Blindness affects tens of million people worldwide and its prevalence constantly increases along with population aging. In some pathologies leading to vision loss, prosthetic approaches are currently the only hope for the patient to recover some visual perception. Here, we review the latest advances in visual prosthetic strategies with their respective strength and weakness. The principle is to electrically stimulate neurons along the visual pathway. Ocular approaches target the remaining retinal cells whereas brain stimulation aims at stimulating higher visual structures directly. Even though ocular approaches are less invasive and easier to implement, brain stimulation can be applied to diseases where the connection between the retina and the brain is lost such as in glaucoma and could therefore benefit to patients with different pathologies. Today, numbers of groups are investigating these strategies and the first devices start being commercialized. However, critical bottlenecks still impair our scientific efforts towards efficient visual implants. These challenges include electrode miniaturization, material optimization, multiplexing of stimulation channels and encoding of visual information into electrical stimuli.

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1. Introduction

Blindness is one of the most debilitating sensory impairment affecting 39 million people worldwide. The leading cause of this sensory disability is cataract accounting for 51% of cases, however, it can be treated very efficiently, but access to treatment remains an issue in most underdeveloped countries. The remaining causes of acquired blindness are glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, and retinitis pigmentosa (RP). Fig. 1 summarizes the global causes of blindness and their prevalence. In these diseases, different cell types can be deficient and degenerate, thereby triggering blindness. For instance, photoreceptors are degenerating in RP and AMD whereas retinal ganglion cells sending visual information to the brain are lost in diabetic retinopathy or glaucoma. For some of these diseases, there is currently no efficient treatment for preventing severe visual loss or blindness. This is the case for RP accounting for 1 million patients worldwide. In these pathologies, photoreceptor degeneration leads to a progressive reduction of the visual field often declining to legal blindness. For the past 40 years, tremendous efforts towards visual rehabilitation through electrical stimulation of the neural tissue with implanted electrodes have been conducted. We will present here the recent developments and our latest advances in the field of visual prosthetics and the current technological and conceptual bottlenecks that will need to be overcome to restore functional vision in blind patients.

2. Prosthetic rehabilitation

In 1755, Charles LeRoy applied the electric discharge of a Leyden jar – an ancestor of capacitors – on the ocular surface of a patient blind from cataract (Fig. 2). This stimulation elicited vivid flashes of light or phosphenes, reported by the patient. It was the starting point of visual prosthetics and from this point, various strategies have been investigated to restore visual perception through electrical stimulation.

Electrical stimulation of the visual system can be performed on multiple locations along the sensory pathway. First, the retina can be stimulated in case of ganglion cell survival and preservation of the information flow through the optic nerve. Stimulating the optic nerve directly is also possible, although the high density of nerve fibers is an issue for stimulation control. And finally, it is possible to stimulate brain structures such as the lateral geniculate nucleus (LGN) or the visual cortex directly, even in case of complete retinal degeneration or optic nerve injury. However, these strategies are much more invasive. In all cases, the device consists in a photosensitive part – i.e. camera – a processing stage and an array of electrodes in contact with the targeted structure (Fig. 3).

We will present here the latest advances in visual implants and the major challenges that need to be addressed.

2.1. Epiretinal implants

Epiretinal implants electrically target the ganglion cell layer. A matrix of electrodes is directly fixed on the surface of the retina with a tack and connected to a stimulator receiving data and power through coil–coil interaction and radio-frequency (RF) signal.

Humayun et al. were the pioneer of epiretinal implants (Humayun et al., 2003, 2009, 2012). The first epiretinal device to be chronically implanted in patients – the Argus I – developed by Second Sight Medical Products was composed of 16 Pt electrodes (Humayun et al., 2003; Caspi et al., 2009). Their report confirmed that light perception could be achieved through epiretinal stimulation. The implanted patient was able to recognize shapes, gratings orientations, and had a restored visual acuity of 20/3240.

The next generation of their epiretinal device named Argus II was designed to reach a higher resolution. Fig. 4 describes the Argus II device containing a 6 × 10 electrode matrix implanted in 30 subjects from 2007 to 2009.
This implant recently received CE mark for commercialization in Europe and will be sold around 100,000$. With this device, a significant ratio of patients could achieve complex visually guided tasks such as object localization (96% of subjects), motion discrimination (57%), and discrimination of oriented gratings (23%) (Humayun et al., 2012). The best acuity that could be measured

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**Fig. 3.** Summary diagram of the visual system and approaches to restore vision. Six main strategies are currently investigated to restore vision through electrical stimulation. Retinal approaches including subretinal, epiretinal and suprachoroidal strategies; optic nerve stimulation and brain stimulation including lateral geniculate nucleus (LGN) and cortical targets. Among the suprachoroidal strategies, both Osaka University and Seoul National University devices are inserted between the sclera and the choroid whereas Bionic Vision Australia is developing a completely extra-ocular strategy.

**Fig. 4.** The first commercialized visual implant: the ARGUS II from Second Sight Medical Products. (A) External part of the device consisting in a pair of glasses carrying the camera and the Video Processing Unit (VPU). (B) The implanted components including the coil for RF communication, the stimulators and the electrode array. (C) Fundus of the implanted retina. (D) Optical Coherence Tomography (OCT) image of the implanted retina with the 60-electrode array. Reproduced with permission from Elsevier from (Humayun et al., 2012).
with the system was 20/1260, still six times lower than the legal blindness limit of 20/200. Two of the implanted patient could also perform reading task with a rate of up to 10 words per minute.

The device stimulates epiretinally by modulating current amplitude linearly with pixel intensity. The stimulus frequency (around 20 Hz), the pulse duration (100 µs to 1 ms), the polarity (cathodic first versus anodic first) are set equally for all the electrodes (McClure et al., 2009). This strategy provides the same information to all ganglion cell types and does not account for retinal adaptation. ON and OFF ganglion cells are stimulated according to the same pattern so that conflicting information reaches the brain. It might explain why there is a large variability in patients performances – with only 7 out of 30 patients able to reliably perform visual acuity tasks (Humayun et al., 2012).

Other groups are investigating epiretinal stimulation. Intelligent Medical Implants (IMIs) in Switzerland developed a 49 platinum electrode prosthesis in which power is transmitted through a RF-link and data, through infra-red pulses. Four patients were chronically implanted with this device (Hornig et al., 2008) and were able to perform localization tasks and recognize simple light patterns.

The EPI-RET group in Germany also performed clinical trials with their EPIRET3 device implanted in six patients (Klauke et al., 2011). This epiretinal prosthesis contained 25 stimulating gold electrodes coated with iridium oxide. In all patients, electrical stimulation could elicit visual percepts. Some of them were even able to discriminate stimuli applied at different locations of the array as well as discriminate pattern orientations. Interestingly, they

![Fig. 5. Summary picture of the different visual prosthetic devices discussed here. (A) Argus I device from second sight (from Humayun et al. (2003)). (B) The Argus II device with 60 electrodes, first prototype on the market (from Humayun et al. (2012)). (C) The IRIS device from Intelligent Medical Implant AG (from Hornig et al. (2008)). (D) The EPIRET-3 device (from Roessler et al. (2009)). (E) The STS suprachoroidal implant (from Fujikado et al. (2011)). (F) The optic nerve implant developed by Louvain's university (from Veraart et al. (2003)). (G) Dobelle's seminal cortical implant (from Dobelle (2000)). (H) The Boston Retina Implant Project device (from Rizzo (2011)). (I) The subretinal device from Retina Implant AG (from Zrenner et al. (2010)). (J) The subretinal microphotodiode array developed by Pr. Palanker's group at Stanford university (from Wang et al. (2012)). (K) The ASR device from Optobionics (from Chow et al. (2004)). (L) The diamond coated subretinal implant from our group at the Vision Institute of Paris. (M) The Utah electrode array for cortical stimulation (from Normann et al. (2009)). All figures were reproduced with permission from their respective editors.](image-url)
found that, for the same amount of injected charges, longer pulses were more efficient to elicit visual perception and the authors suggest to use ~1 ms pulse durations.

Epiretinal strategies provide some great advantages such as the direct immersion in the vitreous which dissipates heat from electrical stimulation. Moreover, it is easily implantable and is less likely to induce retinal detachment or injury compared to subretinal prostheses (Fernandes et al., 2012). However, some drawbacks are also inherent to such a strategy. First, the high density of axon fibers in the central area of the retina introduces a collateral stimulation of cell that are located far from the area of interest (Wilms and Eckhorn, 2005; Behrend et al., 2011; Rizzo et al., 2003), although modulated 20 Hz sine wave stimulation could limit axonal stimulation (Weitz et al., 2012). As a consequence of this stimulation of passing fibers the retinotopy of the stimulation patterns could be lost in some cases (Humayun et al., 2003). Moreover, as stated earlier, epiretinal implants do not benefit the inner layers of the retina that naturally act as an amplification and encoding system. Therefore, the adequate encoding of stimulation pulses remains an unsolved issue. That is why other groups focused their efforts on subretinal strategies.

2.2. Subretinal implants

Subretinal implants primarily target the inner nuclear layer of the retina. In retinitis pigmentosa, the primary loss of photoreceptors is followed by a reorganization process (Marc et al., 2003; Jones and Marc, 2005) and the partial degeneration of the other retinal cell types. However, morphometric analyses of post-mortem eyes from RP patients showed a significant preservation of neurons in the inner nuclear layer as well as in the ganglion cell layer, even in late stages of the disease (Santos et al., 1997; Humayun et al., 1999). In the macular region, Santos et al. showed that 78% and 88% of the inner nuclear layer cells were preserved in moderate and severe RP respectively. This survival was not statistically dependent on the inheritance mode of the disease. Moreover, Busskamp et al. were able to show that optogenetic reactivation of cone cell bodies in a mouse model of retinal degeneration could restore natural processing such as lateral inhibition and even direction selectivity (Busskamp et al., 2010). These findings suggest that the inner retinal network remains functional even in a late stage of retinal degeneration. Therefore, despite the wide heterogeneity of RP types, there is a good chance that the subretinal approach could be relevant and effective in a majority of cases.

Subretinal implants are inserted below the retina and are therefore maintained between the choroid and the retina itself without additional tack for fixation. This position increases implant stability along with risk of retinal detachments. In 2001, Optobionics, Inc. developed the first implanted subretinal device called Artificial Silicon Retina (ASR). This device consisted in a 2 mm diameter autonomous array of 5000 photodiodes directly converting light into electrical stimulation. This very elegant strategy did not require any power supply nor data transmission to the chip. Once implanted, the device was completely autonomous, thereby limiting the risks of complications. A pilot clinical trial was conducted and in six patients were implanted (Chow et al., 2004, 2010). These patients suffered from autosomal dominant, isolated, X-linked and Usher II RP. Vision improvement was found in the implanted patients, however, they were not necessarily correlated with the chip location, suggesting that the implantation benefits were indirect – through neuroprotection for instance. These results suggested that ambient natural light was not powerful enough to provide supra-threshold stimulation of the retina. Therefore, subsequent research introduced amplification systems for subretinal implants.

The first strategy to amplify the signal was developed by the group of Pr. Zrenner in Tübingen. They coupled each photodiode to an amplifying circuit. This device required a battery to power the circuit delivering current to the electrodes. This battery was located at the eye periphery whereas the implant was in a very central position. The device contained 38 × 40 photodiodes (Zrenner et al., 2010) plus 16 larger electrodes (50 μm) that were used in light independent stimulation (Wilke et al., 2011). With this system, the implanted patients could perceive bright objects, discriminate simple grating patterns and read letters in some cases. They reported a visual acuity of 20/1000 in these patients that is no better than patient implanted with the Argus II and its 60 electrodes. It was somehow disappointing that 25 times more electrodes did not improve visual restoration. This could be explained by the crosstalk between neighboring electrodes that are separated only by 70 μm and share a distant ground (see (Joucla and Yvert, 2009) for the effect of the ground on stimulus focalization).

Retina Implant AG device uses limited processing. The light reaching the photosensitive array is converted into electrical current according to a sigmoidal law. The operating range of the sigmoid is set by a voltage bias thus providing sensitivity across four log units and a dynamic range of two log units when this voltage is set. The stimulation frequency is set from 2 to 20 Hz with a pulse duration of 1–4 ms. More recently, D. Palanker’s group at Stanford reintroduced the concept of an autonomous implanted chip (Mathieson et al., 2012; Wang et al., 2012) similar to the ASR device. In this prototype, each electrode is connected to three photodiodes in series providing enough current to reliably evoke ganglion cell spiking. The photodiodes are sensitive to infrared light that is projected by an head mounted beamer. An external camera acquires the visual information that is processed to provide the stimulation pattern. With this device, the authors were able to show a reliable activation of ganglion cells in both normal rats and Royal College Surgeon (RCS) rats – animal models of retinal degeneration. This subretinal autonomous strategy offers appealing advantages because infrared light provides enough power to the photodiodes to elicit reliable responses while avoiding photophobic effects that have been previously described in RP patients (Hamel, 2006). Moreover, the photosensitive elements are enslaved to ocular movements meaning that the patient will scan the projected image naturally without any need of eye tracking system. Finally this procedure allows the implantation of multiple independent units under the same retina to increase the coverage of the visual field without increasing retinal detachment risks. This device is still on a preclinical stage but should be implanted in patients in the following years and should progressively catch up with already clinically tested implants.

In addition, the same group has addressed the difficulty to generate very focal stimulation and prevent spill over activation from one electrode to another. They indeed proposed to generate 3D implant designs to restrict activation to cells between bipolar electrodes (Palanker et al., 2004). Using blind rats and polyimide prototypes, they could show further that retinal cells can integrate into cavities of 3D implants (Butterwick et al., 2009). However, the technology retained to examine the tissue did not allow them to control the neuronal nature of these cells. In reaction to the implant, one could easily imagine that fibrotic or glial cells could multiply to fill empty cavities.

The Boston Retinal Implant Project that started in the 80s intends to achieve maximum development before starting clinical trials in human (Rizzo, 2011). They developed a first generation of implant containing 15 electrodes that were implanted in animals for biocompatibility and insulation assessment. Their next generation will contain more than 200 electrodes to provide useful perceptions to human patients.

Subretinal approaches present multiple advantages. First, the implantation under the retina guarantees a good contact between the electrodes and the targeted bipolar cells after retinal
reattachment. Some studies even reported bipolar cell integration in three dimensional implant structures (Palanker et al., 2004; Butterwick et al., 2009), thereby increasing implant stability. Moreover, subretinal stimulation threshold were found to be lower than for epiretinal stimulation (Jensen and Rizzo, 2006). This lower threshold could be due to the better contact between the electrode and the retina, or to an amplification mediated by convergence of bipolar cells onto ganglion cells.

As for epiretinal implants one of the remaining challenges for subretinal strategies is to achieve selective activation of ON and OFF pathways separately. ON and OFF bipolar cells morphologically differ in the depth of their axon terminal. OFF bipolar cells contact ganglion cells in the outer part of the inner plexiform layer, whereas ON bipolar cell terminals are located in the inner part of the layer. A theoretical study has quantified the effect of stratification depth on the response to electrical stimulation (Gerhardt et al., 2010) and showed that OFF bipolar cells would be preferentially addressed by small bipolar electrodes (diameter <100 μm) and short pulse durations (<150 μs) whereas ON bipolar cells would be selectively activated by large monopolar electrodes (diameter >100 μm) and long pulse durations (>150 μs). However, this study modeled bipolar cells as linear passive and single-compartment components. They did not include morphological properties such as dendritic arborization and soma size nor physiological properties of specific ionic channels. A more recent study (Freeman et al., 2011) accounted for these properties and in particular for the effect of calcium channel subtypes, differentially expressed in bipolar cells (Muller et al., 2003; Ivanova and Muller, 2006; Hu et al., 2009). They studied the effect of calcium channel expression, axonal resistivity and soma size on the responses to a sinusoidal electrical stimulation. They conclude that high frequency stimulations (500 Hz) cannot preferentially activate ON or OFF bipolar cells specifically. At lower frequencies (20 Hz) ON bipolar cells would be 20% more sensitive than OFF bipolar cells. However, the lack of knowledge on the distribution of other voltage gated ion channels across different bipolar cell types does not allow to conclude on the specific activation of different subtypes of bipolar cells.

Finally, important reorganization of the inner retina occurs after photoreceptor degeneration (Marc et al., 2003; Jones and Marc, 2005). These studies describe the reorganization process starting before any detectable cell death: photoreceptor terminal projection into the inner nuclear layer and ganglion cell layer, horizontal cell dendritic reorganization, Muller cell hypertrophy, amacrine cell migration and general cellular death. Subretinal strategies will need to account for this remodeling process or try to delay it.

2.3. Transchoroidal prostheses

Transchoroidal implants stimulate the retina from the outer part. This approach benefits from an easier implantation with no risk of retinal detachment or choroidal hemorrhage. With this strategy, two patients were implanted and stimulated for few weeks (Fujikado et al., 2011). Although this device developed by Osaka University contained 49 electrodes in theory, only 9 were active and among these nine electrodes, they were only able to elicit phosphenes through 5 and 6 of them in each patient respectively. However, this was sufficient to allow object localization and grat- ing discrimination. In this prototype, the active electrode array was placed in a scleral pocket and a return electrode was inserted inside the vitreous cavity allowing the current to flow across the retina.

Benefiting from a strong background in cochlear implants, a recent Australian initiative led by Bionic Vision Australia is also developing suprachoroidal devices. In initial studies in cats, they showed that they could evoke cortical activity by stimulating the retina from outside the sclera (Chowdhury et al., 2005). The strategy was efficient in different stimulation configurations – monopolar between an electrode of the implant and a corneal return electrode, monopolar between one of the electrodes and all the others acting as a common ground, and bipolar stimulation between two neighboring electrodes. In all these configurations, no incision of the sclera was necessary. Very recently, they implanted three patients with a 24 channel implant that could already evoke visual percepts. A next generation of implant called “Wide-view device” consisting in 98 electrodes is under development and will be implanted in the suprachoroidal space. They are expecting the first clinical trials with this device by 2013 while they will keep on developing the second “High-acuity device” with 1024 electrodes. This latest version should be implanted in patients by 2014.

Finally, another Korean team is experimenting suprachoroidal stimulation (Zhou et al., 2008). Similarly to the device from Osaka university, the device containing 7 electrodes was inserted between the sclera and the chorioid. However, in this case, the return electrode was not inserted inside the vitreous cavity but placed on the posterior surface of the sclera, reducing thereby the risk of complications.

Although the suprachoroidal technique allows low tissue damage when implanted, it requires higher current intensities to elicit visual percepts because of the increased distance between the electrodes and the inner retinal neurons.

2.4. Optic nerve prostheses

Optic nerve stimulation has been investigated as a potential target for electrical stimulation because it conveys the information of the entire visual field in a very small area. It is possible to stimulate peripheral and central vision at the same time. However, this nerve fiber concentration is also a disadvantage for very focal stimulation as more than 1 million axons are contained into the 2 mm diameter optic nerve.

One patient with retinitis pigmentosa was implanted with an optic nerve prosthesis (Veraart et al., 1998; Veraart et al., 2003). This device consisted in a 4 contact cuff-electrode placed around the optic nerve. The four contacts were placed around the cuff at 90° intervals, allowing to stimulate the four quadrants of the visual field. The stimulations were biphasic, charge balanced with durations varying from 20 μs to 420 μs (Veraart et al., 1998). By varying the stimulation amplitude, duration, frequency and number of pulses per phase, the patient was able to perceive different phosphenes (Delbeke et al., 2003). More than 100 of them could be reliably elicited and were used to encode a visual scene from a camera into electrical stimulations. With this strategy, the patient was able to reach 85% success rate on a pattern recognition task where symbols consisting in two or three bars randomly oriented were presented (Brelén et al., 2005). This high recognition score could be achieved with only four electrodes, suggesting that precise encoding of the visual stimulus is critical in the case of optic nerve stimulation. More recently, a second patient was implanted with a eight contact electrodes and the cortical evoked potentials were recorded as an objective measurement to better understand optic nerve stimulation (Brelén et al., 2010).

A chinese initiative – the C-sight project – is also developing optic nerve stimulation (Chai et al., 2008; Wu et al., 2010). Instead of surface stimulation the authors designed penetrating electrodes. They implanted rabbits with two-electrode devices and recorded cortically evoke potentials. They showed that different stimulation parameters could result in different cortical activity and therefore that the resolution of the device was not limited by the number of electrodes only. This group also developed image processing strategies in order to encode complex visual scenes with a limited number of pixels. They established different processing algorithms...
according to the complexity of the scene and tested these strategies in psychophysiological experiments in healthy subjects.

Finally, a Japanese group is also investigating optic nerve stimulation but through an intraocular prosthesis, stimulating the optic nerve head (Fang et al., 2006). This strategy would benefit the less invasive surgical approach of retinal implants as well as the coverage of the entire visual field in a limited stimulation surface. Such a device with four electrodes has been implanted in rabbits and could evoke cortical activity. However, they observed an increase of perceptual threshold after 1 month of implantation that could be due to a glial coverage of the electrodes as revealed by histological evaluation.

Together, these studies have demonstrated that optic nerve stimulation is an appealing strategy but that stimulation design will remain a major challenge to achieve fine spatial resolution rehabilitation in patients.

2.5. Cortical and LGN implants

Whenever retinal ganglion cells degenerate or after optic nerve injury, it is no longer possible to use the previous strategies. This is the case for glaucoma and optic neuropathy. Brain stimulation becomes the only available strategy for prosthetic visual rehabilitation.

The seminal work of Brindley and Lewin (1968) followed by Dobelle et al. (1974); Dobelle (2000) were the first attempts in providing a functional cortical prosthesis. Dobelle’s implant was placed on the surface of the visual cortex in eight blind patients. Some of them were implanted for 20 years without infection or other complication. With this device containing 64 electrodes, one patient was able to reach 20/1200 visual acuity. With a digital zooming function, he was even able to recognize 2-inch high letters at 5-feet distance corresponding to 20/400 visual acuity. This patient had been able to learn to interpret this stimulation in one day and could use it for 20 years. He was able to recognize characters and navigate in a room, performing complex tasks such as finding a hat and placing it over a mannequin’s head. This early breakthrough opened the field of cortical visual implants.

Because superficial stimulation of the visual cortex is not very efficient and in order to reduce perceptual thresholds, some teams investigated cortical penetrating electrodes. Penetrating electrodes were shown to elicit visual percepts with stimulation thresholds two to three times lower than for surface stimulation (Schmidt et al., 1996). The Utah Electrode Array consists in a device with 100 electrodes at the tip of acute pillars. This device that has been extensively used for neuronal recordings (Maynard, 2001) will be used for stimulation. The first functional experiments in non-human primates confirmed the perception of electrically elicited phosphenes (Torab et al., 2011). However, behavioral responses of monkeys could be observed on 8 electrodes out of 82 only. This low success rate could be due to the positioning of the electrodes within V1 (because the majority of successful electrodes were spatially clustered) or to the inability of non-human primates to report visual phosphenes. The authors observed a cellular death around the electrodes but without apparent impairment in visual function. Although this cortical strategy provides the only hope of visual restoration in case of ganglion cells and optic nerve degeneration, it still need to face critical challenges. The implantation itself is highly invasive with major risks of infection and inflammation due to foreign body introduction. Additionally, cellular death around the electrodes occurring after electrical stimulation (McCreery et al., 2010) could lead to an increase of activation thresholds.

Stimulation of the lateral geniculate nucleus (LGN) is also under investigation. It presents the advantage of targeting relatively simple and well characterized cells compared to cortical neurons. Moreover, magnocellular and parvocellular pathways are spatially segregated in the LGN, allowing to adapt image processing to the targeted area. Additionally, the foveal region projected on the LGN is larger than on the retina, allowing to achieve higher resolution with a given electrode size and finally, implantation techniques are similar to those already implemented for deep brain stimulation. Performing stimulation of the LGN in alert monkeys, Pezaris and Reid (2007) confirmed the evocation of visual percepts and their spatial localization. However, this proof of concept was performed with only two tetrodes implanted at the same time and the increase in number of electrodes may represent an additional challenge.

3. Global challenges

3.1. Electrode configuration and materials

In order to provide the best visual acuity to the patient, the resolution of the implant must be maximum. Psychophysical experiments (Sommerhalder et al., 2004) estimated that 1000 pixels where sufficient to perform basic tasks such as face recognition or reading. Fig. 6 summarizes the relationship between electrode size and restored acuity in the best patients for the different implanted devices. In theory, the acuity is linearly dependent on the size of the stimulation and a 20/20 acuity corresponds to a stimulation surface of 1 arcmin on the retina. Although the experimental curve does not follow the theoretical relationship exactly, there is a strong correlation between electrode size and restored acuity. Interestingly, the early device from Dobelle as well as Second Sight Argus I and II are close from their theoretical limit suggesting that the stimulation extent does not exceed the size of the electrode. In contrast, the ASR device from Optobionics and the MDPA chip from Retina Implant AG perform much worse than expected from the size of their electrodes, suggesting a saturation of the restored acuity. However, this saturation may be due to crosstalk between neighboring electrodes. The retina behaves as an inhomogeneous conductive medium in which ion species are acting as charge carriers. A good electrical contact between the electrodes and the tissue is critical for local stimulations along with the location of the return electrode. It was recently shown that local grounds surrounding each electrodes could provide more focal stimulations (Joucla and Yvert, 2009). Geometric properties of the electrodes can also contribute to a better resolution of the implant (Palanker et al., 2005) and three dimensional structures have been shown to allow retinal integration with limited glial reaction and reduce the spatial extent of electrical stimulation (Djilas et al., 2011).

Developments in electrode miniaturization are also tightly linked to materials engineering. Any electrical stimulation of a neural structure involves an electrode-tissue interface where charge movements occur. Two types of currents can be generated by the electrodes: Faradic currents involve chemical reactions – oxidation/reduction – at the interface whereas capacitive currents are induced by charge accumulation only. In the case of neural prosthetics, capacitive stimulations are preferred because they limit modifications of the electrode surface as well as pH modifications in the tissue (Cogan, 2008). In the context of visual implants, smaller electrodes introduce higher charge densities and therefore higher risks of irreversible reactions with risks of electrode degradation and tissue damage. Finding materials with high charge-injection limits is critical to decrease electrode size. Platinum (injection limit ~0.35 mC cm\(^{-2}\)) (Robblee et al., 1983), titanium nitride (1 mC cm\(^{-2}\)) and iridium oxide (4 mC cm\(^{-2}\)) are the commonly used material for neural stimulation. In order to improve biocompatibility and charge injection limits, some teams are...
investigating the behavior of doped-diamond electrodes (Bongrain et al., 2011; Kiran et al., 2012; Hadjinicolaou et al., 2012) that will be incorporated in future generations of implants.

3.2. Image processing for visual rehabilitation

Obviously, the amount of processing necessary to translate the acquired image into useful electrical stimulation patterns depends on the targeted structure. Stimulating retinal cells will – a priori – be easier than mimicking the entire visual processing up to the visual cortex.

One hypothesis is that the visual system is still plastic enough to interpret non-physiological stimulation patterns. This theory is supported by several experiments underlining the reorganization and physiological modifications of the visual system after blindness onset (Bavelier and Neville, 2002; Merabet et al., 2005). In blind patients, indeed, the visual cortex can be recruited by other sensory modalities introducing a cross-modal plasticity (Cohen et al., 1997). In this study, Braille reading performances of blind subjects were altered by transcranial magnetic stimulation of the primary visual cortex, thus implying a functional activation of the visual cortex by tactile inputs. It would suggest that the adult visual system is still plastic and that this plasticity would allow patients to learn and interpret new kinds of signals. With this hypothesis, processing algorithm should focus on conveying a maximum amount of relevant information through the limited number of electrodes. Some teams are currently simulating complex processing such as contour extraction (Dobelle, 2000), motion detection (Ouarti et al., 2012), saliency extraction (Parikh et al., 2009), complexity analysis (Sui et al., 2009) or even non purely visual inputs such as depth encoding (Lieby et al., 2012). All these strategies suppose that the visual structures downstream to the targeted cells will be able to interpret such signals. However, current experiments in implanted patients showed that only a minority of them were actually able to interpret complex visual inputs such as letters when non-physiological signals were applied (Humayun et al., 2012). This suggests that the plasticity of the system is limited and that providing more physiological signal would improve patients percepts and reduce the learning phase.

In this context, one of the major challenges in visual prosthetics is to develop real time processing algorithms to provide relevant physiological stimuli. Regardless of the implant location, it is necessary to perform the adequate filtering corresponding to the upstream computation. Subretinal stimulation targets bipolar cell terminals and requires to account for photoreceptor adaptation (Schnapf et al., 1990; Schneweiss and Schnapf, 1999), surround inhibition from horizontal cells (Yang and Wu, 1991) as well as activation kinetics. Epiretinal approaches need to predict action potential patterns for different subtypes of ganglion cells. Finally, cortical stimulation needs to account for specialized areas and complex processing such as orientation, color and motion. Current devices do not allow single cell stimulation and generally target many cells with different functions. In the primate retina, some 20 types of ganglion cells are meshed together (Field and Chichilnisky, 2007) and electrical stimulation from a single electrode will correlate the activity of all these cell types, introducing interferences between the information channels. Because of this lack of specificity, current image processing strategies are relatively simple and do not account for specific cell types.

There is no need of cell specific processing as long as each electrode elicits a phosphene with a broad spatial extent. But as micro-fabrication processes are developed, it will soon be possible to target a small group of neurons (Sekirnjak et al., 2008). In this context, it is critical to study information coding by specific ganglion cell types and to predict the accurate spike train for each cell. First models of ganglion cell behavior emerged from early electrophysiological experiments (Enroth-Cugell and Robson, 1966; Victor, 1988; Victor, 1987) in cat ganglion cells. These studies already emphasized major differences between X and Y ganglion cell types. The X type was found to exhibit a roughly linear response to spatial gratings while Y-cells behaved non-linearly to the same stimulus. More recent models successfully reproduced some ganglion cell properties. Linear non-linear Poisson (LNP) models consist in modeling ganglion cells as spatial and temporal linear filters followed by non-linearities and a Poisson process for spike generation. This method has been extensively used (Berry et al., 1997; Keat et al., 2001; Chichilnisky and Kalmar, 2002; Uzzell and Chichilnisky, 2004; Pillow et al., 2005; Pitkow and Meister, 2012) and provided satisfying predictions of ganglion cell responses to simple stimuli. However, having a model that predicts the responses to complex natural stimuli remains an open challenge (review in Gollisch and Meister, 2010).

In particular, Nirenberg and Pandarinath recently implemented a LNP-like model to encode visual scenes into stimulation patterns

Fig. 6. Acuity and electrode size. Correlation between electrode size and measured visual acuity is present although it does not follow perfectly the theoretical relationship – i.e. 5 μm ~ 1 arcmin ~ 20/20.
for ganglion cells (Nirenberg and Pandarinath, 2012). In their study, they did not use electrical but optogenetic stimulation using expression of channel-rhodopsin 2 (ChR-2) in ganglion cells. This principle allowed them to reliably evoke ganglion cell activity matching natural responses to some stimuli. Stimulus reconstruction accuracy as well as performances in behavioral tasks were shown to depend on the encoding process. Therefore, this work provides evidence that accurate encoding of ganglion cell activity will increase prosthetic efficacy. A major challenge is now to be able to target specific cell types independently (e.g. ON and OFF) in degenerated retinas.

### 3.3. Importance of ocular movements

Our eye is in constant motion. These movements are key components of normal vision and their disruption – in case of nystagmus – can lead to severe vision impairments. Ocular movements allow to scan the environment and center the foveal part of the retina on a region of interest to achieve high acuity tasks. They prevent perceptual fading due to photoreceptor adaptation and allow super-resolution (Martinez-Conde et al., 2009). Gilchrist et al. described a patient who completely lost the ability to perform ocular movements (Gilchrist et al., 1997). This patient performed head scanning of the scene, matching natural eye movements, to prevent perceptual fading and achieve high acuity tasks.

Visual prosthetic strategies need to account for this critical feature of natural vision. Blindness triggers the loss of the oculomotor control pathway and blind patients are not able to direct their gaze anymore. However, electrical stimulation of the optic nerve and cortex of blind patients confirmed that the expected location of a stimulus was highly dependent of the gaze direction (Dobelle, 2000; Veraart et al., 1998). Moreover, stimulating the retina independently of the eye position leads to unwanted pursuit motions (Wang et al., 2008). It is therefore crucial to be able to enslave the electrical stimulation to the position of the eye.

### 3.4. Comparison of the different strategies

In Table 1, we summarize the major clinical trials that have been conducted so far. It presents different prototypes with the number of implanted patients along with the implant characteristics and the restored acuity while Fig. 5 presents the physical aspect of the different devices.

Each of the targeted locations that we described above presents its own advantages and drawbacks. While cortical prostheses can benefit to all kind of blindness conditions including glaucoma, the other strategies require an intact connection between the retina and the brain, thereby reducing the number of potential patients. The downside of such an approach is the highly invasive surgical procedure with non-zero risk of lethal complications – hemorrhages and infections.

Non cortical approaches would apply to a smaller number of patients – 9% of blindness cases. However, they are much less invasive and do not threaten the life of the patients. We can divide them between optic nerve stimulation and retinal approaches. Despite a relatively preserved retinotopy inside the optic nerve, the very high fiber density is a real challenge for foci stimulation. More than 1 million axons are packed within a two millimeter diameter fiber so that the retinal surface is projected to the optic nerve section.

#### Table 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Prototype</th>
<th>Team</th>
<th>Electrodes</th>
<th>Size (µm)</th>
<th>Distance (µm)</th>
<th>Type</th>
<th>Patients</th>
<th>Acuity</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974</td>
<td>Cortical</td>
<td>Dobelle</td>
<td>64</td>
<td>0.25</td>
<td>0.75</td>
<td>Cortical</td>
<td>2</td>
<td>20/400</td>
<td>Dobelle (2000)</td>
</tr>
<tr>
<td>2000</td>
<td>ASR</td>
<td>Optobionics</td>
<td>5000</td>
<td>0.031</td>
<td>0.087</td>
<td>Subretinal</td>
<td>6</td>
<td>20/400</td>
<td>Capsi et al. (2009)</td>
</tr>
<tr>
<td>2002</td>
<td>Argus I</td>
<td>SSMP</td>
<td>16</td>
<td>1.6–0.8</td>
<td>2.8</td>
<td>Epiretinal</td>
<td>6</td>
<td>20/3200</td>
<td>Hornig et al. (2008)</td>
</tr>
<tr>
<td>2005</td>
<td>IRI S</td>
<td>IMI</td>
<td>49</td>
<td>1.25</td>
<td>1.4</td>
<td>Epiretinal</td>
<td>20</td>
<td>OL</td>
<td>Humayun et al. (2012)</td>
</tr>
<tr>
<td>2006</td>
<td>Argus II</td>
<td>SSMP</td>
<td>60</td>
<td>0.69</td>
<td>1.7</td>
<td>Epiretinal</td>
<td>32</td>
<td>20/1260</td>
<td>Roesler et al. (2009)</td>
</tr>
<tr>
<td>2008</td>
<td>EPIRET2</td>
<td>RWTH</td>
<td>25</td>
<td>0.34</td>
<td>1.7</td>
<td>Epiretinal</td>
<td>6</td>
<td>LP</td>
<td>Zrenner et al. (2010)</td>
</tr>
<tr>
<td>2010</td>
<td>MDPA</td>
<td>RIAG</td>
<td>1500</td>
<td>0.17</td>
<td>0.25</td>
<td>Subretinal</td>
<td>3</td>
<td>20/1000</td>
<td>Fujikado et al. (2011)</td>
</tr>
<tr>
<td>2011</td>
<td>STS</td>
<td>Osaka University</td>
<td>49</td>
<td>1.7</td>
<td>2.4</td>
<td>Suprachoroidal</td>
<td>2</td>
<td>OL</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2

| Prosthetic strategies advantages and drawbacks. Retinal and optic nerve implantation are safer than brain stimulation approaches. Implant stability has been demonstrated in all techniques however, the electrode-tissue contact is improved in subretinal approaches. The processing complexity increases in higher visual streams so that retinal approaches only need limited computation. The potential acuity restoration is highly dependent on the ability to stimulate a limited corresponding visual field. Retinotopic area is higher in the brain and smaller in the optic nerve, therefore resulting in different angular resolution for a given electrode size. Finally, retinal and optic nerve strategies are only suited for patients with intact ganglion cells and optic nerve – mainly retinitis pigmentosa and AMD. Brain stimulation in contrast can be used in any visual impairment when it is the only solution.  

<table>
<thead>
<tr>
<th>Implantation safety</th>
<th>Implant stability</th>
<th>Processing ease</th>
<th>Spatial resolution</th>
<th>Potential patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiretinal</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Subretinal</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Suprachoroidal</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brain</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

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Among retinal approaches, suprachoroidal implantations are the safest ones because they do not imply incision of the choroid, thus limiting risks of hemorrhages and retinal damage. However, the electrical threshold and current diffusion will be higher because of choroidal and pigmented epithelium resistivity. Finally, epiretinal and subretinal approaches differ in a few ways. Epiretinal devices benefit from the vitreous as a natural cooling system but the contact between the retina and the electrodes is only maintained by a single tack, thereby reducing the electrical contact. Targeting ganglion cells directly also implies a complex image processing before electrical stimulation whereas subretinal stimulation assumes that only photoreceptor function should be accounted for. Table 2 summarizes this comparison of the different strategies.

4. Conclusion
We presented here the current prosthetic strategies for visual rehabilitation in blind patients. The variety of possible locations for stimulation offers a wide field of research. Current implanted devices allow patients to perceive light, recognize shapes and objects and even read for some patients reaching 20/200 visual acuity. However, it is still well below the legal blindness limit (20/200) and does not allow patients to recover their autonomy. Current technological bottlenecks include electrode miniaturization maintaining safe stimulations; design of hundreds-channel stimulators and the associated data and power transmission; and design of real-time video processing algorithms providing useful percepts to the visual cortex. The Journal of Physiology 196, 479–493.

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References