



BIOENG-457

Neuroengineering of vision's Group Project

LGN prosthesis to partially restore vision in glaucoma blind patient

Group 5

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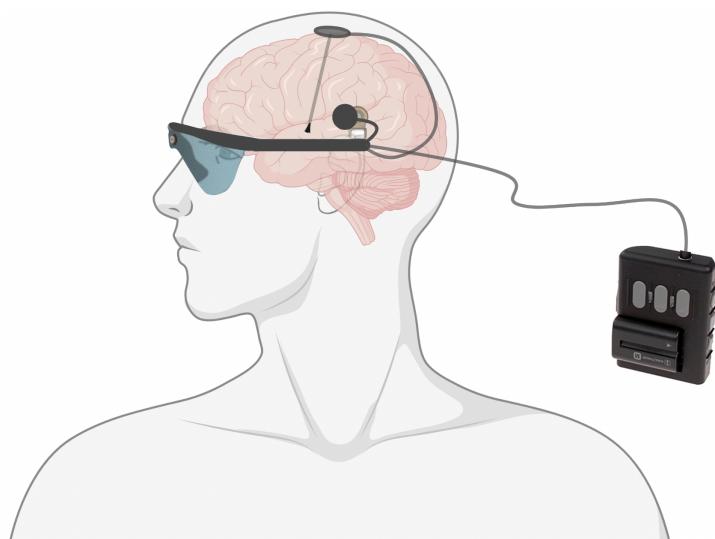


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1 Introduction

This report presents a novel approach to partially restore vision in glaucoma-blind patients by targeting the LGN. We will start by introducing the disease, and the target's choice. Then we will describe the general design of our prosthesis, how to transfer data and power to it, and finally how we will analyze the results in order to test our device.

1.1 Glaucoma and objective

Over 60 million individuals worldwide suffer from glaucoma, which accounts for 8.4 million cases of blindness [1]. Although there are different kinds of glaucoma affecting patients in various ways, this study will concentrate on patients who are legally blind. There are numerous causes for the condition, but increased intraocular pressure is the main risk factor (IOP). The loss of the retinal ganglion cells (RGC) and optic neuropathy are typically the outcomes of this elevated IOP [1]. This results in both an impaired retina and a damaged optic nerve head.

Despite this impairment, the downstream visual pathway remains unaltered offering an ideal target (see figure 1). More precisely, we chose to work on the lateral geniculate nucleus (LGN) of the thalamus. Hence, this report aims to propose enhancements to the study of J. Pezaris and R. Clay, 2007 [2] which targeted the LGN of monkeys. Although Pezaris managed to elicit phosphenes, their concept was rather rudimentary. Our study will add the various components of a visual prosthesis, namely a camera capturing images, a video processing unit, and an implant containing both more and different electrodes than in [2].

Ideally, our prosthesis would be able to restore vision. But in practice, the minimal goal is to reach a device allowing the patient to move out of legal blindness (i.e. a score of logMAR 1.3) [3]. And the best case scenario would be to recover full trichromatic, stereo vision at logMAR 0. Of course, this ultimate goal is not reachable with current technology. Hence, we will focus on demonstrating the feasibility of scaling up previous experiments on monkeys and eventually moving to human subjects.

1.2 Motivations for our design

1.2.1 Anatomical motivations

From the retina to the primary visual cortex (V1), many structures are potential candidates to receive visual implants. Here we will go through the pros and cons in anatomical order (see figure 1). The first possibility is to implant the retina. This technique is suitable for patients suffering from photoreceptors disease, such as retinitis pigmentosa. However, most of the methods target retinal ganglion cells [2] which are dead in the case of glaucoma. Hence, despite having many advantages, retinal prostheses are not suited for treating glaucoma patients. Then one could implant the optic nerve where the advantages are minimally invasive surgery, mechanical stability and functional flexibility [2]. However, following the death of RGCs the optic nerve can be damaged in glaucoma patients (with a varying impact across individuals) [4]. Hence, it discards the optic nerve as a candidate for a robust

and automated protocol designed for glaucoma patients. Another important point is the lack of fine retinotopy in the optic nerve, preventing a precise stimulation in the visual field [5]. Right before the LGN, the following anatomical structure is the optic tract, which combines the disadvantages of the LGN and optic nerve, while only retaining a few of their advantages, hence making it a less attractive candidate [2][6]. Then comes the LGN which will be described in more detail below. Next, there is optic radiation, where its major drawback lies in its complex 3D diffuse structure [2]. Thus stimulating the visual field's entirety implies a more complex implant, making it less convenient. Before last, there is V1, which has been thoroughly studied and already implanted [2]. The downside lies in the complexity of the signals in this structure. Indeed, much more processing has been done on the visual inputs at this stage than on any other prior structures. This complicates the treatment of the video signals into stimulating pulses for the cortex. Moreover, part of V1 is hidden within cerebral sulci which renders a portion of the primary visual cortex harder to stimulate. Finally, all structures that lie after V1 have an even higher degree of abstraction in terms of signal processing. Additionally, these structures are poorly documented compared to the ones described before. Therefore, we chose not to pursue research on these.

The aspects mentioned above as well as those we are about to develop motivated us for selecting the LGN as a good compromise between the stability of the implant, compactness of the region to stimulate, and representation of the visual signals.

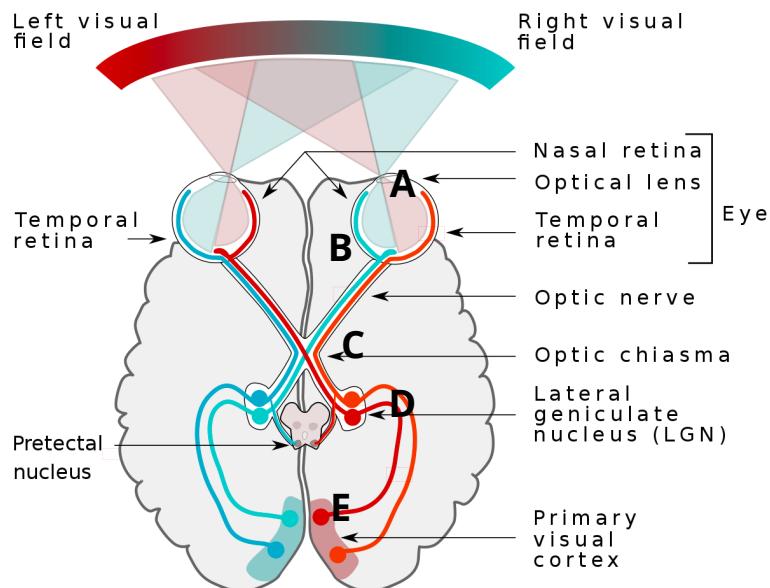


Figure 1: The downstream visual pathway remains unaltered in case of glaucoma. **A:** Retina; death of RGCs. **B:** Optic nerve; partially damaged and lack fine retinotopy. **C:** LGN; good compromise. **D:** Optic radiation; complex 3D diffuse structure. **E:** V1; complex signals and part of V1 is hidden. Higher-level of visual processing structures are not shown in this graph; too high degree of abstraction.

1.2.2 LGN overview and motivations

For a long time, the LGN has been considered a simple relay nucleus between the retina and V1. Yet scientists are starting to reconsider this structure as a more complex and active component of the visual pathway, performing non-linear filtering and perhaps some role in object-vision and attention [7]. For

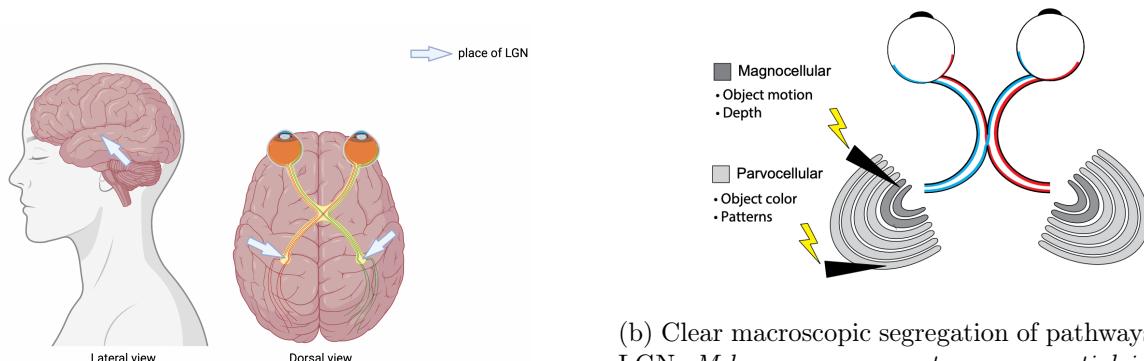
instance, the LGN's inputs have been underestimated, as 50% of its inputs come from the visual cortex while only 10% of the visual information received comes from the retina [5]. Hence the thalamocortical loop probably plays an important role in LGN's functions and should not be underestimated. This illustrates a part of this "relay nucleus" complexity as well as the mystery surrounding the LGN's purpose. These are aspects that we will need to take into consideration while designing our prosthesis (see figure 2c)

Nonetheless, there are several advantages when targeting the LGN. For instance in terms of stability, as it is located centrally deep inside the brain, once the electrodes are placed, their stability would be guaranteed (see figure 2a). Moreover, the LGN's location is about 10 mm away from subthalamic structures targeted for deep brain stimulation (DBS) implants [2]. These surgeries are well established and the proximity suggests that only minor modifications from a typical DBS surgery will be required. Then structurally, as the LGN surface is compact (only about 10 mm across), it becomes easier to cover the surface with electrodes and stimulate the full extent of the visual field [2]. Compared to the retina where the entirety of the eye needs to be stimulated (which represents an averaged surface of 1094 mm^2 [8]), the required implant can be smaller (i.e. easier to insert). Another advantage compared to the retina is the LGN's consistent density of "receptors" with respect to the visual field. While the retina contains a denser concentration of receptors in the fovea, the LGN neurons density remains the same [9]. Compared to the retina, this means that the surface representing the high acuity central vision is bigger due to what is called foveal magnification [2]. It will facilitate the electrical stimulation as the size and spacing of the electrodes can be increased (compared to the fovea), and spacing evenly between our contact points will still result in a greater density of phosphenes in the central visual field [3]. Another advantage is the compactness of the visual representation in the LGN. For instance in V1, the foveal neurons are concealed within interhemispheric and calcarine fissures [3].

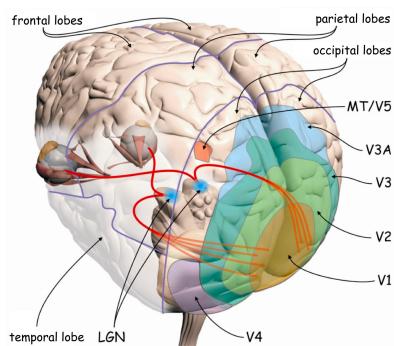
Another structural advantage arises from the highly organized pathways (magnocellular, parvocellular, and koniocellular). Indeed, the LGN is the only location in the early visual system where these three structures are macroscopically segregated [6] (see figures 2b and 2d). Although there is much to uncover about their functions, it is assumed that the M-layers code primarily for movement, coarse spatial information, and high contrast whereas cells of the P-layers code for fine detail and red/green color discrimination [10]. Another potential asset worth mentioning regarding LGN stimulation is that LGN layers 3 and 4 were found to process signals from OFF-center RGCs, while layers 5 and 6 supposedly process signals from ON-center RGCs [10]. Signals from these cell types are in part responsible for the detection of edges and gradients in images. In the long run, selectively accessing these subdivisions will imply a more amenable control of luminance and chrominance levels compared to other locations, and potentially enable us to encode our stimulation to effectively allow prominent feature extraction from images [2]. Finally, in terms of signal processing, the LGN receives signals that are only slightly pre-processed and maintain much of the primary input from the retina [2]. This is another factor facilitating the phosphenes generation, especially compared to structures even further away from the retina. Despite these advantages, one should keep in mind the vertical segregation of the visual field. Indeed, the LGN lies after the optic chiasm, hence the visual field is already separated into the left and right hemifields. Thus, one needs to implant both LGNs to cover the full visual field [2]. However, this could enable great stereo-vision.

1.2.3 Stimulation type motivations:

We considered three main approaches for stimulating the visual system: optogenetics, magnetic and electrical stimulation. The former presents many advantages in terms of: spatial and temporal resolution, non-invasive (if used in the retina) and cell specificity [9]. However, deeper brain structures are not accessible, the side effects are poorly understood, and most importantly: this method requires novel gene editing techniques which are far from being approved in humans. Magnetic stimulation has the advantage of being non-invasive and not introducing exogenous agents within the body [9]. Yet this method has a low spatial resolution, requires high-power electromagnetic devices (not suitable for wearable designs) and has also been less thoroughly researched than electrical stimulation. Although the electrode-based approach is more invasive and does not match the resolution reached by optogenetics [9], the technology is well understood, and wearable devices already exist and are commercially available for human use. Thus we decided to use electrical stimulation for our project.

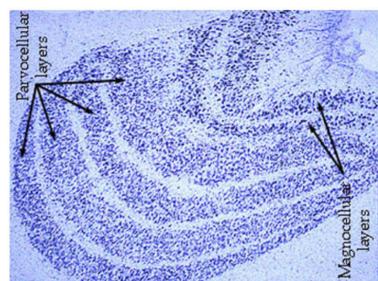


(a) Location of the LGN in the thalamus. *It is located centrally deep inside the brain, only 10 mm away from subthalamic structures.*



(c) Flow of information through the LGN. *It Receives slightly pre-processed info from both eyes and from the visual cortex. It transmits info to V1 after performing non-linear filtering. Then, it receives a feedback loop from V1.*

(b) Clear macroscopic segregation of pathways in the LGN. *M-layers: movement, coarse spatial information, high contrast (colour blind system). P-layers: detail and red/green color discrimination. K-layers: between each of the M and P layers (unclear role).*



(d) Staining of LGN.

Figure 2: LGN overview

1.3 Previous studies on LGN

Visual prostheses implanted in the LGN have been demonstrated in monkeys, rats and rabbits [9]. A study evaluated the crude resolution of LGN implants by using microwire bundle electrodes to induce visual percepts in healthy monkeys [2][11]. The percepts were similar to the sudden illumination of a bright point outside of the gaze direction. The authors took advantage of the natural primate reaction which is to focus vision on the stimuli through direct eye movement. Hence, they could monitor the stimulation by measuring saccades: either electrically (stimulation) or optically on a computer screen (control). This study demonstrated the feasibility of inducing phosphenes via LGN electrical stimulation and paved the way for the emergence of a new type of visual prostheses. Another study focused on implanting rats and rabbits [5], where the main objective was to determine which type of electrical stimulus could trigger reliable responses of cortical neurons similar to those induced by images seen through the eyes. After some fine-tuning, the authors succeeded in eliciting artificial visual responses (in V1) similar to natural visual responses. This reinforces the feasibility of using the LGN as a stimulation target.

Building upon these two experimental kinds of research (as well as other theoretical ones), we want to further animal experimentation by increasing the number of electrodes (such that we could create basic patterns) and integrating an image acquisition system which, ultimately, could be translated to glaucoma blind patients.

2 Device design

As the problem and goals have been described, we can now focus on the components required for creating a comprehensive visual prosthesis. These prostheses require the following set of system components: 1) a device to capture images, 2) electronic circuitry to process the images and create stimulation patterns that would mimic the firing of neurons, and 3) an array of miniature electrodes, each of which can stimulate a small number of visual neurons [10].

This section of the report aims to illustrate external hardware components and internal hardware of the proposed LGN visual prosthesis (see the sketch of the entire prosthesis in figure 4). And the focus of our project is to investigate the electrodes and stimulation types in a study conducted on non-human primates.

2.1 External hardware

The image-capturing device should be convenient and comfortable to wear on a daily basis for the wearers. This is why we have been inspired by the Argus II technology idea and decided to go for a video camera that is mounted on a pair of glasses for real-time image acquisition.

For the electronic circuitry processing the images and creating stimulation patterns, a video processing unit (VPU) is necessary. Because the VPU is too large to be attached directly to the glasses, it will be worn on the subject's belt. The VPU has adjustable settings that transform the images from the camera into electrical stimulation, which is then transmitted using an antenna via a coil,

wired to the side of the glasses, transmitting to another customised receiving coil on the skull. This information is then sent through a cable to the electrode array implanted in the LGN [12]. As we want to implement a near-field wireless power transmission (WPT) for reasons mentioned further in section 3.1, the idea is to create a design similar to the well-established WPT of cochlear implants that are already FDA-approved such as MED-EL, Cochlear Corporation or Advanced Bionics [13][14].

The inductive coupling will be used, where one coil will be located on the glasses frame (or connected through a wire to the glasses) and the other coil on the skull above the ear. Both data and power will be transmitted. To design this, we would simply adapt a commercially available solution from the field.

2.2 Internal hardware

2.2.1 LGN's characteristics

Before diving into the details, one needs to understand the anatomical structure we want to stimulate. The LGN has a typical volume of 250 mm^3 and a maximum extent of $\sim 10 \text{ mm}$ along the cardinal axis [2]. The visual field in this volume is not spread uniformly as mentioned before. For instance, the central 10° of the visual field is treated in the posterior half. More precisely, the anatomical mapping of the retinotopic field onto the LGN allowed the discovery that 60% of the LGN's volume is dedicated to the central 3° of the visual field [9]. This is advantageous as we want to trigger the central visual field in priority. This would allow a less densely packed electrode array than in the retina (where the central vision is tightly packed in the fovea). Hence reducing the mechanical and electrical damage to the tissues.

2.2.2 Electrode choice

As discussed above, we intend to interface the visual pathway through the LGN, which is a structure deeply enclosed within the brain. Although we need to get access to this structure, it is also necessary to bear in mind that for our implant to present a significant advantage for blind individuals suffering from glaucoma, we need a decent phosphene resolution. One of the first means of evoking a large number of phosphenes through electrical stimulation that comes to mind is the microelectrode array (i.e. Utah array) that is conventionally used for V1 stimulation. However, in our case, bringing such an array of electrodes to deep structures within the brain is, as far as we know, impossible without causing a tremendous amount of damage to the tissues. Henceforth, it appeared to us that a possible optimal way to address this was to use electrodes typically involved in Deep Brain Stimulation (DBS).

The type of DBS electrodes that we deemed fit to carry out our task is brush-style electrodes (see figure 3c). In terms of electrode density, if we assume a spacing of 1 mm in three dimensions using brush-style electrodes, around 250 tips could fit in theory into one LGN, resulting in 500 phosphenes across both hemifields [2]. The resulting space used would be only 0.6% of the area if $40 \mu\text{m}$ wires are used. This is an improvement compared to a Utah array (estimated 1%), or DBS electrode (between 0.7% to 3% of the space) [2].

By using customized Ad-Tech brush-style stimulation electrodes it would be possible to gain access to the LGN while potentially having around 60 contact points to stimulate from [2]. Ad-tech brush style stimulation electrode is normally used for deep brain stimulation in the subthalamic nucleus which is a biconvex structure of approximately 180 mm^3 [15]. As discussed above, the size of LGN is approximately 250 mm^3 , and Ad-tech electrode size is, therefore, suitable for stimulation in the LGN (see figure 3b).

As an outcome, there is no need to fabricate the electrodes ourselves because they are already commercially available for 9 contact points, and according to Pezaris in 2009 [16], it is possible to request an increase in the number of contact points directly from the manufacturer. You can see details about the length and the diameter of an electrode in figure 3a.

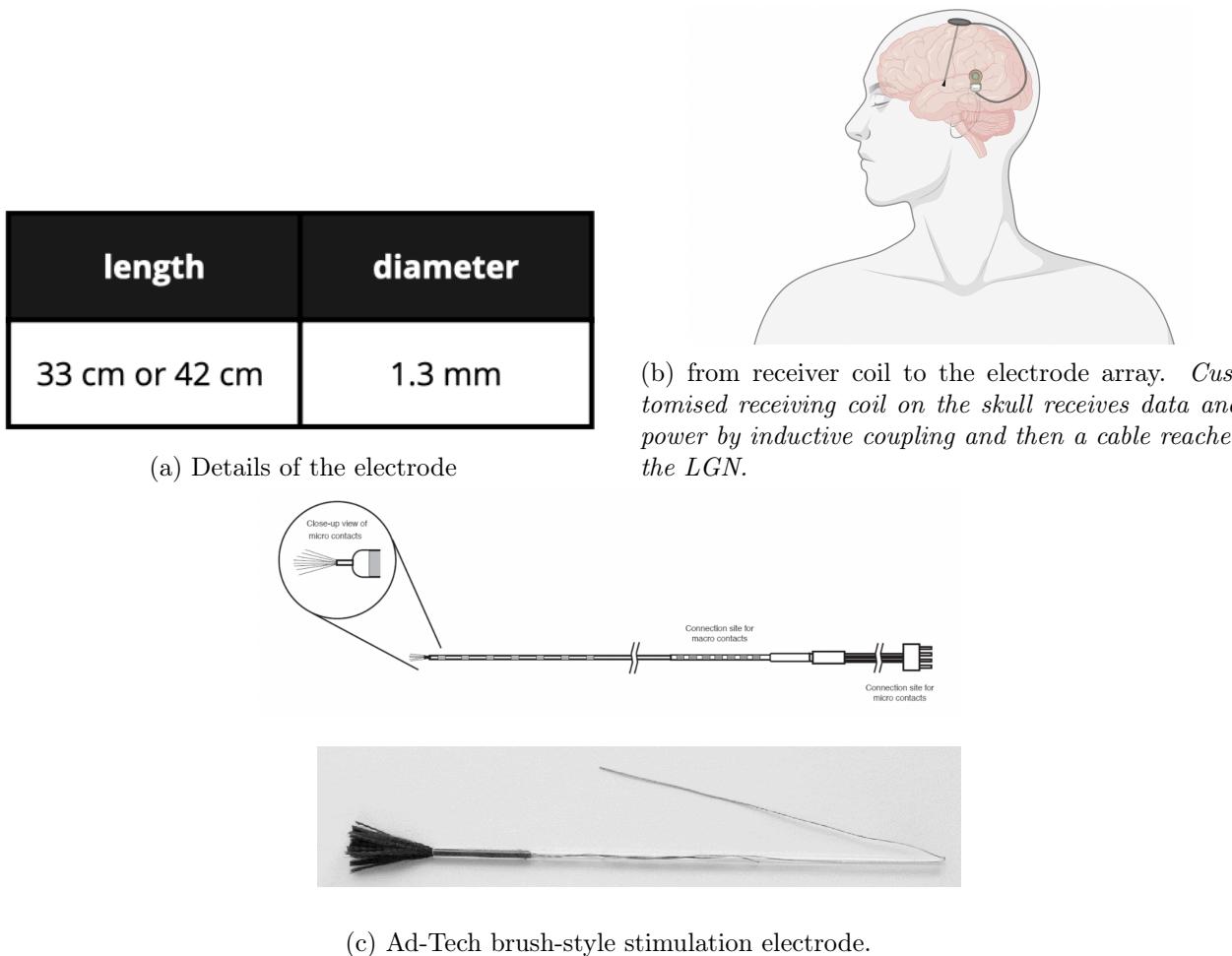


Figure 3: Design of the brush-style electrodes

2.3 Evoked phosphenes

Once subjects are implanted with brush-style deep brain stimulation electrodes, it will be possible to stimulate the LGN at various locations using up to hundreds of different contact points. Each contact point would then allow for the evocation of single phosphenes across the visual field through electrical microstimulation of the most proximal nerve cells around electrode contact. The shape and

location of phosphenes will probably depend on our stimulation parameters, such as amplitude, frequency, stimulation length and so forth. Assuming that cross-talk is possible among our contact points, predicting the result of a given subset of spatially close stimulations across the LGN becomes a more cumbersome task. For now, however, we assume that phosphenes produced through the stimulation of close contact points will mostly have a round-like shape and there could be up to as many phosphenes as there are contact points. We can already expect them to become bigger as we move away from the central foveal representation of the visual field on the LGN, as we know the size versus eccentricity distribution of phosphenes is not uniform [2]. We will start by using stimulation parameters based on a Pezaris study on LGN microstimulation: 80-200 ms long trains of 1ms sinusoidal pulses repeating at 100 to 200 Hz for 20 pulses [11].

2.4 Phosphene mapping

Being able to evoke a high number of phosphenes is not sufficient to restore (even partially) vision. We also need to know their location in the patient's visual field. This is a problem because retinotopy is much more complex in post-optic chiasm structures as it loses its geometrical coherence. Indeed, the geometry of phosphene induced with retinal implants reflects the geometry of the electrodes: aligned electrodes induce aligned phosphenes, electrode in the top-right corner of the retina induces a phosphene in the top-right corner of the visual field, and so on [17]. However, this is not the case for LGN. Phosphenes forming a straight line in the visual field can be induced by electrodes in a triangular conformation and multiple electrodes can induce phosphene in nearly the same location, making them indistinguishable [17]. This property prevents us from sending the processed optical information directly to the electrodes. We first have to perform an individual phosphene mapping to determine which electrode in the LGN corresponds to which phosphene when it lights up in the visual field. In animal models, this mapping can be complex to perform as it is impossible to obtain a description of the scenery resulting from stimulation. However, it is still possible to do it on monkeys through tasks and electrode readings. The different methods and setups we used to perform this mapping on animals will be described in the section Animal testing on NHP.

3 Power and data transmission

3.1 Power

Powering our device is not straightforward. First, our LGN implants will probably require significantly more power than simple DBS implants. Currently, DBS technology uses implanted battery, similar to those used in a cardiac pacemaker, with a cable spanning from the chest to the skull's top [18]. The problems are: due to higher power, the battery will not last for long, plus we need to transmit continuous data from the video camera. These factors motivate the use of continuous power and data transfer. Then, as using a trans-cutaneous cable is not a suitable long-run solution (due to infection risk) we want to opt for a wireless solution. Hence we chose to use near field approach for wireless power transmission (WPT) as well as for data transmission. This technology is the best-suited for biomedical implants, avoiding eddy current losses, tissue heating, and electromagnetic compatibility

issues with electronic circuitry [14].

More precisely, we selected inductive coupling with one external transmission coil and one internal receptive coil. As mentioned earlier, only research has been conducted on wirelessly powered DBS-implant. There are FDA-approved solutions coming from the field of cochlear implants which is well established and where companies such as MED-EL, Cochlear Corporation, and Advanced Bionics are now commercializing such devices [13].

Finding exact figures on the power consumption of these cochlear implants was no easy task. The manufacturers do not disclose the technical specifications of the audio processor's battery, nor the required power of their electrodes. Fortunately, a doctoral thesis on cochlear implant modeling provided some numbers [19]. The author managed to communicate with a scientist at Cochlear Corporation and estimated the power requirements. A total of 40 mW are needed, from which 5 mW is actually needed for electrical stimulation, while 15 mW is dissipated in the transmission (about 30% efficiency), and the rest is drawn by the audio processor. The manufacturers claim to have a battery lasting for at least a day, so it is safe to assume that the energy stored in the battery is at least $40 \text{ mW} \cdot 24 \text{ h} = 0.96 \text{ Wh}$. Although this number is estimated from Cochlear™ the two other companies should produce devices consuming the same order of magnitude of power. As the thesis dates back to 2012, technological advances will occur. The sound processing part will likely increase in complexity and requires more power, while the electronics will become more efficient and consume less. In the end, the power requirements are expected to remain similar [19].

Thus, cochlear implants are expected to readily provide 40 mW of power. Now, what is the expected power consumption for our DBS-like technology? According to a research paper, a typical four-channel DBS electrode (quadripolar macro electrode, model 3389 from Medtronic) used in adaptive mode requires $132 \pm 21 \mu\text{W}$ and in continuous mode $270 \pm 37 \mu\text{W}$ [20]. Ideally, we want to include a bilateral implant containing a maximum of 256 electrodes in each LGN. Hence, we would need $512/4 = 128$ times more electrodes, meaning at least 128 times the power (i.e. worst case $128 \cdot (270 + 37) \mu\text{W} = 39.3 \text{ mW}$ in continuous mode). Implying that our DBS-like- and cochlear-technology use the same power's order of magnitude.

The calculations above assumed a stimulation type similar to the ones used in DBS implants. However, the pulses used might differ for LGN stimulation. As Panetsos, 2011 [5] did not provide the details of the electric pulses used, we will take Pezaris, 2007 [11] numbers. They generated trains of pure sinusoids with specific frequencies within the train and between the trains. More precisely, the mean current and voltage required to elicit phosphenes were $40 \pm 12 \mu\text{A}$ and $2.5 \pm 0.6 \text{ V}$. The pulses were 1 ms long sinusoid with up to 40 pulses in 200 ms trains. In order to have some margin we will estimate the worst-case scenario which corresponds to five trains per second, two times 256 electrodes and taking two standard deviations (with respect to Pezaris's current and voltage values). We recall that the average AC power is equal to: $P_{AC} = I_{RMS} \times V_{RMS}$ ($\text{RMS} = \text{Root Mean Squared}$). Taking all these parameters into account, we estimated a power consumption of 12.1 mW. Which is suitable for the power delivery of the cochlear implant.

Note that the implanted receiving antenna will be laid between the skin and the skull. Minor drilling into the skull will be required, such that the implant's pins will be fixed into the holes enabling a better stabilization [21]. The link to the LGN will be achieved through a cable connecting the power

receiver (implant) to the electrodes' implant. This wire will slide underneath the skin to the top of the skull where the DBS-style electrode connector is located. On the outside, a device similar to the audio processor will be used to transmit power and data from the glasses. Ideally, the surgical procedure should be modified such that the receiver implant would be located below the glass frame and the transmitter antenna would be mounted within the glass frame. Thus limiting the number of moving parts and size of the wearable device.

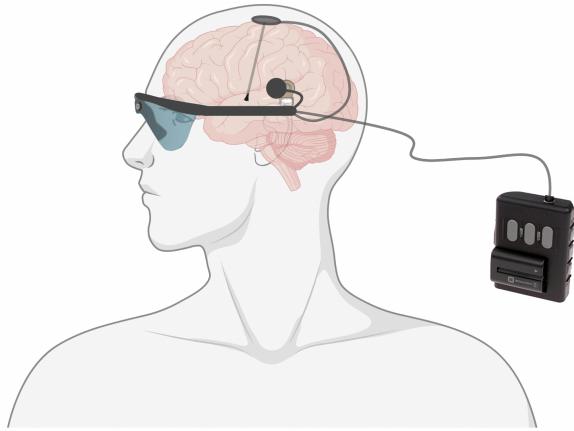


Figure 4: Sketch of the proposed visual prosthesis targeting the LGN. 1) *A device to capture images (Glasses with camera).* 2) *Electronic circuitry to process images and create stimulation patterns (VPU, WPT with transmitter coil on the glasses frame and the receiver coil on the skull around the ear).* 3) *Brush-style electrodes to stimulate visual neurons; received data and power through cables.*

3.2 Data

As we said before, the electrodes are linked to the antenna in order to receive and transmit data throughout the LGN. One must convert the visual stimuli into electrical stimulations to the electrodes in order to elicit a visual percept. But before forming the stimulation mode, our VPU will apply image processing to optimize the visual perceptions of the patients.

3.2.1 Image processing

The usual artificial prosthetic vision consists of phosphenes that have the disadvantages of irregular shapes, distorted topological arrays, and partial loss. This makes the visual percepts far less detailed than the captured image. For the last two decades, in the hope of improving visual perception, researchers proposed to apply certain image processing techniques before forming the stimulation mode. Some prosthetic devices such as Argus II already remove colors and extract edge information. However, even with the help of this retinal prosthetic device, recognition of single letters can take up to a few hundred seconds. It is then difficult to assess how many useful details these elementary image processing methods can extract for visual tasks. This is why we took an interest in optimizing prosthetic vision with the help of computer vision to extract meaningful information such as saliency detection [22]. Indeed, many visual tasks involve object detection in the visual scene. Several proposed strategies have been studied under simulated prosthetic vision. Researchers concluded that with the

help of saliency detection, the recognition accuracy of objects has significantly improved [23].

We would use a real-time image processing strategy based on saliency models developed by Li's research group since most of the other models cannot achieve real-time processing. Indeed, Li's group was able to set up to 24 fps. The processing functions as follows: First there is the global contrast saliency detection (based on color and intensity difference) where for each frame a saliency map is built by the global saliency detection algorithm. For further explanations on the saliency detection algorithm, we refer to [23]. On the same frame, an edge map is extracted after some graying. An output stream is then obtained from saliency and edge maps thanks to weighting (see Figure 5).

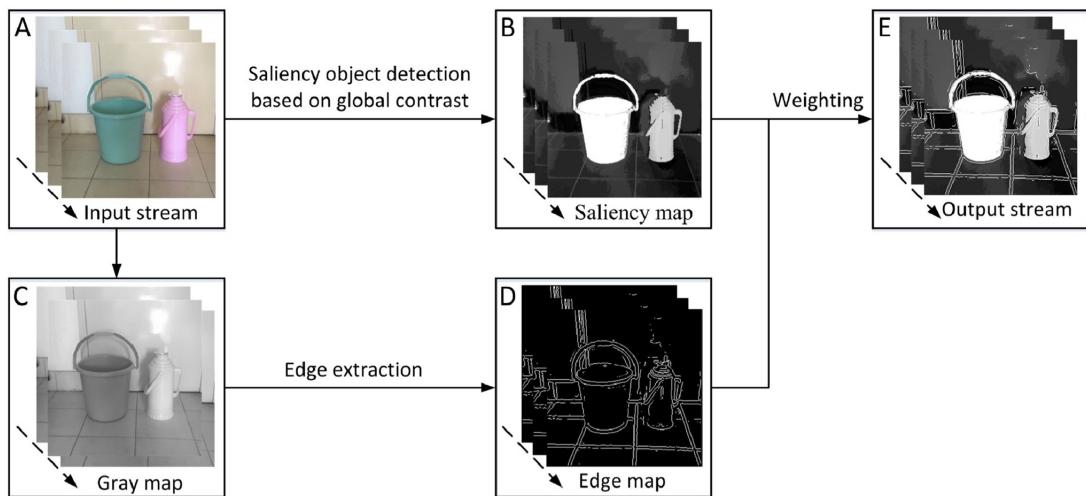


Figure 5: Diagram of the image processing strategy. *Based on Li's research group global contrast saliency model [23].*

Then, this output passes through a visual stimulus encoder in order to be converted into neural code [24], which allows selection of activated electrodes based on subject's phosphene mapping and selection of their waveforms. This encoder should mimic the input from the optic nerve, although the uncertainty of which encoding method to convert the image into neural stimulation for the LGN still remains today [6]. It is also important to note that patterned stimulation across multiple electrodes has not been attempted in the LGN [16].

Finally, the information is sent to the electrode stimulator [6] using the Pezaris stimulation parameters : 80-200ms long trains of 1ms sinusoidal pulses repeating at 200 Hz for 20 pulses [11].

4 Device testing

4.1 Preclinical testing

Because an LGN implant necessitates an invasive approach, it is more than necessary to conduct preclinical testing on an animal model to improve the procedure before proceeding with the implant's

development for human testing. Indeed, the main limitations of this visual prosthesis are the LGN's small size and depth, which limit the number and size of implanted electrodes [25].

Previously, some preliminary experiments were conducted in papers to ensure that we could proceed to preclinical testing. For example, it ensures that simulating the LGN can generate phosphenes in NHP [11]. Only a few groups have previously worked on Lateral Geniculate Nucleus Visual Prostheses [25]. One famous type is Bionic Eye Technologies Inc. and the VISNE system developed by Nerve Biomed S.L. However, no clinical studies have been reported by any groups as of yet, only pre-clinical testing [25].

Reaching the LGN and incorporating a wire from the receiver coil to the brush electrodes without damaging the brain structure is a major challenge. Due to the fact that each LGN represents only one of the two hemifields, bilateral LGN implants are required to create a full visual field prosthesis [2]. To avoid multiple operations and the risk of complications associated with skull opening and anesthesia, the two implants will be placed during the same surgery. In humans, the LGN is about 1 cm away from subthalamic structures, which are already stereotactically implanted with DBS electrodes. STN, for example, is an effective target for the motor symptoms of movement disorders such as Parkinson's. It is also advisable to follow the same procedure. DBS electrodes are implanted through small craniotomies near the top of the head using a rigid frame carefully aligned to the skull. The procedure is considered minimally invasive because the craniotomies are small in comparison to those used in other brain surgeries, despite the fact that there are significant potential risks.

Using CT and MRI scans prior to surgery, the LGNs could be located relatively precisely. A personalized surgical plan for implanting electrodes in each animal could be developed. Additionally, before surgery, monkeys must stop eating or drinking for at least 8 hours [26] to prevent vomiting under general anesthesia.

4.1.1 Anaesthesia

Animals are sedated, and the procedure will be monitored using an electroencephalogram (EEG) recorded directly in the frontal cortex using a small electrode. It allows us to add an anesthetic dose in the event of a decrease in wave amplitude and reaction to noxious. Of course, other vital signs are monitored throughout the experiment.

4.1.2 Set-up of the surgery

Monkeys must be placed in a stereotaxic device to fix the animal's head in a fixed position in order to pinpoint the precise location of brain sections. The platform is created using CT and MRI scans and is designed to fit onto the bone anchors placed subcutaneously at least one week before electrode insertion. The electrodes are precisely aligned for permanent placement on this platform. Animals require artificial ventilation. To keep the rectal temperature at $38\pm0.2^{\circ}\text{C}$, a servo-controlled abdominal heating pad will be used. There is a special emphasis on maintaining aseptic conditions in the environment.

4.1.3 Surgery

The skin must first be incised, and muscles must be removed. It allows us to reach the animal's skull, where small holes are drilled at strategic locations to expose both hemispheres of the LGN. Before inserting the brush electrodes, the dura is removed. Because the surgery can be time-consuming, vaseline oil will keep the exposed surface of the brain from drying out.

The brush electrodes are inserted deep into the brain through the planned target area guided by X-ray imaging. Thanks to the EEG, monitor electrical activity is recorded to listen for hyperactive areas that need to be treated. The effects of stimulation on movement are tested, as are any side effects of the stimulation. The skull is sealed with acrylic cement after the brush-style electrodes are correctly inserted. It is then necessary to extend the wire connecting the electrodes from the top of the head to the temple ipsilaterally by having the wire go under the skin. The electrodes can then be connected to the subcutaneous receiving coil. If there are no complications, the other LGN implant can be placed during the same procedure on the other side, along with its' corresponding receiving coil and extended wire. Finally, the muscles and skin are sutured, and the animals are placed in boxes and allowed to wake up. For pain relief, antibiotics must be administered for at least four days.

Experiments, animal handling, housing, surgery, and sacrifice must be approved by the UCM ethical committee and carried out in accordance with national legislation (R.D. 1201/2005) and EU Directives (86/609/EC) [5].

Because the LGN is a deep and compact area, electrodes would be stable once placed [2]. Even so, CT scans are conducted after surgery to record electrode placement and to look for signs of hemorrhage or even a stroke.

4.1.4 Animal testing on NHP (non-human primate)

During the animal testing phase, we will use NHP with normal vision and blindfold them with eye patches to simulate blindness. This solution is convenient because it is simple to implement, reversible and it avoids unnecessary burdens for monkeys. It allows us to recover monkeys' vision to train them for different experiments. Otherwise, we would have to perform all the training before the implantation, with a high risk of monkeys forgetting some of the training.

There will be different levels of testing based on how well the monkey performs with the device. The phosphene mapping process will serve as the first major round of tests. We will be able to determine how many phosphenes can be created and their locations in the visual field. If the mapping results are good enough (at least 60 unique phosphenes), we will go on with the two other tests. First, we will perform a pattern/object recognition task. Then, we will continue with a motion detection task. Both tests will be performed in the same head-restrained setup as for the phosphene mapping.

In order to verify that our implant is indeed working, we will not blind the first implanted monkeys and use different mapping methods that are easier to implement and perform. Monkeys are placed in a head-restraining setup for the entirety of the trials. It will ensure the most precise and reliable measurements by preventing subjects from moving their head or tearing off the outer part of the implant.

Non-blind monkeys

The experimental setting would be to present stimuli on a pixel grid to implanted monkeys, with the grid taking up the entirety of the subject's visual field. By sequentially presenting our stimulus on each pixel of our visual grid and recording implanted electrodes individually, we can determine which electrodes successfully interfaced with the LGN and which portion of the visual field is dedicated to them. By dividing the grid into an increasing amount of pixels we can improve our resolution and obtain a finer grasp of the receptive field devoted to each micro-contact.

Another process through which mapping can be conducted is by training our subjects. Using a screen that presents a stimulus at various locations in the form of a white dot on top of a black background, we can train monkeys to touch dots wherever they appear on the screen. Once they achieve an acceptable level of success over this task, we can successively use each one of our micro-contact to trigger the appearance of a phosphene in their visual field while they are looking at a black background. If the stimulation is successful, the monkeys should per their training reach for the location at which the phosphene appears and thus inform us about the whereabouts of our stimulation site on the LGN and its' match in the visual field.

Blind monkeys

It is almost impossible for blind monkeys to give proper, conscious feedback on what they see as they cannot locate precisely their body (especially their fingers) in space. To overcome this problem, we chose to make use of the saccadic eye movement. It is possible to train monkeys to perform a saccade to focus their vision on a visual stimulus [11]. After the training, we stimulate multiple times the LGN with the implant, to repetitively elicit the same phosphene, and track eye movements. If the saccades' endpoints are roughly on the same spot in the visual field then it means the stimulation is perceived as a phosphene by the monkey. Even though vision is required for the training process, we can then make use of saccades once monkeys are blind (temporarily or definitely). However, using saccadic eye movements on blind monkeys to determine the position of a phosphene in such a simple configuration is not possible due to a major limitation: drift. Once monkeys are blind, it is impossible to define an absolute central point because the monkey's eyes, head, or even the monkey itself can move slightly, thus creating a shift between measured phosphene locations before and after the movement. One solution to this issue is to use double a saccade pattern. In this case, we assume the initial eye's position to be random so we elicit a first phosphene to focus the monkey's vision. Shortly after, we elicit a second phosphene while tracking the eye. This allows us to determine the relative location of the second phosphene compared to the first one. By repeating this task with enough phosphene pairs, we can construct a relative phosphene map.

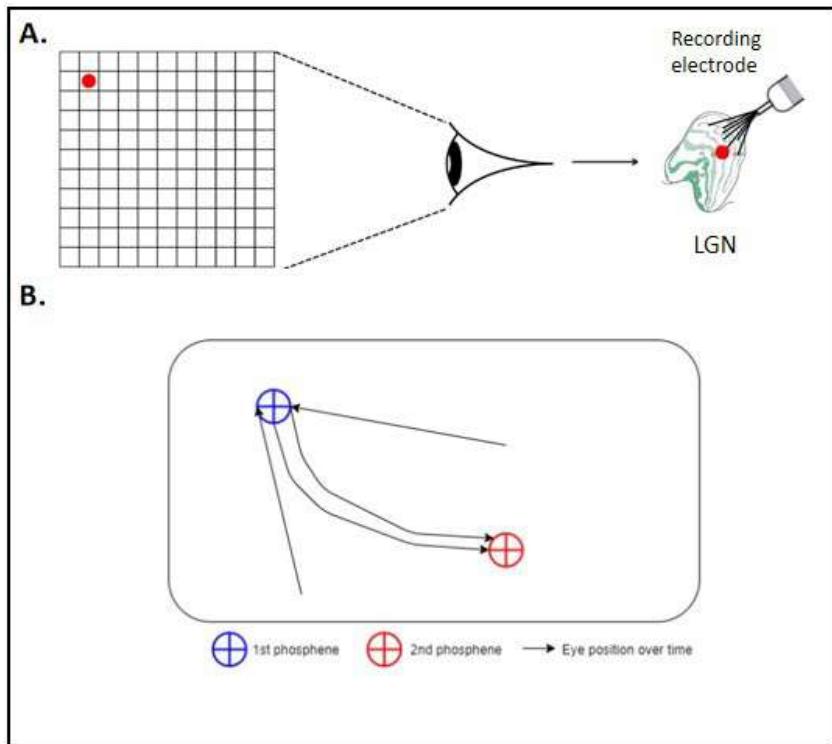


Figure 6: Phosphene mapping strategies for non-blind and blind NHPs. **A:** *Mapping through visual stimulation* **B:** *Mapping through use of saccades*.

For the pattern/object recognition task, we will train monkeys, without patches, to discriminate objects or patterns in sets of four different ones. They will give their answer by moving a joystick in one of the four directions (left, right, top or bottom) with their hands. Once they perform consistently with their normal vision, we blind them with patches and activate the implant. The pattern or object will be displayed on a screen in front of the monkey. During the experiment, we will record both the accuracy of the recognition (how often the monkey makes a good guess) and the time they take to commit to an answer. These results will help us determine if the number and placement of phosphenes are good enough to recognize a pattern or an object. If monkeys are able to see phosphenes (through the mapping step) but fail this task, we will have to work on improving these characteristics. Solutions could be to either increase the number of stimulation electrodes or spread them more widely in the LGN. If monkeys still fail after these improvements, we could also improve the image processing algorithms of our VPU.

The motion detection task will follow the same process flow as the pattern/object recognition task. Monkeys will first be trained with their normal vision to detect a moving target (i.e a square) on a screen. They will then be trained to move a joystick in the direction of the target's movement. Once they are sufficiently good at this task, we blind them with patches, put them in the head-restrained setup with a screen in front, and repeat the same task. We will record the accuracy of the detection (how often they can detect the moving object), the maximum time during which they can follow the square without losing track of it by keeping the joystick in the corresponding inclination, and the maximum speed of the square at which it is still detectable. These results allow us to evaluate how responsive the device is. If monkeys that succeed in previous tasks fail this one, we will have to improve

the time required to compute one frame. It can be done by optimizing our device and object detection program (lowering the computational cost or increasing the performance of the VPU).

4.2 clinical testing

At this time, all researches about LGN visual prosthesis remain at the stage of preclinical testing. In order to develop clinical testing, the protocol could be inspired by clinical testing done for cortical visual prostheses. We would need patients suffering from acquired bilateral blindness, and who became blind at different times before the trials begin. This will allow us to investigate how stimulation effectiveness changes with the time spanned since blindness onset.

5 Limitations

We are aware that our device has shortcomings, and here are some we could foresee.

One of the limitations of targeting the LGN is its lack of experimentation. To the best of our knowledge, only a few retinal implants have been approved for commercial use in Europe and the US [9], while no other structures described in the introduction have been approved. Hence, a lot of effort will need to be oriented toward the (pre)clinical testing as described in the sections above.

One of the issues with glaucoma, as with other neurological disorders, resides in the degeneration of the brain structures not being stimulated. In a study comparing the LGN's size of glaucoma versus control patients, MRI images showed atrophy of LGN height [27]. The authors also underwent a neuro-histological study of the LGN. They found similar shrinkage of the structures and determined that magnocellular and parvocellular LGN neurons were the most affected populations [27]. In another study, the researchers determined through an autopsy that the magnocellular cell density was significantly lower than in the control group [28]. However, there was no statistical difference in the parvocellular layer. These studies emphasize the importance of acting early in vision loss, to limit the damage to the visual pathway. In terms of the plasticity of the brain, it was shown that some areas can be reallocated if not stimulated anymore. This is of course an issue as the LGN functions could be altered.

Another important LGN aspect is the thalamocortical loop. Indeed it is estimated that only 10% of the visual information received by the LGN comes from the retina. On the other hand, 50% is inputted from the visual cortex [5]. Hence it will be crucial to not disturb this loop with our electrodes.

6 Conclusion

In conclusion, we presented the case of glaucoma-blind patients and a device to partially restore vision through stimulation of the LGN. To accomplish this we started our reasoning from the study of Pezaris in 2007 [11], which demonstrated the feasibility of inducing phosphene by targeting the LGN. Upon this, we designed a device able to capture and process images which are then converted to electrical signals sent to electrodes inside the brain. To implement this, we based our design on an already proven and used solution: a camera embedded in a glasses pair, connected to an external

VPU. To properly power and transfer data, we took inspiration from the field of cochlear implants which already designed an efficient, reliable, and FDA-approved transcutaneous wireless communication system. By using a similar system as MED-EL implants, we can manage to provide enough power and transfer data for our implant. Concerning the implant itself, we improved upon Pezaris by using novel brush-style electrodes from Ad-Tech. By adapting the surgery from DBS implants, we showed that we could precisely insert these electrodes. Finally, we detailed several ways to test and improve our device once inserted into monkeys' brains, in order to pave the way for human testing.

7 Perspectives

One of the flaws the device suggested in this paper has is that it doesn't account for gaze and head movements compensation, which means that subjects implanted with it would have to move their head around in a non-natural way. Studies have shown that adding gaze-compensation methodology to already existing implants allowed patients to increase their performances when doing specific tasks while decreasing the amount of head movements necessary to perform them [29]. Avi Caspi et al. not only showed that performances increased when using the Argus II in reaching tasks with blind individuals when using a setup allowing eye-head scanning, but also that calibration of said setup could be done even with blind individuals using the self-calibration of the eye-tracker [29]. The eye tracking technology (Eye Tracking Glasses 2.0, ETG 2.0; SensoMotoric Instruments, Teltow, Germany) [29] was efficiently paired up with the Argus II structure. This means that in theory the device concept we develop in this paper, which already leverages some of the Argus II technology, could also benefit from this eye-tracking setup by adding infrared illuminators to the frame. However, they specified that the region of interest (ROI) was obtained using the eye-trackers and the camera through means of laptop computations. We are unsure as of yet about the computational cost of this process and if it could be performed without adding consequent weight to the base device, which is why it is only a perspective.

For the VPU's power consumption, according to the Argus II's surgeon manual [30], the medium battery last at best 6 hours, and has a 19 Wh storage capacity. This means that the VPU consumes at best 3.16 W, which is orders of magnitude higher than the implant (max 40 mW). This will be a challenge for the miniaturization part because such batteries cannot fit into the glasses' frame. Hence mounting the VPU onto the glasses is a major challenge that we will need to work on by taking advantage of the 2020s miniaturized and efficient electronics.

We could draw some inspiration from MED-EL and its audio processor. The external component of their hearing aid is a single oval-shaped device that is magnetically connected to the implant on the skull. The audio processor can be wirelessly recharged, has a battery lasting for a day, and can be connected to a smartphone to directly stream phone calls or other sounds. One could imagine doing the same for our implant, perhaps streaming images from the phone screen instead of passing through the camera.

Improving the electronics of the LGN implant would also be important, by increasing the number of wires (to create more detailed patterns) and diminishing the size of the wires (to get a higher resolution), the quality of patterns created would be greatly increased.

But most importantly, implanting humans and testing our devices on them is the main goal. This will allow us to fine-tune the phosphene shape, overlap (or lack thereof), alignment, and colour which is harder to perform on animals. This fine-tuning will inherently improve the electrical pulses which also need to be refined.

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Sources of the images

- Front page: EPFL logo from EPFL official website & figure of the device created on Canva.com on 16/12/2022.
- Figure 1: visual pathway from wikipedia.
- Figure 2a: brain views created with BioRender.com on 16/12/2022. Figure 2b: scheme of the LGN layers from S. Meikle (2021). Figure 2c: brain design from P.A. based on Logothetis (1999) and Zeki (2003). Figure 2d: stained LGN image from Webvision website.
- Figure 3a: table created on Canva.com on 16/12/2022. Figure 3b: device created with BioRender.com on 16/12/2022. Figure 3c: Electrode designs from Ad Tech website and picture from Skopalová, Jana, et al. (2018).
- Figure 4: sketch of the visual prosthesis created on Canva.com on 16/12/2022.
- Figure 5: image of the image processing strategy from Heng Li et al.
- Figure 6: image of the phosphene mapping strategy build from canva.com on 14/01/2023, and based on images from our group.