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Spotlight on vision

Retinal prostheses: Clinical results and future challenges

Les prothèses rétiniennes : résultats cliniques et défis futurs

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ABSTRACT

Retinal prostheses aim at restoring visual perception in blind patients affected by retinal diseases leading to the loss of photoreceptors, such as age-related macular degeneration or retinitis pigmentosa. Recent clinical trials have demonstrated the feasibility of this approach for restoring useful vision. Despite a limited number of electrodes (60), and therefore of pixels, some patients were able to read words and to recognize high-contrast objects. Face recognition and independent locomotion in unknown urban environments imply technological breakthroughs to increase the number and density of electrodes. This review presents recent clinical results and discusses future solutions to answer the major technological challenges.

RÉSUMÉ

Les prothèses rétiniennes ont pour objet de restaurer la perception visuelle de patients devenus aveugles dans des pathologies reposant sur la perte des photorécepteurs, comme la dégénérescence maculaire liée à l'âge ou la rétinopathie pigmentaire. Les essais cliniques récents ont démontré la faisabilité de cette approche pour redonner une certaine vision. Malgré un nombre limité d'électrodes (60) et donc a fortiori de pixels, certains patients étaient en mesure de lire des mots ou de reconnaître des objets très contrastés. Le retour à l'autonomie pour la locomotion en milieu urbain inconnu ou la reconnaissance des visages impose des sauts technologiques pour augmenter le nombre et la densité des électrodes. Cette revue expose les résultats récents des essais cliniques et discute les solutions d'avenir envisagées pour résoudre les défis technologiques posés.

1. Introduction

Although blindness is one of the most feared handicaps, 39 million people worldwide are blind (WHO, 2012: http://www.who.int/blindness/en/). The first cause of blindness (51%), cataract, can be efficiently treated to recover vision. Other major causes of blindness are due to ocular diseases leading to loss of retinal cells: photoreceptors in age-related macular degeneration (ARMD) and retinitis pigmentosa (RP) or retinal ganglion cells in glaucoma. Photoreceptors are transforming luminance changes into an electrical activity while retinal ganglion cells are the output retinal neurons extracting and

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compressing visual information to be sent to the brain via the optic nerve. For some of the considered diseases, there is currently no effective treatment to prevent vision impairment leading to blindness or treatments are only efficient for a limited number of patients. For patients who became blind, visual prostheses aim at restoring some visual perception. Although the idea of restoring vision in blind patients by electrical stimulations was originally proposed by Charles Leroy in 1755, its re-examination was recently highly motivated by the success of cochlear implants to restore audition or the success of deep brain stimulation to treat Parkinson disease. Depending on the pathology and therefore the degenerated cells, it is possible to intervene at different levels in the visual system. When it comes to loss of photoreceptors, retinal prostheses are designed to stimulate the residual retina, while, in diseases with optic nerve atrophy, devices have to activate the visual cortex. For such cortical implants, clinical tests conducted in the 70s and 80s showed functional visual recovery, often transient, with prostheses comprising 100 electrodes [1,2]. The lack of persistence of vision restoration resulted in the cessation of clinical trials, in the expectation of a stable solution.

For diseases affecting the photoreceptors (PR in Fig. 1), retinal prostheses have been introduced at different ocular levels. Indeed, the loss of photoreceptors leaves two neuronal layers in the retina:

- the inner nuclear layer containing cell bodies of the bipolar cells (BC in Fig. 1), the neurones postsynaptic to photoreceptors;
- the ganglion cell layer where all retinal ganglion cells (RGC in Fig. 1) are generating visual information sent to the brain by their axons via the optic nerve (NO).

In the normal operation of the retina, these two layers process neuronal information for converting the analogue visual information of photoreceptors (their membrane potential is a linear function of the light intensity) into a digital code at retinal ganglion cells (information is coded as spike frequencies). Different positions were assessed for stimulating the residual retina after the photoreceptor loss:

- into the subretinal space where photoreceptors were originally located (subretinal implant);
- on the vitreal side of the retina close to the ganglion cell layer (epiretinal implant);
- around the optic nerve as an optic nerve cuff (Fig. 1).

If all of these implants induced the perception of phosphenes, optic nerve cuffs were not able to generate coherent images because phosphenes are scattered throughout the visual field [3,4]. A trans-choroid approach that prevents the introduction of the implants into the eye was also recently proposed [5]. This review will focus on the recent clinical trials of subretinal and epiretinal implants with their future challenges to increase electrode resolution and the resulting visual performances.

2. Clinical trials

At the early phase of the retinal prosthesis development, investigators started by asking whether activating the residual tissue following photoreceptor degeneration could elicit visual perception. This question was not trivial because neurons in the residual tissue undergo a secondary degeneration [6]. Histological examination of postmortem tissue indicated that patients in advanced stages of retinitis pigmentosa retain only a third to a quarter of their retinal ganglion cells [7]. Remodelling of retinal tissue and loss of ganglion cells have also been reported in animal models of the disease [8–12]. Different causes of this degeneration have been proposed in the literature, from axonal compression to taurine deficiency [8,13]. It was unclear if such cells in a degenerative state would still transmit visual information to the brain, which could then be interpreted as visual perception. The first clinical trials thus consisted in acute stimulations of the degenerated retina. An electrode or an electrode array was introduced on the vitreal side of the retina and patients were asked if they perceived electrically elicited phosphenes. In these clinical trials, patients reported the perception of phosphenes taking different forms depending on the stimulation protocols [14–18]. These results demonstrated that residual neurones in blind patients could elicit visual perception when electrically activated.

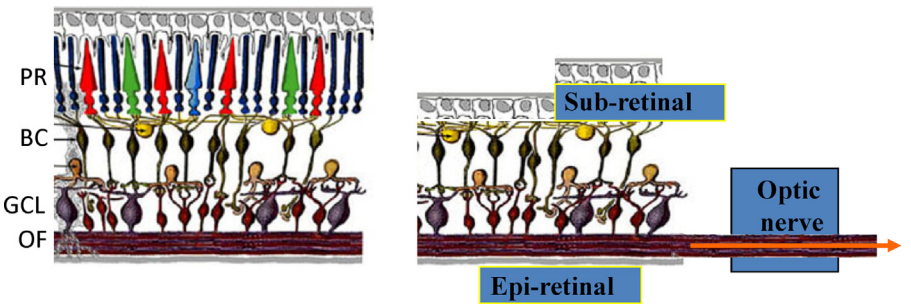

Fig. 1. (Colour online.) Concept of retinal prostheses. A. Schematic of a retina with different neuronal layers: the photoreceptor layer (PR), the inner nuclear layer containing bipolar cells (BC), the ganglion cell layer (GCL) and optic fibres or axons (OF) pointing to the optic nerve (NO). B. Diagram showing the position of subretinal implants between residual retinal pigment epithelium, epiretinal implants on the retina at the vitreous side, and finally the cuff of electrodes around the optic nerve.
Adapted from Webvision.

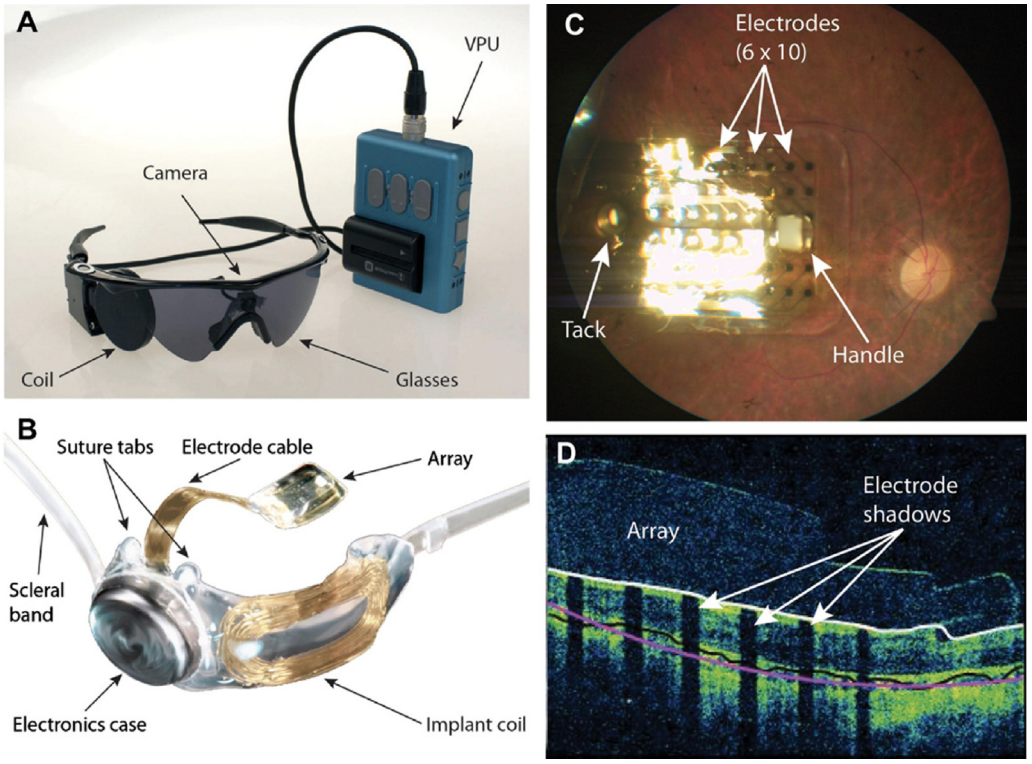

Fig. 2. (Colour online.) First marketed retinal prosthesis: the Argus II from the company Second Sight Medical Products. A. Part of the external device containing the microprocessor (VPU) and the pair of glasses, on which both the camera and the coil for radio frequency transmission are located. B. Part of the implantable device containing the electronic box tied around the eye by a scleral band, with the coil for the radiofrequency reception on one side, and the electrode cable entering the eye on the other side. The electrode cable is connecting the electrode array to the electronic box. C. Image of the fundus with the electrode array and tack fixation. D. In vivo image of the electrode array by optical coherence tomography. Electrodes are generating shadows preventing the retinal tissue examination.
From [21].

2.1. Epiretinal prostheses

Following this key demonstration, clinical trials have subsequently focused on retinal stimulations with retinal prostheses chronically fixed on the vitreal side of the retina. These epiretinal prostheses illustrated in Fig. 2 are composed of the following elements:

- a camera located on eyeglasses for acquiring images of the visual environment;
- a microprocessor which converts the image into stimulation codes;
- a transmitter located on the eyeglasses which transmits the information by radio frequency to the implanted device;
- an implanted device containing the radio frequency receiver (coil-coil interaction), which is connected to an ASIC (chip) converting stimulation codes into electric currents;
- extending from the implanted device, a foil composed with the electrical lines leading to the electrodes at its end, the end being attached to the retina and eye by a tack or nail through the choroid.

The company, Second Sight Medical Products, Inc, had initially produced an implant with 16 electrodes (Argus I), which enabled blind patients to identify light targets, recognize white objects on a black background with a 20/3240 restored visual acuity [19,20]. The following generation of epiretinal implant, Argus II (see Fig. 2), from the Second Sight Company has been evaluated in an international multicentre clinical trial including 30 patients between 2007 and 2009. Four blind patients were operated in the department headed by Professor Sahel (author of this publication) at the Quinze-Vingts National Eye Hospital in Paris. With this device, the majority of patients could perform complex visual tasks such as object location (96% of subjects), discrimination of movement (57%), and discrimination oriented networks (23%) [21]. The best-corrected visual acuity was measured at 20/1260, still six times lower than the limit of legal blindness (20/200). Two of implanted patients were also able to perform reading tasks with a rate of up to 10 words per minute [22]. Patients could also read Braille symbols with the device [23]. These successes have allowed the medical device Argus II to obtain European CE marking approval (selling price of € 80,000) and already its repayment in Germany by the national health agency was agreed. More recently, Argus II obtained the FDA approval for US marketing. Other groups have also conducted clinical trials confirming the possibility of restoring some visual perception with epiretinal implant [24,25]. The company Pixium Vision

has recently started clinical trials in Europe with a similar device.

The Argus II device stimulates retinal cells by currents whose amplitude is a linear function of the pixel light intensity at a frequency of about 20 Hz with a pulse duration of 100 μs to 1 ms applying biphasic stimulations, cathodic first then anodic. This strategy provides exactly the same information to all types of ganglion cells and does not take into account their diversity [26]. Cells activated at the light onset, ON cells, thus receive the same stimulation as those normally activated at the extinction of the light phase, OFF cells. In addition to this identical stimulation of all retinal ganglion cell types, the epiretinal approach also activates fibres passing by from the periphery toward the optic disc [18,27]. This fibre stimulation corresponds to the activation of retinal ganglion cells peripheral to the implant and thus to the perception of an unwanted peripheral arc of light. These various difficulties associated with epiretinal stimulation could explain the great variability in patient performances using Argus II, only 7 patients out of the 30 implanted were able to reliably perform complex tasks of visual acuity [21,22].

2.2. Subretinal implants

Subretinal implants are introduced in the subretinal space at the position of degenerated photoreceptors. In this case, electrical stimulations aim at activating retinal bipolar cells (or eventually residual non-photosensitive photoreceptors [28], which can then transfer visual information to the retinal ganglion cells as in the normal retina. Prof. Chow and the company Optobionics were the first to evaluate this strategy [29]. Implant contained solar photodiodes which could directly generate current at the stimulation electrodes. The device was thus very simple because it contained no external component or wire to power or transmit visual information. The circular device (diameter of 2 mm) was simply inserted into the subretinal space of blind patients. Unfortunately, the photodiodes did not allow conversion of enough photons to cause the activation of the degenerated retinal tissue. However, a positive trophic effect has been observed at a distance of the device on residual photoreceptors [29]. To increase the delivered current, Prof. Zrenner and the company Retina Implant AG have introduced an amplifier circuit between the photodiodes and their corresponding electrodes [30]. The chip exactly reproduces the operation of a photoreceptor receiving photons and amplifying this signal to finally deliver a current at the electrode. However, the presence of the amplifier circuit requires the addition of a battery, which is linked to the chip by wires and also inserted in the subretinal space but at the periphery. This whole device is therefore much more complex to install in the eye because the chip is introduced into the subretinal space from the periphery and then pushed to a central position. At first, 16 passive electrodes were also added to the device and activated from the outside. These 16 subretinal passive electrodes enabled the investigators to demonstrate that subretinal stimulations could elicit visual perceptions [31,32]. In a second phase, the chip, which contains 1500 diodes/electrodes, was activated by the ambient light as expected. With this device, patients perceived objects, discriminated simple test patterns and could, in some cases, read letters or even words. The restored visual acuity was 20/1000 in these patients [33]. These results were therefore in the same range as those obtained with the epiretinal implant, Argus II, despite a greater number of electrodes. Psychophysical experiments had suggested that implants with 600 independent pixels would provide facial recognition, reading complex texts and autonomous locomotion [34–38]. Therefore, the clinical results from Retina implant AG suggest that patients equipped with their implants do not perceive 1500 independent pixels despite 1500 electrodes. These different clinical trials have generated very important knowledge for future development of retinal prostheses:

- both epiretinal and subretinal stimulations can induce visual perceptions;
- epiretinal stimulations can stimulate by-passing fibres;
- the brain can understand this recovered visual information;
- increasing the pixel number does not only rely on increasing the number of electrodes. In the next paragraphs, we will therefore discuss how to increase the number of electrodes and their individual spatial resolution.

3. Future challenges

3.1. The electrode distribution

The work of Professor Zrenner on subretinal implants has shown that increasing the number and density of electrodes is a complex objective. The electrode distribution, the implant design and new materials have to be considered for improving further the resolution of individual electrodes. A model study has thus investigated how the electrode distribution could affect the current distribution. Three different configurations were examined: a distant common ground, a bipolar stimulation between a central and an annular return electrode, and a ground grid surrounding all stimulating electrodes [39]. If the concentric electrodes were improving the current spread, it doubled the number of wires in the foil, complicating thereby the device. Ground grids could further limit the current spread, provided this grid has low impedance. As a consequence, we have introduced such ground grid in our recent retinal implant model [40]. Prof. Palanker similarly inserted such a ground grid in his autonomous photodiode array [41,42]. In this device, each electrode is connected to three photodiodes in series and light is projected on the implant in the infrared to reach light intensities that are sufficient to generate enough current for activation of the retinal cells. The advantage of this design would be to remove the power supply or battery, which complicates the surgery to establish the wire connection. However, goggles would be required to transform visual scenes into infrared stimulations of the implant.

3.2. The design of the interface

Prof. Palanker has also proposed new tissue/implant interface to improve further the electrode resolution. On each side of the residual retina, a glial cell layer acts as an insulating layer between the implant and the retinal neurones. Therefore, stimulation currents are more likely to flow into the space between the implant and the tissue rather than penetrate into the retinal tissue. To circumvent this difficulty, Prof. Palanker generated 3D design to move retinal neurones between electrodes of opposite polarity [43]. Such 3D structures can be pillars gradually penetrating into the neuronal tissue [44]. More recently, we generated a model to define the optimal 3D structures [40]. Instead of pillars rendering the implant removal difficult if not impossible, we introduced wells with a bottom electrode and a ground grid on the implant surface [40]. The model suggested that electrode stimulations with such 3D implants would activate independent neuronal columns corresponding to individual pixels (Fig. 3A). This strategy was finally validated by producing 3D implant prototypes, which were introduced in the subretinal space of blind rats [40]. Indeed, this strategy relies on the hypothesis that the retinal tissue will mould itself into the wells. In fact, when the 3D implants were introduced into the subretinal space of blind rats (Fig. 3B–C), the residual retina had remained sufficiently plastic to fill the wells with retinal bipolar cells (Fig. 3D). Therefore, in stimulating conditions, bipolar cells in a well would be in a position to be selectively stimulated by the electrode located at the bottom of the well, whereas bipolar cells found in neighbouring wells would not be affected [40]. The 3D implant designs could therefore be able to generate independent pixels from each individual electrode.

3.3. Materials

For the electrical stimulation of a neural structure, electrodes can generate two types of currents:

- faradic currents that involve chemical reactions of oxidation/reduction and;
- capacitive currents resulting from the charge accumulation only.

In the case of neural prostheses, capacitive stimuli are preferred because they limit pH changes at the electrode surface [45]. In the context of visual implants, the need for small electrodes introduces additional risks of tissue and electrode damages by injecting high charge densities. Finding materials with high charge injection limits is therefore a major challenge. Materials conventionally used are platinum (0.35 mC/cm^2 limit injection), titanium nitride (1 mC/cm^2) and iridium oxide (4 mC/cm^2). Biocompatibility studies for these materials were performed on retinal cells in culture as for titanium nitride [46]. Diamond is also considered because:

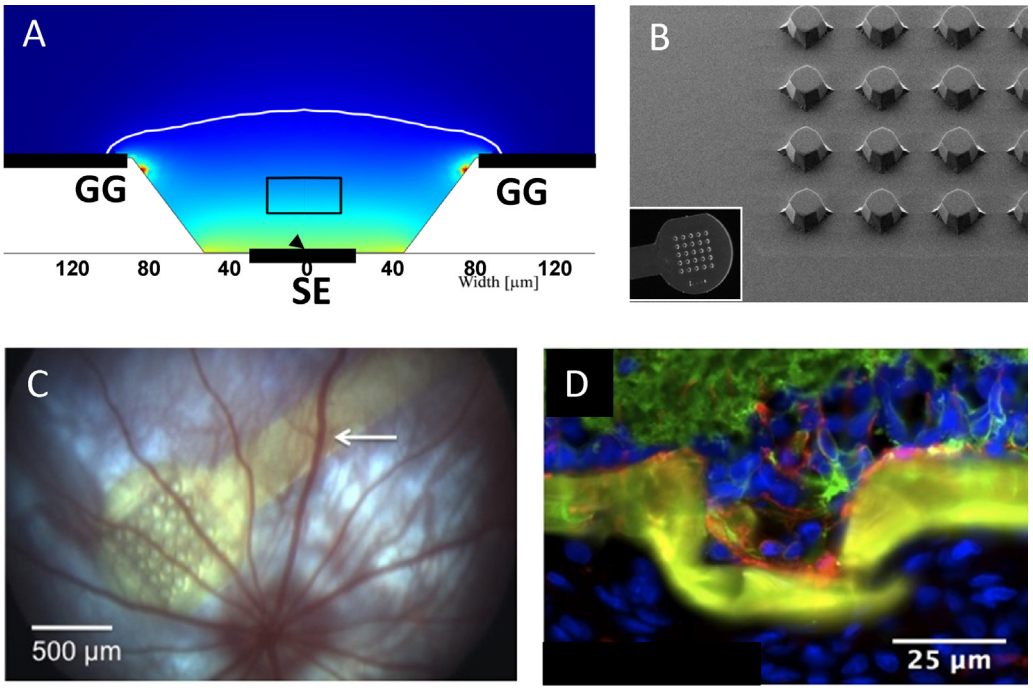

Fig. 3. Restricted stimulations by 3D implant interfaces. A. Modelling current intensities in the retinal tissue on a 3D implant with a stimulation electrode (SE) at the bottom of the well and ground grid (GG) at the surface of the implant. The colour code indicates a current confinement in the well and in particular in the target area represented by a rectangle. B. Mould used for producing a three-dimensional prototype implant (see insert). C. Fundus of a blind rat showing the three-dimensional implant beneath the retina and therefore under retinal vessels (arrow). D. Histological section of the retina showing the bipolar cells (green) in the well.
Adapted from [40]. For interpretation of references to colour, see the online version of this article.

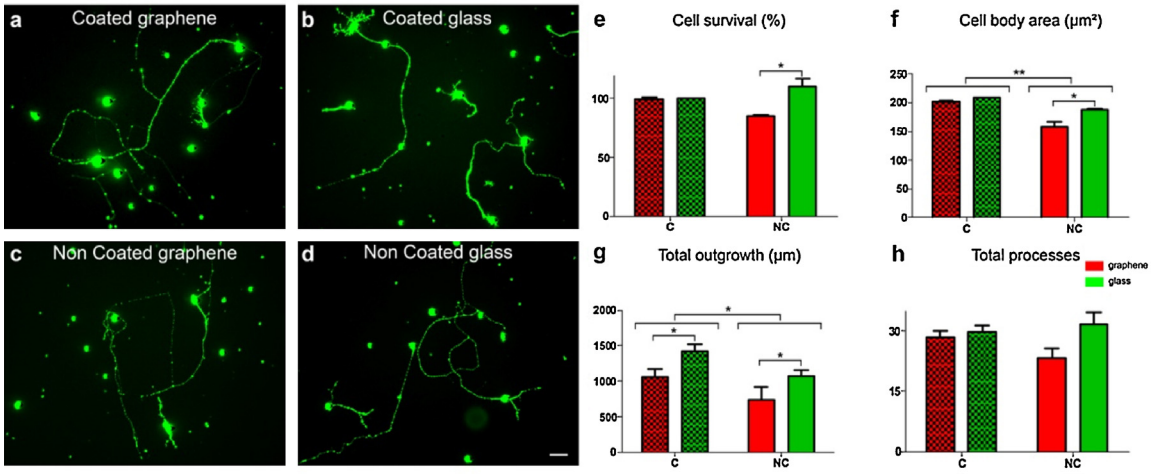

Fig. 4. (Colour online.) Survival of adult retinal ganglion cells on graphene or glass with or without a protein coating (poly-D-lysine and laminin). A–D. Visualization of viable cells using the calcein dye on these different materials. E–F. Quantification of viable cells and their neurites. (Mean ± s.e.m. $n = 4$). ** $P < 0.01$, * $P < 0.05$. The scale bar represents 50 microns.
Adapted from [50].

- it becomes a semiconductor when doped with boron atoms;
- it has a high mechanical stability;
- its carbon structure appears very likely biocompatible.

We have characterized the electrochemical properties of such diamond electrodes [47] and evaluated their biocompatibility for cultured retinal cells [48]. Others have also assessed the value of diamond electrodes to perform electrical stimulations of retinal cells [49]. In parallel, we have also analyzed the biocompatibility of graphene for retinal neurones [50]. Fig. 4 shows for instance the survival of pure adult retinal ganglion cells on bare graphene or on peptide-coated graphene. All studies suggest that these new carbon-based materials could provide excellent biocompatible electrode materials likely to generate less electrochemical damages.

3.4. Encoding visual information

Currently, visual information coding remains relatively simple with a conversion of light intensities into amplitude stimulations. This simple coding relies on the assumption that the cortex should be able to learn reading such crude signals and extract the relevant information. The potential for plasticity of the visual system from blind patients is based on reported functional reorganizations after the onset of blindness [51,52]. In blind patients, the visual cortex can in fact be recruited by other sensory modalities introducing a multi-modal plasticity; the visual cortex can also contributes to tactile Braille reading [53]. However, stimulating with signals as close as possible to the physiological retinal response would facilitate understanding the newly proposed visual language. The current difficulty to properly encode visual information could explain the lack of understanding of signals in some patients.

In this context, one of the major challenges of visual prostheses is to develop algorithms for processing visual information operating in real time. These algorithms have to model all retinal cell types to prepare specific cell stimulations because it remains unknown if some cell populations are more affected by the secondary tissue degeneration and plasticity. Different models have already tried to reproduce the ganglion cell function [54,55]. If newer models reproduce quite successfully the properties of ganglion cells, they cannot yet satisfactorily predict responses to complex natural stimuli [56]. Recently, we have addressed this issue through an innovative approach based on a new asynchronous dynamic visual sensor whose function mimics photoreceptor and retinal cell responses [57]. The advantage of these cameras is the absence of a clock, which constrains signal processing by the acquisition of visual information at regular time intervals (video rate: one image/30ms). Each pixel of this asynchronous visual sensor operates completely independently by indicating through positive and negative events at their exact timing of occurrence all increases or decreases of light intensities with respect to defined thresholds. Using this visual information, we were able to reconstruct the physiological responses of retinal ganglion cells previously described by Werblin and Roska [26]. Using our model, we reached at a millisecond precision of cellular responses, thereby extrapolating responses to complex stimuli [58]. Fig. 5 illustrates such visual images sent by the retina to the brain. This new coding strategy of visual information should allow us to provide patients with visual information similar to those normally generated by retinal cells and thus more easily understandable by the visual system.

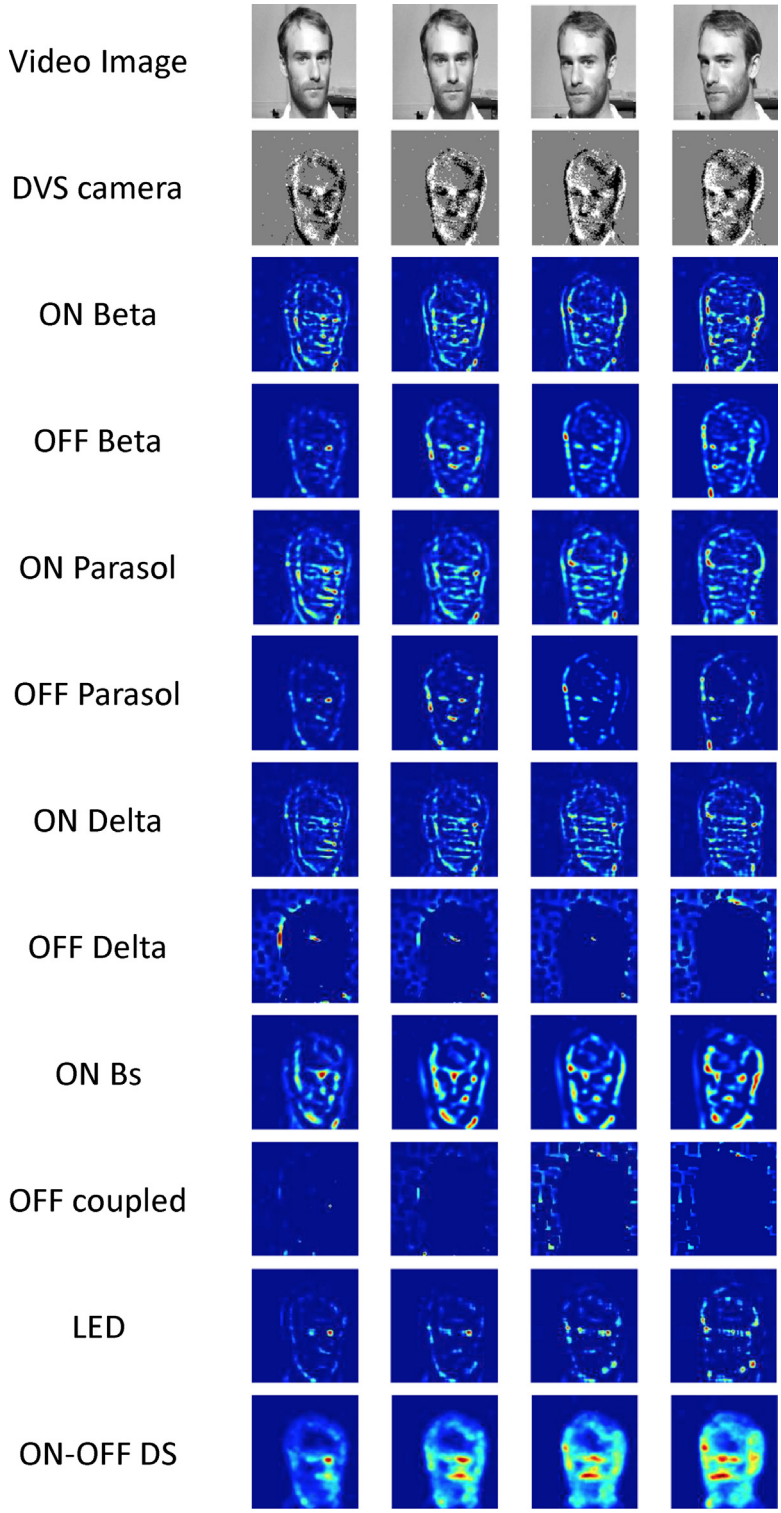

Fig. 5. Modelling visual information sent to the brain by different populations of retinal ganglion cells. The model is using positive and negative events (white and black dots) generated by an asynchronous DVS camera. Response intensities of cells are represented by a colour code at the corresponding pixel. See [58]. For interpretation of references to colour, see the online version of this article.

4. Conclusions

Restoration of some visual functions by retinal prostheses becomes a realistic approach. Some patients already exhibit remarkable visual performances with implants containing only 60 electrodes. Many challenges are facing the scientists in the fields to improve existing systems. However, like cochlear implants, which required 20 years of development from the first implant allowing the mere recognition of a word to current implants allowing phone conversations, a similar path of development is expected for blind patients to recover a degree of autonomy in their locomotion, face recognition and common task achievements such as reading. Innovation is a source of hope for many blind patients and the developments in the visual system could then pave the way for other neural prostheses in the treatment of various handicaps.

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