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Electrodes and Chronic Optic Nerve Stimulation

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Visual pathways are often schematized as a parallel afferent transmission of pixel image matrices. Suggested interfaces would thus have numerous contacts in close proximity to the target elements. However, well organised tissue reactions would actively keep electrodes away from the neural units.
Alternatively, self sizing spiral cuffs were wrapped around the optic nerve of two blind volunteers in an attempt to develop a visual prosthesis. Unexpected features of the optic nerve code have emerged. This interface remained well tolerated for more than ten years. However, there is still a long way to go before to reach the useful vision rehabilitation.

K e y w o r d s: implantable electrodes, foreign body reaction, visual prosthesis, optic nerve code, neural interface

1. Introduction

The visual pathways are very much seen as a parallel structure with some degree of retinotopy, that is a point-to-point topological correspondence between the retina (or the visual field) and more central structures. This fundamental organisation has suggested that an artificial visual prosthesis should interface with the neural tissue through some grid of contacts, each transmitting a point or 'pixel' of an image captured by a camera [1]. This basic model supports the pioneering work of Brindley who implanted an 80 contact electrode array over the cortex of two human volunteers [2]. This massive parallel approach is also the main encoding scheme used in more recent retinal approaches [3], including the sub-retinal replacement of cones and rods by artificial photo-sensors, in an attempt to restore the natural eye camera [4]. At that level, the images of the outside world indeed take the shape of a straightforward array

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of pixels. However, further in the retina and down the visual pathways, a complex and largely unknown spatio-temporal encoding takes place. The visual areas of the brain are nothing like an internal projection screen upon which image pixels could be transferred in parallel.

Much work has been devoted to the development of miniature electrodes carrying an array of numerous contacts [5]. For an efficient stimulation, that is a selective activation with minimal currents, the electrode must be placed in close proximity to its target. However, any foreign material, even clean and sterile, devoid of toxicity or allergens will trigger protein adhesion and a well organised [6, 7] physiologic inflammatory reaction with fibrosis and neovascularisation (Fig. 1).

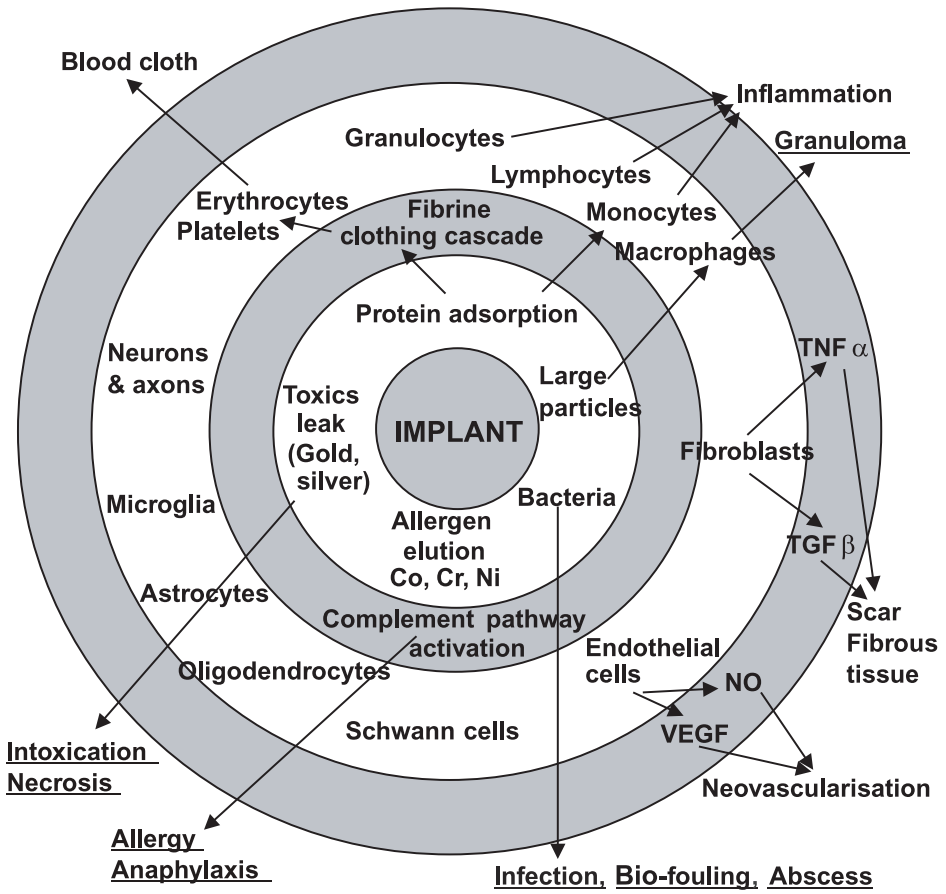

Fig. 1. Schematic view of events and actors activated by a neural implant. From the central circle (implantation) to the periphery: surface interactions (seconds), cell migrations (minutes), cell multiplication / differentiation (hours), paracrine cascades (days), matrix formation (weeks). The arrows underscore some major links. Underlined font is used for the adverse events

Indeed, as soon as an electrode is implanted, even if it is totally non-toxic and biocompatible, the protein adhesion will trigger a cascade of events. If things go wrong, activation of the complement pathway will manifest itself as an allergic reaction or even an anaphylactic shock Local fibrin deposits and blood clothing are activated. In addition, specialised leucocytes will trigger repair and defence mechanisms. In the presence of bacteria, this inflammation will degenerate in biofouling or local infections. Specific cells will produce specific cytokines such as (TNFa and TGFb) that control the production of scar tissue and a fibrous capsule [6]. Other messenger molecules such as NO and VEGF [7] will set up a new vascularisation as required by the anatomical changes. The details of the messenger distribution and their effects vary among the different kinds of tissue involved (endoneurium, perineurium, epineurium). When any particles are present, 'frustrated phagocytes' will induce an exaggerated and prolonged inflammatory reaction that will lead end up in a granuloma. These changes take place in the brain as well. Here, blood toxicity is a major issue leading to neuronal destructions even in the case of minor traumatic bleeding. Fibroblasts and endothelial cells play a major role here as well. The microglia will supplement the leukocytes in the tissue reactions. If micro-needles are used, breakage and some unavoidable local bleeding will kill local neurones through blood toxicity [8]. In all cases, the target will become separated from the contact again with the result of reduced selectivity. Then, there is a good chance that the stronger currents needed to reach the activation thresholds cannot be sustained by the small contact areas available.

For those reasons, massively parallel interfaces still represent a major challenge. On the other hand, gradual recruitment of axons can be achieved by controlling the stimulation intensity applied through external electrodes [9]. Cuff electrodes implanted around a peripheral nerve have selective activation properties [10]. It seemed therefore a good idea to apply the same principle to the optic nerve, considering that a cuff electrode would be more easily tolerated and larger contact areas could provide adequate stimulation currents [11]. Here we describe long term observations in two blind volunteers who received a prosthetic device connected to their optic nerve more than respectively ten and five years ago in the frame of two European projects MiViP (Microsystems based Visual Prosthesis) and OPTIVIP (OPTImization of Visual Implantable Prosthesis).

2. Material and Methods

The projects were approved by the 'Comité d'éthique Biomédicale Hospitalo-Universitaire de L'Université catholique de Louvain' and comply with the Declaration of Helsinki. Both our volunteers suffered from a familial form of retinitis pigmentosa. Our first volunteer, a 59 years old lady, had suffered total blindness (no light perception) for two years when, on 05/02/1998, she was implanted with a four

contact spiral cuff electrode around the intracranial portion of her optic nerve [12]. This electrode was firstly connected to the outside world through a subclavicular percutaneous lead until, 30 months later, the stimulator and the antenna were secondarily implanted under the scalp above the parietal and mastoid bones respectively.

Our second patient, a 68 years old man, was implanted on May 18th 2004. He had been totally blind for 33 years [13]. In his case, the electrode had two rings of four staggered contacts, thus providing the eight stimulation positions around the nerve. The electrode, the stimulator and the antenna were implanted during a single surgical procedure. For this second trial, the electrode was placed on the intra-orbital portion of the nerve just behind the eye [13]. Although technically difficult, this surgery was extremely benign compared to the craniotomy required for the former intra-cranial surgery. The procedure was followed by a temporary mydriasis, a ptosis and a limitation of all eye movements. These symptoms disappeared within two months but a slight miosis and some limitation in the operated right eye adduction can be seen years later. However, there is no visible scar and the patient is not aware of any sequel.

The stimulation applied consists in single pulses or trains of current controlled pulses of variable frequency and pulse numbers. Each pulse has a rectangular biphasic shape of variable duration. The second, charge balancing, phase is five times longer with a five times lower current than the initial stimulating cathodic phase. The monopolar stimuli can be applied to each of the electrode contacts referred to the implanted stimulator titanium encasing which forms the anode. Bipolar and simultaneous stimuli have been tested as well but did not lead to any significantly different findings.

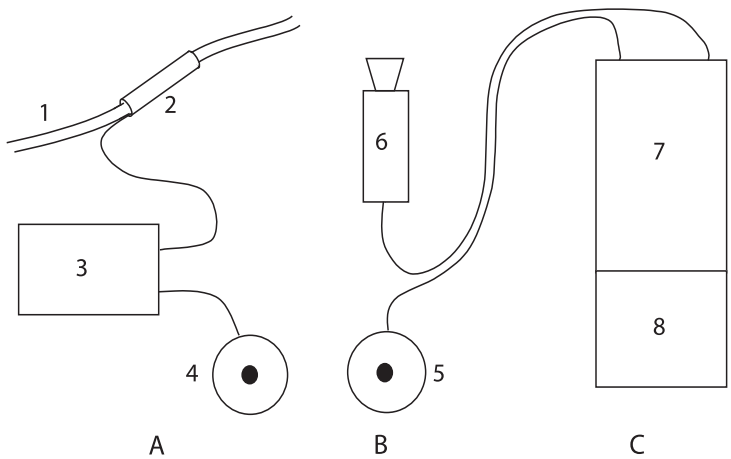

Fig. 2. Schematic representation of the visual prosthesis with implanted parts in A, elements attached to the spectacles in B and C – the belt carried devices. The numbers refer to: 1 – the optic nerve; 2 – the cuff electrode; 3 – the implanted stimulator; 4 – the implanted antenna (with central magnet); 5 – the external antenna; 6 – the miniature camera; 7 – the signal processor; 8 – the batteries

For the initial calibrations, the volunteers sat with their right (implanted side) eye in the centre of a graduated hemisphere, holding one index finger straight ahead in the middle of the hemisphere. This reference point was also used as a fixation point. A whole spectrum of stimulus parameter (Intensity, Duration, pulse Frequency, pulse Number) combinations was successively applied while the volunteer carefully indicated the location and extends of the resulting perceptions with his/her free hand. This procedure was used to establish a list of available phosphenes. Other perception characteristics such as brightness, colour, structure and movement where noted as well.

The external components of the complete prosthesis (Fig. 2) include a miniature black-and-white camera attached to spectacles and connected to an image processor. This device applies a decimation that reduces the image to 90 vertical and 60 horizontal 1° square pixels. Thresholding and edge detection further reduce the data. The remaining active pixels are compared to a stored list of available pixels and whenever there is an overlap, the parameters of the corresponding pixel is send through the transcutaneous antennas to the implanted stimulation unit.

3. Results

Because of the expected recruitment of fibres in a nerve stimulated from its periphery and because of the known central magnification phenomenon [14], it was anticipated that most stimuli would induce large flash perceptions encompassing almost half the visual field (Fig. 3). Nothing like that was ever seen in our first volunteer who described small spots of light. Somme patches have a diameter of 10 degrees and more but usually, they are much smaller and often point-like. The average size of the phosphenes depends on the stimulus strength defined as the ratio between the stimulus current and the threshold intensity for a similar train with pulses of the same duration (Fig. 4).

The larger phosphenes typically have a structure made of rows or columns of dots. Various colours can be perceived and a single phosphene often combines several colours, often one colour for the dots and another colour for the background. Different colours are described for the same stimulus on different days. A movement perception is rarely reported and is often found to be related to inadvertent eye movements. The perception location is indeed clearly referred to the retina so that a corresponding perception position shift is reported when the eyes are turned away from the fixation point during the stimulation.

Phosphenes have a retinotopic localisation in the sense that the two temporal contacts induce phosphenes in the nasal visual half-field and vice-versa for the two nasal contacts. Also the two upper electrode contacts yield phosphenes in the lower half-field while the lower contacts generate phosphenes above the horizon line. Curiously, the phosphenes obtained with one contact remain restricted within one

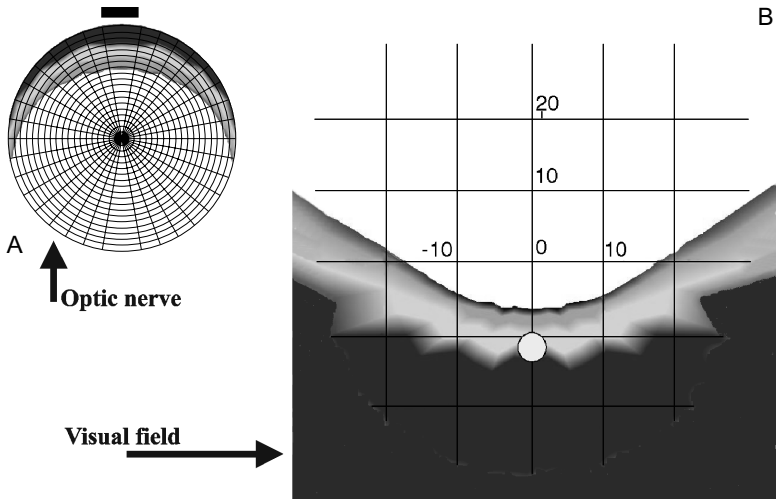

Fig. 3A. The circular picture represents a nerve section where different gray levels mark the margins of the expected activation fields for fibres of 0.6 µm, 0.9 µm and 1.2 µm, the last ones being activated deeper into the nerve. The active electrode contacts are represented by a black bar just outside the circle; **B.** On the right, the corresponding visual field as expected from retinotopy and the central magnification rules. Only part of the visual field has been represented. This model shows why phosphenes encompassing almost half the visual field were anticipated even for relatively weak stimuli. In contrast, the small white disk on the right represents the size and location of a typically observed phosphene

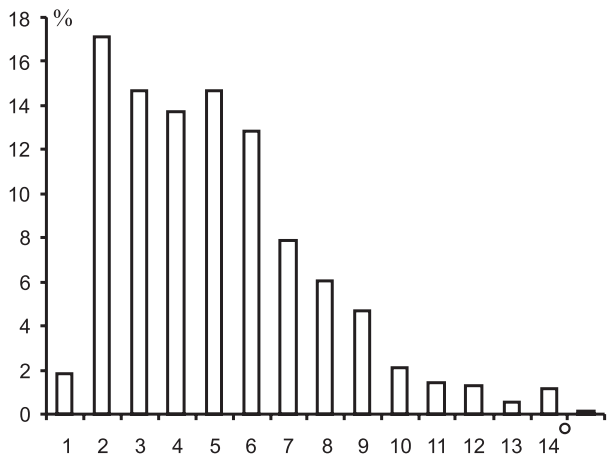

Fig. 4. Phosphenes were elicited by 957 different supra-threshold stimuli obtained while systematically exploring the effect of the electrode contact, the current amplitude, the pulse duration, the pulse frequency and the pulse train durations. The resulting phosphene size was reported by the volunteer as the diameter of an equivalent circular area. A histogram was constructed of the percentage of phosphenes reported to have a given diameter in degrees (the limit in precision). Note the multiple peaks. When separating the data in three subgroups according to the stimulus intensity (1.3 times threshold, between 1.3 and 2 times threshold and twice threshold or more for otherwise identical conditions), this histogram can be fitted to the sum of three Poisson distributions with averages 2.7°, 4.1° and 5.9°

quadrant of the visual field and do not appear in the opposite hemi-field while it is obvious that stronger currents stimulate the entire optic nerve section. The retinotopy described above is however seriously restricted by the fact that perceptions were never located outside a narrow vertical band from 10° above horizon to 50° down, 15° to the left and 15° to the right.

In the first year after the implantation, the light perception on prolonged pulse trains faded and disappeared within 200 to 500 ms (Fig. 5). This clearly reminds of the stabilized image phenomenon [15]. Ten years after the implantation, this phenomenon has completely disappeared and a 5 s long train is fully perceived during the whole five seconds.

Strength-duration curves based on the subjective perception yielded a chronaxie of about 130 µs in the first year of stimulation. Ten years later, this value has not changed. The thresholds however have come down (Fig. 6) from 834 µA (SD = 502 µA) to 275 µA (SD = 91 µA) for single pulses of 100 µs duration. For trains of 17 pulses at 160 Hz the average threshold did not change significantly (from 55 µA (SD = 27 µA) to 63 µA (SD = 16 µA). Pulses of 170 µs were used in the second volunteer in order to take into account the longer (but also stable) chronaxie of 190 µs. Again, a drop of the average threshold current was observed over a two year period for single pulses: from 1740 µA (SD = 458 µA) to 277 µA (SD = 59 µA). In this case, the threshold for 16 pulse trains at 300 Hz also decreased from 1600 µA (SD = 331 µA) to 325 µA (SD = 84 µA).

The perceived phosphene brightness is typically weak and not linearly proportional to the stimulus intensity but rather exhibits an all or nothing character except

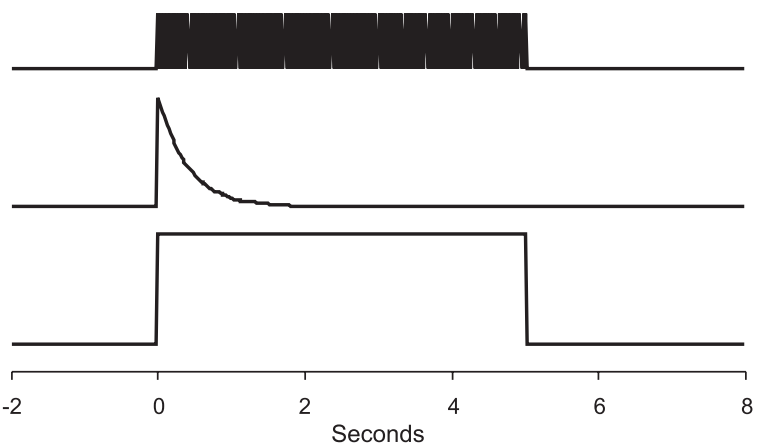

Fig. 5. The abscissa represents the time in seconds. The top trace shows the stimulation (a continuous pulse train of 5 second). The second and third traces schematically represent the descriptions given by the blind volunteer of the perceived brightness of the phosphenes induced by the stimulus above. The middle trace represents the perceptions in 1999 when the perception quickly faded out (stabilized image phenomenon) and the bottom trace corresponds to the constant luminosity reported in 2009

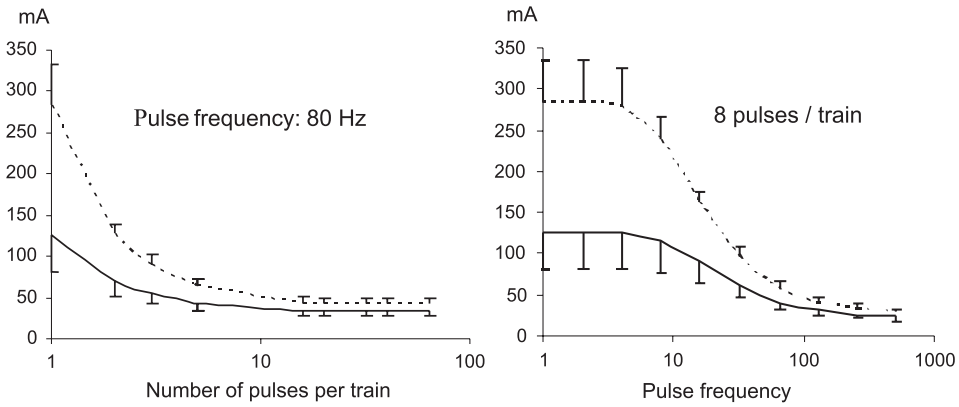

Fig. 6. Left: the perception threshold current to the pulse train stimulations as a function of the number of pulses/train for a pulse frequency of 80 Hz. Right: the perception threshold current to the pulse train stimulations as a function of the pulse frequency for trains of 8 pulses. The dotted lines correspond to the data obtained in 1998 (146 thresholds). The solid line represents the results of 2008 (230 thresholds). A separate best fit to the data for each electrode contact 0°, 90°, 180° and 270° was first obtained. The traces above represent the average and standard deviation (error bars) of those four functions

very near the threshold where occasional very faint perceptions are reported. Normal stimuli only induce light perception and no other sensation whatsoever. An occasional sensation of pressure in the eye was reported by the second volunteer (intra-orbital) with the strongest current trials but these sets of parameters are avoided and thus remain rare. Such sensations were never reported by the first volunteer with the planned settings. However, very few accidental stimuli with much larger intensities and pulse durations than intended resulted in pain and very bright light perception.

The effect of the pulse duration on the threshold is very well described by the classical chronaxie and rheobase parameters. The chronaxie is found to be independent of the pulse number and frequency. On the other hand, these parameters clearly reduce the rheobase and hence the threshold (Fig. 6), clearly pointing to a spatial and temporal summation effect. The pulse duration, intensity, frequency and number not only prove to contribute to the stimulus strength in relation to the threshold, but also affect the size and the position of the perceptions along a radius from the stimulating contact to the centre of the nerve. Modelling of the optic nerve fibre recruitment (Fig. 3) suggests that phosphenes are perceived at the edge of the stimulated field. Using single pulses, it is possible to obtain small (near threshold i.e. strength < 1.3 threshold) central phosphenes because of the required spatial summation to reach threshold. Then the activation field (region of the nerve section where the nerve fibres are activated) reaches the centre of the optic nerve and correspondingly of the visual field. On the other hand, the near-threshold high-frequency prolonged stimulation trains yield peripheral phosphenes by temporal summation of low amplitude stimuli (Fig. 7).

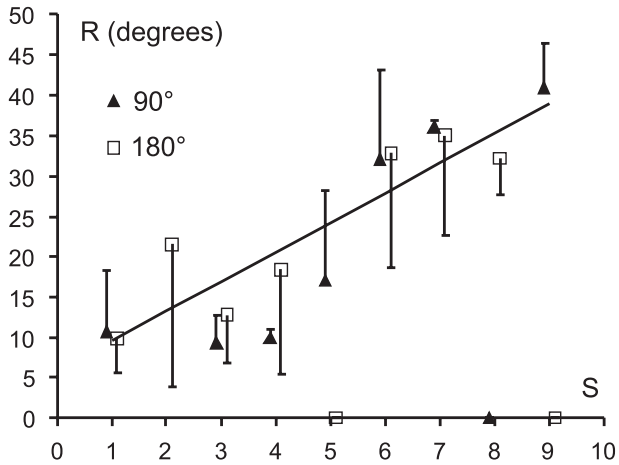

Fig. 7. The results reported here have been obtained with 185 stimuli consisting in the trains of 1 to 33 pulses at frequencies between 40 and 320 Hz. The individual pulse duration varied between 21 and 400 μs. The pulse current intensity was just above the threshold for the phosphene perception. This threshold current appears to be lower for high frequency and/or the long trains than for single pulses of the same duration (not shown). This effect corresponds to a stimulus effectiveness summation (*S*) quantified by the ratio between the threshold current for a single pulse (T_1) and the threshold for the train (T_T) of similar pulses. Eccentricity (*R*), in degrees from the centre to the periphery of the visual field, is plotted against the summation factor ($S = T_1/T_T$). The data shown are for the two electrode contacts corresponding to the lower visual field and yielding the largest position ranges. The figure indicates that the near-threshold long and/or high frequency stimuli yield eccentric phosphenes as opposed to the rather centrally located phosphenes obtained with single pulses

When a selected set of about 110 to 120 phosphenes is used with a head-worn camera to transmit visual information, it is possible for the volunteer to identify large characters projected in front of her. High scores (80%) are obtained after a few weekly training sessions but the time required to identify of a single character could never be brought down much below 1 minute. Similarly, the volunteer can locate, recognize and seize simple objects placed in a black-and-white environment. The performances after training quickly reached 100 % but again, at the cost of far too much time (about 40 s) to perform a useful task. The same performances are still obtained 10 years later. However, any attempt to work in a less restricted environment faces the problem of controlling the eye position within the orbit. For example, locating and recognising of relatively small objects works fine, but when trying to evaluate how broad an item is, uncontrolled lateral eye movements almost invariably lead to an overestimation. Part of the time cost to complete functional tasks is due to the scanning head movements required to bring all the object details under the limited field of usable phosphenes. In addition, a significant part of the time simply consists in a waiting time as if the volunteer needed some thinking before identifying or grasping of an object.

The observations above were made with the first volunteer (intra-cranial electrode). In the second volunteer, phosphenes are obtained as well. However, despite a high education level and a strong motivation for the study, this person is unable to precisely describe the induced perceptions. These are very variable and most often extremely faint. Phosphene generation by the implant can be confirmed but they cannot be exploited functionally.

4. Discussion

The effect of the number of pulses within a stimulation train clearly indicates that a single action potential in the optic nerve does not lead to the perception but that convergence or repeated activity at a sufficient frequency are necessary to reach the threshold [16]. Despite the fact that a clear retinotopy was found, the results above are quite unlike what was anticipated. There is no simple one-to-one correspondence between the activated axons and the pixels of a perceived shape. This clearly reminds of the discrepancies observed when acutely stimulating the retinal ganglion cells [17]. Some spatial differentiation could be a part of the visual information encoding scheme in the optic nerve. The observed spatial summation suggests that axons spread all over the nerve section converge to influence each particular pixel of the visual field. On the other hand, the multiple Poisson distribution of the phosphene sizes is compatible with just a few (2 to 6 as suggested by the shapes [18]) inputs to control the phosphene size. That the neural code pertaining to a single pixel tends to be distributed all over the optic nerve section can also be deduced from the fact that the perceptions generated by one contact remain within an hemi-field even with stimuli several times stronger than the threshold, when the whole nerve section is expected to be activated [18]. Although unexpected, these findings turn out to be most favourable to provide a large number of different perceptions to convey visual information through the prosthesis. On the other hand, a dense parallel point-to-point connection between the peripheral and central visual pathways is clearly naïve. This might explain contradictory findings in the literature about retinotopy in the optic nerve [19].

Poor brightness, which has remained constant over ten years, is a problem that could not be overcome. Accidental stimuli indicate that higher luminosity might require the stimulation of very high threshold fibres that could not be activated safely at the level of the nerve. Again, the observed dissociation between luminosity and pulse strength is rather puzzling and underscores the complexity of the visual encoding scheme. It should be pointed out that our findings are in sharp contrast with the brightness modulation by the stimulus intensity observed in an epiretinal prosthesis project [20].

Neural code however is not the only issue. We are working here with the patients suffering a chronic evolving disease of their visual pathways. In our first

volunteer, the exploitable visual field is very restricted laterally and in the upper hemi-field. This is so severe that it would clearly limit the performances of any prosthesis. The poor results in our second volunteer seem to be related to the 30 years of disuse of the visual pathways before the implantation [21]. Other factors may have to be considered as well such as the presence of the dura mater between the optic nerve and the electrode contacts in the case of the intra-orbital implantation. This clearly increases the thresholds, but the current sources used remain within their functional range so that the same stimulation current probably reaches the optic nerve as in the case of intra-cranial electrode where no dura mater surrounds the nerve.

High scores [22] are obtained during functional testing are jeopardized by the required time. Training does lead to some improvement but still falls short of minimal requirements for practical usefulness. Also, a subjective sense of vision is never attained and the perceptions remain described as very artificial, requiring some 'thinking time' [23] before decisions can be made about the perceptions. Noteworthy, localising and grasping of objects after head scanning in a restricted space is very precise in comparison with the important variability, perhaps in part due to superimposed spontaneous neural activity, of the localisation of the phosphenes obtained by pointing in the hemi-sphere. The errors linked to uncontrolled eye movements in the open space trials indicate that sight is very much a matter of eye and head position control rather than a feature of the eye seen as a mere camera. An integrated gaze orientation compensation system is clearly more important than anticipated and to be considered as an essential requirement.

Finally, the lowering of thresholds (over more than ten years in our first volunteer) is excellent news. Despite the fact that these persons are ageing and suffer a degenerative disease, no degradation was observed. There is no change in the threshold to the high frequency or prolonged pulse train stimuli, thus the optic nerve fibres are well preserved. On the other hand, the thresholds to single pulses have gone down quite significantly. A central origin of these changes is the most plausible explanation and would correspond to some plasticity whereby the spatial and temporal summation required for the brain to consciously perceive a stimulus has been clearly reduced.

5. Conclusions

Perhaps the most important result of this study is the urgent need for a much better understanding of the neural codes carried by the very heterogeneous fibre population of the optic nerve. The same question will be raised at any level of the visual pathways where a connection is to be attempted.

It is often expected that the brain plasticity would compensate for imperfect signal coding. A better knowledge of plasticity would indeed help to organise the information in such a ways that the brain can fill in the gaps but we know that

not all limitations can be compensated for. On the other hand, this topic quickly leads to even more elusive questions about the nature of visual perception and consciousness.

Another important problem to deal with is the secondary degradation of the patient's visual pathways as a result of disuse or transsynaptic degeneration. In this study, the volunteers with any remnant light sensitivity had been discarded to avoid misinterpretation of the implant performances because of temporary partial recovery due the stimulation or to the stress of surgery [24]. The present paradox is that for better results, the visual prosthesis should be implanted as early as possible, that is, before the presently primitive prosthesis can be of any use to the patient. Electrical stimulation itself could perhaps be a solution to maintain the visual pathways while photosensitive cells degenerate [25, 26, 27]. This application might in turn become a first indication for the implants.

Interfacing the prosthesis at the level of the optic nerve is certainly feasible and has produced much new knowledge but also raised many questions. One is about what would be the optimal site to interface the prosthetic devices with the visual system. The optic nerve approach is certainly very well tolerated. The rediscovered importance of integrated gaze orientation certainly gives an advantage to the subretinal approach [28]. However, only retinitis pigmentosa patients are candidates for these 'anterior' approaches while there is so much pressing demand from other patients suffering from more acute conditions such as traumatic optic nerve lesion. In these, the cortical approach of the very first attempt by Brindley remains a most valuable goal [29].

Acknowledgments

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