CONSISTENT CORTICAL RESPONSES FROM SUBCORTICALY DELIVERED ELECTRICAL STIMULI

A Study Oriented to Visual Prostheses

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Abstract: Loss of vision is one of the most important challenges for science nowadays and a large amount of work has been done in the development and implant of visual neuroprostheses. The applicability of retinal implants is restricted either because healthy retinal neurons and/or optic nerve are not always available or because of problems related to the retinal implants themselves. At the present alternatives are restricted to cortical prostheses which in turn have several physiological and technical limitations. In our communication we describe a direct proof for the feasibility of subcortical visual prostheses that would solve several of the limitations of the cortical ones. Our approach consists in stimulating the visual cortex of intact animals by means of visual stimuli and then to generate similar responses by means of electrical stimulation of the lateral geniculate nucleus.

1 INTRODUCTION

1.1 General Context

Loss of vision is one of the most important challenges for science nowadays. Vision impaired people are among the most vulnerable and emarginated, normally with low incomes or unemployed, with poor education, inadequate social protection, many problems for public or private transport, perception of the environment, access to the buildings, etc. In addition to these adversities, the negative attitudes of the society create a hostile environment to both, the blind people and their families.

For all these reasons the development of visual prostheses represents one of the highest priorities in the field of Biomedical Engineering, despite vision is the most complicated of our senses and several extremely complicated physiological, computational and engineering problems have to be solved at every step. Up to now, a large amount of work has been done in the development and chronic implants of visual neuroprostheses (for a thorough review see (Maynard, 2001)) including chronic implants in the retina, optic nerve and occipital cortex of blind human subjects (Cohen, 2007; Dobelle, 2000; Gerding, 2007; Humayun et al., 2003; Javaheri et al., 2006; Lakhanpal et al., 2003; Margalit et al., 2002; Shenoy et al., 2006; Thanos et al., 2007; Veraart et al., 1998; Winter et al., 2007).

Retinal prostheses are very useful for the impaired people but they need functional retinal neurons and intact optic nerve, thalamus and cortex. On the other hand cortical prostheses have to be directly interfaced and inject visual signals to a high-level neural structure, the visual cortex, designed by nature to receive and analyse complex information.

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Moreover, such information is previously pre-processed by the retina and visual thalamus and this process includes an open loop formed by the corticothalamic and thalamocortical projections (Mason et al., 1991) the function of which is not taken into account in the design of cortical prostheses.

Most of the problems related to the architecture of the visual cortex and the input of visual signals could be solved if visual prostheses would be implanted to the previous relay station of the visual system, the lateral geniculate nucleus of the thalamus; such prostheses would also benefit from the processing capabilities of the thalamocortical loop (see Section 1.2). But to our knowledge there is not available experimental work on visual prostheses to implant in subcortical structures and in particular in the visual thalamus, except the work of Pezaris and Reid (2007) in the generation of visual percepts after stimulation of the lateral geniculate nucleus.

In the present paper we describe our work on visual prostheses implanted in the lateral geniculate nucleus of the thalamus and a direct way to demonstrate the appearance of artificially generated cortical responses similar to those elicited by natural visual stimuli.

1.2 The Visual System

The visual system processes information in a hierarchical manner from the retina to the cortex through increasing the complexity of feature extractions using a chain of three neurons and two neural relay stations connected in a massively parallel fashion. The first information processing station is the eyeball's inner lining, the retina, where a bidimensional sheet of photoreceptors transform the image of the external world to a multi-dimensional spatiotemporal and intensity pattern of electrical signals (Baylor et al., 1979; Saito et al., 1978) further processed by the bipolar, horizontal, amacrine and ganglion cells (Kuffler, 1953). Via the optic nerve, the outputs of the two retinas are transmitted to the lateral geniculate nucleus of the thalamus (LGN) where are processed (Kastner et al., 2006; Derrington and Fuchs, 1979) and integrated into a binocular representation of the world (Murphy and Sillito, 1989).

LGN output goes directly to the primary visual cortex (V1) which gives in turn a massive feedback to LGN and also sends information to higher visual cortical regions for further processing (Mason et al., 1991). The corticothalamic information feedback plays a major role to information processing of the visual signal, selecting the most interesting inputs and imposing processing rules to the thalamus (Sillito et al., 2006).

1.3 Visual Prostheses

Blindness results from either an inability of the visual system to transduce light energy into electric signals or a failure of the generated electrical signals to reach the higher relay stations of the visual pathway. It is classically accepted that electrical stimulation of V1 can elicit a visual percept of light denominated phosphene (Tehovnik and Slocum, 2007; Krisch and Hosticka, 2007).

In retinal prostheses arrays of electrodes are placed either on the retinal surface or in the subretinal space where they stimulate ganglion cells (Humayun, 2003). A new approach to retinal prosthesis is electrical stimulation of the retina with extraocular electrodes (Chowdhury et al., 2008). However they need an undamaged retina and an intact optic nerve (Margalit, 2002).

Cortical prostheses consist of arrays of electrodes which are placed to or penetrate the cortical surface and stimulate layer VI of the visual cortex to create discrete phosphenes (Brindley and Lewin, 1968; Dobelle, 2000) and have the advantage to be suitable for almost any kind of blind patients.

However the visual cortex is non-linear and non-conformal with visual space, not letting us to predict in a precise way where will phosphenes be elicited when stimulating with each electrode (Warren et al., 2001). Moreover, the power of cortical processing is mainly based to the continuous feedback of the thalamocortical loop and to the influence V1 exercises to the thalamus, both of them excluded due to the direct introduction of visual information to V1.

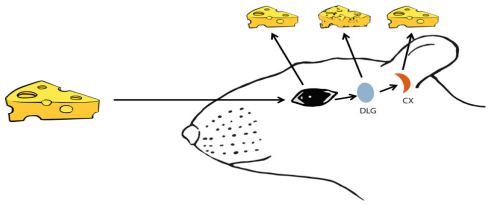

Figure 1: Schematic representation of the visual pathway.

In the cases in which the retina and/or the optic nerve are damaged or not functioning, the target with more advantages and less technical, experimental or clinical problems for visual prostheses seems to be the thalamus:

1) the receptive fields (RFs) of LGN neurons are simple, well characterized, and similar to those of their retinal afferents (Hubel and Wiesel, 1961; Wiesel and Hubel, 1966)

2) fovea and parafovea are spatially represented in the LGN facilitating the accessibility of neurons with central visual fields (Pezaris and Reid, 2007)

3) LGN cells give rise to axons that terminate in primary visual cortex, in a highly specific manner making monosynaptic connections with simple cells predominantly when the pre- and postsynaptic receptive fields overlap and match in sign, size, and time course (Alonso et al., 2001), consequently stimulation of a small number of LGN neurons should achieve simple, focal percepts (Pezaris and Reid, 2007)

4) LGN cells receive a massive cortical feedback that directly control the processing capabilities of these neurons conditioning and selecting the visual information from LGN to the cortex (Sillito et al., 2006). Consequently, LGN implants will use the plasticity and adaptability of the Central Nervous System to modify the responses of its own neurons to recognize the artificial signals through the influence of the corticothalamic LGN-V1 loop.

Despite the above considerations LGN has never been taken into account in the development of prosthetic visual devices, except the mentions in Pezaris and Reid (2007).

The direct test of the feasibility of visual devices implanted in the thalamus is just the target of the present work. The data we present here come out from our research carried out within the framework of our projects on visual neuroprostheses. In this work our objective was to generate perception sensations similar to the natural ones and assess them by comparing the responses of the cortical neurons to electrical stimulation of the thalamus with those generated by visual stimulation of the eye (see Section of Materials and Methods).

2 EXPERIMENTS

2.1 General Approach

Data were obtained from 36 urethane- (1.5g/kg i.p.) or sodium pentobarbital (35mg/Kg i.p.) anaesthetized Wistar rats of both sexes, weighting 200-240g. Experiments were carried out according to the national legislation (R.D. 1201/2005) and EU Directives on this matter (86/609/EC). Rats have been used due to their simple but complete visual system. In a previous work we had realised a mapping of the thalamic and cortical visual areas and to characterized the responses of their neurons to simple and complex visual stimuli. The 36 animals were used in a series of combined experiments in which one group of electrodes was placed in the LGN and another group in V1.

Our approach consisted in: 1) presenting a series of visual stimuli to one eye and record the responses of the contra lateral LGN and V1, R_{Th} and R_{V1} respectively, by means of the implanted multielectrodes, 2) inject to LGN an electrical pattern R_{Th}^* similar to the previously recorded R_{Th} during the presentation of the visual stimuli; at the same time record the cortical responses R_{V1}^* to this electrical stimulation of LGN and 3) modify the parameters of R_{Th}^* looking for the best matching between R_{V1} and R_{V1}^*, that means between the response to natural and the response to the electrical stimuli.

The ability to elicit R_{V1}^* responses similar to R_{V1} for a large number of natural visual stimuli would be a proof of the feasibility of visual prostheses implanted to the thalamus.

In total, 216 complete cycles of experiments (visual stimulation – LGN & V1 recordings, electrical stimulation – V1 recordings were performed.

2.2 Stimulation and Recordings

Animals were placed in a stereotaxic device that enables the conduct of visual experiments. An incision was performed and two holes were made in the skull to allow access to the rat brain in the appropriate coordinates. Recording and stimulating multielectrodes were developed and tested in our lab following the methodology described by Neuralynx (http://www.neuralynx.com) and then introduced in the brain. Anaesthesia level was controlled by the amplitude of the EEG waves. A frontal hole was made to record the electroencephalogram (EEG). EEG recordings were performed through an insulated (except in the tip) 1mm diameter Cr-Ni macroelectrode introduced in the frontal cortex at 1.0mm from the surface. The EEG was continuously monitored in the oscilloscope. In case of reduction of the amplitude of the waves supplementary doses of anaesthesia were administered.

2.3 Data Acquisition and Analysis

Single channel recordings were performed using tungsten microelectrodes (2.0MΩ) and Micro1401 hardware by Cambridge Electronic Design with

accompanying software Spike2. Multichannel recordings were performed using the above described multielectrodes and neural activity was acquired using a PCI-6071E E Series data acquisition card from National Instruments, with accompanying Recorder software amplified and displayed on a Plexon Inc PCI device, stored and then imported to a Spike2 software and analyzed using MATLAB (©MathWork corporation) and Spike2 software. Data were sampled and digitalized at 20 KHz, stored in personal computers and then processed off-line. We first performed single channel recordings both in LGN and V1 with tungsten electrodes in order localize a region with response to visual stimulation.

Once the most suitable region was identified the tungsten electrode was substituted by a 4x4 multielectrode array. The neural tissue was then let to recover its normal activity for 20 minutes and then we started with the standard recording/stimulation procedure. The exact location of the recording electrode was also confirmed on subsequent histological preparations.

Spikes were threshold-isolated offline using Spike2 software (Cambridge Electronic Design) taking as threshold a value equal at least three times the level of the noise, and converted into discrete processes. To determine basic features of neuronal response and behaviour we performed peristimulus histograms, interspike interval histograms, auto- and cross-correlation histograms.

2.4 Histology

To ascertain the localization of the electrodes, the histology of the brain was analyzed 1 mm rostral and dorsal to the electrodes placed in the LGN and the occipital cortex, respectively.

Briefly, after recording, and because the electrodes are too thick to easily identify the cerebral structured where they are placed into, a 2mA electric current was passed though them for 10s in order to electro coagulate the recorded structures. Then the animals were sacrificed with an intracardiac injection of NaCl hypertonic solution (3ml) and the brain was quickly removed and whole fixed in Bouin's fixative for 24 hours, then dehydrated through increased concentrations of ethanol (from 70º to absolute) and xylene to remove the picric acid, and embedded in paraffin.

The blocks were cut serially to obtain coronal sections 10µm thick, deparaffinized, rehydrated and stained with methylene blue-eosin. The sections were then washed in tap-water, dehydrated and mounted with Entellan®, and studied in a light photomicroscope. The electrode implanted into the lateral geniculate body has a trajectory perpendicular to the brain surface. The structural techniques used to identify the lesioned zones were routinely haematoxylin & eosin and alzian blue & haematoxylin. Both techniques consented identify the structure of the brain and the electrocoagulation-induced lesion.

2.5 Stimulations and Responses

In a first phase, visual stimuli of increasing complexity were used to determine the response patterns evoked in both LGN and V1. Two types of visual stimuli were used, flashes (Grass model PS33, 20-40 stimuli at 1Hz) and persistent geometric black and white figures (see figure 2): horizontal stripes, circle, ring of light, cross and black cross on a white background. Persistent stimuli were generated on the screen of a PC (324 X 244 mm and 1024 x 768 pixels resolution) applied for 3 seconds at 0.3Hz. Every stimulus had a TTL synchronization signal toward the data acquisition system.

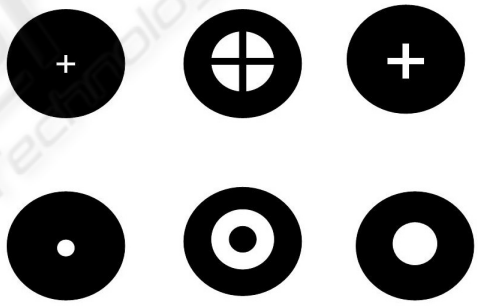

Figure 2: Geometric stimuli used in the experiments.

Responses were analyzed, correlated and patterns of electrical stimuli were generated and applied to the LGN according to the procedure described in Section 2.2. Then it has been possible to extract basic characteristics of the electrical stimulation that evoked cortical responses comparable to those of the visual stimuli.

After that, each animal was applied a battery of visual stimuli, thalamic and cortical activity were recorded, online analyzed, and sets of electrical stimulation patterns were generated. Such stimulation patterns were then applied to the LGN, and cortical responses were recorded and compared to those generated by the visual stimuli (see figure 3).

Current was applied across the four electrodes in the geniculate nucleus using SIUs (World Precision Instruments, A365 and A360 Stimulus Isolator Unit) controlled by the Spike software with the Micro1401 mkII data acquisition unit (Cambridge Electronic Design). We used intensities between 100μA and 600μA and applied different patterns of stimulation differing in the number of stimuli trains, the interval between trains, the number of stimuli per train and their duration and the number of electrodes and the temporal relation between the current applied by each electrode.

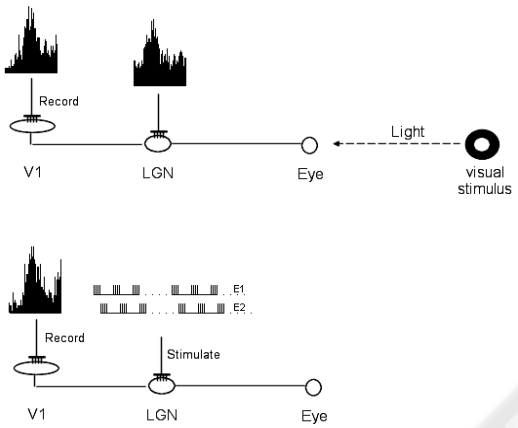

Figure 3: A visual stimulus is presented to the eye and neural responses are recorded from the lateral geniculate nucleus in the thalamus and the primary visual cortex (up). The characteristics of the thalamic electric activity are extracted and an artificial electrical stimulus is generated and delivered to the thalamic neurons in absence of external (natural) visual stimulus (down). A fine adjustment of the spatiotemporal and intensity characteristics of the artificial stimuli delivered through the multiple electrodes implanted to the thalamus allow us to obtain responses from the cortical neurons that are very similar to those induced by the natural stimulation using geometric stimuli. Similar results were obtained from the entire set of visual stimuli (geometric forms) and the corresponding electrical stimuli.

3 CONCLUSIONS

Due to the architectonic organisation of the lateral geniculate nucleus and the lower complexity of the processing of visual information it performs (if compared to the visual cortex) LGN is the best candidate for visual implants when the retina and/or optic nerve are not functional. Moreover, the direct action of the visual cortex to the thalamic neurons through the thalamocortical loop allows a better adaptation of the Central Nervous System to the artificial input to the thalamus than to the cortex.

In the present paper we prove that electrical stimulation of the lateral geniculate nucleus can generate neural responses in the visual cortex that resemble those elicited by natural visual stimuli. Such responses can be achieved after a sampling of the thalamic responses to the natural stimuli by means of multielectrode recordings, the extraction of their basic spatiotemporal characteristics and a subsequent fine tuning of the electrical stimuli delivered through the same electrodes implanted into the thalamus.

Our results are important for the development of visual prostheses implanted in the subcortical structures of the brain of blind people although an extensive work has to be done: in addition to anatomophysiological problems related to the implants of the electrode, damages to the brain due to the chronic stimulation, etc., research on coding complex visual stimuli, images in movement, reduction of the complexity of the visual image. So future steps to solve these problem will be recordand stimulate with more channels (up to 100), applied visual stimuli in movement, implant multielectrodes chronically, mathematical study of the interactions between recording/stimulating channels to develop more precise microstimulation, etc.

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