BRAIN RESEARCH 1595 (2015) 51–73

Available online at www.sciencedirect.com
ScienceDirect
www.elsevier.com/locate/brainres

Review

Restoration of vision in blind individuals using bionic devices: A review with a focus on cortical visual prostheses

Philip M. Lewis[a,b,c,d], Helen M. Ackland[a,e], Arthur J. Lowery[c,d,f], Jeffrey V. Rosenfeld[a,b,c,d,g,*]

[a]Department of Neurosurgery, Alfred Hospital, Melbourne, Australia
[b]Department of Surgery, Monash University, Central Clinical School, Melbourne, Australia
[c]Monash Vision Group, Faculty of Engineering, Monash University, Melbourne, Australia
[d]Monash Institute of Medical Engineering, Monash University, Melbourne, Australia
[e]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
[f]Department of Electrical and Computer Systems Engineering, Faculty of Engineering, Monash University, Melbourne, Australia
[g]F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, USA

ARTICLE INFO

Article history:
Accepted 8 November 2014
Available online 15 November 2014

Keywords:
Bionics
Vision
Bionic eye
Cortical implant
Blindness

ABSTRACT

The field of neurobionics offers hope to patients with sensory and motor impairment. Blindness is a common cause of major sensory loss, with an estimated 39 million people worldwide suffering from total blindness in 2010. Potential treatment options include bionic devices employing electrical stimulation of the visual pathways. Retinal stimulation can restore limited visual perception to patients with retinitis pigmentosa, however loss of retinal ganglion cells precludes this approach. The optic nerve, lateral geniculate nucleus and visual cortex provide alternative stimulation targets, with several research groups actively pursuing a cortically-based device capable of driving several hundred stimulating electrodes. While great progress has been made since the earliest works of Brindley and Dobelle in the 1960s and 1970s, significant clinical, surgical, psychophysical, neurophysiological, and engineering challenges remain to be overcome before a commercially-available cortical implant will be realized. Selection of candidate implant recipients will require assessment of their general, psychological and mental health, and likely responses to visual cortex stimulation. Implant functionality, longevity and safety may be enhanced by careful electrode insertion, optimization of electrical stimulation parameters and modification of immune responses to minimize or prevent the host response to the implanted electrodes. Psychophysical assessment will include mapping the positions of potentially several hundred phosphenes, which may require repetition if electrode performance deteriorates over time. Therefore, techniques for rapid psychophysical assessment are required, as are methods for objectively assessing the quality of life improvements

*Corresponding author at: Department of Neurosurgery, Level 1, Old Baker Building, The Alfred, 55 Commercial Road, Melbourne, VIC 3004, Australia.
E-mail addresses: p.lewis@alfred.org.au (P.M. Lewis), h.ackland@alfred.org.au (H.M. Ackland), Arthur.Lowery@monash.edu (A.J. Lowery), j.rosenfeld@alfred.org.au (J.V. Rosenfeld).

http://dx.doi.org/10.1016/j.brainres.2014.11.020

obtained from the implant. These measures must take into account individual differences in image processing, phosphene distribution and rehabilitation programs that may be required to optimize implant functionality. In this review, we detail these and other challenges facing developers of cortical visual prostheses in addition to briefly outlining the epidemiology of blindness, and the history of cortical electrical stimulation in the context of visual prosthetics.

Contents

1. Introduction

Neurobionics is the direct interfacing of electronic devices with the nervous system. This interface may be exploited to facilitate exogenous stimulation of the nervous system or for single and multi-unit recording of neural activity. The significant therapeutic potential offered by neural recording is evident in recent reports of multi-electrode prostheses implanted in the motor cortex of humans and non-human primates, enabling the dextrous operation of a robotic arm and hands (Collinger et al., 2013; Hochberg et al., 2012). This dexterity will undoubtedly be greatly enhanced by the integration of sensory feedback (e.g. mechanosensation), which has already been demonstrated in macaques via microstimulation of somatosensory cortex (Berg et al., 2013; O'Doherty et al., 2011; Tabot et al., 2013). Beyond the experimental domain, electrical stimulation of the brain, spinal cord and peripheral nerves via implanted electrodes is in use clinically for the treatment of movement disorders (Williams and

Okun, 2013), psychiatric disorders (Williams and Okun, 2013), chronic pain (Plow et al., 2012), epilepsy (Bergey, 2013), neurogenic bladder (Lay and Das, 2012) and for the restoration of lost sensory functions such as hearing (Carlson et al., 2012; Shepherd et al., 2013). Currently, the most commercially successful sensory prosthesis is the cochlear implant for treatment of neural deafness, of which the US National Institutes of Health reports there were 324,200 recipients worldwide in December 2012 (National Institute on Deafness and Other Communication Disorders, 2013). Restoration of visual perception to the blind or severely vision impaired is another area of intense research effort and two retinal bionic vision devices are now commercially available (Weiland and Humayun, 2014). We briefly review these and other devices being developed for the restoration of functional vision in blind individuals, before focusing on cortical visual prostheses and the challenges facing developers of these devices. We describe an implant currently being developed by the Monash Vision Group which is currently in the preclinical testing phase.

2. Epidemiology of blindness

Recent meta-analyses examining the global burden of blindness and vision impairment highlight the scale of these ongoing public health concerns. In two separate studies, the total number of people with vision impairment in 2010 was estimated at 191 million (Stevens et al., 2013) and 285 million (Pascolini and Mariotti, 2012) globally, with the number of those legally blind estimated at 32 and 39 million respectively. The most recent of these studies found the most common causes of blindness to be cataract (33%), uncorrected refractive error (21%) and macular degeneration (7%) across all regions studied (Stevens et al., 2013). As would be expected, there is significant regional variation in these figures; in high-income regions including Western Europe, Australasia (Australia and New Zealand), Asia-Pacific and North America, the most common causes are macular degeneration (16.1–19.5%), uncorrected refractive errors (14–14.1%) and cataract (12.7–14.5%), with glaucoma and diabetic retinopathy comprising a further 14.5–16% combined (Bourne et al., 2013). In Australia specifically, a 2005 study found age-related macular degeneration (48%), glaucoma (14%), cataract (12%) and diabetic retinopathy (11%) to be the most common causes of blindness, with neuro-ophthalmic conditions accounting for an additional 3% of cases (Taylor et al., 2005).

There were an estimated 530,000 vision impaired people in Australia as of 2004, including 50,600 who were categorized as legally blind (visual acuity of $\leq$6/60). This figure is predicted to rise as a result of population ageing; Taylor et al. (2005, 2006) estimated that approximately 70,000 Australians would be legally blind by 2014, and almost 90,000 by 2024 (Taylor et al., 2005, 2006). Moreover, increasing rates of obesity-related Type II diabetes (Shaw et al., 2010) will undoubtedly contribute further to these figures.

3. Economic impact

The direct health system costs in Australia for age-related macular degeneration, glaucoma and cataract alone were A$490 million in 2004. Indirect financial costs relating to lost income and carer costs for all visual impairment were estimated at A$3.2 billion, exclusive of transfer costs including lost tax revenue and the expenditure related to carer and welfare payments, which were estimated at A$850 million (Taylor et al., 2006). Visual impairment has been associated with a 2.3 fold increase in mortality (McCarty et al., 2001) and the costs specific to loss of well-being due to the impact of disease and premature mortality have been estimated using daily adjusted life years (DALY) at A$4.8 billion (Taylor et al., 2006).

4. Treatment options for blindness

4.1. *Biological therapies*

While not a major focus of this review, biological therapies represent a promising suite of existing and emerging therapeutic options for blindness caused by retinal disease. Gene replacement therapy (McClements and MacLaren, 2013; Petrs-Silva and Linden, 2014), modulation of ocular autoimmune responses (Ambati et al., 2013; Buschini et al., 2011; Rieck, 2013), transplantation of stem cells, photoreceptor precursor cells or bioengineered sheets of retinal tissue (Barber et al., 2013; Fernandez-Robredo et al., 2014; Pearson, 2014) plus intraocular administration of neurotrophic, anti-angiogenic, intraocular pressure-lowering and antioxidant agents (Zarbin et al., 2013) are all techniques that are either currently in use, at clinical trial stage or being investigated in the laboratory.

4.2. *Sensory substitution*

Among the rehabilitative options available to the blind, sensory substitution is a concept that has been explored extensively. Sensory substitution operates on the principle of replacing input from a lost sensory organ with an artificial sensor, with the output of that sensor redirected to the input of one or more remaining senses. A simple example of sensory substitution is the mobility cane, wherein a representation of the blind user's physical environment is obtained via a tactile method (Bach-y-Rita and Kercel, 2003). The representation of visual information by a tactile system was suggested in the late 19th century by Noiszewski, (Collins, 1971) with practical implementations of vibro- or electrotactile stimulation of the back, abdomen, fingertips and tongue demonstrated by Bach-y-Rita and others over the last 50 years (Bach-y-Rita et al., 1969, 1998; Collins, 1971; Deroy and Auvray, 2012; Loomis, 2010). Alternatives to the tactile approach include encoding visual information into audible signals (Capelle et al., 1998; Hanneton et al., 2010; Loomis, 2010; Meijer, 1992). Such devices have shown great promise, however their uptake has been limited and development is ongoing (Loomis, 2010; Reich et al., 2012).

4.3. *Visual prostheses*

Another approach to vision rehabilitation involves the generation of functionally useful visual perception by direct electrical stimulation of the visual pathway (Fig. 1).

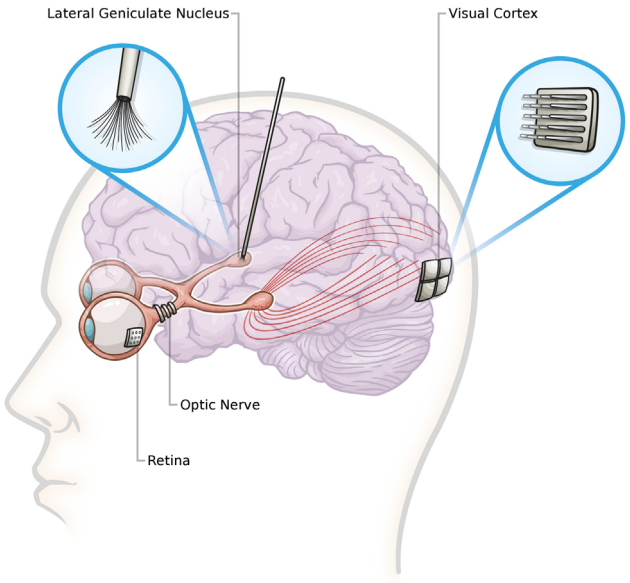

Fig. 1 – Graphical depiction of the visual pathways and electrical stimulation targets for developing a visual prosthesis. Small arrays of electrodes can be implanted epiretinally, subretinally or suprachoroidally to stimulate retinal ganglion cells and generate phosphenes. Similarly, the axons of these cells can be stimulated as they pass along the optic nerve, using "cuff-style" electrodes. The lateral geniculate nucleus can be accessed using conventional deep-brain stimulation electrodes, or newer-generation devices incorporating a "tuft" of microelectrodes. Lastly, the visual cortex may be stimulated directly using surface (not shown) or penetrating microelectrodes.

The application of such stimulation relies on three physiologic principles (Maynard, 2001):

1. Light can be replaced by electric current to stimulate the perception of vision.
2. Blindness due to retinal degeneration does not affect signal transmission from the retinal ganglion cells through the visual pathways.
3. Electrical stimulation of the visual pathways and visual cortex can elicit visual percepts in blind subjects.

Volta (1800) was among the first to describe the visual percepts, or *phosphenes* resulting from electrical stimulation of the eye. In the two centuries since this observation, countless experiments on both animals and humans have confirmed that electrical stimulation of the major anatomical landmarks in the human visual pathway produces phosphenes of varying character.

4.3.1. *Retinal*

Retinal stimulation has been covered extensively in the recent literature, and the reader is directed to reviews by Shepherd et al. (2013), Guenther et al. (2012), Ong and da Cruz (2012), Fernandes et al. (2012), Theogarajan (2012) and Merabet (2011) for additional details. Briefly, visual prostheses based on electrical stimulation of surviving populations of retinal ganglion cells have progressed substantially in recent years. Retinal stimulation takes advantage of the significant visual information processing that occurs not only in the retina itself (Freeman et al., 2011), but also the lateral geniculate nucleus (Cudeiro and Sillito, 2006; Wiesel and Hubel, 1966).

Electrical stimulation of the retina may be achieved via placement of epiretinal, subretinal, or suprachoroidal stimulating electrode arrays. One such device, the Argus II epiretinal implant developed by Second Sight (Sylmar, California, USA), has recently obtained regulatory approval for marketing in Europe and the United States. The Argus II is based on a 60-electrode array and a spectacles-mounted digital camera. Clinical trials of the device have shown improved reading (da Cruz et al., 2013) and motion detection (Dorn et al., 2013) abilities in many recipients.

A variety of other implant designs are in development worldwide. Stingl et al. (2013) recently described the clinical trial results of a subretinal array (Alpha IMS) incorporating 1500 embedded photodiodes and matching stimulating electrodes. In this device, incoming light is received by photodiodes, the signals from which are then processed and amplified before being sent to matching electrodes. The combination of photodiodes and electrodes therefore provides point-to-point stimulus of retinal bipolar cells, eliminating the need for an external camera and permitting object tracking via saccadic eye movements. The device was trialed on 9 patients with retinitis pigmentosa ($n=8$) and cone-rod dystrophy ($n=1$), resulting in light perception by 8 patients with one excluded due to complications during the implantation procedure (Stingl et al., 2013). Functionally, the results were variable, with 7/8 patients able to localize a light source, 5/8 able to detect motion and grating acuity testing able to be performed in 6/8 recipients. The device was recently approved for marketing in the European Union (Retina Implant AG, 2014).

Whilst Alpha IMS is wirelessly powered via a subdermal coil behind the ear that is tethered to the implant (Stingl et al., 2013), Chow et al. (2004) recently described an alternative photodiode-based array with 5000 stimulating elements that is powered by incident light. This device, referred to by its developers as the "Artificial Silicon Retina" (ASR), has undergone limited clinical trials (Chow et al., 2010).

Bionic Vision Australia is also developing a suprachoroidal retinal implant. In the popular press, the group recently reported on the first human implantation of a 24-electrode prototype device (Bionic Vision Australia, 2012), with development and testing of improved devices ongoing (Villalobos et al., 2013).

4.3.2. *Optic nerve*

Veraart et al. (1998) were the first to attempt electrical stimulation of the optic nerve as a basis upon which to develop a visual prosthesis. The method can be applied in blind patients with surviving retinal ganglion cells and/or an intact optic nerve, and was initially trialed on a 59-year old female with retinitis pigmentosa (Veraart et al., 1998). After demonstrating that phosphenes could be reproducibly elicited at safe stimulation currents, the group developed a computational model that could predict the location and size of percepts as a function of stimulus parameters (Delbeke

et al., 2003). With sufficient training, recipients could recognize and orient complex shapes (Brelen et al., 2005; Veraart et al., 2003) and perform object localization, discrimination and grasping (Duret et al., 2006). Phosphenes could be elicited in all four visual field quadrants, although they were irregularly distributed and subtended a relatively narrow portion of the horizontal field (Delbeke et al., 2003). The surgical technique was relatively simple, with the first patient receiving an implant consisting of a four-electrode, non-penetrating silicon cuff implanted around the optic nerve, accessed via a pterional craniotomy and a trans-Sylvian approach (Veraart et al., 1998). The second recipient received an intraorbital implant, which also produced phosphenes although it was noted that higher stimulation currents were required, most likely due to the impedance of the dural sheath that lay between the electrodes and the nerve itself (Brelen et al., 2006). Veraart's group are continuing testing of their device (Brelen et al., 2010), and have since been joined by two others developing optic nerve prostheses using electrodes stimulating either the optic nerve or the optic disk (Lu et al., 2013; Sakaguchi et al., 2009; Wu et al., 2010).

4.3.3. *Lateral geniculate nucleus*

The lateral geniculate nucleus (LGN) is considered a favorable stimulation target due to its compact dimensions, retinotopic organization and the physical separation of pathways specific to color and motion (Mullen et al., 2008; Wiesel and Hubel, 1966). The proximity of the LGN to structures targeted surgically for pain control and movement disorders resulted in reports of visual phenomena experienced during thalamic stimulation procedures over three decades ago. Some of these reports were published by Marg and Driessen (1965), with their patients describing highly complex visual phenomena during deep brain stimulation. In a recent macaque study however, it was shown that simple, discrete visual percepts could be elicited by microstimulation of LGN (Pezaris and Reid, 2007). While in that study Pezaris et al. analyzed visual saccades in response to LGN stimulation, Panetsos et al. (2011) recently analyzed rat and rabbit cortical responses to LGN stimulation, concluding that such stimulation could generate visual cortical responses resembling those elicited by natural vision. While much work remains to be done, both groups report plans for further studies in support of developing a functionally useful visual prosthesis based on LGN stimulation (Panetsos et al., 2011; Pezaris and Eskandar, 2009).

4.3.4. *Geniculo-calcarine tract (optic radiations)*

Reports exist of complex visual percepts elicited by stimulation of the optic radiations during neurosurgical procedures (Chapanis et al., 1973; Marg and Driessen, 1965), however to date there are no groups known to us for whom this site is a stimulation target for developing a visual prosthesis.

4.3.5. *Visual cortex and the case for a cortical implant*

Primary visual cortex, or V1, is an area of the occipital lobe that encompasses the buried portions of cortex in the calcarine sulcus and its upper and lower banks, extending posterolaterally to the occipital pole. The reported surface area of V1 varies between 1400 and 6300 mm^2, depending on

Table 1 – List of institutions known to us, who report plans to develop a cortical visual prosthesis at the time of writing.

	Lead Institution			
	Monash University	University of Illinois	Universidad Miguel Hernández	École Polytechnic
Selected relevant publications	Brunton et al. (2012), Lowery (2013), and Wang et al. (2013)	Lane et al. (2012), Rush et al. (2011), Srivastava et al. (2009), and Troyk et al. (2005)	Ferrandez et al. (2007), Marin and Fernandez (2010), and Morillas et al. (2007)	Coulombe et al. (2007), Mohammadi et al. (2012), and Simard et al. (2010)
Web Address	http://www.monash.edu.au/bioniceye/	http://neural.iit.edu/research/icvp/	http://cortivis.umh.es/	http://goo.gl/zuzcxk [a]
Proposed implantation site	Occipital pole	Occipital pole	Not stated	Not stated [b]
Proposed total # of electrodes	300–500	600–650	Not Stated	960 [c]
Electrode array size (mm)	9 × 9 × 2.9	3 × 3 × ? [d]	Not stated	3 × 3 × ? [e]
# of electrodes per array	43	16	Not stated	16

[a] The address was shortened to minimize the table size. The link provided is accessible, however the full address at the time of writing was: http://www.polymtl.ca/polystim/en/navigation/Prothesevisuelleintra-corticale.php.

[b] To our knowledge the group's publications do not specifically state the proposed site of implantation, however the design of the system has been described as supporting implantation of electrodes on flexible substrates over medial calcarine cortex.

[c] The group have not explicitly stated plans to implant 960 electrodes, however a recent publication by the group (Mohammadi et al., 2012) described simulated phosphene vision using 960 phosphenes, and the group's detailed implant specification (Coulombe et al., 2007) supports up to 992 stimulation channels.

[d] The depth of the electrode array was not stated.

[e] Estimated from the microphotograph in (Coulombe et al., 2007), no depth information was available.

the method of estimation (Andrews et al., 1997; Genc et al., 2014; Stensaas et al., 1974), with approximately 67% of that area buried inside the calcarine fissure (Stensaas et al., 1974). Most efferent fibers from the LGN synapse with layer 4 of V1, from which numerous connections to other layers within V1 and those of higher visual centers are made (Troncoso et al., 2011). Human trials of visual cortex electrical stimulation with both surface and penetrating electrodes have demonstrated the viability of this brain region as a target for a visual prosthesis (Dobelle, 2000; Schmidt et al., 1996). While no cortical visual implant has obtained regulatory approval to date, Dobelle did achieve limited commercial and functional success with his system prior to his death in 2003 (Anon., 2005; Dobelle, 2000).

The attractiveness of visual cortex as the stimulation site for a visual prosthesis is based on several factors. Firstly the large surface area of visual cortex and the cortical magnification factor combine to render it more amenable to implanting large numbers of electrodes in cortical areas subserving central vision (Daniel and Whitteridge, 1961; Harvey and Dumoulin, 2011), potentially offering a higher-resolution visual experience than either LGN or retinal implants. Secondly, the stereotactic implantation of small occipital cortical electrode arrays is a relatively straightforward procedure compared to implanting deep LGN electrodes or microarrays onto, or under the retina. Lastly, the utility of direct cortical stimulation extends to all causes of visual impairment in patients with late blindness due to retinal or optic nerve disease or injury. Cortical visual prosthesis research therefore has enormous potential for future treatment of visual impairment, and three research groups known to us report ongoing plans, either in the scientific literature or via their institutional websites, to develop a cortical visual prosthesis (Table 1). Many other research groups are conducting research within the general domain of neural prosthetics, much of which may translate to a cortical visual prosthesis. A number of these studies are covered throughout this review.

5. A brief history of cortical electrical stimulation and cortical visual prosthesis development

Visual cortex electrical stimulation has a rich history spanning almost a century, beginning with the early 20th century observations of Löwenstein and Borchardt (1918), who stimulated the occipital cortex of soldiers with occipital bullet wounds. Research involving such patients provided a wealth of data, with Krause and Förster subsequently demonstrating that stable, punctate phosphenes could be elicited by electrical stimulation of occipital cortex (Förster, 1929; Krause, 1924; Krause and Schum, 1931). These studies also confirmed that the retinotopic map of visual cortex was roughly equivalent to that proposed by Inouye and Holmes, who examined visual field defects of soldiers with occipital bullet wounds and concluded that the occipital pole subserved central vision (Glickstein and Whitteridge, 1987; Holmes and Lister, 1916).

After Penfield's extensive mapping studies (Penfield, 1947) and Button and Putnam's rudimentary but groundbreaking attempts to provide visual perception to four blind volunteers (Button and Putnam, 1962; Button, 1958), the first attempt to produce a genuinely functional visual prosthesis was made by Brindley and Lewin (1968). Their implant was a significant advance on Button and Putnam's four stainless steel wires, consisting of an array of eighty 1 mm^2 platinum electrodes embedded in a silicon substrate and molded to the recipient's occipital cortex. These were tethered to a subcutaneously-implanted set of radio receivers containing basic circuitry that permitted wireless stimulation of individual electrodes in the array. The recipient was able to perceive phosphenes from stimulation of 39/80 electrodes, with the nature of elicited percepts varying from discrete, clustered, diffuse and elongated points of light. While the system was ultimately of no practical use to the recipient, it demonstrated that stimulation of visual cortex with a fully-implanted, multi-electrode implant was feasible and could produce visuotopically organized percepts. Moreover, it suggested that with an increased number of electrodes and phosphenes, providing the blind with useful visual perception via cortical stimulation may be possible.

Brindley's success was followed by a significant increase in research effort towards the development of a cortical visual prosthesis, with a number of other groups publishing the results of experiments directed at visual prosthesis development in subsequent years (Dobelle and Mladejovsky, 1974; Pollen, 1975; Talalla et al., 1974). Both Brindley and Dobelle's groups separately progressed their implants, eventually demonstrating that phosphenes could be assembled into simple patterns for the purpose of reading Braille characters (Brindley and Rushton, 1974; Dobelle, 1974).

The goals of visual prosthesis designers at the time were generally centered on providing the blind with the ability to read text or to improve their level of independent mobility. Brindley had previously determined that 50 favorably placed phosphenes would be required to permit the reading of idealized letterforms, however up to 600 would be required for the reading of handwriting (Brindley, 1965). Dobelle was less focused on reading and more so on mobility (Dobelle et al., 1979a) and his group reported plans to implant 512 electrodes towards that goal (Dobelle et al., 1979a). Brindley made no further reports on his visual prosthesis development program after 1982 (Brindley, 1982), however Dobelle continued development, incorporating a camera and miniaturizing the system to the point of portability. With ongoing improvements in the sophistication of computing hardware, Dobelle's (2000) system was ultimately capable of providing limited object recognition and mobility to one of its recipients with only 21 phosphenes. Despite this, it was similar to Brindley's device, based on an array of surface electrodes that required currents up to several milliamperes to elicit phosphenes (Brindley and Lewin, 1968). Aside from limiting the minimum spacing between electrodes and therefore any resultant phosphenes, these large currents also increased the risk of seizures for implant recipients (Naumann, 2012), a problem that had previously plagued other researchers in the field (Pudenz, 1993). A further disadvantage was the bulk of the cabling that connected to the electrodes via a transcutaneous connector fixed to the skull.

An alternative, intracortical microstimulation (ICMS) with miniature penetrating electrodes had already been established

as a potentially safer alternative to surface stimulation. A number of studies provided clear evidence that primates could detect ICMS of visual cortex at much lower current levels, also using electrodes more closely-spaced than those of Brindley and Dobelle (Bartlett et al., 1977; Bartlett and Doty, 1980; Doty, 1965). Intracortical microelectrodes were not benign however; chronic implantations revealed astrocytic proliferation around the electrode shank (Schmidt et al., 1976), and unbalanced or excess charge delivery could damage both the electrodes and neuronal tissue (Bartlett et al., 1977; Brummer et al., 1983).

A preliminary human study examining ICMS of visual cortex was published in 1990, the results of which added significant impetus to the effort to develop a cortical visual prosthesis (Bak et al., 1990). Bak et al. reported that three sighted volunteers were able to perceive phosphenes from ICMS at currents up to 100 times lower than those required by surface stimulation. Moreover, the phosphenes were discriminable when stimulated by electrodes 700 μm apart (Bak et al., 1990). Further work identifying thresholds of total charge delivered and charge *density*, beyond which neuronal damage could be expected to occur (McCreery et al., 1994), supported the progression to a more systematic evaluation of ICMS of visual cortex in a blind volunteer in 1996 (Schmidt et al., 1996). A key finding from this study was that the chronically blind subject, who was unable to perceive phosphenes from surface stimulation, perceived phosphenes from ICMS in a similar manner to sighted volunteers in the previous report (Schmidt et al., 1996).

While this study represents a milestone in the development of a cortical visual prosthesis, significant engineering, surgical, biological and psychophysiological issues still remained to be addressed before an implant fit for human use could be realized. In the period since, significant work has been undertaken in understanding and addressing these problems, with the goal of developing a functional, wirelessly-operated cortical visual prosthesis with stable long-term performance and an acceptable safety profile.

6. Current challenges and potential solutions

6.1. *Selection of potential recipients*

The recent approval of Second Sight's Argus II retinal implant in both the US and Europe, and Retina Implant AG's European approval of the Alpha IMS implant represents a significant step forwards in the regulatory environment for visual prostheses. Cortical devices remain experimental, however one group recently reported plans to apply for US FDA approval to proceed with human clinical trials (Lane et al., 2012). Given the relatively uncertain outlook for the balance of risk versus benefit for cortical visual prostheses, great rigor must be exercised in the preclinical testing and the recipient selection process.

6.1.1. *Suitability for a retinal implant*

The choice of a cortical approach to prosthetic visual rehabilitation should only be made after careful screening for residual retinal functioning, to determine possible suitability for a retinal implant (Merabet et al., 2007). Screening techniques may include tests of residual vision and the measurement of thresholds for light perception in response to retinal electrical stimulation (Yanai et al., 2003); the majority of potential cortical implant recipients will likely be those with complete failure of both retinae or optic nerves, in whom no responses to light will be observed.

Potential recipients of a cortical visual prosthesis will need further assessment to determine the likelihood of successfully eliciting visuotopically ordered phosphenes via ICMS of visual cortex.

6.1.2. *Responses to electrical stimulation of visual cortex*

In the normally-sighted, the functional development of visual cortex is guided by the presence of both spontaneous (prior to eye opening) and stimulated (after eye opening) retinal and cortical activity (Espinosa and Stryker, 2012). In the absence of visual input, the connectivity and architecture of visual cortex are altered. While magnetic resonance imaging (MRI) studies of the congenitally blind (CB) have shown preservation of geniculocalcarine tract fiber integrity (Schoth et al., 2006; Zhang et al., 2012), reductions in the volume of the LGN, geniculocalcarine tract and visual cortex (Ptito et al., 2008b; Qin et al., 2013), increased thickness of primary visual cortex (Anurova et al., 2014; Qin et al., 2013), and increased functional connectivity between visual and non-visual cortices (Collignon et al., 2013; Qin et al., 2013) are seen in this subject group. From a functional perspective, this reorganization of visual cortex is believed to reflect the process of sensory cross-modal adaptation, in which visual cortex is recruited for non-visual tasks, including Braille reading and auditory processing (Burton et al., 2002; Collignon et al., 2013). Such changes clearly have significant implications for the selection of potential visual prosthesis recipients, and the preoperative evaluation of responses to visual cortical stimulation will be an important component of the process.

Direct electrical stimulation of visual cortex in the preoperative setting is not feasible, however transcranial magnetic stimulation (TMS) is a tool that may offer a method for noninvasively assessing potential cortical visual prosthesis implant recipients prior to surgery. Previous studies of occipital TMS in normally-sighted subjects have demonstrated that it can elicit simple phosphenes (Marg, 1991; Merabet et al., 2003), while in blind subjects the responses to TMS differ between the early (EB) and late blind (LB). Gothe et al. (2002) used TMS to stimulate the occipital cortex of blind individuals subgrouped by the presence or absence of residual vision. Notably, no EB study participants without memory of vision reported phosphenes from occipital TMS. In the remaining subjects, 60% (6/10) of those with residual vision perceived phosphenes compared to 20% (2/10) of those with no residual vision, and the lack of phosphene perception was significantly correlated to the time since blindness onset. In another study, Kupers et al. (2006) stimulated the occipital cortex of a group of blind subjects trained in the use of a tongue-based tactile sensory substitution device. Importantly, no EB study participants experienced phosphenes in response to occipital TMS, whereas 2/5 LB participants reported phosphenes.

It remains unclear as to whether those who are unresponsive to occipital TMS would also be unresponsive to ICMS of

visual cortex. Previous studies have shown that EB subjects may experience phosphenes in response to either surface (Brindley and Rushton, 1974) or intracortical (Button and Putnam, 1962) stimulation of visual cortex, however the diffuse nature of the percepts may severely limit their application in a visual prosthesis. Moreover, the absence of residual vision may also not be predictive of a poor response to ICMS of visual cortex; a subject with a 22-year history of blindness and no residual vision reported no phosphenes from surface stimulation (Schmidt et al., 1996), whereas ICMS elicited stable, punctate percepts consistent with those described by sighted volunteers (Bak et al., 1990). TMS is itself a fairly blunt instrument with relatively poor focality, and it may be that the diffuse nature of TMS emulates that derived from stimulation with cortical surface electrodes. Further work is necessary to address these questions.

Further complicating the question of implant recipient selection is the potential for occipital stimulation to disrupt any cross-modal sensory adaptations upon which a potential recipient's activities of daily living depend (Fernandez et al., 2005). For example, previous work has demonstrated that TMS over the occipital cortex of CB and EB subjects proficient in Braille can significantly impair their reading accuracy (Kupers et al., 2007). Other groups have reported that this phenomenon may be specific to these groups only, with LB subjects not experiencing the same degree of disruption (Cohen et al., 1999). There is little data on whether repeated stimulus to the visual cortex of a blind subject, demonstrating sensory cross-modal adaptation, may produce a more permanent impairment of their adaptations. Such changes would be of particular concern if a cortical implant were to eventually fail, after which a return to the pre-implant functional state would be required. Recent work showing that normally-sighted individuals deprived of visual input show rapid functional recruitment of visual cortex after 5 days of Braille training suggests that even in adulthood, neuroplasticity is preserved to a level that supports relatively rapid shifts in the functional organization of visual cortical networks (Merabet et al., 2008). If such plasticity is preserved in adult LB subjects, this may suggest that a return to pre-study levels of cross-modal sensory adaptation may be possible in the event of a persistent impairment resulting from long-term visual cortical stimulation.

From another perspective, an established state of cross-modal sensory adaptation may in fact impair the ability of an implant to elicit simple phosphenes at all, in favor of phantom perceptions related to extra-visual sensory cortices, e.g. touch (Kupers et al., 2006; Merabet et al., 2007; Ptito et al., 2008a). More research needs to be done to determine the impact of neuroplasticity on the likely performance of an implant in the long term, or conversely any negative influence of the implant on the recipients' adaptations to blindness.

6.1.3. *General and psychological health*

The implantation of penetrating cortical electrode arrays is a major neurosurgical procedure. As with any surgery involving the opening of the skull and intradural space, there is a demonstrable risk of acute and longer-term complications resulting in a poor surgical and clinical outcome. These risks include but are not limited to postoperative hemorrhage, swelling, tissue infarction, infection, seizures and neurological deficits, each of which may delay or preclude progressing to the implant testing stage (discussed in more detail in Section 6.2).

A key component to minimizing these risks will be the selection of candidate recipients in whom the burden of comorbidities known to negatively impact on neurosurgical outcomes is acceptably low. For example, the risk of postoperative bleeding is increased by hypertension, diabetes and coagulopathy (Seifman et al., 2011). Poor nutritional status due to advanced age, malignancy or obesity may increase the risk of infection (Walcott et al., 2012), and preoperative screening for MRSA colonization may be helpful in avoiding a complicated postoperative course in the event of infection (Harrop et al., 2012). Patients with a history of epilepsy are innately at greater risk of suffering postoperative seizures, and should be excluded (Weiss and Post, 2011).

The complexity and experimental status of the implant procedure and rehabilitation process dictates that obtaining informed consent, for which a detailed discussion of surgical risks is required, will need to be undertaken carefully to ensure a thorough understanding by potential recipients. The mental health and capacity of a potential recipient is therefore of paramount importance in this context, as it may potentially impact on the treating physician's ability to ensure that a truly informed consent can be obtained (Lane et al., 2012; Merabet et al., 2007). Moreover, it may impact on the perception of the soundness of potential recipients' motivation to participate, or the likelihood of effective rehabilitation (Dagnelie, 2008; Merabet et al., 2007). Lane et al. (2012) studied motivation as a core theme when surveying potential implant recipients, noting that individual reasons for wanting to pursue implant surgery included participation in cutting-edge research, the more benevolent ideal of contributing to the future development of visual prostheses, and of course deriving personal benefit through improved visual perception.

Importantly, the likely benefits of even limited visual restoration to a blind individual are often under appreciated by sighted individuals (Lane et al., 2012). Even rudimentary prosthetic vision in the setting of profound blindness may have significant positive psychological and functional ramifications for a blind individual, contributing to reduced feelings of isolation and depression (Dagnelie, 2008). Only a few reproducible phosphenes may be required to improve an individual's quality of life. For example, a recipient of the Dobelle implant was able to navigate independently and read letters on a Snellen chart with only 21 phosphenes at his disposal (Dobelle, 2000). In the most simple of demonstrations, the reported elation felt by blind volunteers stimulated with only 4 occipital electrodes, in addition to their ability to independently locate a light source (Button and Putnam, 1962), suggests that questions of what constitutes “acceptable” performance by both recipients and treating physicians alike, needs to be carefully balanced.

6.2. *Postoperative care*

Progression to functional testing of a cortical implant is predicated on an uneventful implantation procedure and

postoperative recovery. As discussed in Section 6.1.3, optimal surgical outcomes will depend partly on careful selection of implant recipients, for whom good general health will likely be a pre-requisite. Beyond this, there is a paucity of data on which to base firm statements about the risk of postoperative complications in current-generation cortical visual prosthesis recipients per se, however inferences can be made by drawing from older studies, the general neurosurgical literature and recent reports on neuroprostheses implanted for other CNS disorders.

The works of Brindley and Dobelle provide historical insights into the risks of cortical implant surgery, although miniaturization of implant hardware, and improvements in operative technique and infection prophylaxis probably render these of little contemporary relevance. Nonetheless, recipients of implants from both groups reportedly suffered implant-related infections (Naumann, 2012; Rushton et al., 1989). More recent large-series reports describe infection rates of 3.1% following the implantation of deep brain stimulators (DBS) (Fenoy and Simpson, 2014), 3.5% for hydrocephalus shunts (Parker et al., 2014) and 2.3% for subdural recording electrodes (Arya et al., 2013). While these figures are more informative, several factors suggest that these studies may overestimate the likely risk for future visual cortex implant recipients. Firstly, shunt candidates often present with comorbidities that increase their infection risk, while subdural recording electrodes incorporate externalized wires that provide a pathway for the intracranial migration of bacteria. On the other hand, while deep brain stimulators are fully implanted, DBS patients tend to be older (Fenoy and Simpson, 2014), and full dural closure is not possible due to the presence of lead wires connecting the electrode to the subcutaneous stimulator hardware. Future cortical visual prosthesis implants will likely be universally wireless in operation, permitting full implantation, dural closure and therefore a lower infection risk that we estimate to be 1–2%. Standard infection prophylaxis will nonetheless be required, including broad-spectrum and staphylococcus-specific antibiotics.

Where symptomatic postoperative bleeding is concerned, a prevalence of 0.8% has previously been reported for the general neurosurgical population (Kalfas and Little, 1988), which is consistent with the figure of 1.1% reported by Fenoy and Simpson (2014) for intracerebral hemorrhage resulting from DBS lead insertion. However, comparing the likely risk of clinically significant intracerebral hemorrhage resulting from the insertion of DBS electrodes vs. cortical electrode arrays is difficult. A DBS electrode penetrates both cortical and subcortical tissue, with tissue damage localized to the penetration trajectory. In the case of cortical electrode arrays, a greater cortical surface area is compromised, however using tiled electrodes will permit the avoidance of large vessels. Moreover, the electrodes in a cortical prosthesis will only penetrate to 1.5–3.0 mm. We therefore consider that the figure of 1.1% reported for DBS implantation is a reasonable estimate of the likely risk of clinically significant intracerebral hemorrhage resulting from cortical visual prosthesis implantation.

There is also a risk of extracerebral (extradural or subdural) bleeding after neurosurgical procedures. For epileptic patients undergoing implantation of subdural recording electrodes, Arya et al. (2013) reported that 3.53% of patients in their systematic review required postoperative evacuation of intracranial hemorrhage, the most common being subdural. Importantly, the size of the grids in this review varied greatly; Wong et al. (2009) reported grid size as an independent risk factor for postoperative complications in subdural grid surgery, reflecting the increased risk with greater surgical exposure.

The craniotomy required for a cortical visual prosthesis will be smaller than that required for large subdural grid implantations. For example, one group report plans to implant up to 650 electrodes across the dorsolateral surface of the occipital pole, covering an area approximately 3 cm in radius or approximately 7 cm^2 (Srivastava et al., 2007). Our group is planning for implantation of up to 500 electrodes over an area covering approximately 9–10 cm^2 (Lowery, 2013). Taking into account the relatively small craniotomy required for a cortical visual prosthesis, we estimate that the risk of symptomatic postoperative extracerebral bleeding (e.g. subdural/extradural) will be consistent with that of the general neurosurgical population.

Postoperative cerebral edema and subsequent neurological deficit is another potential complication requiring careful consideration. Fenoy and Simpson (2014) reported that 0.3% (2/728) of DBS patients demonstrated evidence of postoperative edema, localized to the electrode tip and causing only a transient motor deficit. Arya et al. (2013) reported a higher prevalence of 2.4% for patients undergoing implantation of subdural monitoring electrodes. The risk of postoperative edema is increased by lengthy and/or forceful brain retraction, and intraoperative tissue ischemia, for example due to venous hypertension (Weiss and Post, 2011). Moreover, as described previously, the complication rate for subdural grid electrodes is higher for large grids, and the area of exposed cortex in visual cortical implant surgery will be relatively small. We therefore estimate the likely risk to implant recipients to be in the order of 1–2%, based on the existing literature and the relative simplicity of the implant procedure. Nonetheless, the risk of postoperative swelling after visual cortical electrode array implantation will minimized by the sparing use of brain retraction and unilateral implantation of electrodes. In the unlikely event of clinically relevant postoperative cerebral edema, standard medical management may include pharmacologic interventions such as osmotic agents and steroids where required.

In summary, the risk of clinically significant adverse events following visual cortical implant surgery is likely to be low. This statement is supported by the existing neurosurgical literature, as well as the growing number of reports describing uneventful temporary (House et al., 2006; Waziri et al., 2009) and longer-term (Collinger et al., 2013; Hochberg et al., 2012) implantations of high-density electrode arrays into human cerebral cortex.

A key non-surgical element to the postoperative care of visual cortical implant recipients will be the provision of ongoing, subject-specific psychological support. This approach has been taken by other groups following implantation of a cortical motor neuroprosthesis (Collinger et al., 2014) and retinal visual prostheses (Peters et al., 2013). Both groups describe the involvement of psychologists throughout

the life-cycle of their respective studies, helping study participants adjust to the ongoing demands of participating in a high-profile research project, along with ensuring outcome expectations and wellbeing were carefully monitored throughout. We anticipate this will become a standard element in the postoperative management of cortical visual prosthesis recipients also.

6.3. *Implant assessment*

6.3.1. *Psychophysical testing*

After implantation and recovery, a significant amount of testing will be required to establish the most effective stimulation parameters for each individual electrode. Given the large numbers of electrodes likely to be implanted, this represents a formidable task; reports of lengthy phosphene threshold testing procedures in implants with approximately 150 electrodes suggest that it has the potential to be an arduous process (Naumann, 2012; Rushton and Brindley, 1977). Moreover, alterations in phosphene thresholds over time (Davis et al., 2012) may require this process to be repeated to ensure a consistent visual experience. Improved tools to speed up the establishment of appropriate stimulus parameters across large numbers of electrodes are required, and these will support the long-term efficacy of cortical visual prostheses.

Beyond the establishment of appropriate stimulus parameters for reliable phosphene generation, the elicited percepts also need to be integrated into a visuotopic map linking cortical electrodes to phosphenes in visual space. The inherent inter-individual variability in anatomical and visuotopical arrangement of visual cortex, in addition to the potential for long-term blindness to influence visual cortical functional organization dictates that this process must be undertaken on a per-recipient basis (Stronks and Dagnelie, 2011). Moreover, some mapping techniques, for example tracking eye saccades to the location of remembered phosphenes (Bradley et al., 2005; Dagnelie et al., 2003), may not be applicable in blind individuals where the eye muscles do not function normally. Pointing methods (Brelen et al., 2005; Brindley and Lewin, 1968) have proven useful in the past for mapping of phosphenes elicited by visual cortical and optic nerve stimulation, although a relatively wide area of visual field was covered by phosphenes in both cases with an approximately 41° vertical × 14° horizontal distribution for the optic nerve device (Brelen et al., 2005), and a similar distribution, albeit in a single hemifield in Brindley's first patient (Brindley and Lewin, 1968).

The distribution of phosphenes elicited by intracortical microstimulation will also depend on the extent of electrode implantation across visual cortex. Whilst implantation of penetrating electrodes within the anterior zone of medial V1 may not be feasible due to the difficulty of access, stimulation of peristriate cortices (V2/V3) can also elicit phosphenes (Dobelle et al., 1979b). Moreover, these phosphenes may conform to alternate visuotopic maps, potentially filling in gaps in the visual field that would otherwise exist when stimulating V1 only (Srivastava et al., 2007 [Fig. 2]). Nonetheless, most phosphenes will likely be clustered near the center of the visual field, given that the occipital pole

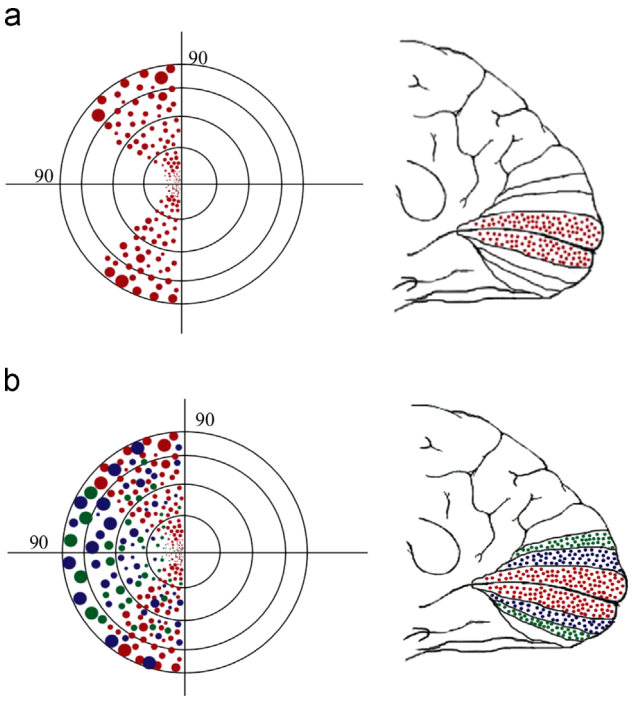

Fig. 2 – (a, b) Possible distribution of phosphenes from cortical microstimulation of V1 alone (a) or in combination with V2 and V3 (b).
Figure reproduced from (Srivastava et al., 2007) with permission.

represents the most likely implantation site (Lowery, 2013; Srivastava et al., 2007). Precisely mapping such large numbers of small, closely-spaced phosphenes will undoubtedly require rapid, potentially automated techniques in order to generate consistent maps.

The problem of phosphene maps moving proportionally with eye saccades is well known (Brindley and Lewin, 1968; Dobelle and Mladejovsky, 1974). Not only does this complicate the generation of consistent phosphene maps, but it also introduces a requirement for central gaze fixation during head turning, or sophisticated eye tracking technology to ensure image stability during changes in eye position. Retinal implants incorporating a light-sensitive electrode array may circumvent this problem (Chow et al., 2004), as would an intraocular camera (Hauer, 2009), which may possibly be adapted for a cortical prosthesis. Importantly, such techniques may only be useful in those subjects not demonstrating significant gaze instability or suffering from nystagmus (Schneider et al., 2013).

6.3.2. *Image processing*

The work of Dobelle (2000) provided clear evidence that preserved neuroplasticity in visual cortex can permit a blind individual, who had an initially poor response to patterned stimulation, to gradually recognize shapes, letters and features in a relatively complex physical environment. According to Dobelle (2000), a key factor in achieving this goal was increased computing power, which permitted the use of more sophisticated image processing algorithms providing enhanced edge detection, whilst keeping frame rates at acceptable levels.

Future cortical visual prostheses will likely elicit several hundred or more phosphenes (Lowery, 2013; Normann et al., 2009; Srivastava et al., 2007), many more than were reported by any previous cortical implant recipient (Brindley and Lewin, 1968; Brindley et al., 1972; Brindley, 1982; Dobelle, 2000; Naumann, 2012). The manner in which visual imagery is preprocessed prior to reconstruction with phosphenes is therefore of great importance, and is a subject of ongoing research.

Early studies of simulated phosphene vision used simple perforated masks of varying density and "pixel" count, which provide a crude estimate of the likely pattern of percepts experienced by a cortical prosthesis recipient (Cha et al., 1992a). This technique provides a model for many subsequent reports of simulated phosphene imagery, namely that the phosphenated image is a grayscale, "downsampled" version of the original, with multiple levels of brightness allowable per pixel. Some more recent studies have added irregularities in the distribution and character of percepts including variable size, brightness, density, overlap and a restricted spread of phosphenes across the visual field to more accurately estimate the perceptual experience (Chen et al., 2009b; Srivastava et al., 2009). Nonetheless, the same approach is essentially employed, wherein the resultant image remains a downsampled version of the original, albeit with phosphenes conforming to a more realistic electrode/phosphene coordinate system.

Chen et al. (2009b) discussed in detail the likely implications of phosphene maps with poor resolution and contrast, restricted fields of view, high eccentricity in the main phosphene field, geometric distortions in images and other such limitations for the rehabilitation of visual prosthesis recipients. While well-designed training programs may permit recipients to work around or adapt to these limitations, modifications or extensions to the basic idea of representing imagery in an "intensity-based" (McCarthy et al., 2011) fashion have been described that may minimize the functional impact of the relatively poor quality of prosthetic vision. For example, Parikh et al. (2013) used feature extraction algorithms to identify the most relevant parts of an image, with a blinking phosphene guiding prosthesis recipient's attention to a particular part of the visual field. The authors reported improvements in object avoidance, reductions in head scanning and more rapid object location with the use of cues. In a similar fashion, Mohammadi et al. (2012) propose the use of a range-finding algorithm to estimate the distance to objects, which would be relayed to the prosthesis wearer using a group of phosphenes reserved for this purpose.

The use of more advanced image processing techniques derived from the field of robotics may provide further improvements in the way in which phosphenes are utilized to represent the physical environment. For example, recognition of the ground plane to clearly identify unobstructed areas when walking may permit better obstacle avoidance (Lui et al., 2012; McCarthy et al., 2011). Object recognition and location, particularly in complex environments, may be improved by using symbolic or iconographic techniques akin to those used in computer graphics (Lui et al., 2012). Facial recognition in particular may benefit from these techniques, whereby simplistic representations of faces (Lui et al., 2012) could be assembled using far fewer phosphenes than would be possible using an intensity-based method (Bradley et al., 2005). Such techniques may be particularly useful in the case of long-term phosphene dropout and map degradation, allowing the available phosphenes to be used to maximal effect. The choice by Brindley and Dobelle to present Braille characters instead of conventional lettering could be considered a conceptually similar "repurposing" of a poor quality phosphene map to maximize its utility (Brindley and Rushton, 1974; Dobelle, 1974).

As demonstrated by the success of Dobelle's (2000) last reported patient (in the scientific literature), the ongoing development of image processing techniques applicable to prosthetic vision should continue to provide improvements in the likely outcomes of visual prosthesis recipients, both cortical and retinal. Even further improvements will undoubtedly come from an improved understanding of the encoding of the more complex features of imagery, such as color, form and motion in visual cortex neurons, possibly offering a richer visual experience (Normann et al., 2009). Moreover, with reductions in the size of the stimulated neuron pool, possibly via increases in the density of electrode arrays (e.g. Wark et al., 2013), and a "bioinspired" approach to encoding information into neuronal spike trains, continued improvements in the quality and functional utility of prosthetic vision may be realized in the future.

6.3.3. *Outcome measures*

Once visuotopic mapping of phosphenes is complete, the ability of the implant to provide the recipient with functionally useful visual perception must be tested.

As discussed in detail by Dagnelie (2008) and others (Chen et al., 2009a), tools for prosthetic vision assessment should permit the quantification of implant performance across a variety of domains, ranging from simple light, direction and motion perception, to improvements in the ability of recipients to complete routine daily tasks such as obstacle avoidance, self-grooming and food preparation. As recently highlighted by Rizzo and Ayton (2014), a key concern in this context is the lack of standard tests and scoring systems, limiting the ability of researchers to compare results.

Recipients of the early Brindley (Brindley and Rushton, 1974) and Dobelle (Dobelle et al., 1976) cortical implants were assessed in terms of their ability to read Braille characters and conventional letters. Later iterations of the Dobelle system were tested using more conventional tools such as Landolt rings and Snellen charts, with which the visual acuity of one implant recipient was estimated at 20/1200, achieved via head scanning (Dobelle, 2000). Since Dobelle's last publication in the scientific literature, there have been no further reports of visual acuity or functional performance testing in cortical visual prosthesis recipients.

Conversely, the development and subsequent implantation in humans of retinal devices has enabled the application of newer testing paradigms to patients experiencing real-world prosthetic vision. For example, recipients of the Alpha IMS (Stingl et al., 2013) and Argus II (da Cruz et al., 2013; Dorn et al., 2013) retinal implants have been assessed using a variety of visual acuity tests including the Basic Assessment of Light and Motion (BALM) (Bach et al., 2010; Wilke et al.,

2007) and Basic Grating Acuity (BaGA) (Wilke et al., 2007) tests, Landolt rings, individual letters and words of 2–4 letters in length or motion of high-contrast rectangles on computer screens. Stingl et al. (2013) also reported on the recipients' experiences with activities of daily living (ADL), such as recognition and location of objects, and navigating the environment, with one recipient achieving poor ADL results, despite satisfactory tests of visual acuity. Notably, the authors report that recipients for whom positive results were obtained on the ADL tasks described the ADL improvements as the most rewarding benefit provided by the implant (Stingl et al., 2013).

Direct translation of the applicability of these vision scoring techniques to cortical implant recipients may be complicated by differences in the nature of cortical vs. retinal prosthetic vision. While such considerations remain speculative in the context of large-scale patterned ICMS, it is known that the cortical magnification factor theoretically allows for significantly larger numbers of small phosphenes in the central visual field, with expected increases in visual acuity (Dagnelie, 2008). Moreover, we expect phosphenes to be largely limited to this area unless electrode implantation extends to the medial primary and secondary visual cortices (Srivastava et al., 2007). Techniques such as head scanning will likely be necessary to optimize the functionality of future cortical prosthesis implants, and will therefore need to be incorporated into prosthesis assessment procedures (Cha et al., 1992b, 1992c; Chen et al., 2006).

The types of vision assessment tasks most appropriate for cortical prosthetic vision may also depend on the method of image processing employed in the system design. For example, system designs utilizing the aforementioned intensity-based image processing techniques vs. those employing a machine vision type of symbolic image representation may dictate a radically different approach to prosthetic vision assessment.

In summary, functional measures will form a central component of any post-implant assessment regimen, however regulatory authorities focus more on tests of visual acuity as measures of functional success (Dagnelie, 2008). This may only change with a concerted effort by visual prosthesis researchers to develop a framework for standard testing paradigms appropriate to prosthetic vision (Rizzo and Ayton, 2014).

6.4. *Stability of the electrode–brain interface*

One of the key obstacles to developing a cortical visual prosthesis is the observed deterioration of the interface between the electrode and brain tissue. Studies of implanted electrodes for both neural recording and cortical stimulation show highly variable patterns of stability over time (Polikov et al., 2005). In some cases electrodes may simply fail to function after implantation (Torab et al., 2011), or failure manifests gradually over a period of months to years as a loss of recording capability (Hochberg et al., 2012; Rousche and Normann, 1998) or increases in stimulation threshold currents to excessive levels (Davis et al., 2012). The implications of this loss of electrode performance may depend on the application. For example, in the case of a motor neuroprosthesis, loss of signals from some electrodes may not grossly impair system functioning as demonstrated by the successful operation of a robotic arm and hand by a tetraplegic volunteer with a neural recording array implanted 5 years prior (Hochberg et al., 2012). As described previously, a loss of the ability to elicit phosphenes from some electrodes may require advanced image processing algorithms to maximize the utility of remaining phosphenes. However, there will undoubtedly be a threshold below which implant functionality deteriorates to the point that neither software nor behavioral changes can compensate. Thus regardless of the application, long-term efficacy of a neural prosthesis is predicated largely on the electrode/tissue interface remaining viable.

There are a variety of proposed mechanisms underlying the gradual loss of electrode functionality, which largely center on the reactive tissue response to the insertion, continued presence of, and adverse effects of electrical stimulation with intracortical electrodes (Polikov et al., 2005).

6.4.1. *Electrode encapsulation, chronic inflammation and neurodegeneration*

The cortical tissue response to passive (i.e. unstimulated) electrode insertion and chronic presence has been examined in a variety of experimental conditions involving both animals and humans. Immunohistochemical studies at varying time points after implantation reveal acute and chronic astrocytic and microglial encapsulation of electrodes (Biran et al., 2005; Edell et al., 1992; Kozai et al., 2012; Szarowski et al., 2003), and chronic inflammation with localized neurodegeneration (Azemi et al., 2011; Biran et al., 2005; McConnell et al., 2009) that combine to increase the separation of viable neurons from the electrode surface. Importantly, this response may be highly variable, even within an individual electrode array. The factors mediating the extent of tissue response are still being characterized, however a number of mechanisms have been examined or proposed. These include the extent of vascular injury occurring during electrode insertion (Bjornsson et al., 2006; House et al., 2006; Kozai et al., 2010), the amount of strain experienced by cortical tissue during penetration of the pia mater (Bjornsson et al., 2006; Rennaker et al., 2005; Rousche and Normann, 1992), the geometry of electrodes (Seymour and Kipke, 2007; Skousen et al., 2011) and micromotion-induced injury due to a stiffness mismatch between electrodes and cortical tissue, or by electrode tethering (Biran et al., 2007; Freire et al., 2011; Lind et al., 2010).

A variety of approaches are being explored to minimize the extent of glial encapsulation and chronic neuroinflammation. A reduction in vascular injury may be achieved by careful placement of electrodes deliberately avoiding surface vessels (Kozai et al., 2010), implanting flexible electrodes that can deflect off vascular structures (Bjornsson et al., 2006), or by customizing electrode arrays to account for the distribution of vessels at the cortical surface of the recipient (Ortmann and Baziyan, 2007).

Some disagreement exists about the optimal combination of insertion speed and electrode tip sharpness required to penetrate the pia with minimal tissue compression; Nicolelis et al. (2003) advocate for the ultra-slow insertion (100 μm/min)

of arrays containing blunt-tipped electrodes, while Rousche and Normann (1992) suggest that to minimize cortical compression and achieve uniform insertion depth of the 100-electrode Utah Electrode Array (UEA), very high speed (>8.3 m/s) insertions of electrodes with sharp tips are required in cats. Notably, the same group suggest that even higher speeds may be required for implantation of arrays into the larger human brain, with its differing biomechanical properties and thicker pial layer (House et al., 2006). Weakening of the pia by pretreating with collagenase prior to electrode insertion has also been shown to reduce insertion forces (Paralikar and Clement, 2008).

Reductions in glial encapsulation and neuronal loss may also be achieved by using electrodes with very low surface areas (Skousen et al., 2011), or greater flexibility (Harris et al., 2011).

Alternative approaches to controlling the tissue response that have been suggested or are being explored include biologically-active electrode coatings (Azemi et al., 2010, 2011; He et al., 2007; Zhong and Bellamkonda, 2007), immunomodulation via drug delivery through microfluidic channels in the electrodes (Abidian et al., 2009), or systemic administration of immunomodulatory agents (Freire et al., 2011; Shain et al., 2003).

6.4.2. *Adverse effects of stimulation*

Complicating the chronic tissue response to the presence of intracortical electrodes is the influence of chronic electrical stimulation itself. Histologically confirmed neuronal degeneration can be seen following electrical stimulation of cortex, which is unrelated to the presence of electrodes (McCreery et al., 1988). This damage manifests acutely as edematous, hyperchromic and shrunken neurons, progressing to vacuolation, degeneration and cell death (McCreery et al., 1988).

Of the factors mediating the degree of tissue damage, irreversible electrochemical (Faradic) reactions occurring at the electrode/tissue interface are a well-known problem. These reactions may lead to electrode degradation or delamination of oxide layers, in addition to hydrolysis causing gas bubble formation and injurious pH shifts within surrounding tissue (Cogan, 2008). The risk of irreversible electrochemical reactions is lowered by using electrodes with high charge injection capacity (CIC), enabling neuronal stimulation while allowing electrode voltages to remain within safe levels (Negi et al., 2010). Well-studied materials with high CIC include iridium oxide films (Negi et al., 2010), with newer options offering even higher CIC including electrodes coated with poly(3,4-ethylenedioxythiophene) (PEDOT) (Wilks et al., 2009), roughened silicon coated with platinum (Negi et al., 2012) or silicon electrodes containing embedded carbon nanotubes (Musa et al., 2012).

Aside from electrochemical reactions at the probe/tissue interface, neuronal stimulation at levels required for elicitation of behavioral responses can be injurious to tissue. The likelihood of damage is related to the amount of electric charge delivered per stimulus pulse (charge per phase), acting in combination with the surface area of the electrode stimulating surface, which determines the *density* of charge (McCreery et al., 2010b, 1990). Therefore, the *density* of charge is also seen to be a mediating factor in determining the likelihood of tissue damage. In a study of the effects of chronic (7 h per day) stimulation over periods of 30 days, McCreery et al. (2010b) noted that the duty cycle, which refers to the ratio of time spent in the stimulus-on vs. stimulus-off state, can also influence the degree of tissue damage. The authors pointedly commented on the requirement for further study to determine whether the degree of neuronal damage due to the 50% duty cycle stimulus regimen represented a steady-state condition.

The likelihood of damage at higher levels of charge per pulse may be reduced by using electrodes with higher geometric surface areas (GSA) (McCreery et al., 2010b), or by increasing the real surface area (RSA) via surface roughening while maintaining the GSA (Negi et al., 2012). While increasing the GSA may be at the expense of stimulating larger populations of cortical neurons and therefore reducing the potential resolution of a visual prosthesis, it may result in improved electrode stability and performance over time (Davis et al., 2012). An electrode design with a large GSA was tested recently by Wang et al. (2013), in which the stimulating area was an annulus of exposed electrode distal to the tip. These electrodes were chronically implanted into rat motor cortex, and demonstrated stable current thresholds for evoking whisker movement over a period of 100 days, at charge levels beyond those previously defined for inducing neuronal injury (Wang et al., 2013). Notably, the charge was delivered only intermittently over a period of three months, so longer-term trials are required to establish the validity of these findings in the chronic setting.

The precise biological mechanisms underpinning neuronal degeneration due to electrical stimulation are relatively poorly understood. McCreery et al. (1988) observed that neuronal loss was independent of electrode type (i.e. faradic vs. capacitative), suggesting that the phenomenon can occur in the absence of electrochemical reactions occurring at the electrode/tissue interface. The authors hypothesized that the damage may be mediated by stimulation-induced neuronal hyperactivity, notably observing the relative preservation of glial cells in the presence of neuronal degeneration (McCreery et al., 1988). Support for this theory was provided by administering an N-methyl D-aspartate (NMDA) receptor antagonist during stimulation of cats with surface electrodes, which reduced the degree of neuronal damage compared to untreated animals and suggested a glutamate-mediated mechanism (Agnew et al., 1993).

A key question surrounding stimulation-induced neurodegeneration and chronic tissue responses is whether the degree of damage is sufficient to cause device failure. The functional relevance of neuronal loss may depend on the relative excitabilities of and proximity to stimulating electrodes of neurons mediating phosphene induction (McCreery et al., 2010a; Tehovnik and Slocum, 2013). Examining the ability of an electrode array to elicit phosphenes 2 years after implantation into the visual cortex of a macaque, Davis et al. (2012) reported that 77/96 individual electrodes failed to consistently elicit behavioral responses at currents up to 200 μA. The authors then stimulated with groups of four and nine contiguous electrodes, finding that 24/36 four-electrode groups produced functional responses at approximately 200 μA per electrode, and all 8 nine-electrode groups

produced responses at currents of approximately 90 μA (Davis et al., 2012).

Taken together, these studies suggest that while stimulation-induced efficacy of individual electrodes may be preserved over a period of months, the chronic tissue response to penetrating electrodes may require reconfiguration of stimulus parameters to maintain device efficacy over time. An obvious drawback to increasing the number of concurrently stimulated electrodes in particular is the potential for a gradual reduction in the resolution of the resulting phosphene map. Davis et al. (2012) reported that the precision of saccades to percepts elicited with multiple-electrode groups was less than those to photic stimuli, suggesting that the percepts elicited with larger groups of electrodes were larger. However, the same authors point out that a previous study (Bradley et al., 2005) also showed inferior precision of saccades to percepts elicited by stimulation with single electrodes compared to photic stimuli. In that study Bradley et al. (2005) suggested that this loss of precision may be the result of differences in the way electrically-evoked percepts are committed to short-term memory, a question that remains unresolved.

6.5. *Seizure risks*

Additional considerations in the context of chronic stimulation include the risk of stimulation-induced alterations in neuronal excitability. From a safety perspective, the risks of seizure induction cannot be understated. Parker et al. (2011) noted that simultaneous stimulation of 72 cortical electrodes at 25 μA induced a tonic seizure in cats. Given this observation of a seizure in an animal model, and previous reports of seizures in human recipients of cortical surface implants (Naumann, 2012; Pudenz, 1993), it is pertinent to discuss the risk of cortical kindling.

Cortical kindling describes the evolution of electrical stimulus response from the expected transient increase in neuronal firing, to the development of after discharges and eventually seizures with no increase in stimulus current (Goddard et al., 1969). This phenomenon is readily observed in the amygdale (Goddard et al., 1969), and the susceptibility of visual cortex to kindling is of direct relevance to the long-term safety of a cortical visual prosthesis. Previous studies have demonstrated the development of neuronal afterdischarges or generalized seizure progression (kindling) in the visual cortex of cats (Pollen, 1977; Wada et al., 1989), rabbits (Jibiki et al., 1988) and primates (Goddard et al., 1969; Poggio et al., 1956). Comparing the susceptibilities of the amygdala and visual cortex to kindling in cats, Wada et al. (1989) noted that visual cortex required much higher currents to elicit afterdischarges. Moreover, the same authors noted that once progression to a seizure response had been achieved through repeated stimulation, there was frequently regression to a non-convulsive response by visual cortex, whereas the amygdala retained its kindled state (Wada et al., 1989). Wada's observations in cats are consistent with the earlier macaque studies of Poggio et al. (1956), in which repeated stimulation of occipital cortex produced less frequent and shorter visual cortical afterdischarges, and with less subcortical progression than other parts of the brain. Bartlett et al. (1977) also noted that even with high current (5.0 mA) stimulus of macaque visual cortex, afterdischarges did not propagate beyond 6 mm from the site of stimulation.

The influence of long-term blindness on the susceptibility of visual cortex to the development of seizures and/or kindling following long-term electrical stimulation is poorly understood. Examining the susceptibility of visual cortex to kindling in immature and adult cats, Moneta and Singer (1986) noted that the developing visual cortex had a higher afterdischarge threshold and was more resistant to the kindling effect. In discussing potential mechanisms for the observed reduction in cortical excitability in kittens, the authors postulated that visual input may antagonize any kindling response (Moneta and Singer, 1986). Importantly, in the blind human subject, there would be no such visual input, potentially increasing the risk of a kindling response. Clearly this is an area requiring further research.

Seizure risk mitigation may be achieved with anticonvulsant medications such as phenytoin, which is known to suppress both neuronal afterdischarges in cats by raising the threshold current for their elicitation (Pollen, 1977; Wada et al., 1990), in addition to suppressing kindled seizures (Wada et al., 1990). Alternatives include sodium valproate, which has been shown to elevate afterdischarge threshold and prevent convulsions in a rat model of amygdala kindling (Salt et al., 1980). There is little data on the prevention of kindled occipital seizures in humans, however occipital epilepsies generally respond equally well to a wide range of antiepileptics, although if a photosensitive component is present, then sodium valproate may be more effective (Taylor et al., 2003). Whether or not photosensitive epilepsy is a more appropriate model for kindled visual cortex seizures is a subject that requires further investigation.

One possible seizure risk mitigation strategy proposed by Parker et al. (2011) was the interleaving of stimuli, maximizing the distance between any two individual, or groups of stimulated electrodes. This may have the added benefit of reducing another undesired side-effect of chronic stimulation, being the depression of neuronal excitability that is seen following 7 h of constant stimulation and may persist for several days (McCreery et al., 1997, 2002). Therefore by avoiding parallel stimulation of electrodes with overlapping current spread, reduction in the multiple deleterious effects of prolonged, chronic and constant stimulation may be avoided.

6.6. *Electrode array design*

Several considerations in the design of penetrating cortical electrode arrays for a visual prosthesis have been discussed throughout previous sections. Several additional major concerns are worthy of discussion, and these are briefly covered here.

6.6.1. *Electrode penetration depth*

Multiple studies report a clear depth–threshold relationship for phosphenes elicited by electrical stimulation with penetrating microelectrodes (Bak et al., 1990; Bartlett and Doty, 1980; Bartlett et al., 2005; DeYoe et al., 2005; Koivuniemi et al., 2011; Tehovnik et al., 2003). These studies consistently show

a dramatic reduction in threshold with increasing depth from the surface, to the extent that the ratio of maximum to minimum thresholds may be as high as 100:1 (Bak et al., 1990). Thus, penetration of electrodes to a depth at which the stimulus threshold for phosphene perception is minimized will be an important consideration in not only preventing current spread overlap and therefore maintaining the discriminability of phosphenes, but also for reducing total power consumption by the device. This latter point may be of critical importance in future implant designs employing many hundreds of electrodes.

The precise cortical depth at which phosphene detection thresholds reach a minimum remains a point of some conjecture. The early macaque studies of Bartlett and Doty (1980) concluded that the lowest thresholds were found in layers V/VI of macaque visual cortex, corresponding to a depth of 1.5 mm. More recently, DeYoe et al. (2005) reported that layers III–IVb of macaque visual cortex consistently demonstrated the lowest thresholds. Conversely, Tehovnik et al. (2003) reported the lowest thresholds from the border of layers V/VI (at a depth of 1.75 mm), later contending that the significant variation in threshold beyond layer III reported by DeYoe et al. (2005) may have been due to electrode damage (Tehovnik and Slocum, 2013). Bradley et al. (2005) implanted electrodes varying in length between 0.7 and 1.5 mm into the visual cortex of a macaque, however they made no specific comment on differences in stimulus current threshold at these varying depths. Torab et al. (2011) implanted 2 arrays of 100 electrodes each into the visual cortex of a macaque, noting that behavioral responses could only be elicited from 5/37 stimulated electrodes in one array, and 3/45 electrodes in the other. Notably, the electrodes were 1 mm in length, and the authors commented that the plane within which the electrode tips were situated was likely not parallel with that of the cortical laminae, resulting in variable penetration depth across the array. This also correlated with differences in the level of background neuronal activity, with those electrodes recording the highest levels of activity tending to be those that produced behavioral responses (Torab et al., 2011).

The available data on visual cortex intracortical microstimulation in humans addresses the question to a limited extent only. Bak et al. (1990) recorded threshold minima at depths of 2–3 mm, 4 mm and 4.5 mm in three sighted volunteers undergoing occipital craniotomy for excision of epileptic foci. In the patient with the lowest detection thresholds, they plotted the threshold stimulus current vs. electrode depth, showing the lowest thresholds (20 μA) at a depth of approximately 2.25 mm. In their subsequent study on a blind volunteer, the same group reported thresholds varying from 1.9 μA to 77 μA using fixed-length electrodes implanted to a depth of 2 mm (Schmidt et al., 1996).

As noted by Torab et al. (2011), the undulating nature of the cerebral cortex renders it difficult to ensure consistent penetration depth of all electrodes with an array based on a rigid substrate. Moreover, the ability of electrodes to elicit behavioral responses at current levels not damaging to the electrodes or tissue may be predicated partly on the location of electrode stimulating sites within laminae containing the most excitable neuronal elements. Spatial differences in threshold current (DeYoe et al., 2005) or depth of lowest threshold (Bak et al., 1990) and natural variations in the thickness of V1 (Fischl and Dale, 2000) may therefore combine to present a significant challenge for ensuring implantation of electrodes to the optimal depth in visual cortex. Possible solutions to these problems include the implantation of arrays with electrode shanks of varying length as previously described (Bradley et al., 2005), which may require an increase in the density of electrodes, e.g. (Wark et al., 2013) to preserve the resolution of the phosphene map. Another possible solution could be the incorporation of multiple stimulating sites onto individual electrode shanks (Changhyun and Wise, 1996) or microdrives that allow independent adjustment of electrode penetration depth (Gray et al., 2007; Yamamoto and Wilson, 2008; Yang et al., 2010). For the latter, further reductions in the size of the positioning hardware will be required before integration into high electrode count arrays is a realistic possibility.

Reductions in the size of electrode arrays may also offer some benefits; for example, the Illinois group and EIC Laboratories recently described a 2 × 2 mm, 16-electrode array (Kane et al., 2013) that may permit improved consistency of electrode tip depth relative to the curved cortical surface when implanted over a wide area. One potential disadvantage to this approach is the larger number of arrays to be implanted, and its potential implications for the length of the surgical procedure. For example, implanting 650 electrodes in groups of 16 would require approximately 41 arrays (Srivastava et al., 2007), while implanting 500 electrodes in groups of 43 would require only 11 (Lowery, 2013).

6.6.2. *Accessing the buried calcarine cortex*

Further to the question of variable electrode penetration depth, there remains the problem of the surgical inaccessibility of the significant region of V1 buried within the calcarine fissure, which serves a large area of the lateral visual fields. Brindley and Lewin (1968) illustrated the distribution of phosphenes derived from stimulation of the accessible areas of the medial calcarine cortex and occipital pole, wherein the expected absence of phosphenes in the nasal and temporal hemifields is evident. However, as discussed in Section 6.3.1, stimulation of parastriate visual cortex can also elicit phosphenes, and these may in fact map to areas of the visual field also subserved by primary visual cortex buried inside the calcarine fissure.

Splitting the Calcarine fissure would necessarily result in a degree of vascular trauma over and above that resulting from the electrode insertion itself, increasing the risk of bleeding and disruption to local cortical blood flow. Even if the cortex buried within the fissure was surgically exposed, implanting an array of penetrating electrodes would be a complex procedure. Another approach may be to slide a ribbon of surface electrodes into the fissure, although this would be done at the expense of stimulation power requirements, seizure risk and phosphene size. A patent for such a device has been granted (Lauritzen et al., 2014), however no reports of stimulation of buried calcarine cortex using ribbon electrodes could be retrieved at the time of writing.

Another alternative may be to implant an array of penetrating electrodes on the medial surface of V1, wherein the

electrodes are long enough to reach cortex buried within the fissure. If the electrodes were fabricated with multiple stimulating sites (Changhyun and Wise, 1996), stimulation of both superficial and deeper cortical layers could be achieved from single electrode shanks. A major challenge in this approach would be the insertion of electrodes to the correct depth without electrode bending or breakage, for which the use of a stiff, removable carrier or "shuttle" may be one solution (Kozai and Kipke, 2009).

Given the increased surgical risk associated with splitting the calcarine fissure and the potential for stimulation of secondary visual cortices to expand the phosphene map, there may be minimal requirement for stimulating the buried calcarine cortex. This uncertainty will only be addressed by future human studies.

6.6.3. *Wireless power and data transmission*

Unlike earlier designs (Dobelle, 2000), current-generation cortical (and retinal) visual prostheses are being developed to operate wirelessly. Given the large numbers of electrodes likely to be implanted, it is a major challenge for a wireless interface to transmit data signals and provide enough power to the stimulating hardware.

A common method for wirelessly operating implantable medical devices (IMDs) is by using electromagnetic induction (Rasouli and Phee, 2010), although novel alternatives include using ultrasound (Sanni et al., 2012) or light (Abdo and Sahin, 2011) to transfer power or data through tissue. Using the induction method, an alternating electric current in a wire coil (the transmitter) induces a magnetic field which causes current to flow in a separate coil (the receiver) that has no physical connection with the first. The current in the receiving coil can then be transformed into a power source for the implanted hardware or data signals can be extracted. Several limiting factors in this approach complicate the design of wireless stimulating implants of any kind, neural prostheses included. The first is that the most efficient transfer of electromagnetic energy between the primary and secondary coils occurs when the coils directly appose each other; physical separation and misalignment therefore impose an efficiency penalty due to the "uncoupling" of the transmitting and receiving coils (Rasouli and Phee, 2010). In particular, rapid reductions in power transfer efficiency are seen with relative angles $>20^{\circ}$ between the transmitting and receiving coils (Ng et al., 2011). This is particularly problematic for retinal implants, in which eye movement may require the use of additional coil pairs to ensure consistent coupling (Ng et al., 2011).

In a cortical prosthesis the implanted electrode arrays may be self-contained, including inductive coils for power and data transmit/receive (Lowery, 2013; Rush et al., 2011), or the power/data transfer electronics and coil may be separate from the arrays themselves (Coulombe et al., 2007). An advantage of the self-contained array approach is the lack of any requirement for tethering, which may reduce damage to the cortex from relative motion of the brain and arrays in the long term (see Section 6.3.1). However, a disadvantage of the self-contained coils is the variation in coupling between the individual implanted array coils and the external coil. For example, arrays implanted on the medial surface of the occipital pole may be at a greater angle to the transmitting coil than those on the more lateral surface. Furthermore, if arrays are implanted more anteriorly onto medial calcarine cortex, these would be more distant from, and orthogonal to the external coil than the more superficial arrays, resulting in poor or zero coupling and energy transfer. Aside from tethering medial arrays to a more superficially-mounted coil, alternatives may include the aforementioned optical or ultrasonic approaches to power and/or data transfer.

Another consideration in the use of wireless power and data transfer derives from the absorption of electromagnetic energy by tissue, which increases exponentially with frequency (Al-Kalbani et al., 2012); the need to transfer sufficient power while maintaining high data transfer rates therefore introduces competing constraints that complicate the design process. Moreover, the separate wire coils used for data and power transfer can interfere with each other, introducing complexity to the design of receiving hardware (Kiani and Ghovanloo, 2014; Rush et al., 2011).

Nonetheless, several inductive link designs have been described or developed in recent years that may support the power and data transfer requirements of a high electrode count cortical visual prosthesis. The general specifications of these systems are summarized in Table 2; these have been included either because they were, as stated in each report, specifically designed for use in a high electrode count cortical visual prosthesis, retinal prosthesis, or both. A key requirement for inclusion was that the performance of the inductive link must have been evaluated over a distance of ≥ 10 mm, which we consider as the likely minimum distance between the external coil and the cortical electrode arrays.

6.6.4. *Brain temperature*

Energy dissipated as heat by the implant remains a problem of concern. A high electrode count, continuous stimulation and

Table 2 – Specifications of selected wireless inductive links for power and/or data transfer to a visual prosthesis.

Stated purpose	Kiani and Ghovanloo (2014) Nonspecific neural prosthesis	Lo et al. (2013) Retinal prosthesis	Monge et al. (2013) Retinal prosthesis	Coulombe et al. (2007) Cortical prosthesis
Data direction (up/down/both)	Both	Down	Down	Both
Separate data/power coils	Yes	Yes	Yes	No
Data/power signal frequency (MHz)	50/13.56	20/2	160/10	13.56/1.5
Max. data rate (Mbps)	13.56	2	20	1.5
Max. # of stimulating channels	NA	1024	512	992

the possibility of increasing current requirements if the electrode/tissue interface becomes impaired over time, all contribute to the potential for high power requirements and therefore greater temperature increases. Studies of focal and whole-brain heating over short periods (30 min), have shown that temperature rises up to 43 °C can be tolerated without damage (Coffey et al., 2014; Haveman et al., 2005). In the context of a cortical visual prosthesis, stimulation is likely to be continuous over a period of hours, therefore the implant must remain at low temperatures to prevent tissue damage. There is little data on the damage to neural tissue resulting from chronic, focal cortical hyperthermia, although some information is available from the literature on heating of tissue due to ultrasound exposure. O'Brien et al. (2008) reviewed the literature on thermal effects of ultrasound, including several studies on cat and rabbit brain. From these studies, a conservative temperature–time exposure boundary was produced, which suggests that increases in temperature of 2 °C above 37 can be safely tolerated for lengthy periods (up to 50 h). An important consideration in this context is the normal human brain temperature, which was found in a recent magnetic resonance spectroscopy study to vary regionally between 34.9 °C and 37.1 °C, and to not differ greatly from core body temperature (Childs et al., 2007). The authors commented on some methodological contributions to the measured variation, however it is also known that a temperature gradient exists between cortical and subcortical regions, with cortical temperature typically being lower by up to 1 °C (Mellergard, 1995). Considering the previously-mentioned 39 °C limit (O'Brien et al., 2008), it would seem that the window of thermal safety may vary from one individual to another. Moreover, the stimulation itself may contribute to temperature changes via alterations in oxidative metabolism and cerebral blood flow (Yablonskiy et al., 2000), while increased cerebral blood flow will itself result in greater heat dissipation (Kim et al., 2007); therefore the accurate estimation of the likely temperature increase due to dense, patterned visual cortex stimulation is a complex task. Kim et al. (2007) estimated temperature increases of 0.029 °C per milliwatt of power dissipated by an electrode array with 100 electrodes, however the power dissipation was based on the system operating as a neural recording device only; we expect that a stimulating array would not only influence local temperatures via increasing metabolism, but it would also consume more power and result in greater heat accumulation. While further study in this area is clearly required to determine the safe limits of operation for a multi-array cortical visual prosthesis, a possible solution to the problem may be incorporating temperature sensors into the implants, which was recently demonstrated in a subretinal visual prosthesis (Liu et al., 2014).

6.6.5. *Hermeticity*

Preventing the ingress of bodily fluids will be essential for maintaining the functionality and longevity of a visual prosthesis, and will require the tight sealing of all joins between materials comprising the electrode arrays. A detailed treatment of the engineering, materials design and manufacturing issues involved is beyond the scope of this review, however it is noteworthy that in-vitro testing of an encapsulated Utah slant array over a period of 9 months revealed no deterioration of device performance that would indicate a failure of hermetic sealing (Sharma et al., 2011). Moreover, with reports of neural recording arrays functioning in-vivo in humans (Hochberg et al., 2012) over periods of 5 years, manufacturing techniques have clearly developed to the point that maintenance of array hermeticity over the lifespan of the visual prosthesis will be achievable.

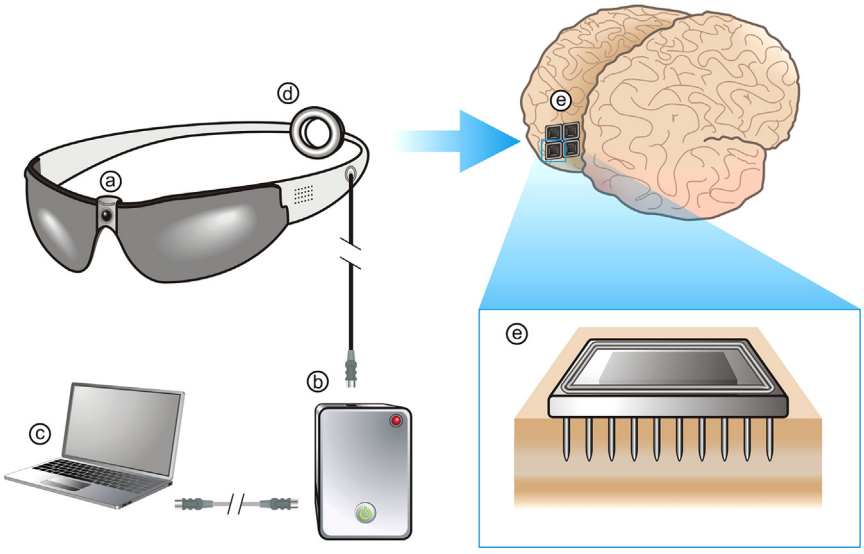

Fig. 3 – A simplified representation of the Monash Vision Group cortical visual prosthesis system. Components of the system include a spectacles-mounted camera (a), which passes digitized visual imagery to a pocket processor (b) that itself processes the image data prior to wireless transmission. The pocket processor can be monitored and reprogrammed via a cabled link to a laptop computer (c). The processed image data is transmitted wirelessly via an antenna (d), which allows bidirectional communication with the wirelessly-powered, tiled electrode arrays implanted into visual cortex (e). The electrodes penetrate to layer IV of visual cortex, indicated by the light shaded area in the exploded view of (e).

7. Conclusions

The rapidly growing field of medical bionics offers the potential of partially restoring visual function in individuals with severe visual impairment. We have summarized the clinical imperative for a cortical visual prosthesis, the general design principles and some of the major hurdles facing research groups who are currently developing this technology. Our research group, based at Monash University in Melbourne, Australia, is developing a wireless prosthetic vision system based on cortical microstimulation (Fig. 3) (Lowery, 2013). The project is nearing technical completion, and preclinical, biocompatibility and functional testing of an implantable device is currently underway in normally-sighted sheep and macaques. We anticipate that the results of this study, and others reporting similar progress in the field, should underpin the imminent trial of a new generation of cortical visual prostheses in humans.

Acknowledgments

The authors would like to thank Dr. Jeanette Pritchard for her assistance with proofreading the manuscript, and Mr. Gavin Hawkins for his assistance with the preparation of Fig. 3.

This project is funded through the Australian Research Council's Research in Bionic Vision Science and Technology Initiative (SRI 1000006).

REFERENCES

Abdo, A., Sahin, M., 2011. Feasibility of neural stimulation with floating-light-activated microelectrical stimulators. IEEE Trans. Biomed. Circuits Syst. 2011, 1.

Abidian, M.R., et al., 2009. Interfacing conducting polymer nanotubes with the central nervous system: chronic neural recording using poly(3,4-ethylenedioxythiophene) nanotubes. Adv. Mater. 21, 3764–3770.

Agnew, W.F., et al., 1993. MK-801 protects against neuronal injury induced by electrical stimulation. Neuroscience 52, 45–53.

Al-Kalbani, A.I., Yuce, M.R., Redoute, J.M., 2012. Safe SAR levels in inductively powered brain implanted visual prostheses. In: Proceedings of 2012 International Symposium on Electromagnetic Compatibility (EMC EUROPE), pp. 1–6.

Ambati, J., Atkinson, J.P., Gelfand, B.D., 2013. Immunology of age-related macular degeneration. Nat. Rev. Immunol. 13, 438–451.

Andrews, T.J., Halpern, S.D., Purves, D., 1997. Correlated size variations in human visual cortex, lateral geniculate nucleus, and optic tract. J. Neurosci. 17, 2859–2868.

Anon., 2005. William H. Dobelle, MD, 1941–2004: ASAIO member, 1970–present. ASAIO J. 51, 1–3.

Anurova, I., et al., 2014. Relationship between cortical thickness and functional activation in the early blind. Cereb. Cortex.

Arya, R., et al., 2013. Adverse events related to extraoperative invasive EEG monitoring with subdural grid electrodes: a systematic review and meta-analysis. Epilepsia 54, 828–839.

Azemi, E., Gobbel, G.T., Cui, X.T., 2010. Seeding neural progenitor cells on silicon-based neural probes. J. Neurosurg. 113, 673–681.

Azemi, E., Lagenaur, C.F., Cui, X.T., 2011. The surface immobilization of the neural adhesion molecule L1 on neural probes and its effect on neuronal density and gliosis at the probe/tissue interface. Biomaterials 32, 681–692.

Bach-y-Rita, P., et al., 1969. Vision substitution by tactile image projection. Nature 221, 963–964.

Bach-y-Rita, P., et al., 1998. Form perception with a 49-point electrotactile stimulus array on the tongue: a technical note. J. Rehabil. Res. Dev. 35, 427–430.

Bach-y-Rita, P., Kercel, S.W., 2003. Sensory substitution and the human–machine interface. Trends Cogn. Sci. 7, 541–546.

Bach, M., et al., 2010. Basic quantitative assessment of visual performance in patients with very low vision. Invest. Ophthalmol. Vis. Sci. 51, 1255–1260.

Bak, M., et al., 1990. Visual sensations produced by intracortical microstimulation of the human occipital cortex. Med. Biol. Eng. Comput. 28, 257–259.

Barber, A.C., et al., 2013. Repair of the degenerate retina by photoreceptor transplantation. Proc. Natl. Acad. Sci. USA 110, 354–359.

Bartlett, J.R., et al., 1977. Deleterious effects of prolonged electrical excitation of striate cortex in macaques. Brain Behav. Evol. 14, 46–66.

Bartlett, J.R., Doty, R.W., 1980. An exploration of the ability of macaques to detect microstimulation of striate cortex. Acta Neurobiol. Exp. (Wars) 40, 713–727.

Bartlett, J.R., et al., 2005. Psychophysics of electrical stimulation of striate cortex in macaques. J. Neurophysiol. 94, 3430–3442.

Berg, J.A., et al., 2013. Behavioral demonstration of a somatosensory neuroprosthesis. IEEE Trans. Neural Syst. Rehabil. Eng. 21, 500–507.

Bergey, G.K., 2013. Neurostimulation in the treatment of epilepsy. Exp. Neurol. 244, 87–95.

Biran, R., Martin, D.C., Tresco, P.A., 2005. Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. Exp. Neurol. 195, 115–126.

Biran, R., Martin, D.C., Tresco, P.A., 2007. The brain tissue response to implanted silicon microelectrode arrays is increased when the device is tethered to the skull. J. Biomed. Mater. Res. A 82, 169–178.

Bjornsson, C.S., et al., 2006. Effects of insertion conditions on tissue strain and vascular damage during neuroprosthetic device insertion. J. Neural Eng. 3, 196–207.

Bourne, R.R., et al., 2013. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob. Health 1, e339–e349.

Bradley, D.C., et al., 2005. Visuotopic mapping through a multichannel stimulating implant in primate V1. J. Neurophysiol. 93, 1659–1670.

Brelen, M.E., et al., 2005. Creating a meaningful visual perception in blind volunteers by optic nerve stimulation. J. Neural Eng. 2, S22–S28.

Brelen, M.E., et al., 2006. Intraorbital implantation of a stimulating electrode for an optic nerve visual prosthesis. Case report. J. Neurosurg. 104, 593–597.

Brelen, M.E., et al., 2010. Measurement of evoked potentials after electrical stimulation of the human optic nerve. Invest. Ophthalmol. Vis. Sci. 51, 5351–5355.

Brindley, G.S., 1965. The number of information channels needed for efficient reading. J. Physiol. 177, 44 P.

Brindley, G.S., Lewin, W.S., 1968. The sensations produced by electrical stimulation of the visual cortex. J. Physiol. 196, 479–493.

Brindley, G.S., et al., 1972. The extent of the region of occipital cortex that when stimulated gives phosphenes fixed in the visual field. J. Physiol. 225, 57P–58P.

Brindley, G.S., Rushton, D.N., 1974. Implanted Stimulators of the visual cortex as visual prosthetic devices. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78, 741–745.

Brindley, G.S., 1982. Effects of electrical stimulation of the visual cortex. Hum. Neurobiol. 1, 281–283.

Brummer, S.B., Robblee, L.S., Hambrecht, F.T., 1983. Criteria for selecting electrodes for electrical stimulation: theoretical and practical considerations. Ann. N. Y. Acad. Sci. 405, 159–171.

Brunton, E., Lowery, A.J., Rajan, R., 2012. A comparison of microelectrodes for a visual cortical prosthesis using finite element analysis. Front. Neuroeng. 5, 23.
Burton, H., et al., 2002. Adaptive changes in early and late blind: a fMRI study of Braille reading. J. Neurophysiol. 87, 589–607.
Buschini, E., et al., 2011. Age related macular degeneration and drusen: neuroinflammation in the retina. Prog. Neurobiol. 95, 14–25.
Button, J., Putnam, T., 1962. Visual responses to cortical stimulation in the blind. J. Iowa State Med. Soc. 52, 17–21.
Button, J.C., 1958. Electronics brings light to the blind. Radio Electron. 29, 53–55.
Capelle, C., et al., 1998. A real-time experimental prototype for enhancement of vision rehabilitation using auditory substitution. IEEE Trans. Biomed. Eng. 45, 1279–1293.
Carlson, M.L., et al., 2012. Cochlear implantation: current and future device options. Otolaryngol. Clin. N. Am. 45, 221–248.
Cha, K., Horch, K., Normann, R.A., 1992a. Simulation of a phosphene-based visual field: visual acuity in a pixelized vision system. Ann. Biomed. Eng. 20, 439–449.
Cha, K., Horch, K.W., Normann, R.A., 1992b. Mobility performance with a pixelized vision system. Vis. Res. 32, 1367–1372.
Cha, K., et al., 1992c. Reading speed with a pixelized vision system. J. Opt. Soc. Am. A Opt. Image Sci. 9, 673–677.
Changhyun, K., Wise, K.D., 1996. A 64-site multishank CMOS low-profile neural stimulating probe. IEEE J. Solid-State Circuits 31, 1230–1238.
Chapanis, N.P., et al., 1973. Central phosphenes in man: a report of three cases. Neuropsychologia 11, 1–19.
Chen, S.C., et al., 2006. Psychophysics of prosthetic vision: I. Visual scanning and visual acuity. Conf. Proc. IEEE Eng. Med. Biol. Soc. 1, 4400–4403.
Chen, S.C., et al., 2009a. Simulating prosthetic vision: II. Measuring functional capacity. Vis. Res. 49, 2329–2343.
Chen, S.C., et al., 2009b. Rehabilitation regimes based upon psychophysical studies of prosthetic vision. J. Neural Eng. 6, 035009.
Childs, C., et al., 2007. Determination of regional brain temperature using proton magnetic resonance spectroscopy to assess brain–body temperature differences in healthy human subjects. Magn. Reson. Med. 57, 59–66.
Chow, A.Y., et al., 2004. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. Arch. Ophthalmol. 122, 460–469.
Chow, A.Y., Bittner, A.K., Pardue, M.T., 2010. The artificial silicon retina in retinitis pigmentosa patients (an American Ophthalmological Association thesis). Trans. Am. Ophthalmol. Soc. 108, 120–154.
Coffey, R.J., Kalin, R., Olsen, J.M., 2014. Magnetic resonance imaging conditionally safe neurostimulation leads: investigation of the maximum safe lead tip temperature. Neurosurgery 74, 215–224 (discussion 224–225).
Cogan, S.F., 2008. Neural stimulation and recording electrodes. Annu. Rev. Biomed. Eng. 10, 275–309.
Cohen, L.G., et al., 1999. Period of susceptibility for cross-modal plasticity in the blind. Ann. Neurol. 45, 451–460.
Collignon, O., et al., 2013. Impact of blindness onset on the functional organization and the connectivity of the occipital cortex. Brain 136, 2769–2783.
Collinger, J.L., et al., 2013. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet 381, 557–564.
Collinger, J.L., et al., 2014. Collaborative approach in the development of high-performance brain–computer interfaces for a neuroprosthetic arm: translation from animal models to human control. Clin. Transl. Sci. 7, 52–59.
Collins, C.C., 1971. Tactile vision synthesis. In: Sterling, T., Bering, J.E.D., Pollack, S., Vaughan, J.H.G. (Eds.), Visual Prosthesis: The Interdisciplinary Dialogue. Academic Press, New York, pp. 267–279.
Coulombe, J., Sawan, M., Gervais, J.F., 2007. A highly flexible system for microstimulation of the visual cortex: design and implementation. IEEE Trans. Biomed. Circuits Syst. 1, 258–269.
Cudeiro, J., Sillito, A.M., 2006. Looking back: corticothalamic feedback and early visual processing. Trends Neurosci. 29, 298–306.
da Cruz, L., et al., 2013. The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. Br. J. Ophthalmol. 97, 632–636.
Dagnelie, G., et al., 2003. Phosphene mapping strategies for cortical visual prosthesis recipients. J. Vis. 3, 222.
Dagnelie, G., 2008. Psychophysical evaluation for visual prosthesis. Annu. Rev. Biomed. Eng. 10, 339–368.
Daniel, P.M., Whitteridge, D., 1961. The representation of the visual field on the cerebral cortex in monkeys. J. Physiol. 159, 203–221.
Davis, T.S., et al., 2012. Spatial and temporal characteristics of V1 microstimulation during chronic implantation of a microelectrode array in a behaving macaque. J. Neural Eng. 9, 065003.
Delbeke, J., Oozeer, M., Veraart, C., 2003. Position, size and luminosity of phosphenes generated by direct optic nerve stimulation. Vis. Res. 43, 1091–1102.
Deroy, O., Auvray, M., 2012. Reading the World through the skin and ears: a new perspective on sensory substitution. Front. Psychol. 3, 457.
DeYoe, E.A., Lewine, J.D., Doty, R.W., 2005. Laminar variation in threshold for detection of electrical excitation of striate cortex by macaques. J. Neurophysiol. 94, 3443–3450.
Dobelle, W.H., 1974. Introduction to sensory prostheses for the blind and deaf. Trans. Am. Soc. Artif. Intern. Organs 20B, 761–764.
Dobelle, W.H., Mladejovsky, M.G., 1974. Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. J. Physiol. 243, 553–576.
Dobelle, W.H., et al., 1976. "Braille" reading by a blind volunteer by visual cortex stimulation. Nature 259, 111–112.
Dobelle, W.H., et al., 1979a. Artificial vision for the blind by electrical stimulation of the visual cortex. Neurosurgery 5, 521–527.
Dobelle, W.H., et al., 1979b. Mapping the representation of the visual field by electrical stimulation of human visual cortex. Am. J. Ophthalmol. 88, 727–735.
Dobelle, W.H., 2000. Artificial vision for the blind by connecting a television camera to the visual cortex. ASAIO J. 46, 3–9.
Dorn, J.D., et al., 2013. The detection of motion by blind subjects with the epiretinal 60-electrode (Argus II) retinal prosthesis. JAMA Ophthalmol. 131, 183–189.
Doty, R.W., 1965. Conditioned reflexes elicited by electrical stimulation of the brain in macaques. J. Neurophysiol. 28, 623–640.
Duret, F., et al., 2006. Object localization, discrimination, and grasping with the optic nerve visual prosthesis. Restor. Neurol. Neurosci. 24, 31–40.
Edell, D.J., et al., 1992. Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex. IEEE Trans. Biomed. Eng. 39, 635–643.
Espinosa, J.S., Stryker, M.P., 2012. Development and plasticity of the primary visual cortex. Neuron 75, 230–249.
Fenoy, A.J., Simpson Jr., R.K., 2014. Risks of common complications in deep brain stimulation surgery: management and avoidance. J. Neurosurg. 120, 132–139.
Fernandes, R.A., et al., 2012. Artificial vision through neuronal stimulation. Neurosci. Lett. 519, 122–128.
Fernandez-Robredo, P., et al., 2014. Current treatment limitations in age-related macular degeneration and future approaches

based on cell therapy and tissue engineering. J. Ophthalmol. 2014, 510285.
Fernandez, E., et al., 2005. Development of a cortical visual neuroprosthesis for the blind: the relevance of neuroplasticity. J. Neural Eng. 2, R1–12.
Ferrandez, J.M., et al., 2007. A customizable multi-channel stimulator for cortical neuroprosthesis. In: 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2007, EMBS 2007, pp. 4707–4710.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. USA 97, 11050–11055.
Förster, O., 1929. Beiträge zur Pathophysiologie der Sehbahn und der Sehsphare. J. Psychol. Neurol. 39, 463–485.
Freeman, D.K., Rizzo 3rd, J.F., Fried, S.I., 2011. Encoding visual information in retinal ganglion cells with prosthetic stimulation. J. Neural Eng. 8, 035005.
Freire, M.A., et al., 2011. Comprehensive analysis of tissue preservation and recording quality from chronic multielectrode implants. PLoS One 6, e27554.
Genc, E., et al., 2014. Surface area of early visual cortex predicts individual speed of traveling waves during binocular rivalry. Cereb. Cortex.
Glickstein, M.F., Whitteridge, D., 1987. Tatsuji Inouye and the mapping of the visual fields on the human cerebral cortex. Trends Neurosci. 10, 350–353.
Goddard, G.V., McIntyre, D.C., Leech, C.K., 1969. A permanent change in brain function resulting from daily electrical stimulation. Exp. Neurol. 25, 295–330.
Gothe, J., et al., 2002. Changes in visual cortex excitability in blind subjects as demonstrated by transcranial magnetic stimulation. Brain 125, 479–490.
Gray, C.M., Goodell, B., Lear, A., 2007. Multichannel micromanipulator and chamber system for recording multineuronal activity in alert, non-human primates. J. Neurophysiol. 98, 527–536.
Guenther, T., Lovell, N.H., Suaning, G.J., 2012. Bionic vision: system architectures: a review. Expert Rev. Med. Dev. 9, 33–48.
Hanneton, S., Auvray, M., Durette, B., 2010. The Vibe: a versatile vision-to-audition sensory substitution device. Appl. Bionics Biomech. 7, 269–276.
Harris, J.P., et al., 2011. Mechanically adaptive intracortical implants improve the proximity of neuronal cell bodies. J. Neural Eng. 8, 066011.
Harrop, J.S., et al., 2012. Contributing factors to surgical site infections. J. Am. Acad. Orthop. Surg. 20, 94–101.
Harvey, B.M., Dumoulin, S.O., 2011. The relationship between cortical magnification factor and population receptive field size in human visual cortex: constancies in cortical architecture. J. Neurosci. 31, 13604–13612.
Hauer, M.C., 2009. (Ph.D. thesis). Intraocular Camera for Retinal Prostheses: Refractive and Diffractive Lens Systems. University of Southern California, California.
Haveman, J., et al., 2005. Effects of hyperthermia on the central nervous system: what was learnt from animal studies? Int. J. Hyperth. 21, 473–487.
He, W., et al., 2007. A novel anti-inflammatory surface for neural electrodes. Adv. Mater. 19, 3529–3533.
Hochberg, L.R., et al., 2012. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature 485, 372–375.
Holmes, G., Lister, W.T., 1916. Disturbances of vision from cerebral lesions, with special reference to the cortical representation of the macula. Brain 39, 34–73.
House, P.A., et al., 2006. Acute microelectrode array implantation into human neocortex: preliminary technique and histological considerations. Neurosurg. Focus. 20, E4.
Jibiki, I., Kubota, T., Yamaguchi, N., 1988. Visual cortical kindling in rabbit—consideration of difference between species. Jpn. J. Psychiatry Neurol. 42, 345–350.
Kalfas, I.H., Little, J.R., 1988. Postoperative hemorrhage: a survey of 4992 intracranial procedures. Neurosurgery 23, 343–347.
Kane, S., et al., 2013. Electrical performance of penetrating microelectrodes chronically implanted in cat cortex. IEEE Trans. Biomed. Eng. 60, 2153–2160.
Kiani, M., Ghovanloo, M., 2014. A 13.56-Mbps pulse delay modulation based transceiver for simultaneous near-field data and power transmission. IEEE Trans. Biomed. Circuits Syst. (in press).
Kim, S., et al., 2007. Thermal impact of an active 3-D microelectrode array implanted in the brain. IEEE Trans. Neural Syst. Rehabil. Eng. 15, 493–501.
Koivuniemi, A., et al., 2011. Multimodal, longitudinal assessment of intracortical microstimulation. Prog. Brain Res. 194, 131–144.
Kozai, T.D., Kipke, D.R., 2009. Insertion shuttle with carboxyl terminated self-assembled monolayer coatings for implanting flexible polymer neural probes in the brain. J. Neurosci. Methods 184, 199–205.
Kozai, T.D., et al., 2010. Reduction of neurovascular damage resulting from microelectrode insertion into the cerebral cortex using in vivo two-photon mapping. J. Neural Eng. 7, 046011.
Kozai, T.D., et al., 2012. In vivo two-photon microscopy reveals immediate microglial reaction to implantation of microelectrode through extension of processes. J. Neural Eng. 9, 066001.
Krause, F., 1924. Die Sehbahn In Chirurgischer Beziehung und die Faradische Reizung des Sehzentrums. Klin. Wochenschr. 3, 1260–1265.
Krause, F., Schum, H., 1931. Die epileptischen Erkrankungen, ihre anatomischen und physiologischen Unterlagen sowie ihre chirurgie. In: Küttner, H. (Ed.), Neue Deutsche Chirurgie. Enke, Stuttgart, pp. 482–486.
Kupers, R., et al., 2006. Transcranial magnetic stimulation of the visual cortex induces somatotopically organized qualia in blind subjects. Proc. Natl. Acad. Sci. USA 103, 13256–13260.
Kupers, R., et al., 2007. rTMS of the occipital cortex abolishes Braille reading and repetition priming in blind subjects. Neurology 68, 691–693.
Lane, F.J., et al., 2012. Responses of potential users to the intracortical visual prosthesis: final themes from the analysis of focus group data. Disabil. Rehabil. Assist. Technol. 7, 304–313.
Lauritzen, T., et al., 2014 Cortical Visual Prosthesis. US Patent US20140222103 A1, Available from: ⟨http://www.google.com/patents/US20140222103⟩ (accessed 22.08.14).
Lay, A.H., Das, A.K., 2012. The role of neuromodulation in patients with neurogenic overactive bladder. Curr. Urol. Rep. 13, 343–347.
Lind, G., et al., 2010. Gelatine-embedded electrodes—a novel biocompatible vehicle allowing implantation of highly flexible microelectrodes. J. Neural Eng. 7, 046005.
Liu, C.Y., et al., 2014. In vivo thermal evaluation of a subretinal prosthesis using an integrated resistance temperature detector. J. Micro/Nanolithogr. MEMS MOEMS 13 (1), 13006, http://dx.doi.org/10.1117/1.JMM.13.1.013006.
Lo, Y.K., et al., 2013. A fully-integrated high-compliance voltage SoC for epi-retinal and neural prostheses. IEEE Trans. Biomed. Circuits Syst. 7, 761–772.
Loomis, J., 2010. Sensory substitution for orientation and mobility: What progress are we making?. In: Wiener, W.R., Welsh, R.L., Blasch, B.B. (Eds.), Foundations of Orientation and Mobility (History and Theory), vol. 1. AFB Press, New York, pp. 7–10.

Löwenstein, K., Borchardt, M., 1918. Symptomatologie und elektrische Reizung bei einer Schußverletzung des Hinterhauptlappens. Deutsch. Z. Nervenheilkd. 58, 264–292.
Lowery, A., 2013. Introducing the Monash Vision Group's Cortical Prosthesis. In: IEEE International Conference on Image Processing. ICIP 2013, IEEE, Melbourne, Australia, pp. 1536–1539.
Lu, Y., et al., 2013. Electrical stimulation with a penetrating optic nerve electrode array elicits visuotopic cortical responses in cats. J. Neural Eng. 10, 036022.
Lui, W.L., et al., 2012. Transformative reality: improving bionic vision with robotic sensing. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2012, 304–307.
Marg, E., Driessen, G., 1965. Reported visual percepts from stimulation of the human brain with microelectrodes during therapeutic surgery. Confin. Neurol. 26, 57–75.
Marg, E., 1991. Magnetostimulation of vision: direct noninvasive stimulation of the retina and the visual brain. Optom. Vis. Sci. 68, 427–440.
Marin, C., Fernandez, E., 2010. Biocompatibility of intracortical microelectrodes: current status and future prospects. Front. Neuroeng. 3, 8.
Maynard, E.M., 2001. Visual prostheses. Annu. Rev. Biomed. Eng. 3, 145–168.
McCarthy, C., Barnes, N., Lieby, P., 2011. Ground surface segmentation for navigation with a low resolution visual prosthesis. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. pp. 4457–4460.
McCarty, C.A., Nanjan, M.B., Taylor, H.R., 2001. Vision impairment predicts 5 year mortality. Br. J. Ophthalmol. 85, 322–326.
McClements, M.E., MacLaren, R.E., 2013. Gene therapy for retinal disease. Transl. Res. 161, 241–254.
McConnell, G.C., et al., 2009. Implanted neural electrodes cause chronic, local inflammation that is correlated with local neurodegeneration. J. Neural Eng. 6, 056003.
McCreery, D., Han, M., Pikov, V., 2010a. Neuronal activity evoked in the inferior colliculus of the cat by surface macroelectrodes and penetrating microelectrodes implanted in the cochlear nucleus. IEEE Trans. Biomed. Eng. 57, 1765–1773.
McCreery, D., Pikov, V., Troyk, P.R., 2010b. Neuronal loss due to prolonged controlled-current stimulation with chronically implanted microelectrodes in the cat cerebral cortex. J. Neural Eng. 7, 036005.
McCreery, D.B., et al., 1988. Comparison of neural damage induced by electrical stimulation with faradaic and capacitor electrodes. Ann. Biomed. Eng. 16, 463–481.
McCreery, D.B., et al., 1990. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. IEEE Trans. Biomed. Eng. 37, 996–1001.
McCreery, D.B., et al., 1994. Stimulus parameters affecting tissue injury during microstimulation in the cochlear nucleus of the cat. Hear Res. 77, 105–115.
McCreery, D.B., et al., 1997. A characterization of the effects on neuronal excitability due to prolonged microstimulation with chronically implanted microelectrodes. Trans. Biomed. Eng. IEEE 44, 931–939.
McCreery, D.B., Agnew, W.F., Bullara, L.A., 2002. The effects of prolonged intracortical microstimulation on the excitability of pyramidal tract neurons in the cat. Ann. Biomed. Eng. 30, 107–119.
Meijer, P.B., 1992. An experimental system for auditory image representations. IEEE Trans. Biomed. Eng. 39, 112–121.
Mellergard, P., 1995. Intracerebral temperature in neurosurgical patients: intracerebral temperature gradients and relationships to consciousness level. Surg. Neurol. 43, 91–95.
Merabet, L.B., Theoret, H., Pascual-Leone, A., 2003. Transcranial magnetic stimulation as an investigative tool in the study of visual function. Optom. Vis. Sci. 80, 356–368.
Merabet, L.B., et al., 2007. 'Who is the ideal candidate?': decisions and issues relating to visual neuroprosthesis development, patient testing and neuroplasticity. J. Neural Eng. 4, S130–S135.
Merabet, L.B., et al., 2008. Rapid and reversible recruitment of early visual cortex for touch. PLoS One 3, e3046.
Merabet, L.B., 2011. Building the bionic eye: an emerging reality and opportunity. Prog. Brain Res. 192, 3–15.
Mohammadi, H.M., Ghafar-Zadeh, E., Sawan, M., 2012. An image processing approach for blind mobility facilitated through visual intracortical stimulation. Artif. Organs 36, 616–628.
Moneta, M.E., Singer, W., 1986. Critical period plasticity of kitten visual cortex is not associated with enhanced susceptibility to electrical kindling. Brain Res. 395, 104–109.
Monge, M., et al., 2013. A fully intraocular high-density self-calibrating epiretinal prosthesis. IEEE Trans. Biomed. Circuits Syst. 7, 747–760.
Morillas, C., et al., 2007. A neuroengineering suite of computational tools for visual prostheses. Neurocomputing 70, 2817–2827.
Mullen, K.T., Dumoulin, S.O., Hess, R.F., 2008. Color responses of the human lateral geniculate nucleus: selective amplification of S-cone signals between the lateral geniculate nucleno and primary visual cortex measured with high-field fMRI. Eur. J. Neurosci. 28, 1911–1923.
Musa, S., et al., 2012. Bottom-up SiO_2 embedded carbon nanotube electrodes with superior performance for integration in implantable neural microsystems. ACS Nano 6, 4615–4628.
National Institute on Deafness and Other Communication Disorders, 2013. Cochlear Implants (NIH Publication no. 11-4798). NIDCD Information Clearing House, Bethesda, MD.
Naumann, J., 2012. In: Search for Paradise: A Patient's Account of the Artificial Vision Experiment. XLIBRIS Corporation, Bloomington, IN, USA.
Negi, S., et al., 2010. Neural electrode degradation from continuous electrical stimulation: comparison of sputtered and activated iridium oxide. J. Neurosci. Methods 186, 8–17.
Negi, S., Bhandari, R., Solzbacher, F., 2012. A novel technique for increasing charge injection capacity of neural electrodes for efficacious and safe neural stimulation. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2012, 5142–5145.
Ng, D.C., et al., 2011. Wireless power delivery for retinal prostheses. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2011, 8356–8360.
Nicolelis, M.A., et al., 2003. Chronic, multisite, multielectrode recordings in macaque monkeys. Proc. Natl. Acad. Sci. USA 100, 11041–11046.
Normann, R.A., et al., 2009. Toward the development of a cortically based visual neuroprosthesis. J. Neural Eng. 6, 035001.
O'Brien Jr., W.D., et al., 2008. The risk of exposure to diagnostic ultrasound in postnatal subjects: thermal effects. J. Ultrasound Med. 27, 517–535 (quiz 537–540).
O'Doherty, J.E., et al., 2011. Active tactile exploration using a brain-machine–brain interface. Nature 479, 228–231.
Ong, J.M., da Cruz, L., 2012. The bionic eye: a review. Clin. Exp. Ophthalmol. 40, 6–17.
Ortmann, V., Baziyan, B., 2007. Intracortical neural interface for prosthetic applications. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2007, 6372–6375.
Panetsos, F., et al., 2011. Consistent phosphenes generated by electrical microstimulation of the visual thalamus. An experimental approach for thalamic visual neuroprostheses. Front. Neurosci. 5, 84.
Paralikar, K.J., Clement, R.S., 2008. Collagenase-aided intracortical microelectrode array insertion: effects on insertion force and recording performance. IEEE Trans. Biomed. Eng. 55, 2258–2267.

Parikh, N., et al., 2013. Performance of visually guided tasks using simulated prosthetic vision and saliency-based cues. J. Neural Eng. 10, 026017.
Parker, R.A., et al., 2011. The functional consequences of chronic, physiologically effective intracortical microstimulation. Prog. Brain Res. 194, 145–165.
Parker, S.L., et al., 2014. Cost savings associated with antibiotic-impregnated shunt catheters in the treatment of adult and pediatric hydrocephalus. World Neurosurg..
Pascolini, D., Mariotti, S.P., 2012. Global estimates of visual impairment: 2010. Br. J. Ophthalmol. 96, 614–618.
Pearson, R.A., 2014. Advances in repairing the degenerate retina by rod photoreceptor transplantation. Biotechnol. Adv. 32, 485–491.
Penfield, W., 1947. Some observations on the cerebral cortex of man. Proc. R. Soc. Lond. B Biol. Sci. 134, 329–347.
Peters, T., et al., 2013. Emotional wellbeing of blind patients in a pilot trial with subretinal implants. Graefes Arch. Clin. Exp. Ophthalmol. 251, 1489–1493.
Petrs-Silva, H., Linden, R., 2014. Advances in gene therapy technologies to treat retinitis pigmentosa. Clin. Ophthalmol. 8, 127–136.
Pezaris, J.S., Reid, R.C., 2007. Demonstration of artificial visual percepts generated through thalamic microstimulation. Proc. Natl. Acad. Sci. USA 104, 7670–7675.
Pezaris, J.S., Eskandar, E.N., 2009. Getting signals into the brain: visual prosthetics through thalamic microstimulation. Neurosurg. Focus. 27, E6.
Plow, E.B., Pascual-Leone, A., Machado, A., 2012. Brain stimulation in the treatment of chronic neuropathic and non-cancerous pain. J. Pain 13, 411–424.
Poggio, G.F., Walker, A.E., Andy, O.J., 1956. The propagation of cortical after-discharge through subcortical structures. AMA Arch. Neurol. Psychiatry 75, 350–361.
Polikov, V.S., Tresco, P.A., Reichert, W.M., 2005. Response of brain tissue to chronically implanted neural electrodes. J. Neurosci. Methods 148, 1–18.
Pollen, D.A., 1975. Some perceptual effects of electrical stimulation of the visual cortex in man. In: Tower, D.B. (Ed.), The Nervous System, Vol. 2: The Clinical Neurosciences, vol. 2. Raven Press, New York, pp. 519–528.
Pollen, D.A., 1977. Responses of single neurons to electrical stimulation of the surface of the visual cortex. Brain Behav. Evol. 14, 67–86.
Ptito, M., et al., 2008a. TMS of the occipital cortex induces tactile sensations in the fingers of blind Braille readers. Exp. Brain Res. 184, 193–200.
Ptito, M., et al., 2008b. Alterations of the visual pathways in congenital blindness. Exp. Brain Res. 187, 41–49.
Pudenz, R.H., 1993. Neural stimulation: clinical and laboratory experiences. Surg. Neurol. 39, 235–242.
Qin, W., et al., 2013. The development of visual areas depends differently on visual experience. PLoS One 8, e53784.
Rasouli, M., Phee, L.S., 2010. Energy sources and their development for application in medical devices. Expert Rev. Med. Dev. 7, 693–709.
Reich, L., Maidenbaum, S., Amedi, A., 2012. The brain as a flexible task machine: implications for visual rehabilitation using noninvasive vs. invasive approaches. Curr. Opin. Neurol. 25, 86–95.
Rennaker, R.L., et al., 2005. A comparison of chronic multi-channel cortical implantation techniques: manual versus mechanical insertion. J. Neurosci. Methods 142, 169–176.
Rieck, J., 2013. The pathogenesis of glaucoma in the interplay with the immune system. Invest. Ophthalmol. Vis. Sci. 54, 2393–2409.
Rizzo, J.F., Ayton, L.N., 2014. Psychophysical testing of visual prosthetic devices: a call to establish a multi-national joint task force. J. Neural Eng. 11, 020301.
Rousche, P.J., Normann, R.A., 1992. A method for pneumatically inserting an array of penetrating electrodes into cortical tissue. Ann. Biomed. Eng. 20, 413–422.
Rousche, P.J., Normann, R.A., 1998. Chronic recording capability of the Utah Intracortical Electrode Array in cat sensory cortex. J. Neurosci. Methods 82, 1–15.
Rush, A., Sungjae, S., Troyk, P.R., 2011. An inductive link for an intracortical visual prosthesis. In: 5th International IEEE/EMBS Conference on Neural Engineering (NER), 2011, pp. 503–506.
Rushton, D.N., Brindley, G.S., 1977. Short- and long-term stability of cortical electrical phosphenes. In: Rose, F.C. (Ed.), Physiological Aspects of Clinical Neurology. Blackwell Scientific Publications, Oxford, pp. 123–153.
Rushton, D.N., et al., 1989. Implant infections and antibiotic-impregnated silicone rubber coating. J. Neurol. Neurosurg. Psychiatry 52, 223–229.
Sakaguchi, H., et al., 2009. Artificial vision by direct optic nerve electrode (AV-DONE) implantation in a blind patient with retinitis pigmentosa. J. Artif. Organs 12, 206–209.
Salt, T.E., Tulloch, I.F., Walter, D.S., 1980. Anti-epileptic properties of sodium valproate in rat amygdaloid kindling [proceedings]. Br. J. Pharmacol. 68, 134P.
Sanni, A., Vilches, A., Toumazou, C., 2012. Inductive and ultrasonic multi-tier interface for low-power, deeply implantable medical devices. IEEE Trans. Biomed. Circuits Syst. 6, 297–308.
Schmidt, E.M., Bak, M.J., McIntosh, J.S., 1976. Long-term chronic recording from cortical neurons. Exp. Neurol. 52, 496–506.
Schmidt, E.M., et al., 1996. Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. Brain 119 (Pt 2), 507–522.
Schneider, R.M., et al., 2013. Neurological basis for eye movements of the blind. PLoS One 8, e56556.
Schoth, F., et al., 2006. Diffusion tensor imaging in acquired blind humans. Neurosci. Lett. 398, 178–182.
Seifman, M.A., et al., 2011. Postoperative intracranial haemorrhage: a review. Neurosurg. Rev. 34, 393–407.
Seymour, J.P., Kipke, D.R., 2007. Neural probe design for reduced tissue encapsulation in CNS. Biomaterials 28, 3594–3607.
Shain, W., et al., 2003. Controlling cellular reactive responses around neural prosthetic devices using peripheral and local intervention strategies. IEEE Trans. Neural Syst. Rehabil. Eng. 11, 186–188.
Sharma, A., et al., 2011. Long term in vitro functional stability and recording longevity of fully integrated wireless neural interfaces based on the Utah Slant Electrode Array. J. Neural Eng. 8, 045004.
Shaw, J.E., Sicree, R.A., Zimmet, P.Z., 2010. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabet. Res. Clin. Pract. 87, 4–14.
Shepherd, R.K., et al., 2013. Visual prostheses for the blind. Trends Biotechnol. 31, 562–571.
Simard, G., Sawan, M., Massicotte, D., 2010. High-speed OQPSK and efficient power transfer through inductive link for biomedical implants. IEEE Trans. Biomed. Circuits Syst. 4, 192–200.
Skousen, J.L., et al., 2011. Reducing surface area while maintaining implant penetrating profile lowers the brain foreign body response to chronically implanted planar silicon microelectrode arrays. Prog. Brain Res. 194, 167–180.
Srivastava, N.R., et al., 2007. Estimating Phosphene Maps for Psychophysical Experiments used in Testing a Cortical Visual Prosthesis Device. In: 3rd International IEEE/EMBS Conference on Neural Engineering, 2007. CNE'07, pp. 130–133.
Srivastava, N.R., Troyk, P.R., Dagnelie, G., 2009. Detection, eye-hand coordination and virtual mobility performance in simulated vision for a cortical visual prosthesis device. J. Neural Eng. 6, 035008.

Stensaas, S.S., Eddington, D.K., Dobelle, W.H., 1974. The topography and variability of the primary visual cortex in man. J. Neurosurg. 40, 747–755.
Stevens, G.A., et al., 2013. Global prevalence of vision impairment and blindness: magnitude and temporal trends, 1990–2010. Ophthalmology 120, 2377–2384.
Stingl, K., et al., 2013. Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS. Proc. Biol. Sci. 280, 20130077.
Stronks, H.C., Dagnelie, G., 2011. Phosphene mapping techniques for visual prostheses. In: Dagnelie, G. (Ed.), Visual Prosthetics: Physiology, Bioengineering, Rehabilitation. Springer, New York, pp. 367–383.
Szarowski, D.H., et al., 2003. Brain responses to micro-machined silicon devices. Brain Res. 983, 23–35.
Tabot, G.A., et al., 2013. Restoring the sense of touch with a prosthetic hand through a brain interface. Proc. Natl. Acad. Sci. USA 110, 18279–18284.
Talalla, A., Bullara, L., Pudenz, R., 1974. Electrical stimulation of the human visual cortex; preliminary report. Can. J. Neurol. Sci. 1, 236–238.
Taylor, H.R., et al., 2005. Vision loss in Australia. Med. J. Aust. 182, 565–568.
Taylor, H.R., Pezzullo, M.L., Keeffe, J.E., 2006. The economic impact and cost of visual impairment in Australia. Br. J. Ophthalmol. 90, 272–275.
Taylor, I., Scheffer, I.E., Berkovic, S.F., 2003. Occipital epilepsies: identification of specific and newly recognized syndromes. Brain 126, 753–769.
Tehovnik, E.J., Slocum, W.M., Schiller, P.H., 2003. Saccadic eye movements evoked by microstimulation of striate cortex. Eur. J. Neurosci. 17, 870–878.
Tehovnik, E.J., Slocum, W.M., 2013. Electrical induction of vision. Neurosci. Biobehav. Rev. 37, 803–818.
Theogarajan, L., 2012. Strategies for restoring vision to the blind: current and emerging technologies. Neurosci. Lett. 519, 129–133.
Torab, K., et al., 2011. Multiple factors may influence the performance of a visual prosthesis based on intracortical microstimulation: nonhuman primate behavioural experimentation. J. Neural Eng. 8, 035001.
Troncoso, X.G., Macknik, S.L., Martinez-Conde, S., 2011. Vision's first steps: anatomy, physiology, and perception in the retina, lateral geniculate nucleus, and early visual cortical areas. In: Dagnelie, G. (Ed.), Visual Prosthetics. Springer, US, pp. 23–57.
Troyk, P.R., et al., 2005. Intracortical visual prosthesis research – approach and progress. In: Proceedings of 27th Annual International Conference of the IEEE EMBS. Shanghai, China, September 1–4, 2005, pp. 7376–7379.
Veraart, C., et al., 1998. Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. Brain Res. 813, 181–186.
Veraart, C., et al., 2003. Pattern recognition with the optic nerve visual prosthesis. Artif. Organs 27, 996–1004.
Volta, A., 1800. On the electricity excited by the mere contact of conducting substances of different kinds. Philos. Trans. R. Soc. Lond. 90, 403–431.
Wada, Y., et al., 1989. Kindling of the visual cortex in cats: comparison with amygdaloid kindling. Jpn. J. Psychiatry Neurol. 43, 245–253.
Wada, Y., et al., 1990. Anticonvulsant effects of zonisamide and phenytoin on seizure activity of the feline visual cortex. Brain Dev. 12, 206–210.
Walcott, B.P., Redjal, N., Coumans, J.V., 2012. Infection following operations on the central nervous system: deconstructing the myth of the sterile field. Neurosurg. Focus. 33, E8.
Wang, C., et al., 2013. Characteristics of electrode impedance and stimulation efficacy of a chronic cortical implant using novel annulus electrodes in rat motor cortex. J. Neural Eng. 10, 046010.
Wark, H.A., et al., 2013. A new high-density (25 electrodes/mm(2)) penetrating microelectrode array for recording and stimulating sub-millimeter neuroanatomical structures. J. Neural Eng. 10, 045003.
Waziri, A., et al., 2009. Initial surgical experience with a dense cortical microarray in epileptic patients undergoing craniotomy for subdural electrode implantation. Neurosurgery 64, 540–545 (discussion 545).
Weiland, J.D., Humayun, M.S., 2014. Retinal prosthesis. IEEE Trans. Biomed. Eng. 61, 1412–1424.
Weiss, N., Post, K.D., 2011. Avoidance of complications in neurosurgery. In: 6th edition In: Winn, H.R. (Ed.), Youmans Neurological Surgery, vol. 1. Saunders, St. Louis, MO, USA, pp. 408–423.
Wiesel, T.N., Hubel, D.H., 1966. Spatial and chromatic interactions in the lateral geniculate body of the rhesus monkey. J. Neurophysiol. 29, 1115–1156.
Wilke, R., et al., 2007. Testing visual functions in patients with visual prostheses. In: Humayun, M.S., Weiland, J.D., Chader, G., Greenbaum, E. (Eds.), Artificial Sight. Biological and Medical Physics, Biomedical Engineering. Springer, New York, pp. 91–110.
Wilks, S.J., et al., 2009. Poly(3,4-ethylenedioxythiophene) as a micro-neural interface material for electrostimulation. Front. Neuroeng. 2, 7.
Williams, N.R., Okun, M.S., 2013. Deep brain stimulation (DBS) at the interface of neurology and psychiatry. J. Clin. Invest. 123, 4546–4556.
Wong, C.H., et al., 2009. Risk factors for complications during intracranial electrode recording in presurgical evaluation of drug resistant partial epilepsy. Acta Neurochir. (Wien) 151, 37–50.
Wu, K.J., et al., 2010. Current research of C-Sight visual prosthesis for the blind. In: Proceedings of 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 5875–5878.
Yablonskiy, D.A., Ackerman, J.J., Raichle, M.E., 2000. Coupling between changes in human brain temperature and oxidative metabolism during prolonged visual stimulation. Proc. Natl. Acad. Sci. USA 97, 7603–7608.
Yamamoto, J., Wilson, M.A., 2008. Large-scale chronically implantable precision motorized microdrive array for freely behaving animals. J. Neurophysiol. 100, 2430–2440.
Yanai, D., et al., 2003. The value of preoperative tests in the selection of blind patients for a permanent microelectronic implant. Trans. Am. Ophthalmol. Soc. 101, 223–228 (discussion 228–230).
Yang, S., et al., 2010. Highly-accurate, implantable micromanipulator for single neuron recordings. In: Proceedings of 2010 IEEE International Conference on Robotics and Automation (ICRA), pp. 5070–5075.
Zarbin, M.A., et al., 2013. Nanomedicine for the treatment of retinal and optic nerve diseases. Curr. Opin. Pharmacol. 13, 134–148.
Zhang, Y., et al., 2012. Diffusion tensor imaging reveals normal geniculocalcarine-tract integrity in acquired blindness. Brain Res. 1458, 34–39.
Zhong, Y., Bellamkonda, R.V., 2007. Dexamethasone-coated neural probes elicit attenuated inflammatory response and neuronal loss compared to uncoated neural probes. Brain Res. 1148, 15–27.