Visual cortical prosthesis : an electrical perspective

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Abstract

The electrical stimulation of the visual cortices has the potential to restore vision to blind individuals. Until now, the results of visual cortical prosthetics has been limited as no prosthesis has restored a full working vision but the field has shown a renewed interest these last years thanks to wireless and technological advances. However, several scientific and technical challenges are still open in order to achieve the therapeutic benefit expected by these new devices. One of the main challenges is the electrical stimulation of the brain itself. In this review, we analyze the results in electrode-based visual cortical prosthetics from the electrical point of view. We first briefly describe what is known about the electrode-tissue interface and safety of electrical stimulation. Then we focus on the psychophysics of prosthetic vision and the state-of-the-art on the interplay between the electrical stimulation of the visual cortex and phosphene perception. Lastly, we discuss the challenges and perspectives of visual cortex electrical stimulation and electrode array design to develop the new generation implantable cortical visual prostheses.

Keywords — visual cortical prosthesis, brain-machine interface, electrical stimulation, prosthetic vision

1 Introduction

In 2019, according to the World Health Organization, there were 1 billion people blind and moderately-to-severely visually impaired in the world. It is predicted that this number will increase significantly in the next decades due to the ageing of the population [67]. Visual deficit can therefore impose a huge social and economic burden. The causes of visual deficits are multiple. It can be due to pathologies of the retina as retinis pigmentosa, age-related macular degeneration, optic nerve, retina traumatisms due to accidents or even tumors surgery [25]. The nature of these last pathologies and traumatisms, destroying the neurons of the retina or the fibers of the optic nerve leads to the conclusion that we can't only rely on retinal prosthetics to treat and restore vision. The visual cortex remains generally intact in these different kinds of visual deficits opening the way to the field of visual cortical prosthesis for treatment.

At the origin of the field of the visual prosthetics, there is the experimental observation reporting the perception of a flash of light called phosphenes in the visual field, induced by electrical stimulation of the visual streams. This has been demonstrated for the visual cortex by [38]. Since this seminal work, different ways of inducing these phosphenes have been developed, in particular through implanted electrodes. The core idea of visual prosthetics is to produce a pixelized vision made of multiple phosphenes induced by electrical stimulation of the visual streams. We can now categorize the main stream of visual cortical prosthetics field according to the used type of electrodes: surface electrodes (subdural electrodes) and intracortical electrodes. We can consider then that the field cortical visual prosthetics with surface electrodes began with

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the work of Brindley and Lewin study [12]. They showed that a blind, 52 years old patient, could perceive phosphenes by electrical stimulation of the visual cortex. This first line of research has been then followed by the Dobelle group [29, 28, 31, 30].

From the nineties, the field see the development of the visual cortical prosthesis with intracortical electrodes. Schmidt and colleagues showed that a phosphene can be induced by electrical stimulation of the visual cortex with microelectrodes penetrating the cortex. This second line of research is now more predominantly followed [89, 10, 64].

But despite these advances in phosphene induction, few visual cortical prosthetis projects have emerged during this period. However, the recent publication of reviews on cortical visual prosthetics emphasize a renewed interest in this topic [5, 63, 64]. Indeed, new advancements in electrodes design and wireless power opened new opportunities. Nevertheless, at present, no cortical prosthesis has restored a useful vision (navigation, reading, object and facial recognition). This therefore represents an important issue and several challenges remain to be overcome.

In this article, we adopt an electrical perspective on the field of visual cortical prosthetics. We first describe the state-of-the-art about the electrode-tissue interface and safety of electrical stimulation. Then we focus on the psychophysics of prosthetic vision and the state-of-the-art on the interplay between the electrical stimulation of the visual cortex and phosphene perception. Lastly, we discuss the challenges and perspectives of visual cortex electrical stimulation and electrode array design for the development of the new generation of visual cortical prostheses.

2 Principles of electrical stimulation of the brain

The electrodes produce an effect on the tissue at short time scales (from millisecond to minutes) during stimulation, depending on the electrical parameters. At longer time scales (hours-years), the electrode effect on the tissue depends on frequency of recurrent stimulation and on the electrode material creating encapsulation of electrodes due to glial reaction, tissue inflammation or neuronal loss [6, 72]. The reaction of biological tissue is complex and the inflammatory response may affect properties of the interface, by keeping the same electrical parameters it may change the effects of the stimulation. The factors influencing the efficiency of electrical neural stimulation seem simple, but they are not completely understood.

The principal focus of electrical stimulation is on the interface between the electrode and the neural tissue. Electrochemistry mechanisms have been extensively studied and described [57, 32]. Charge is carried by electrons in the implant material, and then by ions in the neural tissue. The effect of the electrode on the tissue can be capacitive, where no electrons are transferred from the electrode material to the tissue, or Faradaic, where electrons are transferred from the electrode material to the electrolyte, resulting in the oxidation or reduction of different chemical species in the neural tissue [77]. Ideally, stimulation should remain within the capacitive domain at all times to minimise the risk of damage to the nervous system. Chemical species produced by Faradaic reactions can either be toxic for neurons, or damage them indirectly by decreasing their ability to compensate for toxic substances, and by increasing their sensitivity to other stress factors [23]. The electrolysis of water may appear with a potential of only 1.23 Volt. The corresponding chemical reactions are the following:

$$2H_2O + 2e^- \longrightarrow H_2 + 2OH^-$$

$$O_2 + H_2O + 2e^- \longrightarrow OH^- + O_2H$$

It leads to a pH modification and may damage the tissue. The pH alteration is associated with pathological brain activities such as spreading depression or seizures [61, 74].

Most electrical stimulation of the nervous system consists of biphasic pulses. The first (usually cathodic phase) of the biphasic pulse is used to depolarise the neural membranes in the surrounding tissue and initiate the desired action potentials. Following that, a balanced anodic phase is used to reverse any chemical reactions that might have taken place during the first phase. A brief pause between the cathodic and anodic phase allows the electrode to discharge completely and return to potential equilibrium [22].

Stimulation systems used for experimental or clinical electrophysiology are either current- or voltage- driven. In the first case, a given current value is injected by the stimulator applying the necessary electric potential, while in the second, the electric potential is set and controlled by the user while the device injects the corresponding current. In general, current-driven stimulation is more reliable as it allows a control over the current injected. However, for long-term applications, it is more power consuming [76, 52]. Current-driven stimulation also allows to know the range of the injected charges offering a better safety criterion.

Indeed, Shannon demonstrated that one of the essential parameters for safe stimulation is the charge injected per pulse phase [85]. This is deduced by the current level times the duration of the pulse $Q = I.t$. For constant current stimulation, charge can be easily derived. However, in the case of constant voltage stimulation, the current does not remain stable, allowing only for an approximation of the injected charge per phase. These authors have demonstrated that longer pulse widths require higher charge content to elicit a response, even if their absolute current value may be lower than in the case of shorter pulses [85]. Therefore shorter pulses with minimal amplitude should be favoured to move the injected charge per phase value as far away as from the area of parametric space that can be harmful to the tissue.

In monopolar stimulation, the current flows between the stimulating electrode and the ground, usually placed away from the electrodes. The resulting electric field is diffuse. Bipolar stimulation is between two electrodes in the array, producing a more densely-packed electric field. The choice between the two largely depends on the position of the target neurons relative to the two electrode tips for bipolar stimulation. If the target is placed in between two electrode tips, bipolar stimulation may be preferred, as the generated electrical field is more focal. The decision is largely patient specific in clinical settings, such as in deep brain stimulation [43, 87].

In all cases, the applied voltage values (either through constant voltage stimulation, or as the voltage required to drive set current in constant current stimulation), should remain below the potential levels where irreversible electrochemical reactions begin to occur either in the electrolyte or the electrode surface. Otherwise, this would lead to tissue damage and electrode corrosion respectively. The interested reader can refer to the review of Merrill and colleagues [60].

The material of the electrodes has also an impact on the parameters and safety of electrical stimulation. A major advance in this area is the introduction of PEDOT and PEDOT:PSS electrodes. This kind of electrode presents electrochemical stability, high conductivity and impedance reduction [26, 73].

3 Psychophysics of prosthetic vision

This field explores the design and visual information processing required for the visual tasks necessary in daily life, like reading, navigation, or the recognition of objects or faces under prosthetic vision (for a review, see Chen [20, 21]). This line of research is crucial for electrode array design as its results can set constraints on the number, configuration, interspace and placement of electrodes on the visual cortex. And ultimately, the choice of these parameters has implications on electrical stimulations needed to restore a useful vision as psychophysics can shed light on the need of simultaneous electrode stimulation, time of stimulation etc...

Traditionally, in the studies of prosthetic vision, a video camera is on the head of the subjects recording the visual scene and sending them the visual information on a monitor through a pixelized filter simulating prosthetic vision for different tasks [18, 20, 21]. Cha and colleagues studied the optimal number of electrodes for reading. Their experiment estimated the number of pixels to 600 to restore a vision allowing reading. This minimal number was then increased to 625 (array of electrodes of 25x25) by Cha and colleagues [18]. Sommerhalder [86] reduced this optimal number and showed that 300 electrodes in foveal vision were necessary to reach a quasi-perfect reading of isolated words (almost 90% of words read correctly). They also studied reading in semi-peripheral vision (15° of visual angle) and reported that it is also possible after a period of learning of a month during one hour a day (64-85% of correct reading) with 300 electrodes. This is important given the foveal projection of the visual field on the cortex is in the calcarine sulcus and is therefore more difficult to access [101]. Indeed, if we can't reach it, it would be possible to use electrodes in the projection of the semi-peripheral vision on the cortex. Reading with prosthetic vision is also possible with a smaller number of electrodes. Fu et al. showed that with only a low resolution of 36 (array of 6x6) and 64 phosphenes (array 8x8), reading was also possible but it will strongly affect reading speed [40].

For facial recognition, Vurro et al. showed that 100 electrodes allow a facial recognition included between 70-80% of recognition rates with various configurations of electrodes (squared, hexagonal, log-polar) with an advantage however for the hexagonal after a pre-treatment of the image [100]. Other results also show that a hexagonal matrix would be more successful for the prosthetic vision [19]. More recently, a study suggests that facial recognition requires much more phosphenes than previously reported and at least an array of 32x32 electrodes is needed [44].

In terms of functional performance, a low-resolution electrodes array would allow wayfinding with a 6x10 array [98]. For complex scene recognition, more electrodes are needed, Zhao and colleagues suggested at least 48×48 electrodes for complete recognition would be necessary [107].

In any cases, phosphene density is the main determinant of visual acuity and a low-resolution visual prosthesis would lead to low efficiency on most acuity mediated visual tasks such as reading, object identification, face recognition, obstacle avoidance, etc... [18]. Therefore, a visual cortical prosthesis able to restore a useful general vision in everyday life will likely have hundreds of electrodes inducing phosphenes in the visual field of the patient.

4 Phosphene perception and electrical stimulation

4.1 Visual cortical prosthesis and surface electrodes

This first line of research has been followed by the groups of Brindley [11, 80] and Dobelle [29, 28, 31, 30]. The pioneering work of Brindley [11] showed that the common evoked phosphene is described as a flash of white light, as 'a star in the sky' or having 'the size of a grain of sago at arm's length' and that the phosphene perception change and stretch with the distance from the foveal projection on the cortex [11]. Most of the projects who involved a clinical development have been based on surface electrodes. The advantage of this approach is the minimal invasivity of the electrodes on the cortex.

The brain-machine interface is generally made of platinum electrodes [11, 29, 28, 31, 30], with squared [11], or circulars shapes [28, 31, 30]. The array is set on subdural configuration and the electrode arrangement of the electrodes themselves is squared [11], or hexagonal [28, 31, 30]. The minimal electrode interspace to obtain two distinct phosphenes varies according to the studies. Indeed, it is about 2.4 mm for Brindley first study [11], 1.5 to 3 mm for Dobelle and Mladejovsky [29], 1.5-2 mm for [70] and until 8 mm for Pollen and colleagues [71]. The minimal interspace would vary with the localization, Pollen suggests that this surprising results compared to those of Dobelle and Brindley would be due to the placement of his electrodes in the foveal vision where a large portion of cortex is used to analyze a small region of the visual field [71]. The size of the electrodes would not influence the phosphene perception [28]. But Pollen reported that it was possible to evoke phosphene with electrodes having a diameter of 0.25 mm and that the evoked phosphene are perceived as smaller than those obtained with electrodes of a diameter of 0.5 mm [70].

Winawer and colleagues reported that phosphene size increases with eccentricity and amount of charge but the area activated increases with the amount of charge but not with eccentricity [106] which is in line with non-human primate studies with microelectrodes [91, 92, 89]. Bosking et al. also found with human subjects that the size of the phosphene depends on the amplitude

Phosphene perception	**Subjects**	**Electrodes array**	**Visual task**	**Biocompatibility**	**Ref.**
Circles,without colors Non uniform field of phosphenes 1 stimulation - >several phosphenes Phosphene lengthened with the estrangement of the foveal projection	52-year-old patient affected by a bilateral glaucoma and then by a detachment of the left retina	80 square electrodes of platinum of 0.63 mm^2, Squared configuration, Subdural placement, Electrodes interspace: 2-4mm	None	Headaches	[11]
Sometimes colored phosphenes Non uniform field of phosphenes Variation of the size of phosphenes with the excentricity of the stimulation 1 stimulation - >several phosphenes Coplanar phosphenes	15 sighted or hemianopsic patients	Several implanted types Electrodes of platinum andiridium (90-10%)	Recognition of simple forms	Headaches	[28]
Phosphenes without colors Orange for the youngest patient Non uniform field of phosphenes 1 stimulation - >several phosphenes Coplanar phosphenes	A 43-year-old patient affected by a congenital cataract and then by a glaucoma and a detachment of the retina A 28-year-old patient, who lost both eyes during the Vietnam War	Array of 64 circular platinum electrodes of 1 mm^2 Hexagonal configuration Subdural placement	Recognition of simple forms and letters	2 days of implantation No reported complications	[29]
Phosphenes with the shape of points 1 stimulation - >several phosphenes	33-year-old patient blind by impact of bullet	Array of 64 electrodes of platinum 12 of the 2 mm^2, the rest of 1 mm^2 Hexagonal configuration Subdural placement	Braille reading at 30 words/mn	?	[31]
Phosphenes without colors Non uniform field of phosphenes	62-year-old patient who lost sight at 32-year-old by trauma	Array of 64 platinum electrodes of 0.78 mm^2 Hexagonal configuration Subdural placement A camera on glasses sends the visual information to a computer which translates it into electric impulses	Recognition of letters and numbers Visual acuity of 20/120	Implantation during 20 years for one patient No reported complications	[30]
?	12 patients	68-72 to 242 electrodes	Navigation Driving of cars Recognition of objects	Epileptic seizure	[48]
Phosphene of different brightness according to the stimulation	Blind individual with an 8-year history of bare light perception	NeuroPace stimulator of two four-contact subdural electrode strips implanted over the right medial occipital cortex	None	Headaches and dizziness	[62]

Table 1: Table of the different conditions and reports for clinical implantation of visual cortical neuroprostheses.

Pulse Waveform	Polarity	Amplitude	Frequency	Pulse duration	Train duration	Impedance	Ref.
?	Monophasic (−)	90 mW (mean power)	100 Hz	200μs	?	3000Ω	[11]
Symmetrical	Monophasic (+,−) Biphasic (+/−, −/+)	1-5 mA	30 to 200 Hz	0.25 to 2 ms	5 to 15 pulses	3000Ω	[28]
Symmetrical	Biphasic (+/−)	0.6-9.3 mA	50 Hz	0.5 ms	>3 s	?	[29]
Squared	Biphasic (−/+)	0.5-3 mA	50 Hz	0.25 ms	0.1-1 ms	?	[31]
Symmetrical	Biphasic (−/+)	10-20V	30 Hz	500 μs/phase	Train of 6 pulses	?	[30]
Squared	Biphasic	0.2–5 mA	5-100 Hz	200–1,000 μs	0.2–1 s	?	[106]
Squared	Biphasic (−/+)	0.3-4 mA	200 Hz	0.1 ms	200-300 ms	?	[7]
?	Monophasic Biphasic (−/+)	0.3-7.5 mA	200 Hz	0.1 ms	200-300 ms	?	[3]

Table 2: Electrical parameters of the stimulation of the human visual cortex to induce phosphenes with surface electrodes. The parameters refer to the common satisfactory parameters as reported in the articles.

of the stimulation. In addition, they discovered that phosphene size saturates at a relatively low current levels (around 2 mA) [9]. Various works also show a relation between the amplitude of the pulse and the luminosity of the phosphene [29, 30] although this relationship was observed for a study as non-linear [28]. It also seems that a frequency of stimulation superior to 30 Hz stop the flickering of the phosphene and that the reversal of polarity of pulses (+/−, −/+) has no influence on the perception of the phosphene [29]. Another point is the continuation of the phosphene after the interruption of the stimulus [11, 29]. According to Bak and colleagues [1], this obstinacy would be due to epileptic discharges such as reported by Pollen [71]. The minimum thresholds of stimulation to evoke a phosphene is between 0.2-4 mA depending on the electrodes and the most common stimulation reported in the studies is biphasic and symmetric (see Table 2). Shape and localization seem to stay globally stable over time [80, 62] and multiple induced phosphenes are coplanar [29].

One main challenge of visual cortical prosthetics is the specificity of the stimulation, e.g. for one stimulation, one phosphene. Indeed, the phosphene induction by electrical stimulation with surface electrodes has been reported sometimes as non-specific [11, 80, 29, 28, 31, 30]. An interaction between two adjacent phosphenes is also possible appearing with the shape of a bright cloud [13]. Beauchamp and colleagues also showed that when multiple electrodes were stimulated simultaneously, phosphenes could fuse into larger visual perceptions, not allowing independent recognition of the induced phosphenes [3]. However, more recent studies have shown reliable specific induction of phosphenes with surface electrodes separated by 6-10 mm [8]. They also could stimulate 4-6 electrodes and induce up to 5 phosphenes at the same time [8]. Therefore, it seems that producing a specific pattern using surface electrodes for different visual tasks is feasible and has been achieved for different cases (see Table 1).

Various visual tasks were achieved with these prostheses with surface electrodes. The first studies show that the recognition of letters and simple forms is possible [31, 30]. The last implantation of the team of Dobelle would have allowed the recognition of objects, wayfinding and the driving of a car on a private parking lot by a non-assisted patient [48].

Nowadays, the research on the visual cortical prosthesis with surface electrodes seems only conducted by SecondSight Medical Products with the Orion device [63]. The main arguments advanced against the use of the electrodes of surface are the currents used in the milliampere

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Pulse Waveform	Polarity	Amplitude	Frequency	Pulse duration	Train duration	Impedance	Ref.
Squared	Biphasic (+/-, -/+)	1.9-80 μA	200 Hz	200 μs	125 ms	?	[84]
Symmetrical, not squared	Biphasic (+, -)	10-20 μA	200 Hz	400 μs	1 s stimulus trial with three 200 ms pulse trains, with an intertrain interval of 200 ms	?	[96]
?	Biphasic	1-100 μA (as reported in [35])	?	?	?	?	[37]

Table 3: Electrical parameters of the stimulation of the human visual cortex to induce phosphenes with intracortical electrodes. The parameters refer to the common satisfactory parameters as reported in the articles.

order and the low phosphene resolution obtained with this technology because of the large size and interspace of the electodes at the surface of the cortex. Nevertheless, this technology presents several advantages. Indeed, it is the less invasive approach and it is compatible with the fabrication of arrays of flexible electrodes [99, 56]. This type of array would ease for example the surgical implantation in the calcarine fissure where we can find the most of the retinotopic maps of the foveal vision in humans [101].

4.2 Visual cortical prosthesis and intracortical electrodes

Most of the current projects follow the intracortical electrodes approach for the development of a visual cortical prosthesis. We can cite the Intracortical Visual Prosthesis Project (ICVP) at the Illinois University of Technology [79], the Cortical visual prosthesis for the blind CORTIVIS supported by the European Commission [36] or the Gennaris bionic vision system developed by Monash Vision Group supported by the Australian Research Council [55]. Intracortical electrodes present several advantages: they allow to reduce the necessary current to evoke a phosphene by several orders of magnitude [88, 84] and it is possible to implant hundred of electrodes on a very small surface of the cortex (4 mm^2 with CORTIVIS for example).

Schmidt and colleagues showed that such intracortical electrodes allowed the perception of phosphenes with a patient blind for 22 years after glaucoma [84]. The phosphene is described as having a round shape and of size ranging from 0.2 to 2° of visual angle, without colors or blue, yellow, red but not green [1, 84]. With this kind of penetrating microelectrodes, the luminance of the phosphene increases with the amplitude of pulses but experiments also reported a reduced size [1, 84]. It seems that a non-linear relation exists between the amplitude of pulse and the size of the evoked phosphene. During the stimulation, the luminosity of the phosphene can also decrease through time, maybe exhibiting a saturation effect [84]. Similarly with the results obtained with the surface electrodes, when at least 3 stimulations were simultaneously applied, phosphenes seemed coplanar for the patient and one stimulation can induce several phosphenes [84]. The minimal electrodes interspace to obtain two different phosphenes is 500 μm, but microelectrodes spaced with 250 μm typically did not elicit specific phosphenes [84]. The study of Schmidt et al. [84] on humans has been stopped prematurely because of complications [83]. A similar array of electrodes was then implanted in the macaque [10]. Five months later, the study has also been interrupted, the monkey became lethargic because of a reaction of the nerve tissue at the level of electrodes and thus because of problems of biocompatibility.

The team of Normann developed the Utah Electrode Array (UEA), which has been approved by the Food and Drug Administration (FDA) for long-term human studies [65, 66]. This array is a silicon-based matrix of 10x10 penetrating microelectrodes. Electrodes are long of 1.5 mm and are spaced out of 400 μm. Their tips are covered with platinum to facilitate the injection of currents. The observations on biocompatibility associated with the presence of this type of matrix can vary from an absence of reaction to the development of a gliosis or fibrosis between the array of electrodes and the brain, movement of the array or even bleedings [65]. Fernandez

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and colleagues recently implanted the UEA in the occipital cortex of a 57-year-old person during a six-month period. They found that stimulation thresholds necessary to induce phosphenes were in the 1-100 µA range [35]. This threshold also depends on the depth of stimulation as reported by De Yoe and colleagues in monkeys [27]. The lower threshold has been found in layers 2/3 and more precisely at the level of the frontier between layer 3 and 4A. Another low threshold is found in layer 5. Tehovnik and colleagues, by using a similar protocol, found the lower threshold in layer 5 at a depth of 1.6 mm under the surface of the cortex [93]. These results are coherent with those obtained by Bartlett and Doty [2]. The chronaxies of V1 neurons for the ocular saccades are also lower in the deep layer (0.17 ms) than in the superficial (0.23 ms) [90].

The electrical stimulation parameters leading to phosphene induction have not been well studied in humans. The electrical stimulation parameters with intracortical electrodes (as reported in Table 3) are symmetric and the amplitude range from 1 to 100 μA. The pulse duration when reported is between 200 and 400 μs and train duration range from 125 ms to 1s (three 200 ms pulse trains, with a inter-train interval of 200 ms).

The intracortical approach presents several advantages: current in the microampere order (see Table 3), and the possibility of increasing the spatial resolution on a small part of the visual field. The main inconvenience is probably the biocompatibility. It is the most invasive technology and it could act negatively with the vascularization of the cortex [24]. In addition, damage can be also induced by mechanical micromovements between the pulsating neural tissue and the static implants [69]. Nevertheless, the studies on cats and monkeys seem to show a good reaction of tissues through time [54, 102, 96]. It was shown that the encapsulation of electrodes does not prevent systematically the efficiency of the stimulation [41, 105]. Another disadvantage is the non-soft character of the arrays of intracortical electrodes [79, 97, 36]. As a large part of the visual field map of central vision is located in the calcarine sulcus [101], it seems difficult to reach this zone of interest with such arrays. It could be limiting factor given the importance of the foveal vision in reading, recognition of faces and the vision of details. In addition, it is still not clear if the array of penetrating microelectrodes can induce a complex pattern of phosphenes. Unlike surface electrodes, we didn't find any studies reporting the analysis of simultaneous stimulation of several electrodes or the achievement of visual tasks with such a prosthesis.

5 Electrical stimulation and electrode array design: challenges, potential solutions and perspectives

The studies reporting implantation of a visual cortical prosthesis either with surface or intracortical electrodes allow us to define several important points which need further investigations.

V1 accessibility A large part of the the visual field map of central vision on the cortex lies in the calcarine sulcus [101]. So far, no project has planned to implant a prosthesis in this area [64]. It seems very unlikely that a non-soft electrodes array will be implanted in this sulcus given the difficulty of access. However, flexible electrodes array would be a potential solution and particularly useful in order to induce phosphene in foveal vision. Some prototypes have been already developed for intracortical electrodes [78] and surface electrodes [56]. Cortical arrays of electrodes fabricated on smooth, flexible and ultrathin materials like parylene provide better coverage of the target area by conforming completely to the shape of the cortex. The same advances can also improve penetrating electrodes. By significantly diminishing their diameter and fabricating them on a soft, thin substrate, those implants promise to cause minimal damage during implantation, and no chronic damage, since the mismatch between a rigid material and soft neural tissue is mitigated due to the soft nature of the implant [82, 49]. Nevertheless, the implantation in the calcarine sulcus could lead to other technological problems including wireless transmission of information and long-term stability of the prosthesis.

High-number of electrodes for restoring a useful vision In order to restore a useful vision, it will be likely necessary to induce hundreds of phosphenes to achieve basic tasks of everyday life as psychophysics of prosthetic vision seem to indicate (see section 3). At present, the studies reported

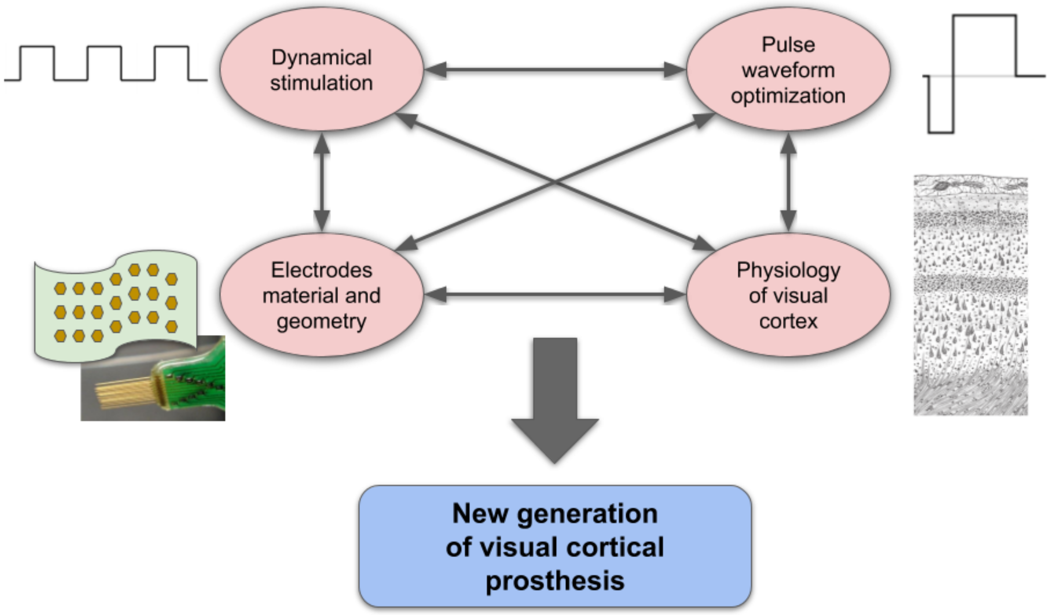

Figure 1: Interaction between different research fields leading to new generation of visual cortical prosthesis.

either development with surface/subdural electrodes or intracortical electrodes. No projects proposed a hybrid way. However, it presents an interesting benefit/cost ratio. Indeed, to minimize invasivity, intracortical electrodes could be implanted only in semi-peripheral vision and the foveal and peripheral vision would be supported by surface electrodes stimulation. The clinician would have the advantages of both techniques and to limit their inconveniences. Intracortical electrodes would allow increasing the spatial resolution in semi-peripheral vision due to their low size and the minimal interspace electrodes of 500 µm to obtain distinct phosphenes. This technology would allow to reach a number of electrodes high enough for acuity-mediated tasks like reading, navigation or object and face recognition. In addition, the amount of current needed to induce the phosphenes will be reduced by the use of intracortical electrodes array while having a good mapping of the rest of the visual field with surface electrodes. The other way, surface electrodes would limit the invasivity of the prosthesis.
Waveform uniformity It seems difficult to conclude on the most adequate parameters of stimulation for the evocation of phosphene in the visual field of the patients: parameters are variable or incomplete between the various studies with surface or intracortical electrodes. More particularly, the shape of the electrical wave is squared or symmetrical in the majority of the studies (or not reported, see Tables 2 and 3). Squared waveforms are a common shape for electrical brain stimulation. But thresholds are similar for cells and axons with the rectangular cathodic stimulation [75, 45, 59]. Different studies demonstrated that asymmetric waveforms can increase the selectivity of the stimulation by modifying the degree of inactivation of voltage-dependent sodium channels [81, 42]. Imbalanced waveform can also mitigate the dissolution of platinum electrodes [50]. This shows the importance of the relationship between the materials used, the electrode tissue interface and the waveform. This approach should be integrated for the development of the new generation of electrode-based visual cortical prosthesis.
Variability in frequency and duration of the pulses We can also observe a strong variability in the duration of the pulse (see Table 2 and 3). This lack of selectivity of the stimulation [29, 28] and the lack of clear data makes difficult the interpretation of the results concerning the optimal electrical parameters for evoked visual responses. The frequency and duration of the pulses can clearly be a criterion to stay in a safe stimulation domain while maximizing the perceptual effect

for long term use. New approaches are also being developed in the field of deep brain stimulation like the technique of current steering. It consists of using multiple electrodes to control the flow of current through the neural tissue, thus allowing a level of fine control over the volume of neural tissue activated by the stimulation. While a novel technique, its combination with high density implants holds promise of improvement, as a higher number of electrodes allows for more options in the way the current can be steered. Such novelties in both stimulation approach and implant hardware could be combined to improve the selectivity of the stimulation for visual restoration [16, 4].

Shape of electrodes The shape of the electrode has two major influences. Firstly, the shape have an impact on the electrode performance and on energy consumption, which can be an important criterion for long term implant and neural stimulation efficiency required for clinical efficacy. The relation of perimeter to surface area have an influence on the spatial distribution of current density [104] and it has been shown for example that fractal-shaped microelectrodes superior have better charge injection capacity, despite having smaller perimeter than other designs [68].

In second, the shape of the electrode has a direct influence on the electrical properties of the stimulation [14]. By changing the shape of electrodes, we can change the shape of the volume of activated neural tissue. Indeed, by segmenting the electrode, or, to change the shape of the contacts can increase the localization of current delivery into specific populations of neuron [103, 15]. A combination of these effects taking into account the spatial non-homogeneity of visual projection in the cortex could significantly improve the resolution of evoked visual perceptions.

Chronic stimulation The early studies report the implantation of cortical neuroprosthesis during years and even one during 20 years [30]. The reported complications are headaches and would be due to an activation of the meningeal fibers [11, 28]. A reported epileptic seizure is also reported, probably induced by an over stimulation [48]. More recently, Niketeghad and colleagues implanted subdural electrodes (a NeuroPace stimulator) in a blind individual [62]. They don't report any serious adverse events except mild headaches and dizziness in three instances. Nevertheless, it is difficult to conclude on the parameters of safe chronic stimulation. Indeed, in addition to not having a clear view on the parameters of electrical stimulation applied in the early studies, no implantation of a fully working neuroprosthesis has been achieved, allowing the induction of hundred of phosphenes via the simultaneous activation of a large number of stimulation electrodes.

Long-term stability The stability of the prosthesis for years is a challenge. Indeed, Towle and colleagues investigated the brain from a blind human subject who had a cortical visual prosthesis implanted for 36 years by Dobelle team [95]. They found a unexpected rotation of the electrode array ranging from 25 to 40 degrees away from the midsagittal plane. They suppose that the torque of the connecting cable could be the cause of this rotation. Wireless prosthesis is a potential solution to this problem [62]. Nevertheless, both approaches in cortical visual prosthetics are not equal in terms of stability. Intracortical microelectrodes are highly invasive. By penetrating the cortex, tissue responses like glial encapsulation, neuroinflammatory reponses or neuronal cell loss can prevent their long-term stability and efficiency [53, 6, 72]. Surface/subdural electrodes are now known to have more reliable long-term stability [94, 47].

Biocompatibility and electrode materials The biocompatibility of the materials used for the implantable part is essential for long-term implantation. In this case, the biocompatibility of a material is assessed by its ability not to induce toxicity, and to produce a minimal inflammatory reaction of the tissues for the long term use. Historically, the materials for implantable electrodes manufacturing are silicone and platinum, and have been well characterized in this context [33]. During the last decade, the development of new materials for electrodes such as the PEDOT:PSS (mixtures of poly (3, 4-ethylenedioxythiophene) and polystyrenesulfonate) has demonstrated progress in terms of biocompatibility [17]. The improved conductivity and impedance of new materials like PEDOT:PSS has a direct positive impact in any kind of brain interface. The improved conductivity allows for electrodes to deliver electrical stimulation with a minimal risk of damage to tissue, while their low impedance provides a much better recording quality, therefore improving both monitoring and evoking neurophysiological activity in patients. PEDOT:PSS has the high conductivity among organic thermoelectric materials and increase charge-transfer

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efficiency [17]. The fact that these improved properties are intrinsic to the material paves the way for fabrication of scalable electrodes down to the micro-scale that can efficiently stimulate and record activity in a very localised and selective manner. In addition, these novel materials are compatible with flexible substrates and microfabrication techniques offers additional possibilities to improve current brain implants. Both surface and intracortical electrodes can be improved through these advances.

Micro-coils Another strategy outside the traditional electrode-based cortical visual prosthetics is the use of magnetic stimulation by means of micro-coils [51, 39]. They are small implantable inductors that magnetically activate neurons. The brain stimulation of cortical pyramidal neurons in vitro has been reported as reliable and could be confined to spatially narrow regions (<60 μm) [51]. Similarly to electrode stimulation, a phosphene can be induced by magnetic stimulation [58, 46] and therefore this strategy could lead to restoration of vision. Other strategies are possible as described in [34].

6 Conclusion

Cortical visual prosthetics spurred a renewed interest these last years thanks to wireless and technological advances. As we saw it, compared to the retina, the optical nerve or with the LGN, the visual cortex presents a large surface of stimulation and remain usually intact after visual impairments. In this study, we focused on the electrical stimulation of the visual cortices and related aspects. We showed that despite several developments, there is still a knowledge gap concerning the safe parameters of electrical stimulation for multi-phosphene induction. To fill this gap and reach a complete clinical efficiency of the electrode-based cortical visual prosthesis seems key for the future. The next generation of visual cortical prosthesis will come hand-to-hand with new technological development of electrodes (in terms of materials and geometry), and the extension of approaches based on temporal sequences and new waveforms of stimulation to increase the efficiency and safety of phosphene induction.

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