

OPINION

What blindness can tell us about seeing again: merging neuroplasticity and neuroprostheses

Lotfi B. Merabet, Joseph F. Rizzo, Amir Amedi, David C. Somers and Alvaro Pascual-Leone

Abstract | Significant progress has been made in the development of visual neuroprostheses to restore vision in blind individuals. Appropriate delivery of electrical stimulation to intact visual structures can evoke patterned sensations of light in those who have been blind for many years. However, success in developing functional visual prostheses requires an understanding of how to communicate effectively with the visually deprived brain in order to merge what is perceived visually with what is generated electrically.

Blindness affects millions of people worldwide, and many prevalent and potentially devastating causes of vision loss cannot be effectively treated. For decades, the possibility of restoring sight to blind individuals has been a subject of intense scientific research as well as of science fiction. Recent advances in bioengineering and microtechnology have led to the development of highly sophisticated micro-electronic devices that are designed to stimulate viable neuronal tissue in the hope of regaining some level of functionality. Human clinical trials with visual prosthetic devices are underway and it seems that this popular subject of science fiction is now becoming a tangible scientific reality. Other new therapeutic interventions are also being pursued. Gene and cell transplantation¹ perhaps represent the best long-term strategy in halting the progression of various eye diseases.

However, research in this area is still in its infancy and many technical challenges remain unsolved. Furthermore, the pervasive question remains as to how these approaches will restore vision after it has been completely lost. Therefore, there is a compelling reason to pursue the development of a micro-electronic prosthesis as a viable therapeutic option to restore sight. In this review, we discuss the current status of visual prosthetic implants and the implications of cross-modal plasticity on future prosthesis development.

Current strategies for restoring vision. All visual neuroprostheses are designed on the basis that focal electrical stimulation of intact visual structures evokes the sensation of discrete points of light (referred to as 'phosphenes' (REFS 2,3)). It has been presumed that geometrical visual percepts can be generated by delivering appropriate multi-site patterns of electrical stimulation. The perception of shapes and images would be perceived in a manner similar to viewing an electronic scoreboard in a stadium (this has been called the 'scoreboard approach').

It is generally acknowledged that complete development of the visual system and prior visual experience are necessary for a patient to be able to correctly and meaningfully interpret these visual patterns. Therefore, it remains unclear whether this approach would be appropriate for a patient who was blind from birth or early infancy (BOX 1).

Many attributes characterize a visual scene, including colour, motion, depth and form. However, current visual prostheses are designed to address only the most basic of these components: spatial detail. To accomplish this goal, several designs are being pursued (FIG. 1) but to provide a comparative and exhaustive inventory of each approach would be beyond the scope of this article. It is nonetheless worthwhile to give the reader an overview of the 'state of the art' in this field. Further technical details can be obtained from several excellent reviews published on this topic⁴⁻⁸.

The cortical approach. Initial interest in visual prosthesis development was aimed at stimulating the visual cortex directly. In the late 60's, Brindley and Lewin conducted seminal work by chronically implanting 80 surface electrodes to overlie the visual cortex of a profoundly blind volunteer⁹. The delivery of electrical current to the visual cortex evoked the sensation of discrete, albeit crude, patterns of bright light (phosphenes). More importantly, it was observed that the location of these phosphenes corresponded roughly to the known cortical topographic representation of visual space. The latter finding was of considerable importance and indicated that predictable patterns of light could potentially be generated using focal electrical stimulation. A more recent effort has managed to incorporate a digital video camera system that captures and transmits encoded visual images to the cortical stimulating array¹⁰. The camera, mounted onto a pair of glasses, sends an image to a portable computer, which, in turn, decodes the signal into appropriate patterns of electrical stimulation. Several blind volunteers have been implanted with this device and one patient (who had been completely blind for over twenty years) could reportedly distinguish the outline of a person and identify the orientation of certain letters¹⁰.

This work has laid down an important foundation for developing a viable visual prosthesis, although the cortical approach

Box 1 | Sight unseen

The restoration of vision following long-term visual deprivation can provide insights into the normal development of visual pathways. Following surgery (for example, removal of congenital cataracts), patients show marked visual deficiencies in recognizing complex objects, depth perception and the detection of illusory contours and figures^{65,66}. These accounts show that even when vision reaches the brain through clear optics, visual perception remains greatly impaired. One of von Senden's patients⁶⁵, having recovered his sight, was unable to distinguish between his cat and dog through vision alone. However, one day he accomplished this feat by touching the cat and matching the new visual percept with his prior tactile experience. Only by touching the animal was he able to learn how to visually identify it. It is unfortunate that many patients have found their new-found sight upsetting and, in some cases, actually preferred their lives as blind individuals⁶⁶.

A recent study used advanced psychophysical testing and functional neuroimaging to reinvestigate restored sight following long-term visual deprivation⁶⁷. In one patient (M.M.), who had been blind since the age of three, a corneal stem-cell transplant was carried out in an attempt to restore his vision. Following the surgery, M.M. was able to instantly identify simple visual shapes (such as a circle) and colours but, as previously reported, showed deficits in identifying more complex objects such as faces and three dimensional forms. Furthermore, he had difficulty in correctly interpreting visual illusions and subjective contours. Interestingly, when many of these same objects were moving, M.M. was able to identify them. Corroborative functional MRI evidence showed decreased levels of activity (measured as the blood oxygen level dependent signal) in areas of the ventral visual pathway compared to normal sighted controls when he viewed complex objects such as faces. Conversely, when viewing moving objects he showed strong levels of activity in areas of the dorsal visual pathway and areas responsible for analysing motion (for example, the middle temporal area). These differences in activity indicate that visual pathways might have different sensitivities to visual deprivation and, specifically, pathways involved in motion processing might be more robust in recovering function⁶⁷.

faces several technical challenges. For example, the invasiveness of surgical implantation and the risk of focal seizures induced by direct cortical stimulation pose serious concerns for a patient's safety. However, despite these limitations, several groups are pursuing this approach and solutions are being developed to address these issues^{11–14}.

Among the greatest challenges in developing prosthetic vision is the puzzle of the neural code. Despite decades of research, a fundamental question remains as to how patterns of neuronal activity give rise to visual percepts and mental events. This is in contrast to micro-electronic devices (for example, digital cameras), which can easily capture patterns of light and recreate an accurate representation of an image. At the level of the visual cortex, neural processing is highly complex, so determining appropriate encoding strategies for electrical stimulation remains daunting, if not elusive. Although blindness can result from a variety of causes, the complexity of the neural code indicates that this problem could be simplified by implanting the prosthetic device at the earliest point along the visual pathway that retains functional integrity. The circuitry of the retina and the optic nerve are by no means simple, but they are less complex than that of the cortex or thalamus. With this in mind, several investigators have recently pursued alternative approaches to stimulate intact visual pathways.

The optic nerve approach. A Belgian group has recently developed a four-contact spiral cuff electrode designed to stimulate the optic nerve rather than the visual cortex. The intracranial electrode is connected to a neurostimulating circuit that is anchored to the cranium below the skin and communicates through wireless transmission with an external processor and camera. This device was chronically implanted in a 59-year-old blind volunteer. In this patient, electrical stimulation evoked the perception of localized, and often coloured, phosphenes throughout the visual field¹⁵. After four months of training and psychophysical testing, it was reported that the patient could recognize and distinguish orientations of lines as well as some shapes and letters¹⁵ despite only a limited number of stimulating electrodes being used.

The retinal approach. Another strategy that is being pursued is to implant a stimulating device at the level of the retina. In two common causes of blindness, retinitis pigmentosa¹⁶ and age-related macular degeneration (ARMD)¹⁷, there is a relatively selective degeneration of the photoreceptor layer of the outer retina. On the other hand, ganglion cells within the inner retinal layers survive in large numbers and respond to electrical stimulation even in advanced stages of the diseases^{8,18}. The premise of the retinal approach is to stimulate these cells and, in essence, to replace lost

photoreceptor function. This strategy has the advantage of delivering input more proximally along the afferent visual pathway, thereby benefiting from early physiological pre-processing and encoding. Furthermore, ganglion cells are tightly packed and arranged in a topographical fashion throughout the retina. In theory, a visual image could be generated in a manner similar to the cortical approach by delivering multi-site patterns of electrical stimulation to the ganglion cells. Two types of retinal prostheses are currently under development, and differ primarily in their location in the retina. One, the subretinal implant, is placed in the region of degenerated photoreceptors by creating a pocket between the sensory retina and retinal pigment epithelial layer. The other, the epiretinal implant, is attached to the inner surface of the retina, close to the ganglion cell side. In order for either design to work, the inner retina and optic nerve must remain functional. So, patients who are blind as a result of conditions such as diabetic retinopathy, retinal detachment or glaucoma would not benefit from a retinal implant.

Subretinal implants. The subretinal design is currently being pursued by several investigators (artificial silicone array¹⁹ and microphotodiode array²⁰). Chow and colleagues have devised an array with approximately 5,000 microphotodiodes, each of which contains its own stimulating electrode¹⁹. When the device is implanted under the retina, photocurrents generated by locally absorbed light stimulate adjacent retinal neurons in a multi-site fashion. There is no camera involved in capturing an image and the array is powered solely by incident light. A phase I feasibility trial has been carried out with six patients with profound vision loss from retinitis pigmentosa. Patients were followed from 6 to 18 months after implantation, and reported an improvement in visual function that was evidenced by an increase in visual field size and the ability to name more letters using a standardized visual acuity chart¹⁹. However, these results have been met with controversy. It seems that the purported beneficial outcome might not be the result of direct and patterned electrical stimulation as initially anticipated, but, instead, an indirect 'cell rescue' effect from low-level current generated by the device.

Epiretinal implants. Large consortium efforts are developing the epiretinal implant design^{21–23}. These groups have concentrated on producing an ultra-thin electrode array that can be safely attached to the delicate retinal surface for long periods of time. Like

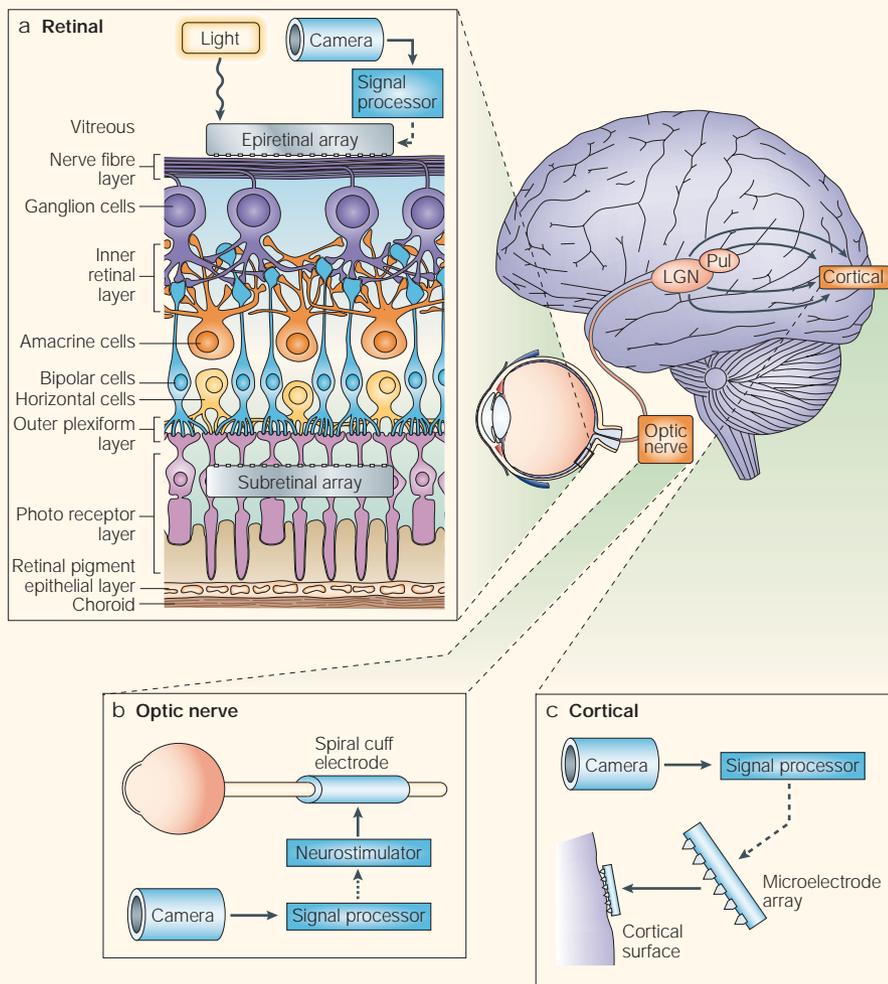


Figure 1 | Summary diagram of the visual system and approaches to restore vision.

Theoretically, any point along the visual pathway can be electrically stimulated and so represents a potential site at which a visual prosthesis could be implanted. The inset figures illustrate several approaches in detail. **a** | Schematic diagram of a retinal cross-section showing two methods of stimulating ganglion cells. The epiretinal device is attached to the inner surface of the retina and stimulates the inner retinal layer based on signals received from a camera and signal processor (mounted externally on a pair of glasses). The subretinal device is powered solely by incident light and is implanted within an area of degenerated photoreceptors. **b** | The optic nerve can be stimulated by implanting a cuff electrode around the nerve. The cuff electrode (located intracranially) and neurostimulator (placed beneath the skin) communicate with an external processor and camera through telemetry. **c** | The cortical approach incorporates a microelectrode array, which is placed either intracortically or on the cortical surface. By stimulating the visual cortex directly, this approach bypasses afferent visual structures. LGN, lateral geniculate nucleus; Pul, pulvinar.

truly functional vision, such as the recognition of objects or skillful navigation in an unfamiliar environment. This issue is complicated by the fact that, often, the geometrical visual percepts reported by study volunteers do not correspond to that predicted based on the delivered patterns of electrical stimulation^{21,22}. Therefore, it seems that our intuitive sense of how to generate patterned visual percepts is not an adequate strategy. This non-conformal relationship might be related to stimulating severely degenerated and, therefore, physiologically compromised retinal tissue or, as in the case of optic nerve and visual cortex stimulation, the topographic complexity between the location of a visual stimulus and the site of the delivered current. The quality of visual percepts is likely to improve as many of the remaining technical challenges are resolved. However, these engineering and surgical issues no longer represent the greatest impediment to future progress. Rather, the greatest barrier lies in our ignorance of how best to introduce meaningful information to the visually deprived brain. It is a misconception that simple percepts generated from light patterns are sufficient to generate meaningful vision. Furthermore, producing more complex patterns by augmenting the resolution of images (for example, by increasing the number of stimulating electrodes), would initially be perceived as visually meaningless rather than perceptually meaningful. A better understanding of how the brain adapts to the loss of sight and how the remaining senses process information in the visually deprived brain are likely to shed light on this issue.

Neuroplasticity in blind individuals

A substantial body of literature has been devoted to understanding the mechanisms of sensory integration and the interplay that underlies neuroplasticity after sensory deprivation²⁴. Clinical evidence and studies using animal models have shown that visual deprivation is associated with superior non-visual skills, such as auditory and tactile abilities^{25–31}. These functionally adaptive changes seem to depend not only on the nature and timing of the visual loss, but also on the complexity of the task being evaluated²⁴. It is also becoming increasingly clear that these neuroplastic changes implicate regions of the brain once dedicated to the task of vision itself³². Specifically, persuasive evidence indicates that, in blind individuals, the visual occipital cortex is engaged in processing tactile and auditory information as well as higher cognitive functions such as grammatical and linguistic processing.

the cortical approach, the design incorporates a digital camera and signal processor mounted on a pair of eyeglasses to capture an image and convert patterns of light into electrical signals. Initial tests have been carried out in volunteers with advanced retinitis pigmentosa^{21,22}. These experiments lasted from minutes to hours while patients remained awake to describe their visual experiences. As electrical currents were delivered to the array, patients reported crude patterned perceptions. In some cases, the gross geometric structure of the phosphene

patterns could be altered by changing the position and number of stimulating electrodes and the strength or duration of the current^{21,22}.

A key milestone. These results are encouraging and show, at least in principle, that patterned electrical stimulation can evoke patterned light perceptions. However, an important milestone has yet to be achieved by all the aforementioned efforts, which is to show that a visual neuroprosthesis can improve the quality of life of a blind patient by restoring

Tactile processing in occipital cortex. An example of this compensatory adaptation was revealed using functional neuroimaging. In both congenital and late-blind individuals, it has been shown that regions of the occipital cortex are activated during tactile Braille reading^{32–38}. The functional relevance of this activation is supported by the fact that reversible disruption of the occipital cortex using transcranial magnetic stimulation (TMS) impairs Braille reading ability^{39,40}. This idea is also supported by clinical evidence. In one report, a patient who was congenitally blind was rendered alexic for Braille following a bilateral occipital stroke⁴¹. She also showed striking deficits in tactile tasks requiring fine spatial judgements, but could easily identify everyday objects through touch⁴².

Auditory processing in the occipital cortex. A similar account also appears to emerge regarding the recruitment of occipital visual areas in the processing of auditory information. Using event-related potentials (ERPs)⁴³ and positron emission tomography (PET)⁴⁴, occipital cortex activation has been shown in congenitally blind individuals while they were carrying out auditory localization tasks. Furthermore, by mapping language-related activity implicated in speech processing²⁸ and auditory verb-generation^{36,38}, it has been shown that in blind adults speech comprehension activates not only classical perisylvian language areas in the left hemisphere (as in sighted adult controls), but also striate and extra-striate regions of the visual cortex. As with Braille reading, the functional relevance of the occipital cortex was tested using TMS. In one study, reversible disruption of occipital cortical areas hindered verb-generating ability in blind individuals but not in sighted controls⁴⁵. This latter study indicates that in blind people, the occipital cortex is implicated in high-level cognitive processing, such as language.

The recruitment of the occipital cortex for tactile and auditory processing in blind

individuals might represent the exploitation of intrinsic spatial and temporal processing strategies necessary to carry out Braille reading or other language related tasks⁴⁶. These neuroplastic changes seem to be functional and compensatory in nature, and further indicate that the potential of the adult brain to 'reprogram' itself might be much greater than has previously been assumed. By studying the cross-modal neuroplasticity that follows visual deprivation, we can begin to elucidate the conditions and constraints that underlie these functional adaptations²⁴. With this in mind, it would not be surprising to learn that these same neuroplastic changes could greatly influence the clinical outcome and success of visual neuroprosthetic devices.

Lesson learned

In addition to developing neuroprostheses to restore vision, progress has been made in other areas. For example, work on artificial limbs and brain-machine interfaces is being pursued with the hope that such tools could assist amputees and paralyzed patients^{47,48}. The development of cochlear implants has been highly successful and has, in many respects, served as an impetus to develop visual prostheses. By combining a strong commitment to clinical and basic science research, cochlear implants have become a viable therapeutic option, allowing many deaf patients to regain functional hearing and even comprehend speech (BOX 2; for a review, see REFS 49,50).

Deaf people learn to use cochlear implants by establishing new associations between sounds generated by the device and objects in the auditory world. However, the ability of individuals to adapt to cochlear implants varies greatly, depending on the age of onset and duration of hearing loss⁵⁰. Not surprisingly, ranges in speech recognition performance vary from very poor to near perfect. In many cases, rehabilitation strategies need to be tailored to the candidate's profile to maximize the likelihood of success.

Visual processing in auditory cortex. In early-deaf subjects, visually presented stimuli activate cortical areas normally associated with hearing (measured with functional MRI)⁵¹. Brodmann's areas 22, 41 and 42, within the auditory cortex, are activated in response to visual stimuli in these individuals, analogous to the occipital cortex activation that is seen in blind individuals in response to auditory stimuli. Studies have also shown that areas of the temporal lobe that are associated with hearing and language comprehension are activated in congenitally deaf individuals when viewing sign-language^{52,53,54}. As with studies of visual deprivation, these results have been attributed to cross-modal plasticity and further expand on the idea that removal of a sensory modality leads to dramatic changes at the level of the cortex. Investigations using animal models have also supported this view. In one study, 're-wiring' of visual inputs to the auditory cortex produced a functional reorganization in this area resembling visual cortex⁵⁵.

Visual-auditory cross-modal plasticity in deaf individuals has also been studied in patients with cochlear implants. In a PET imaging study, the primary auditory cortex was activated by the sound of spoken words in pre-lingual deaf patients (that is, in patients who lost their hearing prior to the development of language) who had received a cochlear implant device⁵⁶. Furthermore, it was noted that the levels of 'resting' hypo-metabolism before implantation were positively correlated with the extent of language improvement following the operation. It was suggested that if metabolism in the auditory cortex was restored by cross-modal plasticity before implantation, the auditory cortex would no longer respond to signals from a cochlear implant and patients would not show improvement, despite concentrated rehabilitation⁵⁶.

These results have important implications. First, they indicate that functional neuroimaging might have a prognostic value. It is conceivable that there is a similar scenario regarding cross-modal sensory interactions in the visual cortex of blind individuals. We propose that a parallel approach might help to identify candidates who are more likely to succeed with a visual prosthesis implant. Second, it is important to note that not all neuroplastic changes that follow sensory loss can be viewed as beneficial or result in functional recovery²⁴. In a sense, plasticity might be viewed as a 'double-edged sword'. On one hand, it can contribute to changes that are functionally adaptive when a sensory modality is lost. On the other, neuroplasticity can also

Box 2 | Cochlear implants

Functional hearing can be restored in individuals with profound deafness by inserting a micro-electrode array into the inner ear. A cochlear implant is an electronic replacement for damaged hair cells of the inner ear, which processes sound waves and creates the sensation of hearing. The device comprises one implanted and several external components. The implanted component includes an electronic circuit that is surgically inserted under the skull behind the ear, and a wire electrode bundle that is inserted into the cochlea. The external components include a microphone that is located next to the outer ear and a portable speech processor that filters, analyses and decodes sounds picked up from the environment. Coded signals are sent by wireless transmission to the internal components which, in turn, drive the electrodes that stimulate the nerve fibres of the cochlea.

limit the degree of adaptation. In either case, these neuroplastic changes need to be considered. Put another way, simple re-introduction of a sensory input by itself is not likely to suffice in restoring that sense. Specific strategies are needed to modulate information processing by the brain and to extract relevant and functionally meaningful information from neuroprosthetic inputs.

Specialization or generalization? The visual cortex encodes specific attributes and localized features within a visual scene⁵⁷. In addition, our sensory world is richly multi-modal and we use other senses to identify objects. It is clear that there is coherence between how an object looks, how it sounds and how it feels when it is explored through touch. Are the neural networks

implicated in visual perception the same as those used by blind individuals to identify objects through touch and hearing? Indeed, functional neuroimaging studies^{58,59,60} have shown that there is notable overlap between cortical areas implicated in object recognition through sight and touch, particularly in a region of the lateral occipital complex (LOC) known as the LOtv (for tactile-visual^{37,61}). It has recently been reported that in sighted individuals, visual and tactile recognition of objects evolves category-related responses in the ventral extrastriate visual pathway⁶². Interestingly, the same category-related responses in extrastriate areas were also reported for two congenitally blind subjects⁶². These results indicate that certain cortical areas might not simply create representations of visual images but also identify more abstract features of object form. In another study, occipitotemporal and visual association areas were also robustly activated when blind individuals were asked to carry out mental imagery tasks triggered by the sound of familiar objects (for example, a ringing bell)⁶³. Although this latter study could not disentangle auditory from tactile components of mental imagery, it is possible that in blind individuals areas such as the LOC are implicated in object identification based on auditory information.

These results force us to re-think how objects might be represented in the brain. It seems that the visual system, considered a highly-specialized sensory processing stream, is also implicated in the processing of other sensory modalities. Furthermore, visual cortical areas seem to be part of a widely distributed and overlapping sensory processing scheme. Such an organization might allow for redundancy of certain cues that are necessary to fully characterize objects, and avoid duplication of similar operations in other modalities⁶⁴. This implies that a crucial aspect of information processing might not depend primarily on the type of sensory input *per se*, but rather on the computational contribution that a given region makes to a task⁴⁶.

Touching and hearing — the new sight
We propose that tactile and auditory inputs (processed in the cross-modally altered brain) can be used to 'remap' restored visual sensations. Given that sensory representations are shared by different pathways and modalities, a blind individual using a visual neuroprosthesis can manipulate concordant tactile and auditory inputs in order to translate visual sensations into functionally meaningful visual percepts (FIG. 2).

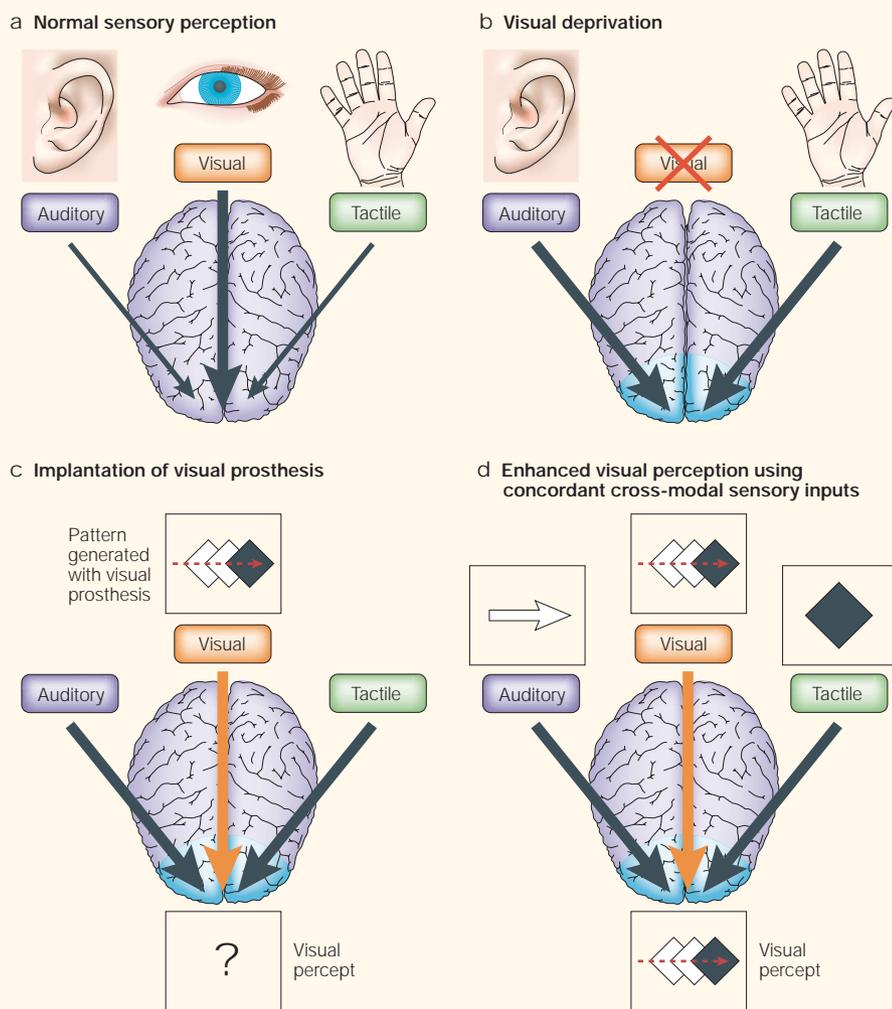


Figure 2 | The multi-modal nature of our sensory world and its implications for implementing a visual prosthesis to restore vision. **a** | Under normal conditions, the occipital cortex receives predominantly visual inputs but perception is also highly influenced by cross-modal sensory information obtained from other sources (for example, touch and hearing). **b** | Following visual deprivation, neuroplastic changes occur such that the visual cortex is recruited to process sensory information from other senses (illustrated by larger arrows for touch and hearing). This might be through the potential 'unmasking' or enhancement of connections that are already present. **c** | After neuroplastic changes associated with vision loss have occurred, the visual cortex is fundamentally altered in terms of its sensory processing, so that simple re-introduction of visual input (by a visual prosthesis; orange arrow) is not sufficient to create meaningful vision (in this example, a pattern encoding a moving diamond figure is generated with the prosthesis). **d** | To create meaningful visual percepts, a patient who has received an implanted visual prosthesis can incorporate concordant information from remaining sensory sources. In this case, the directionality of a moving visual stimulus can be presented with an appropriately timed directional auditory input and the shape of the object can be determined by simultaneous haptic exploration. In summary, modification of visual input by a visual neuroprosthesis in conjunction with appropriate auditory and tactile stimulation could potentially maximize the functional significance of restored light perceptions and allow blind individuals to regain behaviorally-relevant vision.

Furthermore, it could be possible to incorporate patient-directed feedback that would alter the stimulation parameters of the prosthesis based on the user's prior and ongoing sensory experiences. Therefore, rehabilitation with a visual neuroprosthesis could be coupled with sensory-guided plasticity to maximize the 're-learning' process that is necessary to regain sight. If cortical 're-mapping' is possible in the mature brain, there is no *a priori* reason to believe that the reprogramming of 'novel' visual inputs in blind individuals would not be possible.

Future perspectives

Success in restoring functional vision depends on our understanding of how blindness affects the brain. In essence, this represents bridging the gap between how the brain adapts to the loss of sight and what it means for a blind individual to 'see' again. Any successful attempt to restore functional vision will require an understanding of these mechanisms in order to predict the feasibility and to evaluate the success of a proposed implant strategy²⁴. For example, it has been shown that in blind individuals who are proficient in reading Braille, occipital cortical stimulation (using TMS) can result in erroneous and even phantom tactile sensations³⁹. Fitting these subjects with a cortical prosthesis might generate tactile, or synaesthetically joined tactile-visual percepts rather than meaningful and interpretable vision. Furthermore, insight into these neuroplastic mechanisms can be used to devise new and optimal rehabilitative strategies and to guide the implementation of these prosthetic devices and future implant designs.

In conclusion, there remains a considerable gap between a clinically viable visual prosthesis and the technical challenges that need to be overcome. However, the modest success of human experimentation to date is not solely limited to these technical issues, but is more likely to be related to our ignorance of how to communicate with the visually deprived brain. Ultimately, success will necessitate an understanding of the potential and constraints associated with visual neuroplasticity and the subsequent changes that occur in response to new stimuli. These ideas are also likely to extend to the development of non-visual neuroprosthetic devices and bring hope to the people who need them.

Lotfi B. Merabet is at the departments of Ophthalmology and Neurology, the Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

Joseph F. Rizzo is at the Boston Retinal Implant Project, Center for Innovative Visual Rehabilitation, Boston VA Health Care System and Massachusetts Eye and Ear Infirmary, Harvard Medical School, Massachusetts, USA.

Amir Amedi and Alvaro Pascual-Leone are at the Department of Neurology, the Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, Massachusetts 02215, USA.

Alvaro Pascual-Leone is also at the Hospital de Neurorehabilitació Institut Guttmann, Universitat Autònoma, Barcelona

David C. Somers is at the Department of Psychology and Program in Neuroscience, Boston University, 64 Cummington Street, Boston 02215, Massachusetts USA. He is also at the MGH-Martinos Neuroimaging Center.

**Correspondence to L.B.M.
e-mail: lmerabet@bidmc.harvard.edu
doi:10.1038/nrn1586**

- Sharma, R. K. & Ehinger, B. Management of hereditary retinal degenerations: present status and future directions. *Surv. Ophthalmol.* **43**, 427–444 (1999).
- Marg, E. & Rudiak, D. Phosphenes induced by magnetic stimulation over the occipital brain: description and probable site of stimulation. *Optom. Vis. Sci.* **71**, 301–311 (1994).
- Gothe, J. *et al.* Changes in visual cortex excitability in blind subjects as demonstrated by transcranial magnetic stimulation. *Brain* **125**, 479–490 (2002).
- Rizzo, J. F. *et al.* Retinal prosthesis: an encouraging first decade with major challenges ahead. *Ophthalmology* **108**, 13–14 (2001).
- Maynard, E. M. Visual prostheses. *Annu. Rev. Biomed. Eng.* **3**, 145–168 (2001).
- Margalit, E. *et al.* Retinal prosthesis for the blind. *Surv. Ophthalmol.* **47**, 335–356 (2002).
- Zrenner, E. Will retinal implants restore vision? *Science* **295**, 1022–1025 (2002).
- Loewenstein, J. I., Montezuma, S. R. & Rizzo, J. F. Outer retinal degeneration: an electronic retinal prosthesis as a treatment strategy. *Arch. Ophthalmol.* **122**, 587–596 (2004).
- Brindley, G. S. & Lewin, W. S. The sensations produced by electrical stimulation of the visual cortex. *J. Physiol. (Lond.)* **196**, 479–493 (1968).
- Dobelle, W. H. Artificial vision for the blind by connecting a television camera to the visual cortex. *ASAIO J.* **46**, 3–9 (2000).
- Schmidt, E. M. *et al.* Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. *Brain* **119**, 507–522 (1996).
- Normann, R. A., Warren, D. J., Ammermuller, J., Fernandez, E. & Guillory, S. High-resolution spatio-temporal mapping of visual pathways using multi-electrode arrays. *Vision Res.* **41**, 1261–1275 (2001).
- Fernandez, E. *et al.* Towards a cortical visual neuroprosthesis for the blind. *IFMBE Proc.* **3**, 1690–1691 (2002).
- Troyk, P. *et al.* A model for intracortical visual prosthesis research. *Artif. Organs* **27**, 1005–1015 (2003).
- Veraart, C., Wanet-Defalque, M. C., Gerard, B., Vanlierde, A. & Delbeke, J. Pattern recognition with the optic nerve visual prosthesis. *Artif. Organs* **27(11)**, 996–1004 (2003).
- Klein, R., Klein, B. E., Jensen, S. C. & Meuer, S. M. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* **104**, 7–21 (1997).
- Hims, M. M., Diager, S. P. & Inglehearn, C. F. Retinitis pigmentosa: genes, proteins and prospects. *Dev. Ophthalmol.* **37**, 109–125 (2003).
- Humayun, M. S. *et al.* Visual perception elicited by electrical stimulation of retina in blind humans. *Arch. Ophthalmol.* **114**, 40–46 (1996).
- Chow, A. Y. *et al.* The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. *Arch. Ophthalmol.* **122**, 460–469 (2004).
- Zrenner, E. *et al.* Can subretinal microphotodiodes successfully replace degenerated photoreceptors? *Vision Res.* **39**, 2555–2567 (1999).
- Rizzo, J. F., Wyatt, J., Loewenstein, J., Kelly, S. & Shire, D. Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays. *Invest. Ophthalmol. Vis. Sci.* **44**, 5355–5361 (2003).
- Rizzo, J. F., Wyatt, J., Loewenstein, J., Kelly, S. & Shire, D. Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials. *Invest. Ophthalmol. Vis. Sci.* **44**, 5362–5369 (2003).
- Humayun, M. S. *et al.* Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. *Vision Res.* **43**, 2573–2581 (2003).
- Baveller, D. & Neville, H. Cross-modal plasticity: where and how? *Nature Rev. Neurosci.* **3**, 443–452 (2002).
- Hollins, M. *Understanding Blindness* (Hillsdale, New Jersey: Erlbaum Associates, 1989).
- Rauschecker, J. P. Compensatory plasticity and sensory substitution in the cerebral cortex. *Trends Neurosci.* **18**, 36–43 (1995).
- Rauschecker, J. P. & Korte, M. Auditory compensation for early blindness in cat cerebral cortex. *J. Neurosci.* **10**, 4538–4548 (1993).
- Roder, B. *et al.* Improved auditory spatial tuning in blind humans. *Nature* **400**, 162–166 (1999).
- Van Boven, R. W., Hamilton, R. H., Kauffman, T., Keenan, J. P. & Pascual-Leone, A. Tactile spatial resolution in blind Braille readers. *Neurology* **54**, 2230–2236 (2000).
- Hamilton, R. H., Pascual-Leone, A. & Schlaug, G. Absolute pitch in blind musicians. *Neuroreport* **15**, 803–806 (2004).
- Gougoux, F. *et al.* Neuropsychology: pitch discrimination in the early blind. *Nature* **430**, 309 (2004).
- Pascual-Leone, A., Hamilton, R., Tormos, J. M., Keenan, J. & Catala, M. D. In *Neuroplasticity: Building a Bridge from the Laboratory to the Clinic* (eds Grafman, J. & Christen, Y.) 93–108 (Springer, Munich & New York, 1998).
- Sadato, N. *et al.* Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* **380**, 526–528 (1996).
- Sadato, N. *et al.* Neural networks for Braille reading by the blind. *Brain* **121**, 1213–1229 (1998).
- Buchel, C., Price, C., Frackowiak, R. S. & Friston, K. Different activation patterns in the visual cortex of late and congenitally blind subjects. *Brain* **121**, 409–419 (1998).
- Burton, H. *et al.* Adaptive changes in early and late blind: a fMRI study of Braille reading. *J. Neurophysiol.* **87**, 589–607 (2002).
- Amedi, A., Jacobson, G., Hendler, T., Malach, R. & Zohary, E. Convergence of visual and tactile shape processing in the human lateral occipital complex. *Cereb. Cortex.* **11**, 1202–1212 (2002).
- Amedi, A., Raz, N., Planka, P., Malach, R. & Zohary, E. Early 'visual' cortex activation correlates with superior verbal-memory performance in the blind. *Nature Neurosci.* **6**, 758–766 (2003).
- Cohen, L. G. *et al.* Functional relevance of cross-modal plasticity in blind humans. *Nature* **389**, 180–183 (1997).
- Hamilton, R. H. & Pascual-Leone, A. Cortical plasticity associated with Braille learning. *Trends Cogn. Sci.* **2**, 168–174 (1998).
- Hamilton, R., Keenan, J. P., Catala, M. D., Pascual-Leone, A. Alexia for Braille following bilateral occipital stroke in an early blind woman. *Neuroreport* **7**, 237–240 (2000).
- Merabet, L. *et al.* Feeling by sight or seeing by touch? *Neuron* **42**, 173–179 (2004).
- Kujala, T., Alho, K., Paavilainen, P., Summala, H. & Naatanen, R. Neural plasticity in processing of sound location by the early blind: an event-related potential study. *Electroencephalogr. Clin. Neurophysiol.* **84**, 469–472 (1992).
- Weeks, R. *et al.* A positron emission tomographic study of auditory localization in the congenitally blind. *J. Neurosci.* **20**, 2664–2672 (2000).
- Amedi, A., Floel, A., Knecht, S., Zohary, E. & Cohen, L. G. Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nature Neurosci.* **7**, 1266–1270 (2004).
- Pascual-Leone, A. & Hamilton, R. The metamodal organization of the brain. *Prog. Brain Res.* **134**, 427–445 (2001).
- Donoghue, J. P. Connecting cortex to machines: recent advances in brain interfaces. *Nature Neurosci.* **5**, 1085–1088 (2002).
- Nicoletti, M. A. Brain-machine interfaces to restore motor function and probe neural circuits. *Nature Rev. Neurosci.* **4**, 417–422 (2003).
- Loeb, G. E. Cochlear prosthetics. *Annu. Rev. Neurosci.* **13**, 357–371 (1990).

50. Rauschecker, J. P. & Shannon, R. V. Sending sound to the brain. *Science* **295**, 1025–1029 (2002).
51. Finney, E. M., Fine, I. & Dobkins, K. R. Visual stimuli activate auditory cortex in the deaf. *Nature Neurosci.* **4**, 1171–1173 (2001).
52. Neville, H. J. *et al.* Cerebral organization for language in deaf and hearing subjects: biological constraints and effects of experience. *Proc. Natl Acad. Sci. USA* **95**, 922–929 (1998).
53. Nishimura, H. *et al.* Sign language 'heard' in the auditory cortex. *Nature* **397**, 116 (1999).
54. Giraud, A. L., Price, C. J., Graham, J. M., Truy, E. & Frackowiak, R. S. Cross-modal plasticity underpins language recovery after cochlear implantation. *Neuron* **30**, 657–663 (2001).
55. Sharma, J., Angelucci, A. & Sur, M. Induction of visual orientation modules in auditory cortex. *Nature* **404**, 841–847 (2000).
56. Lee, D. S. *et al.* Cross-modal plasticity and cochlear implants. *Nature* **409**, 149–150 (2001).
57. Grill-Spector, K. The neural basis of object perception. *Curr. Opin. Neurobiol.* **13**, 159–166 (2003).
58. Deibert, E., Kraut, M., Kremen, S. & Hart, J. Neural pathways in tactile object recognition. *Neurology* **52**, 1413–1417 (1999).
59. James, T. W. *et al.* Haptic study of three-dimensional objects activates extrastriate visual areas. *Neuropsychologia* **40**, 1706–1714 (2002).
60. Beauchamp, M. S., Lee, K. E., Argall, B. D. & Martin, A. Integration of auditory and visual information about objects in superior temporal sulcus. *Neuron* **41**, 809–823 (2004).
61. Amedi, A., Malach, R., Hendler, T., Peled, S. & Zohary, E. Visuo-haptic object-related activation in the ventral visual pathway. *Nature Neurosci.* **4**, 324–330 (2001).
62. Pietrini, P. *et al.* Beyond sensory images: object-based representation in the human ventral pathway. *Proc. Natl Acad. Sci. USA* **101**, 5658–5663 (2004).
63. De Volder, A. P. *et al.* Auditory triggered mental imagery of shape involves visual association areas in early blind humans. *NeuroImage* **14**, 129–139 (2001).
64. Johnson, K. O. & Hsiao, S. S. Neural mechanisms of tactual form and texture perception. *Annu. Rev. Neurosci.* **15**, 227–250 (1992).
65. von Senden, M. *Space and Sight: the Perception of Space and Shape in the Congenitally Blind Before and After Operation* (Methuen, London, 1960).
66. Gregory, R. L. & Wallace, J. G. Recovery from early blindness: a case study. *Exp. Psychol. Soc. Monogr.* **2** (Heffers, Cambridge, 1963).
67. Fine, I. *et al.* Long-term deprivation affects visual perception and cortex. *Nature Neurosci.* **6**, 915–916 (2003).

Acknowledgements

Funding for this work is provided by a National Research Service Award fellowship from the National Eye Institute to L.B.M., a Department of Veterans Affairs, Rehabilitation Research and Development Service grant to J.F.R., a National Science Foundation grant to D.C.S. and a National Science Foundation Science of Learning Centers Catalyst Award and National Center for Research Resources grant to A.P.L.

Competing interests statement

The authors declare no competing financial interests.

Online links

FURTHER INFORMATION

Encyclopedia of Life Sciences: <http://www.els.net/>
Cortical plasticity: use-dependent remodelling | Eye anatomy | Macular degeneration, age related
Access to this interactive links box is free online.

OPINION

Reading vascular changes in brain imaging: is dendritic calcium the key?

Martin Lauritzen

Abstract | A key goal in functional neuroimaging is to use signals that are related to local changes in metabolism and blood flow to track the neuronal correlates of mental activity. Recent findings indicate that the dendritic processing of excitatory synaptic inputs correlates more closely than the generation of spikes with brain imaging signals. The correlation is often nonlinear and context-sensitive, and cannot be generalized for every condition or brain region. The vascular signals are mainly produced by increases in intracellular calcium in neurons and possibly astrocytes, which activate important enzymes that produce vasodilators to generate increments in flow and the positive blood oxygen level dependent signal. Our understanding of the cellular mechanisms of functional imaging signals places constraints on the interpretation of the data.

It is often assumed that an increase in the intensity of a functional brain imaging signal indicates an increase in neuronal activity and, in particular, spiking activity. However, recent findings challenge this assumption and have given new impetus to the search for the neural underpinnings of functional brain imaging. Increases in spiking activity of targeted neurons have been correlated to the blood oxygen level dependent (BOLD) signal in functional MRI (fMRI) studies (BOX 1), and it has been suggested that the amplitude of the BOLD signal predicts the spiking activity of neurons in the activated brain regions^{1,2}. The interest in the relationship between spiking and the BOLD signal stems from the fact that the pioneering studies of neural correlates of behaviour used the spiking activity of specific neurons as the marker^{3–5}. Therefore, if the BOLD signal was correlated with, and possibly driven by, spiking activity, functional neuroimaging could be used as a non-invasive tool to map human brain function with the same

validity as electrophysiological recordings. However, several papers have provided evidence that the blood flow and BOLD contrast signal correlate only weakly with spiking activity^{7–10}. In contrast, blood flow and BOLD signals correlate more strongly with local field potentials (LFPs), which are generated by subthreshold synaptic activity, upstream from the axo-somatic level. This finding has paved the way for a better understanding of the constraints of functional neuroimaging in relation to the underlying neuronal processes.

Glutamate

Excitatory glutamatergic synapses dominate the brain's grey matter, and glutamate metabolism and the consequences of glutamate release in the postsynaptic cells are the main energy-consuming processes in the working brain^{11–13}. As a result, there is considerable interest in the relationship between glutamatergic neurotransmission, blood flow, energy consumption and brain imaging signals. Glutamate and its specific analogues evoke increases in cerebral blood flow and BOLD contrast signals, presumably by interacting with glutamate receptors on astrocytes and neurons^{12,14–20}. Antagonists of glutamate receptors attenuate or abolish synaptic and blood flow responses. For example, in the cerebellum, AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor (AMPA) antagonists attenuate the increases in blood flow and postsynaptic activity that are evoked by climbing fibre stimulation by up to 95% (REFS 7,21). Combined treatment with AMPA and NMDA (*N*-methyl-D-aspartate) receptor (NMDAR) antagonists reduced blood flow responses and postsynaptic activity by 90% in the rat sensory cortex during infra-orbital stimulation²². In addition, BOLD and blood flow responses evoked by forepaw stimulation were reduced by substances that attenuated glutamate release²³.

So, glutamate release and the interaction of glutamate with its receptors on neurons are necessary for the production of blood flow and BOLD responses. The close relationship between glutamatergic neurotransmission and increases in perfusion points to the function of the increased blood flow: to provide the substrates for energy metabolism — glucose and oxygen²⁴. It is possible that local blood flow is partially controlled by metabolic end products. However, detailed studies of the time course of blood flow responses²⁵, and quantitative analysis of the relationship between the release of vasoactive cations and blood flow responses²⁶, have led to the hypothesis that the activity-dependent regulation of blood flow is a feedforward (rather than