CORTICAL VISUAL NEUROPROSTHESES FOR THE BLIND

E. Fernández[1*], F. Pelayo[2], P. Ahnelt[3], J. Ammermüller[4], R. A. Normann[5]

[1] Instituto de Bioingeniería, Universidad Miguel Hernández, Elche, Spain

[2] Dept. Tecnología y Arquitectura de Ordenadores, Univ. Granada, Granada, Spain

[3] Dept. Physiology, Medical University, Vienna, Austria

[4] Dept. Biology, University of Oldenburg, Oldenburg, Germany

[5]Dept. of Bioengineering, University of Utah, Salt Lake City, USA

***Address all correspondence and reprint requests to:**

Dr. Eduardo Fernández

Universidad Miguel Hernández

Instituto de Bioingeniería

Fac. Medicina

San Juan 03550 ALICANTE

SPAIN

Tel.: +34/96 591 9439; FAX: +34/96 591 9434

Email: e.fernandez@umh.es

Abstract

A survey of the present state of research on a visual neuroprostheses, interfaced with the occipital cortex, as a means through which a limited but useful visual sense could be restored to profoundly blind people is given. We review the most important physiological principles regarding this neuroprosthetic approach and emphasize the role of neural plasticity to achieve the desired behaviour of the system. While the full restoration of vision is unlikely in the near future, the discrimination of shape and location of objects could allow blind subjects to 'navigate' in a familiar environment and to read enlarged text, resulting in a substantial improvement in the quality of life of blind and visually impaired persons. Moreover, if we can understand more about the fundamental mechanisms of neuronal coding, and to safely and selectively stimulate nervous system, there will real potential to apply this knowledge clinically.

Keywords

Artificial vision, neuroprosthetics, visual prostheses, bioinspired retina, electrical stimulation

1. Introduction

Loss of vision poses extraordinary challenges to individuals in our society which relies heavily on sight. Although in recent years the techniques of molecular genetics have led to a rapid identification of a great number of genes involved in visual diseases [1, 59, 66], the nervous system once damaged is capable of little functional regeneration and currently there is no effective treatment for many patients who are visually handicapped as a result of degeneration or damage to: 1) the retina, 2) the optic nerve, or 3) the brain. While pharmacological interventions provide therapeutic solutions to many physiological problems, a pharmacological approach to the mechanisms of blindness has not been discovered.

A new, human engineered approach to this problem has generated new hope in those suffering from profound vision loss. This approach, a vision neuroprosthesis, is based on the observation that electrical stimulation of neurons at almost any location along the visual path will evoke visual perceptions called "phosphenes" [11, 19, 20, 23, 24, 32, 42, 83, 94]. Recent progress in materials and microfabrication technologies are allowing researchers to build neural prosthetic devices designed to interact at a number of specific sites in the nervous system [27, 58, 61]. Such assistive devices are already permitting thousands of profoundly deaf patients to hear sounds and speech directly and the same hope exists in the field of visual rehabilitation.

The concept of artificially producing a visual sense in blind individuals is founded on our present understanding of the structure of the mammalian visual system, its processing elements, and the relationship between electrical stimulation of any part of the visual pathways and the resulting visual sensations. A number of studies have shown that electrical stimulation of the retina [29, 40, 42, 96, 101, 103], optic nerve [20, 94, 95] and visual cortex [5, 11, 25, 26, 32, 83] evokes the perception of points of light (called phosphenes) at specific regions in space. Based on these findings, several laboratories worldwide are developing microelectronic prosthesis designed to interact with the remaining healthy retina [29, 36, 41, 42, 78, 79, 102] or optic nerve [19-21, 94, 95]. However, although these retinal or optic nerve prostheses may prove to be useful for restoration of sight lost in diseases such as retinitis pigmentosa and age related macular degeneration, the retina, and the output neurons of the eye (ganglion cell neurons, which in turn give rise to the optic nerve axons) often degenerate in many retinal blindnesses [51] so that these approaches may not be always helpful [52, 64].

We have decided to work on stimulation of the primary visual cortex because the neurons in higher visual regions of the brain (visual cortex) often escape from this degeneration. If these higher visual centers can be stimulated with visual information in a format somewhat similar to the way they were stimulated prior to the development of total blindness, a blind individual may be able to use this stimulation to extract information about the physical world around him/her. This concept is supported by several studies, which demonstrate that localized electrical stimulation of the human visual cortex can excite topographically mapped visual percepts. The first report of the appearance of phosphenes after electrical stimulation of the visual cortex was published by Löwenstein and Borchart in 1918 [47]. Subsequently Wilder Penfield and co-workers during neurosurgical operations for epilepsy [71, 72], observed that electrical stimulation of the surface of visual cortex evoked the perception of points of light (called phosphenes). These observations led a number of investigators to propose that electrical stimulation of visual cortex via arrays of electrodes might provide the profoundly blind with a limited form of functional vision. Experiments by the group of Giles Brindley at the Cambridge University in England [9-11], and William Dobelle at the University of Utah [24-26] showed that stimulation of multiple electrodes simultaneously allowed blind volunteers to recognize simple patterns, including letters and Braille characters. The results from these studies however also indicate, that a cortical prosthesis based on relatively large electrodes implanted subdurally, have a limited usefulness because of factors such as the high levels of current required to produce phosphenes (currents in the range of 1-3 mA), interactions between phosphenes ,occasional elicitation of pain due to meningeal or scalp stimulation, and epileptic seizures.

A promising approach, which can activate populations of neurons with greater spatial specificity and lower levels of stimulation than is possible with larger electrodes on the surface of the brain, is the use of intracortical microelectrodes. In this sense, Schmidt et al. [83] described the implantation of 38 floating microelectrodes within the right visual cortex of a 42-year-old woman who had been blind over 22 years. 34 of the microelectrodes were able to elicit phosphenes for a period of 4 months, and most of the microelectrodes had stimulation thresholds below 25 μA. Unfortunately these microelectrodes were not well suited for a long term application. Thus, due to the breakage of lead wires early in the experiment, only limited tests could be done to evaluate pattern recognition. Nevertheless, taken as a whole the previous results suggest that passing electrical currents through an array of electrodes inserted into an appropriate location in the visual pathway, is able to produce the perception of

phosphenes, and that these phosphenes could be useful for restoring some limited but useful sense of vision to the profoundly blind.

The heart and soul of this Cortical Visual Neuroprosthesis research, is based on the work of a group of scientists at the University of Utah under Prof. Richard Normann's leadership, and an European consortium (CORTIVIS; http://cortivis.umh.es) in which researches at the University Miguel Hernandez (Spain), University of Oldenburg (Germany), University of Vienna (Austria), University of Granada (Spain), Centre National de la Recherche Scientifique (France), University of Montpellier (France), Instituto de Engenharia de Sistemas e Computadores (Portugal) and Biomedical Technologies (Spain), are combining their resources and efforts to develop and safely implant an active cortical device able to provide a functional sense of vision to blind persons with dysfunctions located in the periphery of their visual system. Our main long-term objective is to demonstrate the feasibility of a cortical neuroprostheses, interfaced with the visual cortex, as a means through which a limited but useful visual sense may be restored to profoundly blind people. While the full restoration of vision seems to be unlikely in the near future, the discrimination of shape and location of objects could allow blind subjects to 'navigate' in a familiar environment and to read enlarged text, resulting in a substantial improvement in the quality of life of blind and visually impaired persons. In addition, if we can understand more about the fundamental mechanisms of neuronal coding, and to safely stimulate nervous system, there will real potential to apply this knowledge clinically in other sensory or motor pathologies since it is widely accepted that the biophysical processes involved in stimulating and recording from neurons are ubiquitous throughout the nervous system [46].

2. Physiological foundations of a cortical visual neuroprostheses

Before looking at the specifics of a visual neuroprosthesis, it will be helpful to review some of the physiological foundations for this neuroprosthetic approach.

1. **There is abundant and positive clinical experience with many neural prosthetic interfaces.**

   Microdevices for cell-electrode interfacing for both cardiac and neural cells have been available for in vitro and in vivo applications for many years. For example deep brain stimulators have been implanted successfully in patients for pain management and for control of motor disorders such as Parkinson's disease [17, 27, 74], cochlear implants are being used for restoring auditory function and a wide variety of devices have been

developed to control respiration, activate paralysed muscles or stimulate bladder evacuation [16, 56, 69, 73, 100]. As more and more patients have benefited from these approaches, the interest in neural interfaces has grown significantly and today it is feasible to interface the nervous system with safe and effective devices.

2. **Most forms of blindness are of retinal origin and leave the higher visual centers unaffected.**

   This observation is often unstated but is a key to a cortical approach to visual neuroprosthetics. Thus, the output neurons of the eye, the ganglion cells, often degenerate in many retinal blindnesses [43, 51], and therefore a retinal or optic nerve prosthesis would not be always helpful (Figure 1). However the neurons in the higher visual regions of the brain are spared this extensive degeneration. If these higher visual centers can be stimulated with visual information in a format somewhat similar to the way they were stimulated before the onset of the blindness, a blind individual could be able to use this stimulation to extract information about the physical world around him/her.

3. **The visual pathways and primary visual cortex are organized in a relatively rational scheme.**

   A greatly improved understanding of the organization of the visual pathways and the roles of its neural elements has gradually emerged from the early theories of Brodmann [12]. Based upon electrophysiological experiments conducted in monkeys and other mammals, we know that receptive field centers of primary visual cortex neurons correspond in a moderately systematic fashion to locations from the fovea to the periphery [86, 93, 97]. Points located in the right visual field are imaged on the temporal side of the left eye and the nasal side of the right eye. Axons from ganglion cells in these retinal cell regions make connections with separate layers in the LGN and these neurons send their outputs to cortical layers 4Cα and 4Cβ respectively. Thus the overall spatial position of the retinal ganglion cells within the retina is preserved by the spatial organization of neurons within the LGN and visual cortex. This rational mapping of visual space onto the neurons of the visual cortex, is one of the fundamental cornerstones upon which a cortical visual neuroprostheses is based.

4. Electrical stimulation of neurons in the visual pathway evokes the perception of point of light

As Johannes Müller stated with his *law of specific nerve energies* [57], perceptions are determined by which nerve fibers are activated, not by how the nerve fibers are activated. For example, mechanical pressure to the eye produces a sensation of light, and electrical activation of axons in the auditory nerve give rise to a sensation of sound. In this sense, studies during neurosurgical procedures have revealed that localized direct electrical stimulation of the exposed human visual cortex can evoke topographically mapped visual percepts [10, 11, 23-26, 71, 72]. These percepts are generally called "phosphenes" and are usually described as 'stars in the sky', 'clouds', 'pinwheels', and occasionally as complex chromatic or kinetic sensations. The induction of phosphenes by cortical stimulation establishes the visual nature of the stimulated cortex and provides the basis for the development of a cortical visual prosthesis [32, 63, 64, 91, 97].

5. The plasticity of the brain will foster significant functional reorganization.

The mature visual system of primates and other mammals is capable of extensive reorganization as the roles of inputs and pathways are altered by visual experience, sensory loss, or cortical lesions. Although this plasticity declines with age [6], adult visual cortex still respond to experience with plastic changes as shown by the effects of perceptual learning [85] and retinal lesions [28]. This plastic change in the brain probably will allow blind subjects to extract greater information from touch and hearing, thus improving the quality of life and enhancing the integration of the blind in the social and working environment of a sighted society. The understanding of these neuroplastic processes will provide the neuroscientific foundation for improved rehabilitation and teaching strategies for the blind. In addition, the modulation of such plasticity will be crucial in developing and projecting the success of novel, visual neuroprosthetic strategies. It is hoped that this neural plasticity will allow quick re-association of the "phosphenes world" with the physical world. Thus, immediately after the electrode array is implanted, the evoked phosphenes are likely to engender a poor perception of an object (as it happens for example with cochlear implants). However, with the adequate training and after some time the reorganization of the "neural network" will improve the perceptions.

3. Engineering a cortical visual neuroprostheses

The most fundamental requirements of any neurological prosthesis are well understood. In order for a device to effectively emulate a neurological system, it has to do three things:

1. First, it must collect the same kind of information that the system normally collects.
2. Next, it has to process that information.
3. Third, it must communicate the processed information, in an appropriate way with other parts of the nervous system.

Figure 2 illustrates the basic components of our cortically based approach. The system will use a bioinspired retina able to perform some of the image pre-processing functions of the retina. This bioinspired device will transform the visual world in front of a blind individual into electrical signals that can be used to excite neurons at the occipital cortex. These signals will be delivered to intracortical microelectrodes that will excite visual cortex neurons in an appropriate way. Since signals reaching the cortex from the retina and LGN arrive not at the surface of the cortex (layer 1) but a depth of 1-2 mm (layer 4), we need intracortical penetrating electrodes with exposed tips located in layer 4 and with tip sizes of the same order of magnitude as the neurons that are intended to be stimulated. For this reason we are using the Utah Electrode Array (UEA), which has 100 microelectrodes, each 1.5 mm long, arranged in a square grid contained in a package 4.2 mm by 4.2 mm (Fig. 3). This array of penetrating electrodes has been designed to compromise as little cortical volume as possible. Thus, each needle has been made as slender as possible yet retain sufficient strength to withstand the implantation procedure. Further, consistent with concept of blunt dissection used by neurosurgeons, these penetrating structures displace the tissues they are inserted into rather than cut their way through them [64]. Finally an integrated telemetry system will transmit power and data (electric impulses) to the electrode array inserted into the visual cortex. The whole visual neuroprosthetic device is expected to recreate a limited, but functionally useful visual sense in blind individuals allowing them to “navigate” in familiar environments and to read enlarged text.

One strategy we are employing is not to simply record an image with high resolution, but to transmit visual information in a meaningful way to the appropriate site/s in the brain. In order to achieve this, we have to take into account the coding features of the biological visual system and design constraints related with the number and distribution of the set of working electrodes the visual scene is mapped to.

4. Development of a reconfigurable bioinspired visual processing front-end (artificial retina).

One of the major challenges of our approach is the design and development of a bioinspired platform able to transform the visual world in front of a blind individual into a set of electrical signals, that will be used to stimulate, in real time, the neurons at his/her visual cortex [70]. According to our design constraints, these signals should be as similar as possible to the output signals of the real retina. The question of how the information about the external world is compressed in the retina, and how this compressed representation is encoded in spike trains is therefore of seminal importance.

The recent decades have revealed many details about the ways the retina is organized to serve several sub-functions. Sampling across the retina is not uniform [4] and therefore retinotopic gradients and magnification factors [2] have to be introduced to match image representation with cortical topography. It is further clear that several streams of information are processed in parallel from any retinal point by several dozens of interneuronal subtypes [44] before contrast, brightness, orientation movement and colour are finally coded as modulation of ganglion cell action potential series. While chromatic information is not of utmost priority a differential characterization will nevertheless be required when designing "achromatic" processing modules for basic representation of image components. Similarly the high sensitivity pathways originating from rod photoreceptors may be silenced by mimicking daylight intensity (photopic) conditions using adequate pre-amplification of dimmer signals.

Although it is not the purpose of this report to present a detailed study of the problem of coding/decoding of retinal images by ensembles of retinal ganglion cells, increasing evidence suggests that the retina and the brain utilize distributed codes that can only be analyzed by simultaneously recording the activity of multiple neurons [8, 33, 35, 60-62, 65, 84, 97, 98]. Far from a simple transducer of light into electrical neural impulses, the retina performs a locally-computed spatio-temporal contrast enhancement function, and a very efficient compression of visual information. These tasks are essential to provide a high adaptation capability to very different lighting conditions, a high noise immunity, and to efficiently communicate the visual information by means of a limited number of optic nerve fibers. Thus, our entire experience of the external visual world derives from the concerted activity of a limited number of ganglion cells in the retinal output layer which have to represent all the features of objects in the visual world, namely their color, intensity, shape, movement, and the

change of these features in time. This representation has to be unequivocal and fast in order to ensure object recognition for any single stimulus presentation within a few hundreds of milliseconds [7, 18, 88].

Figure 4 shows the architecture of the bioinspired retinal model we are currently using. It is based on electrophysiological recordings from populations of retinal ganglion cells. Through a set of parametrized filters and functions, we obtain a portable model that can be easily translated into a hardware description for automatic synthesis using the appropriate tools. The input images are captured by a photosensor array (preferably a logarithmic response camera) and are processed by a set of separate spatial and temporal filters that enhance specific features of the captured visual information. The model can take into account the irregular distribution of photoreceptors within the human retina: a high density of pixels and smaller receptive field sizes in central areas; lower density and bigger receptive fields in peripheral areas. A gain factor can be specified for every individual channel as well as a global gain. The output of these filters is combined to produce an output map we call the "information figure". The next stage reduces the information figure array to the resolution of the electrode matrix, with the option of defining specific receptive field shapes and sizes. We call "activity matrix" to this low resolution representation (see Fig. 4). Finally, a mapping and neuromorphic coding (into output pulses that can be sent to each electrode) is carried out and feeds the radiofrequency link that goes to the microelectrode array. The model implemented in the present version of the software is a simplified version of an integrate-and-fire spiking neuron [34]. Each neuron accumulates input values coming from its receptive field until it reaches a programmable threshold. Then it fires and discharges the accumulated value. The model also includes a leakage term to make the accumulated value diminish for low or null input values. Figure 5 shows an example of the spike output obtained by a real recording of a population of rabbit retinal ganglion cells and a similar pattern generated by the artificial coding module in response to short repetitive flashes of light. Although the model is essentially analog, we have chosen a digital hardware implementation to have a more flexible and standardizable approach. In the future, this implementation could be easily customized for each implanted device. Thus, the implementation of the model in digital hardware provides a flexible design, achieving a high performance with response times several orders of magnitude lower than that of biological systems. The whole system is presently able to work properly up to 40 MHz. This means that 40,000 electrodes could be stimulated with an inter-spike temporal resolution

equal to or lower than 1msec. The use of reconfigurable circuitry (FPGA) let us to adjust or even change the spiking model easily.

It may be argued that emulation of cortical afferents from the lateral geniculate nucleus will provide a more appropriate sensory signal for stimulating primary visual cortex. In particular it is likely that significant functional transformation of the visual stream occurs at this stage, both as a result of feedforward circuitry, as well as the influence (at present poorly understood) of the very large cortical-fugal feedback pathway. However the functional high-order relationships between the outputs of retinal ganglion cells are probably preserved to some extent at the level of the geniculate output [75-77]. A crucial experimental advantage of using a retinally based model is the ability to make multiple simultaneous recordings that allow derivation of firing statistics between ganglion cells, but at present such technology does not exist for functional (i.e. visually evoked) recordings of the lateral geniculate. This limitation thus necessitates our focus on providing an image of the retinal, as opposed to geniculate, output to the cortical implant.

5. Safe and effective stimulation of neural tissue through multiple intracortical electrodes.

A neuroprosthetic system must be implanted into the nervous system and remain fully functional for periods that will eventually extend to many decades. Therefore these devices must be highly biocompatible and be able to resist the attack of biological fluids, proteases, macrophages or any substances of the metabolism. Furthermore it is necessary to take into account the possible damage of neural tissues by permanent charge injection using multielectrode arrays and the most effective means of stimulating the cerebral cortex. These considerations place unique constraints on the architecture, material, and surgical techniques used in the implementation of neural interfaces [64].

Once a particular type of electrode is selected, the next step is to design a surgical procedure for electrode implantation. Even though the individual microelectrodes of the UEA are extremely sharp, early attempts to implant an array of 10 x 10 electrodes into the visual cortex in different animal models only deformed the cortical surface and resulted in incomplete implantation. A system that rapidly inserts the UEA into the cortex has been developed [81] allowing implantation in a manner that minimizes dimpling and compression of the subjacent structures. The implantation is so rapid that the cortex experience only slight mechanical dimpling and the insertion is generally complete. The most typical findings in acute

experiments are occasional microhemorrhages emanating from the electrode tracks probably due to the high probability of electrode tips encountering one or more blood vessels during implantation. This typically resolves itself and aside from a few mechanically-distorted and somewhat hyperchromic neurons, the neurons near most tracks appear normal (Fig 6). Furthermore single unit recordings of neural activity can often by made within hours after the implantation.

An important problem reported with all available microelectrodes to date, is long-term viability and biocompatibility. Although it has been reported that silicon-based shafts, siliconoxide based surfaces and other glass based products are highly biocompatible [82] there are acute and chronic inflammatory reactions which affect both the neural tissue and the surface of the microelectrodes [3, 37, 39, 45, 48, 54, 92, 99]. These reactions often result in damage to neurons and microelectrodes and lead to the proliferation of a glial scar around the implanted probes which prevents neurons to be recorded or stimulated [31, 92]. Our experiments with the UEA support this notion and show a think capsule (2-5 microns thick) around each electrode track (Figure 6). The reasons for the inflammatory response lie in molecular and cellular reactions at foreign surfaces [30, 37]. These responses can be controlled and one of our goals is to contribute to this field, both in terms of increasing the understanding of how at the nanoscale inflammatory events take place and in terms of creating new, more biocompatible surfaces for use in neurosurgery and brain implants.

Other possible problems are related to motion of the brain with respect to the skull. These devices should stay in place for years, but how to keep them biologically and electrically viable remains a difficult problem. We have described a new surgical technique to minimize the formation of adhesions between the dura and implanted electrode arrays using a 12 mm (0.5 mil) thick sheet of Teflon ® film positioned between the matrix of microelectrodes and the dura [53]. Furthermore we are collaborating with the Department of Medical Physics of the University of Vienna in the developing of a new “in vivo” technique for ultra high resolution optical coherence tomography with unprecedented resolution (< 10 μm). In the future this technique could help to the development of a non-invasive diagnostic technique to obtain precise information about the cortical differentiation of blind persons. It could be also very valuable for determining the required advancement depth of multi-electrode tips to access the most appropriate cortical sublayer (4C).

By implanting penetrating microelectrodes within the visual cortex, with exposed tip sizes the same order of magnitude as the neurons we want to stimulate, much selective stimulation can,

in principle be achieved. However implantation of penetrating electrodes is intrinsically more invasive than application of surface electrodes, and studies regarding safety and preservation of neuronal tissues as well as optimisation of stimulating parameters are needed preceding the actual clinical application. Experiments to determine the levels of current injections that are required to evoke sensory percept via intracortical microstimulation have shown that most of the microelectrodes had thresholds currents below 25 μA [64, 80, 83]. Nevertheless more data on the possible damage of neural tissues by permanent charge injection using multielectrode arrays and the most effective means of stimulating the cerebral cortex are still needed.

Another important issue for the design of a useful cortical visual neuroprosthesis, not yet addressed, is whether a change in retinotopic organization results from electrical stimulation. It is known that repeated sensory stimulation of either primary visual cortex or other primary sensory cortices can lead to changes in the representation of the sensory input. Additionally, it is known that changes in the cortical representation can occur as a result of repeated electrical stimulation of auditory, somatosensory, motor and visual cortex [22, 38, 49, 50, 55, 87, 89, 90]. However preliminary results are inconsistent and more work needs to be done.

6. Development of a non-invasive methodology for selection of suitable subjects for a cortical visual prosthesis.

A major prerequisite for the possible clinical application of this neuroprosthetic approach, aside from safety considerations, is proper, non-invasive patient selection criteria. The visual cortex of potential candidates for such neuroprosthetic devices has to be capable of processing visual information, but there is evidence that the occipital parts of the brain utilized by sighted subjects to process visual information are transformed in some blind subjects and utilized to process tactile and auditory stimuli [13-15, 68]. Figure 7 shows an example. It displays the areas of the brain that are activated when a sighted person reads Braille characters (Fig 7A). The activated areas are displayed in red and represent the activation of the somatosensory and motor cortex on the left side of the brain that process tactile information from the right hand being used for tactile decoding of the symbols. The above figure contrast with Fig 7B, which shows the areas activated when an early blind subject read Braille characters. The areas of activation are not restricted to the somatosensory and motor cortex contralaterally to the right hand used for reading. Rather, there is marked activation of the occipital cortex, the part of the brain that we use to process visual information, the primary visual cortex. This cross-modal plasticity, by which the visual cortex is recruited for

processing of tactile information, is associated with a significant improvement in the tactile reading skill and is supported by a variety of additional, converging data. For example, Pascual-Leone et al. [67], reported the case of a blind woman who was an extremely proficient Braille reader working as an editor for a newsletter for the blind. In a most unfortunate event, this woman became unable to read Braille, Braille alexia, following a stroke. Indeed, she became unable to decode any complex tactile information, while otherwise remaining neurologically intact. Contrary to expectations, the lesion in this patient did not affect the somatosensory cortex but damaged the occipital pole bilaterally. In this case, a cortical neuroprostheses for partially restoring the vision in blind people, would not be useful. Several important questions arise: what happens to the occipital cortex when a person become blind?, and, is the occipital cortex of blind subjects still able to process visual information?.

In order to get insights into these issues, we have developed a reliable, non-invasive method to study the degree of cross-modal plasticity and the degree of remaining functional visual cortex in blind subjects using transcranial magnetic stimulation (TMS). The procedure allows the systematic mapping of the sensations induced by focal and non invasive stimulation of the human occipital cortex and provides a method for their quantification [32]. A total of 25 sighted and 21 blind volunteers have been studied using these techniques. Almost all (96%) sighted subjects perceived phosphenes using single TMS pulses and an intensity of 80% of maximal stimulator output, although not in all sampled positions, hence the relevance of a systematic sampling. The most frequently induced phosphenes were spots of light in shades of gray, which were extremely brief and never occurred after the stimulation. It was more difficult to elicit visual perceptions in blind subjects. Only 33% of the blind subjects reported phosphenes when using single TMS pulses. However, localized phosphenes could be induced in 57% of the blind subjects by using short trains of 4 consecutive 15-Hz TMS pulses (particularly those severely visually impaired but with some residual vision and late blind subjects). These results suggest that TMS might be used to map the function of the remaining visual cortex in blind subjects and hence, aid in the determination of their suitability for the implantation of visual neuroprosthetic devices. Furthermore TMS, in combination with other brain image technologies and methods, could be very useful to improve our present understanding of the physiological reorganization and plastic changes in the brain of blind subjects as a consequence of their adaptation to the loss of sight.

A detailed understanding of the processes and time-course of cross-modal plasticity will provide the neuroscientific foundation for the development of better rehabilitation and

teaching strategies for the blind. At the same time, the determination of the degree of cross-modal plasticity and its modulation will provide the foundation for the evaluation and further development of neuroprosthetic approaches to restoration of functionally significant sight in the visually impaired.

7. Conclusions and future perspectives

Clinical applications such as artificial vision require extraordinary diverse, lengthy and intimate collaborations among basic scientists, engineers and clinicians. On-going research on the anatomy and physiology of the visual pathways will yield a better understanding of the parallel processing capabilities of the central nervous system and the role of neural plasticity in the interpretation of visual information. The strategy of using a combination of experimentation and modelling to understand the mechanisms of visual coding will allow the design and development of fast and flexible bioinspired systems able to process signals from external devices before they are fed into a machine-brain interface to safely stimulate the nervous system. However there are many questions regarding biocompatibility, safety and even nontechnological issues that need to be addressed before a cortical neuroprosthesis can be considered a viable clinical therapy.

The implant is to be inserted directly into the brain, where it will remain without intervention for decades. Further, the system will not be a simple passive device, but it will contain active circuitry for multiplexing and telemetry. While some progress has been made in many of these fields, it is clear that more animal experiments are needed. Although the full restoration of vision seems to be impossible, the discrimination of shape and location of objects could allow blind subjects to "navigate" in a familiar environment and to read enlarged text, resulting in a substantial improvement in the quality of life of blind and visual impaired persons. However it is necessary to go step by step, not creating false expectations that could negatively affect this emerging approach. We are still a long way away from a highly functional visual prosthesis, but the success of the cochlear implant encourges the pursuit of this neurotechnological application.

The plastic changes in the brain of blind subjects allows them to extract greater information from touch and hearing, thus improving their quality of life and enhancing their integration in the social and working environment of a sighted society. The precise understanding of these neuroplastic processes will provide the neuroscientific foundation for improved rehabilitation and teaching strategies for the blind. In addition, the modulation of such plasticity will be

crucial in developing and projecting the success of novel, visual neuroprosthetic strategies, which has implications for rehabilitative training and device development.

Hopefully the advances in medicine, ophthalmology and genetics will be able to devise new ways of preventing diseases of the visual pathways or in transplanting neurons that have been lost. However genetic science and treatment will not help in injuries due to accidents and probably will not eliminate all the visual impairments due to aging. Therefore progress in neuroprosthesis technologies is regarded as a necessity for the future. Society and the research community is becoming aware of this necessity and is beginning to invest time and efforts in this nascent field. The next 15 years will be of seminal importance for these rehabilitative approaches, and we hope that the progresses in medicine, material science, bioengineering, and the increase of intelligence in assistive systems and devices will foster the improvements in the quality of life of people that are affected by visual impairments.

8. Acknowledgements

This report has been carried out with financial support from the Commission of the European Communities, specific RTD programme "Quality of Life and Management of Living Resource ", QLK6-CT-2001-00279. It does not necessarily reflect its views and in no way anticipates the Commission's future policy in this area

References

[1] G.M. Acland, G.D. Aguirre, J. Ray, Q. Zhang, A. T.S., A.V. Cideciyan, P.-K. S.E., V. Anand, Z. Y., M. A.M., S.G. Jacobson, W.W. Hauswirth, and J. Bennet, Gene therapy restores vision in a canine model of childhood blindness, Nat Genet **28** (2001) 92-95.

[2] D.L. Adams and J.C. Horton, Shadows Cast by Retinal Blood Vessels Mapped in PrimaryVisual Cortex, Science **298** (2002) 572-576.

[3] B.J. Agnew, J.G. Duman, C.L. Watson, D.E. Coling, and J.G. Forte, Cytological transformations associated with parietal cell stimulation: critical steps in the activation cascade, J Cell Sci **112** (1999) 2639-2646.

[4] P.K. Ahnelt and H. Kolb, The mammalian photoreceptor mosaic-adaptive design, Prog Retin Eye Res **19** (2000) 711-777.

[5] M. Bak, J.P. Girvin, F.T. Hambrecht, C.V. Kufta, G.E. Loeb, and E.M. Schimidt, Visual sensations produced by intracortical microstimulation of the human occipital cortex, Med Biol Eng Comput **28** (1990).

[6] N. Berardi, T. Pizzorusso, G.M. Ratto, and L. Maffei, Molecular basis of plasticity in the visual cortex, Trends Neurosci **26** (2003) 369-378.

[7] W. Bialek, F. Rieke, R.R. de Ruyter van Steveninck, and D. Warland, Reading a neural code, Science **252** (1991) 1854-1857.

[8] A. Borst and F.E. Theunissen, Information theory and neural coding, Nat Neurosci **2** (1999) 947-957.

[9] G.S. Brindley, Effects of electrical stimulation of the visual cortex, Hum Neurobiol **1** (1982) 281-283.

[10] G.S. Brindley, P.E.K. Donaldson, M.A. Falconer, and D.N. Rusthon, The extent of the region of occipital cortex that when stimulated gives phosphenes fixed in the visual field, J Physiol (Lond) **225** (1972) 57-58.

[11] G.S. Brindley and W.S. Lewin, The sensations produced by electrical stimulation of the visual cortex, J Physiol (Lond) **196** (1968) 479-493.

[12] K. Brodmann, Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, ed., Leizpig 1909.

[13] L.G. Cohen, P. Celnik, A. Pascual-Leone, B. Corwell, L. Falz, J. Dambrosia, M. Honda, N. Sadato, C. Gerloff, M.D. Catala, and M. Hallett, Functional relevance of cross-modal plasticity in blind humans, Nature **389** (1997) 180-183.

[14] L.G. Cohen, R.A. Weeks, N. Sadato, P. Celnik, K. Ishii, and M. Hallett, Period of susceptibility for cross-modal plasticity in the blind, Ann Neurol **45** (1999) 451-460.

[15] L.G. Cohen, U. Ziemann, R. Chen, J. Classen, M. Hallett, C. Gerloff, and C. Butefisch, Studies of neuroplasticity with transcranial magnetic stimulation, J Clin Neurophysiol **15** (1998) 305-324.

[16] G.H. Creasey, K.L. Kilgore, D.L. Brown-Triolo, J.E. Dahlberg, P.H. Peckham, and M.W. Keith, Reduction of costs of disability using neuroprostheses, Assist Technol **12** (2000) 67-75.

[17] R. Davis, Twenty-eight years of clinical experience with implantable neuroprostheses for various applications, Artif Organs **26** (2002) 280-283.

[18] R.R. de Ruyter van Steveninck, G.D. Lewen, S.P. Strong, R. Koberle, and W. Bialek, Reproducibility and variability in neural spike trains, Science **275** (1997) 1805-1808.

[19] J. Delbeke, M. Oozeer, and C. Veraart, Position, size and luminosity of phosphenes generated by direct optic nerve stimulation, Vision Res **43** (2003) 1091-1102.

[20] J. Delbeke, D. Pins, G. Michaux, M.C. Wanet-Defalque, S. Parrini, and C. Veraart, Electrical stimulation of anterior visual pathways in retinitis pigmentosa, Invest Ophthalmol Vis Sci **42** (2001) 291-297.

[21] J. Delbeke, M.C. Wanet-Defalque, B. Gerard, M. Troosters, G. Michaux, and C. Veraart, The microsystems based visual prosthesis for optic nerve stimulation, Artif Organs **26** (2002) 232-234.

[22] H.R. Dinse, G.H. Recanzone, and M.M. Merzenich, Alterations in correlated activity parallel ICMS-induced representational plasticity, Neuroreport **5** (1993) 173-176.

[23] W.H. Dobelle, Artificial vision for the blind by connecting a television camera to the visual cortex, Asaio J **46** (2000) 3-9.

[24] W.H. Dobelle and M.G. Mladejovsky, Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind, J Physiol (Lond) **243** (1974) 553-576.

[25] W.H. Dobelle, M.G. Mladejovsky, J.R. Evans, T.S. Roberts, and J.P. Girvin, 'Braille' reading by a blind volunteer by visual cortex stimulation, Nature **259** (1976) 111-112.

[26] W.H. Dobelle, M.G. Mladejovsky, and J.P. Girvin, Artificial vision for the blind: electrical stimulation of visual cortex offers hope for a functional prosthesis, Science **183** (1974) 440-444.

[27] J.P. Donoghue, Connecting cortex to machines: recent advances in brain interfaces, Nat Neurosci **5** (2002) 1085-1088.

[28] B. Dreher, W. Burke, and M.B. Calford, Cortical plasticity revealed by circumscribed retinal lesions or artificial scotomas, Prog Brain Res **134** (2001) 217-246.

[29] R. Eckmiller, Learning retina implants with epiretinal contacts, Ophthalmic Res **29** (1997) 281-289.

[30] D.J. Edell, V. Van Toi, V.M. McNeil, and L.D. Clark, Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex, IEEE Trans Biomed Eng **39** (1992) 635-643.

[31] J.W. Fawcet and R.A. Asher, The glial scar and central nervous system repair, Brain Res Bull **49** (1999) 377-.

[32] E. Fernandez, A. Alfaro, J.M. Tormos, R. Climent, M. Martínez, H. Vilanova, V. Walsh, and A. Pascual-Leone, Mapping of the human visual cortex using image-guided transcranial magnetic stimulation, Brain Res Protoc. **10** (2002) 115-124.

[33] E. Fernandez, J. Ferrandez, J. Ammermuller, and R.A. Normann, Population coding in spike trains of simultaneously recorded retinal ganglion cells, Brain Res **887** (2000) 222-229.

[34] W. Gerstner and W. Kistler, Spiking Neuron Models, ed., Cambridge University Press 2002.

[35] M. Greschner, M. Bongard, P. Rujan, and J. Ammermuller, Retinal ganglion cell synchronization by fixational eye movements improves feature estimation, Nat Neurosci **5** (2002) 341-347.

[36] A.E. Grumet, J.L. Wyatt, Jr., and J.F. Rizzo, 3rd, Multi-electrode stimulation and recording in the isolated retina, J Neurosci Methods **101** (2000) 31-42.

[37] P. Heiduschka and S. Thanos, Implantable bioelectronic interfaces for lost nerve functions, Prog. Neurobiol. **55** (1998) 433-461.

[38] P. Heusler, B. Cebulla, G. Boehmer, and H.R. Dinse, A repetitive intracortical microstimulation pattern induces long-lasting synaptic depression in brain slices of the rat primary somatosensory cortex, Exp Brain Res **135** (2000) 300-310.

[39] A.C. Hoogerwerf and K.D. Wise, A 3D micro-electrode array for chronic neural recording, IEEE Trans Biomed Eng **41** (1994) 1136-1146.

[40] M.S. Humayun, Intraocular retinal prosthesis, Trans Am Ophthalmol Soc **99** (2001) 271-300.

[41] M.S. Humayun, E. de Juan, Jr., G. Dagnelie, R.J. Greenberg, R.H. Propst, and D.H. Phillips, Visual perception elicited by electrical stimulation of retina in blind humans, Arch Ophthalmol **114** (1996) 40-46.

[42] M.S. Humayun, J. Weiland, G.Y. Fujii, R. Greenberg, R. Williamson, J. Little, V. Cimmarusti, G. Van Boemel, G. Dagnelie, and E. de Juan, Jr., Visual perception in a blind subject with a chronic microelectronic retinal prosthesis, Vision Res **43** (2003) 2573-2581.

[43] B.W. Jones, C.B. Watt, J.M. Frederick, W. Baehr, C.K. Chen, E.M. Levine, A.H. Milam, M.M. Lavail, and R.E. Marc, Retinal remodeling triggered by photoreceptor degenerations, J Comp Neurol **464** (2003) 1-16.

[44] H. Kolb, R. Nelson, P. Ahnelt, and N. Cuenca, Cellular organization of the vertebrate retina, Prog Brain Res **131** (2001) 3-26.

[45] X. Liu, D.B. McCreery, R.R. Carter, L.A. Bullara, T.G. Yuen, and W.F. Agnew, Stability of the interface between neural tissue and chronically implanted intracortical microelectrodes, IEEE Trans Rehabil Eng **7** (1999) 315-326.

[46] G.E. Loeb, Neural prosthetic interfaces with the nervous system, Trends Neurosci **12** (1989) 195-201.

[47] K. Löwenstein and M. Borchart, Symptomatologie und elektrische Reizung bei einer Schubverletzung des Histerhauptlappens, Dtsch Z Nervenheilk **58** (1918) 264.

[48] A.B. Majji, M.S. Humayun, J.D. Weiland, S. Suzuki, S.A. D'Anna, and E. de Juan, Jr., Long-term histological and electrophysiological results of an inactive epiretinal electrode array implantation in dogs, Invest Ophthalmol Vis Sci **40** (1999) 2073-2081.

[49] P.E. Maldonado and G.L. Gerstein, Neuronal assembly dynamics in the rat auditory cortex during reorganization induced by intracortical microstimulation, Exp Brain Res **112** (1996) 431-441.

[50] Reorganization in the auditory cortex of the rat induced by intracortical microstimulation: a multiple single-unit study, Exp Brain Res **112** (1996) 420-430.

[51] R.E. Marc and B.W. Jones, Retinal remodeling in inherited photoreceptor degenerations, Mol Neurobiol **28** (2003) 139-147.

[52] E.M. Maynard, Visual prostheses, Annu Rev Biomed Eng **3** (2001) 145-168.

[53] E.M. Maynard, E. Fernandez, and R.A. Normann, A technique to prevent dural adhesions to chronically implanted microelectrode arrays, J Neurosci Methods **97** (2000) 93-101.

[54] D. McCreery, W.F. Agnew, and L. Bullara, The effects of prolonged intracortical microstimulation on the excitability of pyramidal tract neurons in the cat, Ann Biomed Eng **30** (2002) 107-119.

[55] D.B. McCreery, T.G. Yuen, W.F. Agnew, and L.A. Bullara, A characterization of the effects on neuronal excitability due to prolonged microstimulation with chronically implanted microelectrodes, IEEE Trans Biomed Eng **44** (1997) 931-939.

[56] W.D. Memberg and P.E. Crago, An analysis of the input-output properties of neuroprosthetic hand grasps, J Rehabil Res Dev **37** (2000) 11-21.

[57] J. Müller, Handbuch der Physiologie des Menschen, ed., Verlag von J. Hölscher, Coblenz 1837.

[58] F.A. Mussa-Ivaldi and L.E. Miller, Brain-machine interfaces: computational demands and clinical needs meet basic neuroscience, Trends Neurosci **26** (2003) 329-334.

[59] S.D. Nadine and J. Bennet, Gene therapy and retinitis pigmentosa: advances and future challenges, BioEssays **23** (2001) 662-668.

[60] M.A. Nicolelis, Actions from thoughts, Nature **409** (2001) 403-407.

[61] Brain-machine interfaces to restore motor function and probe neural circuits, Nat Rev Neurosci **4** (2003) 417-422.

[62] M.A. Nicolelis and S. Ribeiro, Multielectrode recordings: the next steps, Curr Opin Neurobiol **12** (2002) 602-606.

[63] R.A. Normann, E. Maynard, K.S. Guillory, and D.J. Warren, Cortical implants for the blind, IEEE Spectrum (1996) 54-59.

[64] R.A. Normann, E.M. Maynard, P.J. Rousche, and D.J. Warren, A neural interface for a cortical vision prosthesis, Vision Res **39** (1999) 2577-2587.

[65] R.A. Normann, D.J. Warren, J. Ammermuller, E. Fernandez, and S. Guillory, High-resolution spatio-temporal mapping of visual pathways using multi-electrode arrays, Vision Res **41** (2001) 1261-1275.

[66] L.R. Pacione, M.J. Szego, S. Ikeda, P.M. Nishina, and R.R. McInnes, Progress toward understanding the genetic and biochemical mechanisms of inherited photoreceptor degenerations, Annu Rev Neurosci **26** (2003) 657-700.

[67] A. Pascual-Leone, R. Hamilton, J.M. Tormos, J.P. Keenan, and M.D. Catala, *Neuroplasticity in the adjustment to blindness*, in *Neuronal Plasticity: Building a Bridge from the laboratory to the Clinic*, J.Grafman and Y. Christen, Editors. 1999, Springer-Verlag: Berlin Heidelber New York.

[68] A. Pascual-Leone, J.M. Tormos, J. Keenan, F. Tarazona, C. Canete, and M.D. Catala, Study and modulation of human cortical excitability with transcranial magnetic stimulation, J. Clin. Neurophysiol. **15** (1998) 333-343.

[69] P.H. Peckham, M.W. Keith, K.L. Kilgore, J.H. Grill, K.S. Wuolle, G.B. Thrope, P. Gorman, J. Hobby, M.J. Mulcahey, S. Carroll, V.R. Hentz, and A. Wiegner, Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study, Arch Phys Med Rehabil **82** (2001) 1380-1388.

[70] F.J. Pelayo, S. Romero, C.A. Morillas, A. Martinez, E. Ros, and E. Fernandez, Traslating image sequences into spike patterns for cortical neuro-stimulation, Neurocomputing **In Press** (2004).

[71] W. Penfield and H. Jaspers, Epilepsy and the functional anatomy of the human brain, ed., Churchill, London, England 1974.

[72] W. Penfield and T. Rasmussen, The cerebral cortex of man, ed., Macmillan, New York 1950.

[73] M.R. Popovic, D.B. Popovic, and T. Keller, Neuroprostheses for grasping, Neurol Res **24** (2002) 443-452.

[74] A. Prochazka, V. Mushahwar, and S. Yakovenko, Activation and coordination of spinal motoneuron pools after spinal cord injury, Prog Brain Res **137** (2002) 109-124.

[75] D.S. Reich, J.D. Victor, B.W. Knight, T. Ozaki, and E. Kaplan, Response variability and timing precision of neuronal spike trains in vivo, J Neurophysiol **77** (1997) 2836-2841.

[76] P. Reinagel, D. Godwin, S.M. Sherman, and C. Koch, Encoding of visual information by LGN bursts, J Neurophysiol **81** (1999) 2558-2569.

[77] P. Reinagel and R.C. Reid, Temporal coding of visual information in the thalamus, J Neurosci **20** (2000) 5392-5400.

[78] J.F. Rizzo, 3rd, J. Wyatt, J. Loewenstein, S. Kelly, and D. Shire, Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays, Invest Ophthalmol Vis Sci **44** (2003) 5355-5361.

[79] Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials, Invest Ophthalmol Vis Sci **44** (2003) 5362-5369.

[80] P.J. Rousche and R.A. Normann, Chronic intracortical microstimulation (ICMS) of cat sensory cortex using the Utah Intracortical Electrode Array, IEEE Trans Rehabil Eng **7** (1999) 56-68.

[81] A method for pneumatically inserting an array of penetrating electrodes into cortical tissue, Ann Biomed Eng **20** (1992) 413-422.

[82] W.L. Rutten, Selective electrical interfaces with the nervous system, Annu Rev Biomed Eng **4** (2002) 407-452.

[83] E.M. Schmidt, M.J. Bak, F.T. Hambrecht, C.V. Kufta, D.K. O'Rourke, and P. Vallabhanath, Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex, Brain **119** (1996) 507-522.

[84] M.J. Schnitzer and M. Meister, Multineuronal firing patterns in the signal from eye to brain, Neuron **37** (2003) 499-511.

[85] A. Schoups, R. Vogels, N. Qian, and G. Orban, Practising orientation identification improves orientation coding in V1 neurons, Nature **412** (2001) 549-553.

[86] M.I. Sereno, C.T. McDonald, and J.M. Allman, Analysis of retinotopic maps in extrastriate cortex, Cereb Cortex **4** (1994) 601-620.

[87] I.G. Sil'kis and S. Rapoport, Plastic reorganizations of the receptive fields of neurons of the auditory cortex and the medial geniculate body induced by microstimulation of the auditory cortex, Neurosci Behav Physiol **25** (1995) 322-339.

[88] S.M. Smirnakis, M.J. Berry, D.K. Warland, W. Bialek, and M. Meister, Adaptation of retinal processing to image contrast and spatial scale, Nature **386** (1997) 69-73.

[89] S.K. Talwar and G.L. Gerstein, Reorganization in awake rat auditory cortex by local microstimulation and its effect on frequency-discrimination behavior, J Neurophysiol **86** (2001) 1555-1572.

[90] G.C. Teskey, M.H. Monfils, P.M. VandenBerg, and J.A. Kleim, Motor map expansion following repeated cortical and limbic seizures is related to synaptic potentiation, Cereb Cortex **12** (2002) 98-105.

[91] P. Troyk, M. Bak, J. Berg, D. Bradley, S. Cogan, R. Erickson, C. Kufta, D. McCreery, E. Schmidt, and V. Towle, A model for intracortical visual prosthesis research, Artif Organs **27** (2003) 1005-1015.

[92] J.N. Turner, W. Shain, D.H. Szarowski, M. Andersen, S. Martins, M. Isaacson, and H. Craighead, Cerebral astrocyte response to micromachined silicon implants, Exp Neurol **156** (1999) 33-49.

[93] R.J. Tusa, L.A. Palmer, and A.C. Rosenquist, The retinotopic organization of area 17 (striate cortex) in the cat, J Comp Neurol **177** (1978) 213-235.

[94] C. Veraart, C. Raftopoulos, J.T. Mortimer, J. Delbeke, D. Pins, G. Michaux, A. Vanlierde, S. Parrini, and M.C. Wanet-Defalque, Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode, Brain Res **813** (1998) 181-186.

[95] C. Veraart, M.C. Wanet-Defalque, B. Gerard, A. Vanlierde, and J. Delbeke, Pattern recognition with the optic nerve visual prosthesis, Artif Organs **27** (2003) 996-1004.

[96] P. Walter, P. Szurman, M. Vobig, H. Berk, H.C. Ludtke-Handjery, H. Richter, C. Mittermayer, K. Heimann, and B. Sellhaus, Successful long-term implantation of electrically inactive epiretinal microelectrode arrays in rabbits, Retina **19** (1999) 546-552.

[97] D.J. Warren, E. Fernandez, and R.A. Normann, High-resolution two-dimensional spatial mapping of cat striate cortex using a 100-microelectrode array, Neuroscience **105** (2001) 19-31.

[98] S.D. Wilke, A. Thiel, C.W. Eurich, M. Greschner, M. Bongard, J. Ammermuller, and H. Schwegler, Population coding of motion patterns in the early visual system, J Comp Physiol [A] **187** (2001) 549-558.

[99] B.J. Woodford, R.R. Carter, D. McCreery, L.A. Bullara, and W.F. Agnew, Histopathologic and physiologic effects of chronic implantation of microelectrodes in sacral spinal cord of the cat, J Neuropathol Exp Neurol **55** (1996) 982-991.

[100] D.T. Yu, R.F. Kirsch, A.M. Bryden, W.D. Memberg, and A.M. Acosta, A neuroprosthesis for high tetraplegia, J Spinal Cord Med **24** (2001) 109-113.

[101] E. Zrenner, Will retinal implants restore vision?, Science **295** (2002) 1022-1025.

[102] E. Zrenner, K.D. Miliczek, V.P. Gabel, H.G. Graf, E. Guenther, H. Haemmerle, B. Hoefflinger, K. Kohler, W. Nisch, M. Schubert, A. Stett, and S. Weiss, The development of subretinal microphotodiodes for replacement of degenerated photoreceptors, Ophthalmic Res **29** (1997) 269-280.

[103] E. Zrenner, A. Stett, S. Weiss, R.B. Aramant, E. Guenther, K. Kohler, K.D. Miliczek, M.J. Seiler, and H. Haemmerle, Can subretinal microphotodiodes successfully replace degenerated photoreceptors?, Vision Res **39** (1999) 2555-2567.

Figure 1

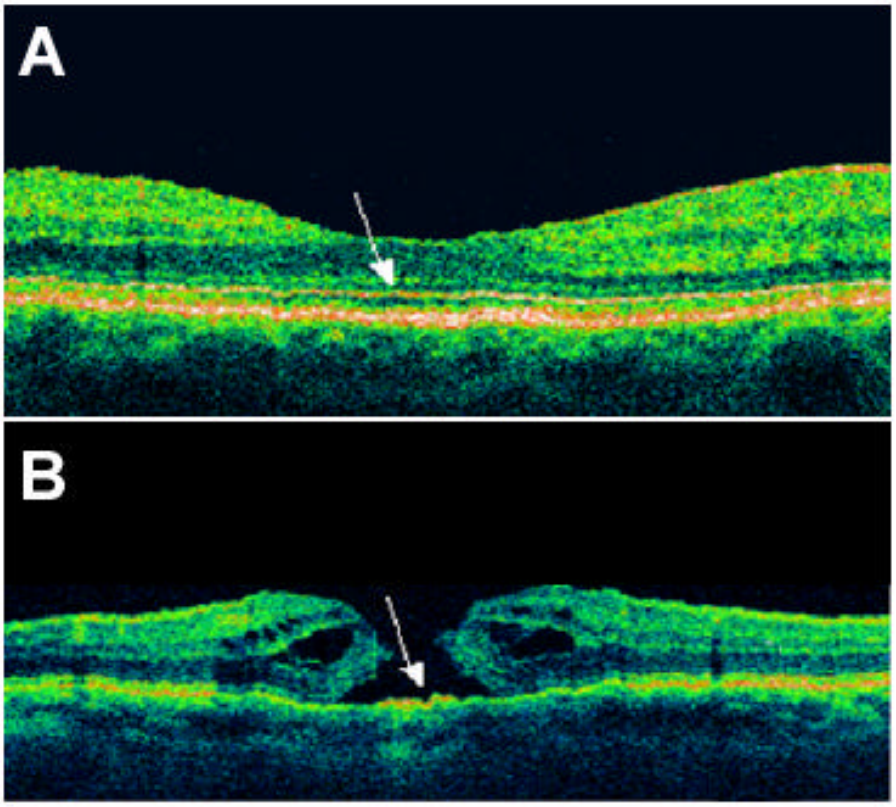

Figure 2

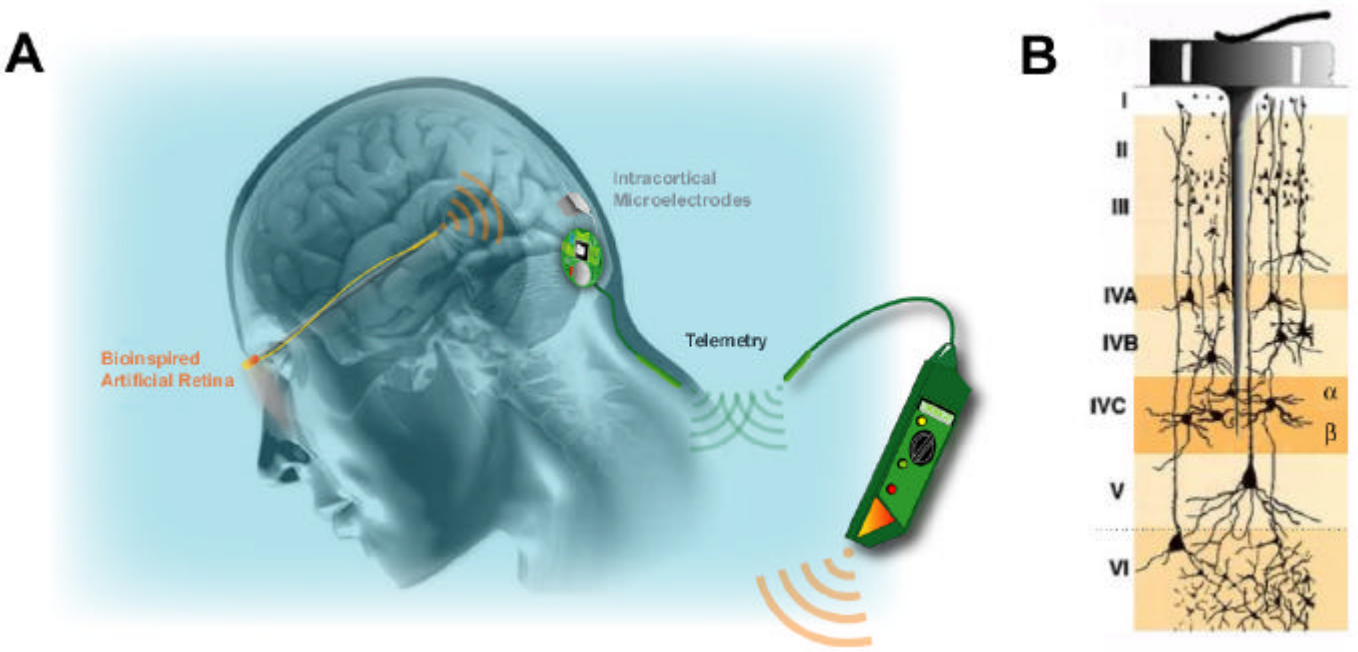
A
Intracortical
Microelectrodes
Telemetry
Bioinspired
Artificial Retina
B
I
II
III
IVA
IVB
IVC
α
β
V
VI

Figure 3

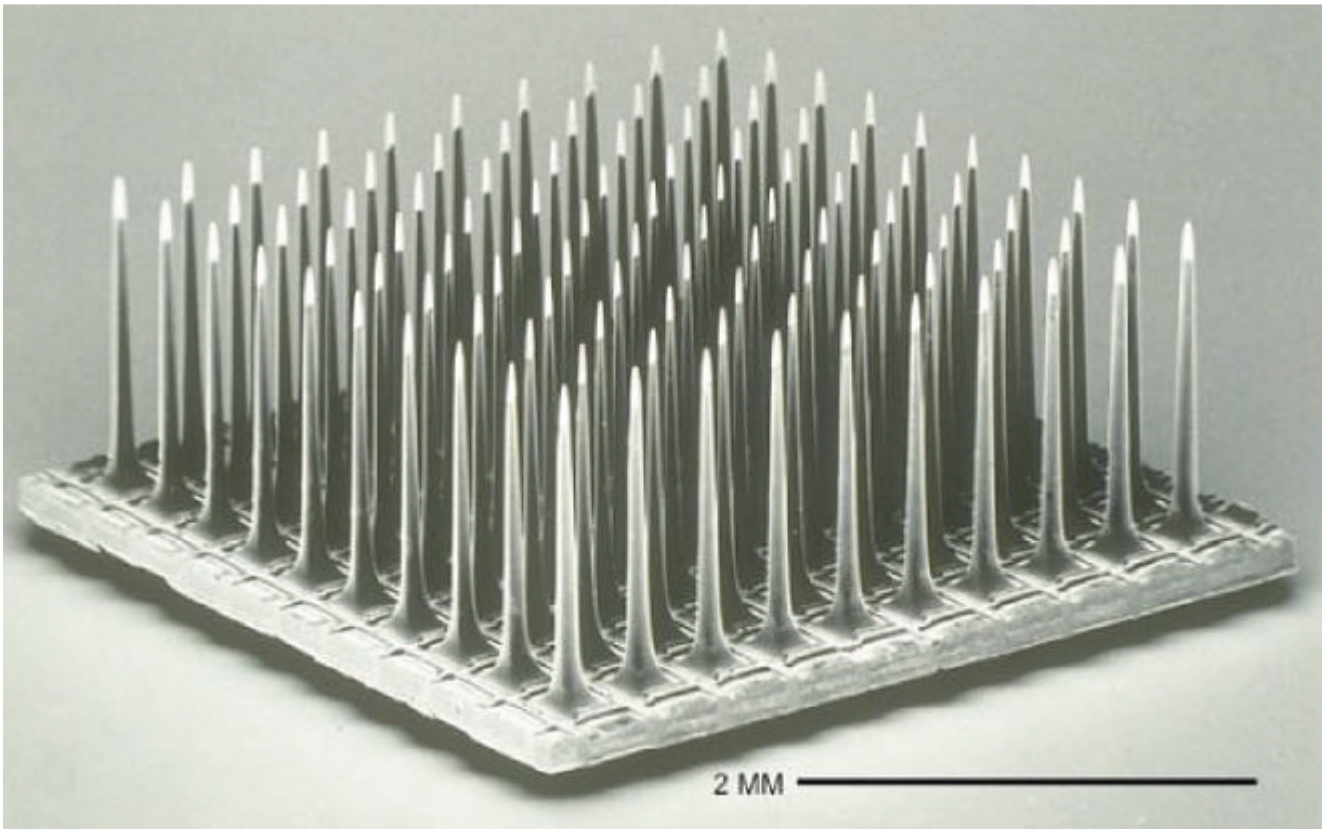

Figure 4

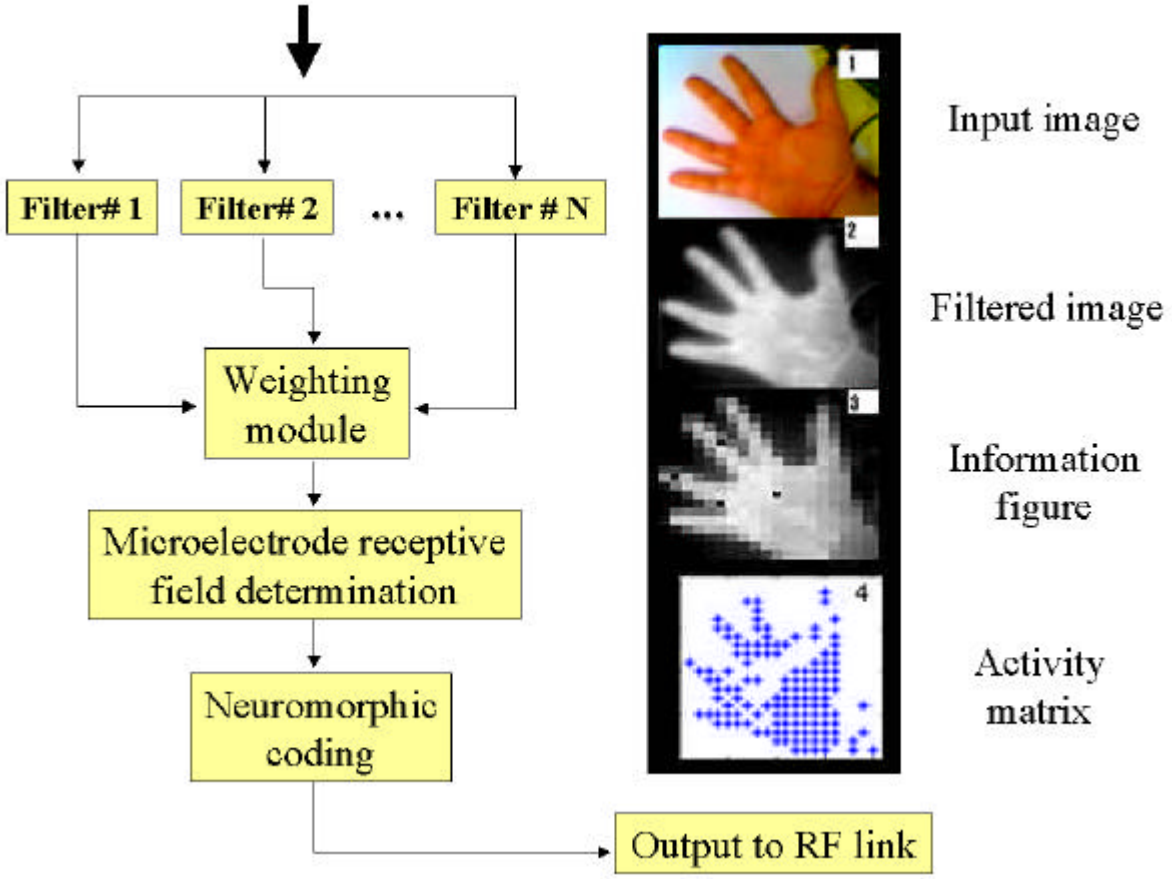
Filter# 1
Filter# 2
...
Filter # N
Weighting module
Microelectrode receptive field determination
Neuromorphic coding
Output to RF link
1
2
3
4
Input image
Filtered image
Information figure
Activity matrix

Figure 5

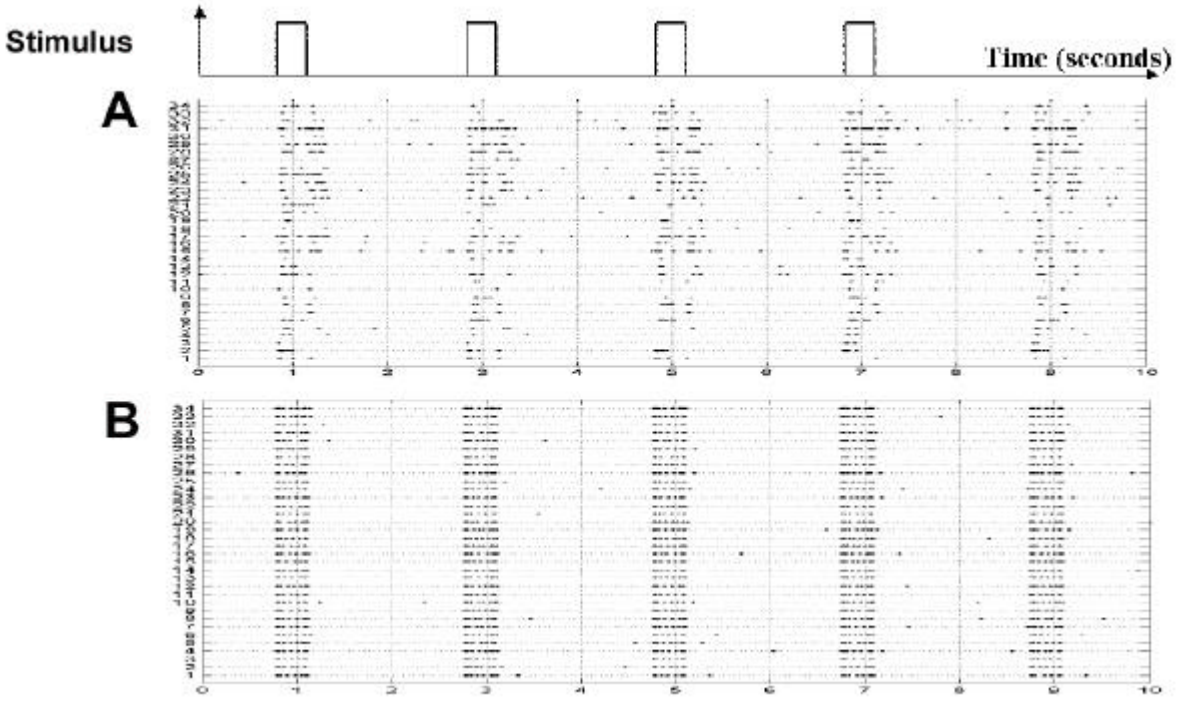

Figure 6

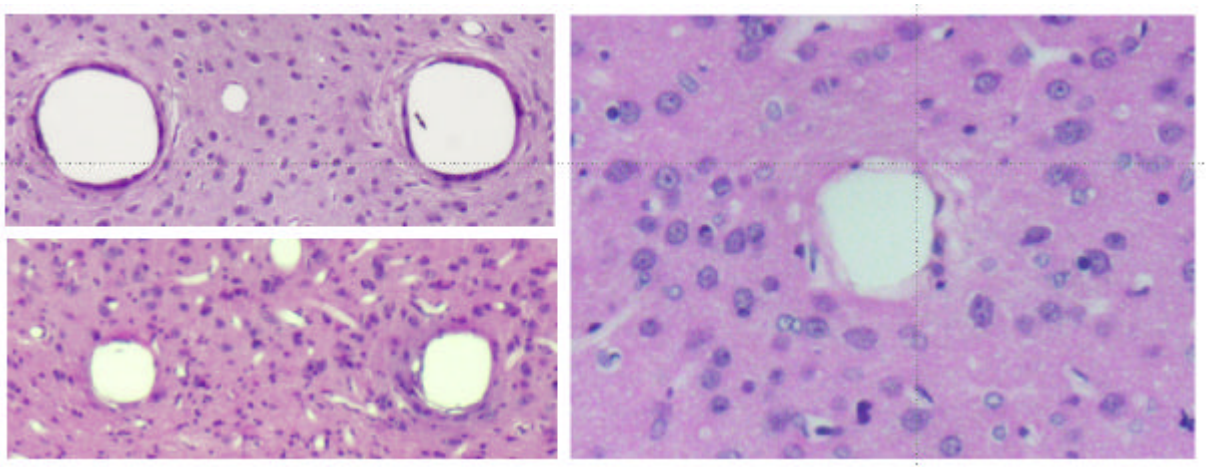

Figure 7