients with an active 4 × 4 subretinal array show they are able to perceive discrete visual phosphenes, lines, and a square (Wilke *et al* 2006, Wickelgren 2006).

5.4. *Extraocular electrodes*

Recently, several groups in Japan and Australia have performed experiments in animals using a stimulating electrode array located inside or on the surface of the sclera of the eye (Kanda *et al* 2004, Sakaguchi *et al* 2004, Nakauchi *et al* 2005, Chowdhury *et al* 2005). These designs have been termed 'suprachoroidal' 'intrascleral' or 'extraocular' electrode arrays. The advantages of these designs are that they appear to cause little risk of retinal detachment, do not occlude the choroidal vasculature, and are adjacent to the outer retina where the visual signal originates. Their disadvantages are that they are located behind the resistive barrier of the pigment epithelium (or R-membrane) which impedes electric current flow into the retina (e.g. Tomita *et al* (1960)). While the resistivity of the retina is quite low to electric current flow ~40–60 Ω cm^2, the resistance of the pigment epithelium is 5–15-fold higher (e.g. frog: Tomita *et al* (1960), rabbit: Karwoski and Xu (1999), macaque: Heynen and van Norren (1985), Tsuboi *et al* (1987), human: Quinn and Miller (1992)).

Experiments in rabbits with suprachoroidal arrays suggest they are well tolerated in the sclera of the eye and no adverse ocular pathology was seen (Nakauchi *et al* 2005). Currently, it is unclear if the currents elicited by these electrodes will be adequate to evoke electrophosphenes in blind patients, however in RCS rats suprachoroidal electrode stimulation elicited evoked-potentials in the superior colliculus (Kanda *et al* 2004). In rabbit retinas, suprachoroidal electrode array stimulation elicited electrically evoked cortical potentials (an index of retinal function), but thresholds were 16× higher than with subretinal stimulation (Yamauchi *et al* 2005). These higher stimulus thresholds may be reduced with a scleral-mounted penetrating retinal implant array currently under development (Gerding 2007).

5.5. *Optic nerve electrodes*

Stimulation electrodes have also been tested on the optic nerve (figure 1). A Belgium-based group has developed a series of four platinum discs (0.2 mm^2) mounted in a spiral cuff electrode to stimulate sectors of the optic nerve. To date, it has been implanted in two RP patients (Veraart *et al* 1998, Delbeke *et al* 2002). Cuff electrodes, mounted on either the orbital or cranial sections of the optic nerve, were attached to a wireless subdermal stimulator located on the side of the head. In the single patient tested, optic nerve stimulation generated a field of phosphene 'dots' whose threshold, area and visual field location depended on pulse train duration and stimulus strength (single pulse threshold, 250 μA). Weaker/shorter stimuli generated more peripherally field percepts while stronger/longer stimuli resulting in more central fields (Delbeke *et al* 2003). While there is little trauma to the eye itself with such a system, it is unclear if optic nerve electrodes can elicit the discrete spatially adjacent phosphene fields needed for generating pattern vision given the large number of axons in the optic nerve.

6. Issues with retinal prostheses

6.1. *Retinotopic stimulation in the fovea*

Theoretically, it would be desirable to stimulate the visual system near the fovea in order to better exploit the remaining high resolution visual pathways. However, there are complexities with stimulating foveal ganglion cell receptive fields. To illustrate these issues, a human fovea is shown overlaid with a model array of epiretinal stimulating electrodes in figure 2(a). Ideally, stimulation by a single epiretinal electrode induces action potentials in the underlying local patch of ganglion cells which would be perceived by the patient as an electrophosphene originating from the overlying photoreceptors. However a problem arises: the central fovea contains no ganglion cells; only cone photoreceptors. Foveal ganglion cell bodies, a typical target of electrical stimulation by visual prostheses, are physically displaced around the edge of the foveal pit in a ring 0.4–2 mm in diameter at a peak density of 25 000–35 000 cells mm^{-2} (Curcio and Allen 1990). The density of ganglion cells across the fovea is shown in figure 2(c). In a single cross section through the foveal edge, ganglion cell bodies are stacked up to six–eight cells deep in a layer some 50–60 μm in thickness (Curcio and Allen 1990). This creates a problem for epiretinal visual prosthesis designs. The annular displacement of the central foveal ganglion cell bodies to the edge of the foveal slope distorts the assumption that electrode stimulation of local ganglion cell bodies generates a local electrophosphene percept. Conceivably, these distortion problems could be reduced by placing a subretinal prosthesis under the fovea, however this could occlude the sole blood supply to the central fovea (see section 10.1). Given the above issues and the variable degeneration found in RP patients, a complex remapping of prosthetic stimulus electrodes to foveal ganglion cell receptive fields may be required in order to generate a uniform 'visual field map' of electrophosphenes.

6.2. *Selective stimulation of local retinal ganglion cells*

An epiretinal prosthesis places stimulation electrodes near the inner retinal surface to induce action potentials in the

underlying local patch of ganglion cells (figure 2(b)). However because the electrodes are *actually* closest to the nerve fiber layer axons overlying the ganglion cells, the possibility exists for the stimulating electrodes to activate these crossing axons from distal retinal ganglion cells before the local cell bodies (e.g. figure 2(b)). In humans and primates, the nerve fiber layer consists of unmyelinated axons 0.5–2 μm in thickness extending around the foveal region in a C-shaped series of decussations (Vrabec 1966). The nerve fiber layer can vary in thickness from around 34–45μm near the foveola to 8 μm in the periphery (Varma *et al* 2003, 1996) and is thinnest about the median raphe (Vrabec 1966).

In patients, stimulation by epiretinal stimulus array electrodes have generated electrophosphenes in their visual fields (Humayun *et al* 2003, Mahadevappa *et al* 2005). Ideally, stimulation by each electrode in the array on the retina surface should elicit a spatially adjacent electrophosphene in the patient's 'visual field'. However the current reported 'visual fields' of a single implanted subject of Humayun *et al* (2003) seem to be considerably larger than the epiretinal electrode array itself, generating the question whether surface electrodes can in some cases activate nerve fiber layer axons from more peripheral ganglion cells rather than the underlying local ganglion cell bodies (Greenberg *et al* (1999); see also Rattay and Resatz (2004)). In theory, smaller more densely packed electrode arrays close to the retinal surface might improve spatial resolution, however higher charge densities might be required to activate local ganglion cells. Modeling studies have suggested that line-shaped stimulation electrodes oriented parallel to the nerve fiber decussations could selectively activate local ganglion cells (Grumet *et al* 2000, Rattay and Rasatz 2004).

Epiretinal electrical stimulation of the retina can potentially activate multiple retinal pathways. In rabbit retina, stimulation studies of a large ganglion cell type with an epiretinal disc electrode have shown that a critical window exists between activation of the adjacent axon fiber bundles, the local ganglion cell bodies and the retinal network circuitry below (Jensen *et al* 2005a, 2005b). To single pulse stimulation, these response components have different latencies of action potentials, with the retinal network response being more delayed. Short duration pulses (0.1 ms) are more selective for direct activation of local ganglion cell bodies and not overlying axons (Jensen *et al* 2005a, Fried and Hsueh 2006). In rabbit retina, cathodic-first stimulation evoked lower spike thresholds than anodic stimulation (Jensen *et al* 2003, 2005a). In epiretinal prosthesis patients, electrode proximity to the retina also plays a role in determining electrophosphene current thresholds (Mahadevappa *et al* 2005). Future designs of epiretinal electrode arrays are slated to contain as many as a thousand electrodes closely apposed to the retina. Contingent on these arrays, given their smaller surface area, is the assumption that the localized electric field density will be sufficient to activate local ganglion cells directly below the electrodes while avoiding activation of more proximal axons crossing in the nerve fiber layer. Classically with electrical stimulation, large diameter axons are recruited before smaller axons. This is known as the 'size principle'. Unmyelinated ganglion cell axons show varicosities inside the human eye, and this could also potentially affect axon recruitment thresholds to epiretinal electrical stimulation (Wang *et al* 2003).

Finally, there are limits to electrical stimulation of the retina using metal electrodes. Most epiretinal prostheses using metal electrodes rely on short charge-symmetric pulses on the order of milliseconds to excite the retinal network. This is because longer current pulses, similar to the natural response of retinal neurons to light, cause metal electrodes to degrade (Rose and Robblee 1990, Robblee *et al* 1983). Consequently, stimulation tends to be limited to biphasic charge-conserving short pulses. Most methods of electrical stimulation cannot distinguish between ON- and OFF-center ganglion cell types (but see Jensen and Rizzo (2006)). It is unclear at present if electrical stimulation can selectively stimulate different ganglion cell types. Different ganglion cell types have different natural firing patterns and spontaneous firing rates; however, they will all be stimulated simultaneously by electrical stimulation. New finer electrode designs may be able to better focus the electric field at the local neurons in the retinal network. None the less, any visual prosthesis that could provide even rudimentary spatial pattern vision would be a major advance for the severely blind patient.

6.3. Eye movements and image stabilization

To be able to see fine detail in the visual world with our fovea. we need to repeatedly shift our direction of gaze through eye movements. The globe of the eye is capable of turning at speeds of up to 900° s^{-1} (Carpenter 1988). This presents severe challenges as to how to send electrical power and signals to prosthetic devices mounted on the surface of the eyeball. The outer surface of the eyeball or sclera, while tough from collagen fibrils, is quite thin in humans. Scleral thickness varies from 0.5 mm near the peripheral surgical limbus to 1 mm at the optic nerve head (Olsen *et al* 1998). Eye movements generated by the six extraocular muscles that surround the eye are of several different types. They include large fast excursions called 'saccades' of up to 100°, smaller 'smooth pursuit' movements and fine 'microsaccades'. Estimates of the daily rate of saccadic eye movements are task-dependent, and vary from 10 000 to 170 000 per day (Dr Jeff Pelz, personal communication, Schiller and Tehovnik (2002)). Seventy-five per cent or more of saccades during ambulatory movement or in tasks such as hand washing are under 15 ° s^{-1} (Pelz and Canosa 2001, Bahill *et al* 1975). To avoid these movements of the globe stressing connecting cables in retinal prostheses, current retinal stimulating prosthetic designs have proposed using devices with telemetry coils mounted to the globe itself, visible or IR light beams as intraocular power/signal sources, or multiple turns of flexible cable to reduce retinal tension (Humayun *et al* 2003, Javaheri *et al* 2006, Wickelgren 2006).

The spontaneous eye movements of visually impaired patients can be a significant problem for prosthesis designs. Adult-onset blind RP patients can exhibit continuous nystagmus or spontaneous eye movements (Ohm 1951, Leigh and Zee 1980, Kompf and Piper 1987, Mahadevappa *et al*

2005), and blindness from birth has been associated with an impaired vestibulo-ocular reflex and an inability to voluntarily initiate saccades (Leigh and Zee 1980). These patient eye movements cause the electrophosphene of a fixed position on the visual cortex/retina to apparently move. As first noted for cortical prostheses, eye movements have made it difficult to generate a 'visual field' map of the electrophosphenes evoked from adjacent electrodes (Brindley and Lewin 1968, Dobelle and Mladejovsky 1974, Schmidt *et al* 1996). Many visual prostheses currently rely on a camera mounted on eyeglasses for transmitting the visual signal sent to their stimulating electrode arrays (e.g. figure 1). These head mounted camera designs do not compensate for patient eye movements. This may require the prosthesis patient to learn additional forms of compensation (e.g. head scanning) in order to navigate the visual environment (e.g. Dobelle (2000)). The problem of remapping the moving visual scene is eliminated only in prosthetic designs that use a 'camera' mounted on the eye, or when eye movement tracking/correction is employed (e.g. Gekeler and Zrenner (2005)).

7. Lateral geniculate nucleus

The lateral geniculate nucleus (LGN) in the thalamus is the first visual area to receive synaptic input from the optic nerves. Its retinotopic organization makes it a potential target for visual prosthetic devices. The human LGN is a rounded structure composed of six concentric slightly bent layers of neurons, and is fairly small (approx. 6 mm × 5 mm). There is considerable variation between individuals in the lateral extent of each layer (Hickey and Guillery 1979, Andrews *et al* 1997). The lower two LGN layers receive input from magnocellular retinal ganglion cells, while the upper four LGN layers receive input from parvocellular cells, with each layer receiving exclusive input from either the ipsilateral or contralateral eye. Most studies on human LGN retinotopy have relied on non-invasive imaging methods particularly functional MRI (fMRI) which relies on the oxygen-dependent hemodynamic response of neural tissue. Studies in primate visual cortex indicate that this fMRI response is roughly correlated with the local field potential activity when both are measured simultaneously (Logothetis *et al* 2001). Functional MRI studies of the human LGN indicate that foveal vision is represented in the posterior and superior sections and is highly enlarged (Schneider *et al* 2004). Magnocellular portions of the geniculate input appeared more inferior and medial in location. From fMRI studies, a 3° retinal area of central vision is magnified anatomically in the lateral geniculate nucleus to occupy ∼60% of the LGN volume (figure 6, Schneider *et al* (2004)). This enlarged LGN foveal representation could facilitate stimulation of the central visual area by a prosthetic device. Electrical stimulation studies of human LGN have been reported by Nashold (1970) and Marg and Dierssen (1965). In some cases, subjects were able to perceive discrete colored dots; however, the surgical difficulty of the deep brain approach to the LGN has hampered prosthetic design. A visual prosthetic design projecting to the LGN has been proposed (Yagi *et al* 1999, 2005).

8. Visual cortex

The primary visual cortex, termed 'V1', 'occipital', or 'striate cortex' serves as the principal way station for visual processing in the brain, and has long been a target for visual prostheses (Marg 1991). Its surface is covered by protective meninges composed of an outer 'dura mater' of tough white fibrous and elastic tissues, a middle 'arachnoid' membrane, and a vascular 'pia mater' that covers the cortical surface. Human visual cortex receives synaptic input from the LGN through a prominent series of axonal fiber tracts termed 'optic radiations' that course to the occipital pole of the cerebral cortex and form part of the white matter below the cortical layers. Stimulation of these radiations can elicit electrophosphenes (Marg and Dierssen 1965).

8.1. Anatomical organization

The visual cortex is composed of ∼100 neuron types irregularly arranged in distinct laminae numbered 1–6 from the cortical surface (Born 2001) A radial section through human visual cortex is shown in figure 3(a). The axonal endings of LGN efferents synapse onto visual cortical neurons located in layers 4Cα and 4Cß. The receptive fields of neurons in these layers have a simple center-surround organization as originally defined by Hubel and Wiesel (1962). More distal layers contain pyramidal neurons that have 'complex' visual receptive fields and dendrites that span the cortical layers. Cells near the visual cortical surface have complex receptive field properties. Perhaps the most striking feature of the visual cortical surface is that it is highly organized by visual modality. Adjacent visual areas termed 'hypercolumns' receive LGN input segregated by right or left eye, stimulus orientation, and also by color in a complex spatial representation of the visual field.

Anatomical studies of human visual cortex using biocytin or DiI to label neurons have found extensive axonal collaterals between adjacent cortical regions (Burkhalter and Bernardo 1989, Kenan-Vaknin *et al* 1992, Burkhalter *et al* 1993). Activation of these axon collaterals by stimulus electrodes have the potential to spatially blur or cause multiple phosphene percepts (Brindley and Lewin 1968). Layer 1 is closest to the cortical surface. It is a largely aneuronal layer, and is composed of many axonal fibers that branch to adjacent local areas in visual cortex. In primates, many of these axons are projections from higher cortical areas such as V2, MT, inferotemporal cortex (Rockland and Knudsen 2000, Rockland *et al* 1994). Layers 2/3 termed the 'supragranular layers' contain many somata and dendrites of pyramidal cells. These cells have extensive axons projecting to extrastriate areas including V2, V3, V4, MT among others. The deeper cortical layers such as layers 4A, 4B and 4C (α, ß) termed 'the granular layers' have few axonal collaterals. Axons in layer 5/6 (infragranular layers) project back to the lateral geniculate nucleus. In addition, there is a series of extensive narrow vertical excitatory axonal connections from infragranular cortical layers to the supragranular layers and inhibitory feeback as well (for more details see Alonso (2002), Burkhalter *et al* (1993), Kenan-Vaknin *et al* (1992)). How

these lateral and vertical feedback axonal pathways respond to electrical stimulation is unknown.

9. Visual cortex prostheses

9.1. An enlarged retinotopic representation

A significant advantage of the human visual cortex (VI) for prosthesis design is that the cortical surface area occupied by the central retinal visual field is highly magnified (figure 4). Visual cortex fMRI studies indicate that the foveal visual field occupies the posterior pole of the occipital lobe (DeYoe *et al* 1996). Using fMRI on seven subjects' cortices, Dougherty *et al* (2003) found a 2° radius of central retinal visual field ~1.0 mm^2, occupied on average 2095 ± 638 mm^2 in the visual cortex: a 2000-fold expansion. Conceivably, this would make the task of central visual field stimulation considerably easier, and one visual prosthetic device using platinum disc electrodes to stimulate the cortical surface was in clinical trials in Portugal (Kotler 2002). However, a portion of the central visual field lies in the calcarine sulcus, so not all of the visual field is surface accessible (figure 3(b)). There is also significant variation in the size of the visual cortex between individuals (Sauer 1983, Stensaas *et al* 1974, DeYoe *et al* 1996, Dougherty *et al* 2003) (figure 4). Two types of electrodes have been tested in visual cortex prostheses: surface and intracortical electrodes.

9.2. Cortical surface electrode arrays

Cortical surface stimulation with disc electrodes, such as those employed originally by Giles Brindley (Brindley and Lewin 1968) and the late William Dobelle (2000, 1996, 2005 obituary) have been tested in significant numbers of patients (see also Lee *et al* (2000a)). This type of cortical implant is the least invasive, beside the inherent risks associated with brain surgery, tissue traction and material biocompatibility. The initial studies of Brindley and Lewin (1968) used a single array of 80 silicon-insulated square Pt electrodes each 0.64 mm^2 that were placed over the pial surface of the visual cortex. Each electrode was connected by wires to a single pedestal interface coil mounted on the skull. Electromagnetic coil induction was used to stimulate individual electrodes (Brindley 1982, Brindley and Lewin 1968). Later prosthesis designs increased the electrode number to 151 (Brindley 1982).

Using surface stimulation, high biphasic current pulse trains (in the 0.5–5 mA range) are necessary to elicit electrophosphenes, necessitating the use of large surface electrodes to avoid electrochemical degradation (e.g. Girvin *et al* (1979)). At threshold levels, patients typically describe stimulation-induced electrophosphenes in the central visual field as being single point-like or pea-sized bright stimuli seen at arm's length. More peripherally located electrophosphenes have been reported as looking like small clouds (Brindley and Lewin 1968). Stronger levels of stimulation elicit electrophosphenes that can appear in multiple regions of the visual field perhaps due to activation of adjacent gyral regions of cortical surface or axon collaterals. High-level stimulation can in some cases elicit frontal headaches presumably due to activation of the meningial pain fibers (Brindley 1982), and in one case convulsions have been reported (Kotler 2002). Using surface stimulation electrodes, two-point discrimination of the cortex is poor and only distances ⩾3 mm can be resolved (Dobelle and Mladejovsky (1974), Dobelle *et al* (1974); see also Talalla *et al* (1974)). Brindley and Lewin (1968) estimated the resistivity of the cortical membrane as 390–500 cm.

When individual electrodes on the cortical surface are stimulated, a retinotopic map of electrophosphene locations in the visual field can be generated. The resulting map appears as a rough sector of some 20° of visual field, giving the patient a pie slice-like region for visual navigation (Brindley *et al* 1972, Dobelle 2000). However map construction is complicated by the fact that during voluntary eye movements, the electophosphenes move with the eyes, except during the vestibular reflex (Brindley and Lewin 1968). When mapped electrodes were stimulated simultaneously in order to generate a 'square' electrophosphene percept, the square became distorted indicating the electrophosphenes were not spatially independent (Dobelle *et al* 1974). Electrodes may also be ineffective in stimulating regions of the visual field that lie in the calcarine sulcus (e.g. figure 3(b)) or under blood vessels. In addition a 'secondary dura' has been reported to form around implanted surface electrode arrays (Brindley and Lewin 1968).

In the Dobelle group cortical prosthesis trials, the patient used a camera mounted to a pair of glasses for visual input (Dobelle 2000, Kottler 2002). The visual processing unit consisted of a belt-mounted computer and utilized an edge detection algorithm for analyzing the visual scene (Sobel 1970). The system was implanted originally in four blind patients (Dobelle 2000). Early studies of the interface Dobelle (2000) were limited to 64 electrodes stimulating one visual cortex. The Teflon-insulated electrode array was connected to the outside electronics through a pyrolytic carbon percutaneous pedestal connector (Klomp *et al* 1977, 1979). More recently, a group of 16 patients were reportedly implanted by Dobelle with bilateral 72 Pt disc electrode arrays in a clinical trial in Portugal in 2002. These trials received great media attention (Kotler 2002) including a video of an implanted individual driving a car around an empty parking lot. To date however, no peer-reviewed published clinical studies have documented patient visual performance or device stability. In addition, the higher stimulation currents required by surface electrode prostheses consume more power, making large batteries needed for portable use.

9.3. Intracortical electrode arrays

Intracortical microelectrode stimulation of the visual cortex has the advantage that significantly lower stimulus currents are needed to evoke electrophosphenes compared to surface electrodes (typically 10–20 μA versus 1–10 mA) (e.g. Ronner (1982), Tehovnik (1996)). Intracortical stimulation is currently being studied by the labs of Troyk and Normann. Typical experiments implant long needle-type electrode arrays (5–150 electrodes) in primate visual cortex (e.g. Bradley *et al* (2005)). However the impalement of visual cortex

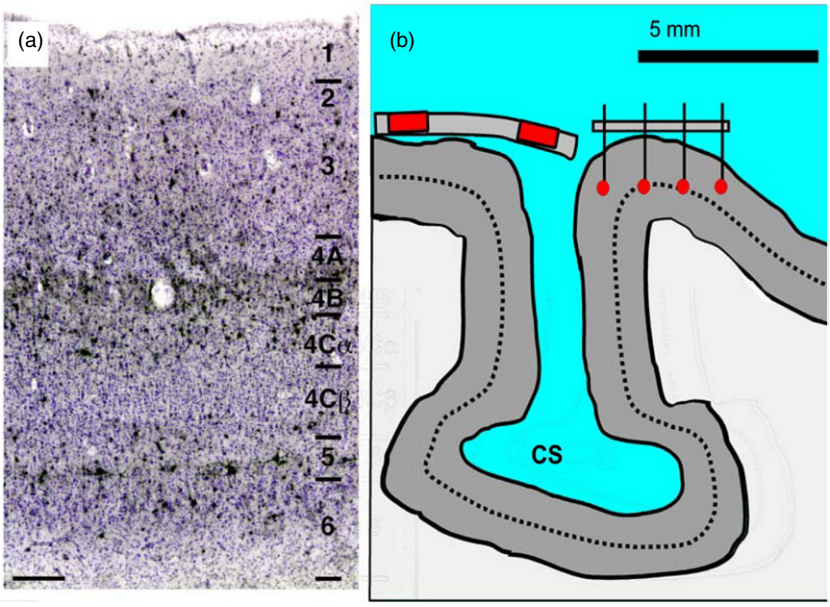

Figure 3. Prosthetic electrode stimulation of the human visual cortex. (a) Neuronal layers of the adult human visual cortex in radial section. Neurons in black are immunostained with an antibody (Cat-301) that labels cells thought to be involved in the magnocellular ganglion cell pathway (black stain), while other neurons are counterstained in blue (Nissle stain). Note layer 1, the uppermost layer near epidural disc electrodes, is largely devoid of neurons. Scale bar: 250 μm. From Preuss and Coleman (2003) with permission. (b) Visual cortex model implanted with epidural (left) and intracortical (right) stimulating electrodes. Red indicates conductive regions. Dotted line shows relative level of layer 4 geniculate efferents to cortex. A portion of the central visual field lies in the calcarine sulcus (CS), which is difficult to contact by current electrode designs. Fixed length intracortical electrodes may not stimulate neurons in the same layer due to variation in cortical curvature. CS: calcarine sulcus. Adapted from a section in figure 1, Stensaas *et al* (1974).

by intracortical electrodes can in some cases injure the brain, cause seizures, or even damage the microelectrodes themselves, and special electrode inserters have been devised (Normann *et al* 1999). In addition, reactive gliosis can in some cases form capsules around implanted electrodes in felines (Schmidt *et al* 1993, Liu *et al* 1999).

A clinical trial of an intracortical electrode array implanted to passively record neural activity in a paralyzed patient's motor cortex is currently ongoing (Hochberg *et al* 2005 abstract). This microarray, termed the 'Utah array' is currently composed of a 10 × 10 array of Pt-tipped silicon microneedles insulated with silicon nitride (Normann *et al* 1999, Warren *et al* 2001). The Utah array is connected by a polyimide cable to a cranial pedestal connector to the skull. Array electrode experiments in primate motor cortex (MI) that indicate arm movements can be predicted from the recorded neural firing patterns (Serruya *et al* 2002). However it is unclear whether these microarray electrodes will be stable enough to pass the larger currents required for stimulation of cortical neurons (see also Warren and Normann (2005)).

Few studies have used intracortical electrodes for stimulation in the human visual cortex (Shakhnovich *et al* 1982, Bak *et al* 1990, Schmidt *et al* 1996). Thirty-eight parylene-insulated iridium electrodes were chronically implanted in pairs in a 42 year old blind patient (Schmidt *et al* 1996). Electrode spacings tested were 250, 500 and 750 μm. Electrophosphene thresholds were complicated by the subject's perception of spontaneous phosphenes (Bak *et al* 1990). Shorter pulse width stimuli (200 μS) aided electrophosphene perception. Electrophosphenes elicited by pulse trains longer than 1 s usually disappeared. Although data were limited, electrophosphenes elicited by two electrodes spaced 250 or 500 μm apart were often reported as being in the same visual field location; implying inter-electrode spacings of $\geqslant$500 μm may be required (Bak *et al* 1990).

9.4. Critical issues for visual cortical stimulation

Given the extensive cortical magnification of the foveal visual field, a critical issue in intracortical electrode design is improving the two-point discrimination between stimulating electrodes. To date, we have little data on what might be the optimal depth(s) or design for intracortical stimulation electrodes in humans. The human visual cortex is about 2.5–3 mm in thickness (Leuba and Kraftsik 1994, Barbier *et al* 2002, Fischl and Dale 2000, Salat *et al* 2004). Although the axons of geniculate fibers lie deep to the cortical surface, electrode activation of more shallow axon feedback collaterals found in the intrinsic organization of the visual cortex itself could enlarge the phosphene. How electrophosphene size varies with cortical depth is unknown in humans. A recent study in primates by DeYoe *et al* (2005) has suggested electrophosphene detection threshold sensitivity in visual cortex is broadly distributed between cortical layers; peaking in layers 3–4B, with a weaker second peak in layer 5. There may also be variations in the optimal phosphene depth depending on cortical layer orientation to the fixed array electrode (figure 3(b)). How intracortical electrodes can be constructed to selectively stimulate adjacent cortical regions situated in cortical sulci is currently unclear. Finally, it

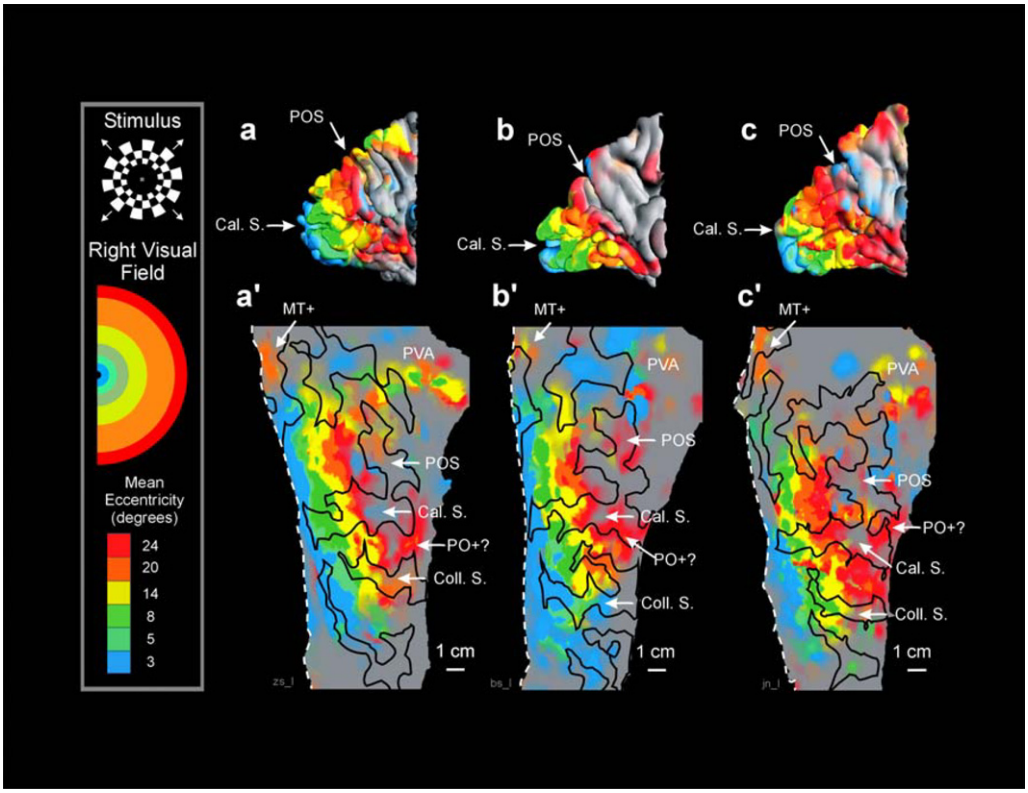

Figure 4. Magnification of the foveal visual field in human visual cortex. Left: legend of retinal visual field regions stimulated by annular test stimuli. Right: retinotopic maps of the visual cortex of three individuals. (a)–(c): Map of the intact visual cortex in medial view. (a′)–(c′): Retinotopy of the flattened visual cortical area. The 3 degrees of central vision that occupy a small area on the retina, in contrast, occupy a long strip on the flattened cortical surface. There is significant individual variation in the size and position of the central fovea cortical area (see also Andrews *et al* (1997)). CalS: Calcarine sulcus; POS: parietooccipital sulcus; PVA: parietal visual areas; Coll S: collateral sulcus. MT: middle temporal cortex. (From DeYoe *et al* **93**:2382–6, Copyright (1996) National Academy of Sciences, USA.)

has been known in primates for many years that pulse train stimulation with intracortical electrodes in the μA range can evoke eye saccades to the presumed electrophosphene, unless the subject is actively fixating on a target (Doty 1965, Talalla *et al* 1974, Schiller 1977, Keating and Gooley1983, 1988). In primates, the current-depth profile for evoking saccade thresholds is lowest near the layer 5/6 border and highest near the dural surface (Tehovnik *et al* 2003).

10. The visual prosthetic implant and the brain vasculature

A final concern for prosthetic device design is the integration of the device with the vasculature of the brain. Like most brain neurons, visual system neurons receive extensive blood flow and are highly sensitive to anoxia. The design and placement of a prosthetic device so that it does not significantly occlude blood flow/tissue oxygenation is an important consideration for stimulating the remaining neural neurons without inducing additional damage.

10.1. The retinal vasculature

The retina is one of the most oxygen-consuming structures in the human body. The bulk of the oxygenation of the retina is delivered through blood flow in the posterior choroidal capillaries located behind the retina. These choroidal vessels form an extensive capillary layer mat directly adjacent to the photoreceptors termed the 'choriocapillaris'. The choriocapillaris receives the greatest percentage of retinal blood flow (65–85%) (Henkind *et al* 1979) and is vital for the maintenance of the photoreceptor layer. A lesser degree of blood flow occurs inside the retina itself via the central retinal artery. These blood vessels service inner retinal layer neurons such as ganglion and amacrine cells (see also Alm and Bill (1973)). The retinal artery capillaries end at the photoreceptor terminals. Thus the bulk of blood flow occurs behind the photoreceptor cells, so as to not obscure the retinal image. Between the choriocapillaris and the retinal artery capillary beds, exists an avascular region some 130 μm in width that depends on diffusion of oxygen from the two capillary beds (Cioffi *et al* 2003). A consequence of this arrangement is that the maximum oxygen tension in a primate eye, some 85–100 mm Hg declines with distance away from the choriocapillaris into the inner retina. The oxygen tension of the inner retinal circulation is weaker and reaches a peak of 30 mm Hg.

Subretinal prostheses can potentially occlude choriocapillaris oxygen diffusion. Studies with impermeable microphotodiode implants in the subretinal space of rats and cats show some thinning of the adjacent photoreceptors, and the bipolar and amacrine cells in the inner nuclear layer

(Chow *et al* 2001, 2002, Volker *et al* 2004); however, implants in pigs showed less degeneration of the inner retina (Zrenner *et al* 1999). For subretinal implants in humans, the central foveal region (500–600 μm diam.) lacks retinal capillaries entirely and is dependent on oxygen diffusion from the choriocapillaris bed (Laatinainen and Larinkari 1977).

10.2. The visual cortex vasculature

The visual cortex vasculature presents different issues for prosthetic designs. It is well known that the visual cortex moves slightly due to the pulsatile nature of arterial blood flow in the brain (Glover and Lee 1995). Significant cortical movement pulsations can also occur during coughing or due to head impact (Maier *et al* 1983, Schmidt *et al* 1996, Goldberg *et al* 2005). A consequence of this issue is that visual prosthetic devices implanted into cortical tissue are subjected to continual flexing which could potentially fatigue fine coatings used to inject current, passivation layers used for insulation, or connections to the skull.

The pial surface of the cortical brain has extensive blood vessels that can be damaged in implanting intracortical electrode arrays. Capillary beds are also found in all cortical layers with the largest numbers of capillaries in layer IVC (Bell and Ball 1985). Close post-operative management of implanted subjects may be needed to avoid seizures, infection, blood hemorrhages, or strokes (Bradley *et al* 2005). However, experiments in primates and cats with implanting intracortical stimulating electrodes by Liu *et al* (1999), Warren and Normann (2005) and Troyk *et al* (2003) show that tissue insult with electrode insertion in most cases attenuates with time.

11. Future visual prostheses

Although current visual prostheses rely on electrical stimulation to excite neurons, researchers are trying more biologically compatible methods of neuron stimulation. These methods include using natural brain neurotransmitters/analogs, ion channels and neuroattractive surfaces to improve signal transmission across the 'machine–neuron' interface.

11.1. Neurotransmitter-releasing visual prostheses

Glutamate is the major neurotransmitter released by many neurons in the retina and visual cortex including retinal photoreceptors and geniculate efferents. In the retina, glutamate is normally stored in the endings of rod and cone photoreceptors as synaptic vesicles (~100 mM) and released onto bipolar cell dendrites. In theory, glutamate released onto bipolar cells would depolarize OFF-bipolar cells, while simultaneously hyperpolarizing ON-bipolar cells. If a glutamate-releasing prosthesis could be placed at the level of the missing photoreceptor endings in RP patients, communication with the remaining bipolar cells could propagate the visual signal to ganglion cells. Two glutamate-releasing prosthetic designs are currently being proposed; one using optical waveguide uncaging of neurotransmitter near retinal neurons (Safadi *et al* 2003), and another using microfluidic neurotransmitter release through miniature orifices (Peterman *et al* 2003a, 2004). Neurotransmitter-releasing prosthetic designs have also been tested in the cerebral cortex by Cheung *et al* (2003), and also in the guinea pig superior colliculus (Rathnasingham *et al* 2004, Wise *et al* 2004, Chen *et al* 1997).

There are also potential problems with this form of more natural neural stimulation. The glutamate-releasing prosthetic device needs to be located extremely close to the glutamate receptors on the dendrites of the postsynaptic bipolar cell targets. Externally applied glutamate, if applied more distally, is rapidly uptaken from the extracellular space by several different glutamate transporter systems present in Müller cells, photoreceptors and some bipolar cells (Grewer and Rauen 2005, Amara and Fontana 2002). Conceivably, this loss could be alleviated by prosthetic devices that 'tether' a neurotransmitter analog as a movable ligand near the receptor (Vu *et al* 2005, Nehilla *et al* 2004). Because the normal resting potential of photoreceptor cells in the dark is partially depolarized, some sustained glutamate release by photoreceptor endings is normally present (Heidelberger *et al* 2005). Bipolar and ganglion cells are also partially depolarized due to resting glutamate release (e.g. Cohen and Miller (1994), Cohen (1998, 2001)). Glutamate diffusion could be limited by growing retinal neurons into small orifices (e.g. Peterman *et al* (2003b)). It is also unclear how a neurotransmitter releasing prosthesis would be refilled. Nonetheless, this neurotransmitter has the greatest potential for duplicating natural vision in an ocular prosthetic device.

11.2. Neural interfaces using light- or mechanically-activated ion channels

It is possible to engineer ion channel interfaces for stimulating neurons that can be gated directly by light. Qiu *et al* (2005) transfected mammalian cells with an endogenous mammalian opsin, melanopsin which caused them to elicit slow light-induced depolarizations. Nagel *et al* (2003) cloned an ion channel termed 'channel rhodopsin-2' from the green algae *chlamydomonas reinhardtii* that was gated directly by light. Upon illumination, a non-selective calcium-permeable cation channel opened causing rapid depolarizations of the membrane. Several groups have transfected cultured hippocampal and retinal neurons with channel rhodopsin-2 and show they are able to gate neuron firing with light; in some cases with near millisecond time control (Banghart *et al* 2004, Bi *et al* 2006, Boyden *et al* 2005). Finally mechanosensitive channels such as the stretch-activated MscL channel in bacteria have been genetically altered to be gated by light directly (e.g. Kocer *et al* (2005)).

11.3. Electrically stimulated cultured neural network interfaces

Neurons can also be stimulated by being grown on silicon substrates with electrical pads. (Matsuzawa *et al* 1994, Fromherz 2003). A 'bio-hybrid' prosthesis has been proposed

Table 1. Retinal prosthesis designs and thresholds in humans (unless noted).

Prosthesis type	Epiretinal	Subretinal	Suprachoroidal	Extracortical	Intracortical
Advantages	Minimally invasive	Near bipolar cells	Minimally invasive. Closer to bipolar cells	Moderately invasive	Low thresholds. Better resolution.
Disadvantages	Must be close to retinal surface	Invasive, may block oxygen diffusion by capillaries in central fovea	Higher thresholds. Pigment epithelium forms resistive barrier	Poor resolution. High thresholds. Secondary dura	Invasive. Blood vessel injury Possible gliosis
Thresholds/ electrode size/ pulse width	25–700 μA 250–500 μm diam 975 μs (Mahadevappa *et al* 2005)	70–100 μA 50 μm diam. 200 μs (pig, Schanze *et al* 2006)	66–94 μA 100 μm diam. 0.5 ms (rabbit, Sakaguchi *et al* 2004)	0.8–4 mA 1 mm^2 0.25 ms (Dobelle *et al* 1976)	1.9–77 μA $\sim$200 μm^2 200 μs (Schmidt *et al* 1996)
Max charge density/phase	0.35 mC cm^{-2}	1.0 mC cm^{-2}	0.4–0.6 mC cm^{-2}	0.1 mC cm^{-2}	0.2–7.7 mC cm^{-2}

where a silicon chip would stimulate cultured retinal ganglion cells which would then form synaptic projections to a blind patient's LGN neurons (Yagi *et al* 1999, 2005). In the neonatal mouse, retinal neurons will grow into sculptured devices and can be electrically stimulated with current (Peterman *et al* 2003b, Leng *et al* 2004). Whether a similar process can be elicited in adult retinal tissue is unclear at present.

12. Conclusions and common issues to visual prostheses

In discussing the status and development of prosthetic devices for the blind, it is instructive to recall the history of cochlear prosthetic implants for the deaf. The cochlea is a one-dimensional neural structure which resolves sound frequency. The human auditory nerve contains $\sim$30 000 axons which cochlear implants currently stimulate with 8–22 electrodes for a ratio of $\sim$1:3000 (ten electrodes). The first cochlear implant was introduced in 1972 over 30 years ago. Cochlear implants had a long history of clinical trial failures, before gaining acceptance (Blume 1999). Initially, patient acceptance of cochlear implants was poor; however with continued use, improved speech processors and electrode arrays the remarkable plasticity of the brain to adapt to new representations of the external auditory environment have made cochlear implants a success.

Visual prosthetic devices may evolve along a similar development path. About a million retinal optic nerve fibers innervate the brain. Future visual prostheses are slated to contain $\sim$250 electrodes resulting in a similar axon to electrode ratio as current cochlear prostheses ($\sim$1:4000) to stimulate a two-dimensional visual structure. Given the adaptability of the human brain, it seems possible visual prostheses could enable the visually impaired patient to gain some functional vision. However like cochlear implants, the visual prosthetic world is likely to differ considerably from our normal visual percepts (Merabet *et al* 2005). Several different designs may be of clinical utility, as not all patients will have similar lesions or diseases of the visual system.

12.1. Common biological issues

Visual prosthetic devices must display some programmable adaptation to the patient's biology. Because the visual abilities/disease state of each implant candidate is different, the placement of stimulation electrodes near visual system neurons will not always achieve the same result. Each implant design has different advantages and electrical phosphene thresholds (table 1). To compensate for two-dimensional variations in retinal and cortical neural tissue, stimulation arrays may require remapping and electrodes may need multiple stimulation zones to optimize a patient's visual phosphene fields. Stimulation patterns may need to be compensated for patient eye movements by mechanisms such as eye tracking to avoid movement of the perceived 'visual phosphene fields'.

New stimulation electrode designs are needed to optimally replicate the natural biological function of the visual pathways and improve the prosthesis–neuron interface. Selective stimulation of ON- and OFF-center retinal ganglion cell pathways may be needed to improve contrast perception. To improve two-point visual discrimination, better electrode designs are needed to stimulate local neurons. Blurring of the visual scene by activation of axonal fibers of passage such as found in the retinal nerve fiber layer or collateral axons in the visual cortex needs to be avoided.

Finally, most visual degenerative diseases affect the retina. Whether a stimulating prosthetic array inserted in the patient's eye can adequately maintain the functional integrity of a diseased retina is unclear at present. In contrast, the visual cortex is unaffected by most diseases causing blindness. However, the ease of insertion and monitoring retinal prostheses may offset the relative risks of seizures, gliosis, hematomas and meningitis associated with implantation of cortical stimulation arrays (e.g. Lee *et al* (2000b)). If visual prostheses follow the development timeline for cochlear implants, durability, long-term patient use, learning and training will be essential for these devices to gain acceptance. In addition, more biologically relevant encoding

strategies and designs of the neuron-prosthetic stimulation interface will enhance patient benefit.

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