BENG 426
HW05: Project Draft
Mach 5th, 2021

A Literature Review of the Development Trends of Visual Neural Protheses

Abstract

According to a systemic review of population-based data sets relevant to global vision impairment and or blindness between 1980 in 2015, there is an estimated 36 million people who suffer from blindness [4]. An additional 405.1 million people with mild to severe visual impairment [4]. Visual impairment of any degree and its growing prevalence are not a new issue. However, recent advancements in neural protheses, such as cochlear implants that aid those who are hearing impaired, leading researchers to turn to visual neural protheses. Visual neural prostheses focus on the concept of artificially inducing vision by using our current understanding of electrical stimulation, visual pathways, and visual sensations. Therefore, all visual protheses focus on creating an artificial sense of vision through the electrical activation of neurons belonging to the visual system of the body [2]. There are a variety of approaches researchers have taken to accomplish this, the approaches differ in the aspects of the visual system they attempt to replace. As of 2019 they are primarily four approaches that encompass most neural prosthetics. Those that focus on the retina, optical nerve, cortical region of the brain, and or the lateral geniculate nucleus (LGN) within the thalamus [2][3]. The most prominent of which is the retina neural prosthetic, having multiple current implants such as the Argus II electronic epiretinal device, this is due to its extracranial location and simpler organization compared to other methods [3][5]. However, the retinal approach is not without faults of its own such as unwanted electrochemical reactions and low resolution. Therefore, in this paper the four approaches of visual neural prostheses will be examined to provide a greater insight into the field.

Introduction:

Blindness and Visual Impairment

Globally as of 2015, there is approximately 36 million people blind and approximately 217 million have moderate to severe visual impairment (will be referred to as MSVI for remainder of paper) [6]. If those who suffered from mild to severe were included this number swells to 405.1 million or 1.1 billion if you include people who have functional from of presbyopia (the loss of elasticity in the lens of the eye that usually occurs because of aging) [4][6]. When looking at these numbers it is clear that there is a sizable portion of the population that suffers from some level of visual impairment. This is not new nor is its prevalence or the knowledge that it will likely increase. Due to its prevalence, we have made many steps forward in limiting the impact at any level of visual impairment can have on one's ability to live a fulfilling life. This sentiment is proven true when accounting for the global population's increase and aging from 1990 to 2015, the percentage of people that suffer from blindness decreased from ~4.58% to ~3.38% [6].

However, the world's population will continue to increase and age leading to the number of people that suffer from MSVI to reach about 703 million by 2050 [6]. As a result of this increase, new methods to prevent and or limit the impacts of visual impairment must be developed. One technology under development for this purpose is visual neural protheses. Visual neural prostheses focus on the concept of artificially inducing vision by using our current understanding of electrical stimulation, visual pathways, and visual sensations. Therefore, all visual prophecies focus on creating an artificial sense of vision through the electrical activation of neurons belonging to the visual system of the body [2]. There are a variety of approaches researchers have taken to accomplish this, the approaches differ in the aspects of the visual system they attempt to replace.

Physiological Background

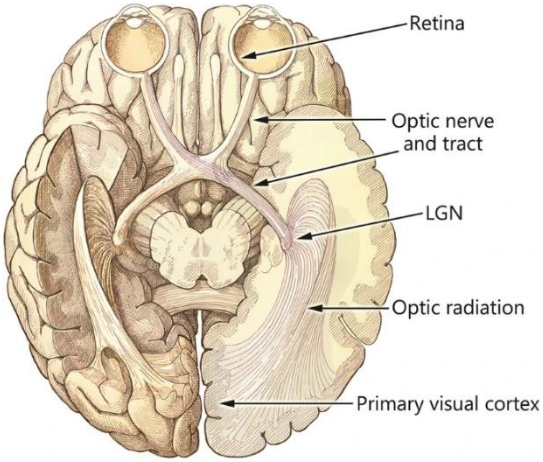

Figure 1: Ventral View That Displays the Visual Pathway and Its Components

Image from: Contemporary approaches to visual prostheses [3]

Recent advancements in neural protheses, such as cochlear implants that aid those who are hearing impaired, leading researchers to turn to visual neural protheses. Visual neural prostheses focus on the concept of artificially inducing vision by using our current understanding of electrical stimulation, visual pathways, and visual sensations. However, the visual pathway is more complex than that of the cochlea. This complexity leads to a more individualized approach when developing visual neuronal protheses, instead of targeting the whole system different aspects of the visual pathway are chosen to be replaced or augmented. Our current understanding of the visual pathway starts with visible light entering the eye. Afterwards it is subsequently the photoreceptors within the retina convert the photons into neuronal signals [3]. The neuronal signals travels down the neurons within the optic nerve tract till it reaches the lateral geniculate nucleus (LGN) within the thalamus [2][3]. Once the signals have reached the LGN it is then directed to the primary visual cortex, where the information is processed [3]. With this current understanding researchers have determined that the retina, optical nerves, LGN, and cortical region of the brain along the visual pathway are our optimal choices for protheses.

Review of Literature:

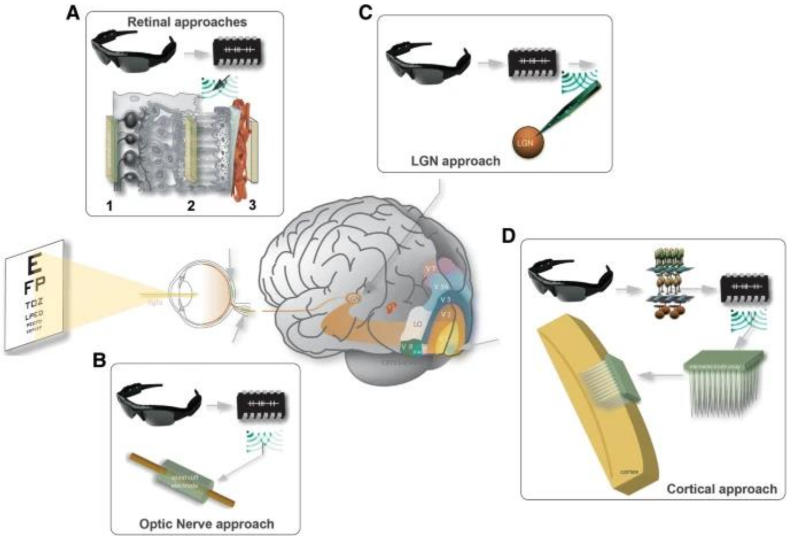

Figure 2: Overview of the Four Primary Locations for a Visual Protheses

Image from Development of visual Neuroprostheses: trends and challenges [2]

Retinal Protheses

Along the visual pathway the retina provides its own complex structure tasked with converting the visual inputs through graded potentials resulting in action potentials at retinal ganglion cells [1]. While all degrees of visual impairment are on the rise due to a variety of causes, severe visual impairment is most commonly a result of retinitis pigmentosa and or macular degeneration [5]. Both lead the photoreceptors to deteriorate and without the retinal photoreceptors working properly the conversion of light to neuronal signals, called phototransduction, becomes unlikely or impossible [1][3][5]. However, as the retinal photoreceptors deteriorate, the neurons within the retina may maintain their ability to respond to electrical stimuli. Therefore, most retinal neural prothesis focuses on providing a connection between an image sensor and the visual pathway by replacing the photoreceptors previous function with artificial electrical impulses that elicit action potentials [1].

There are primarily two methods for retinal neural protheses, the epiretinal approach and the subretinal approach. Epiretinal implants began early development in the 1990’s by researchers and engineers at North Carolina State University eventually leading to the development of models such as Argus I, IMI’s (Intelligent Medical Implants) learning retinal implant system, and Epi-Ret devices [5][7]. The three products listed are vastly different in their size, capability, and durability but the process for how they operate remains the same. For an epiretinal implant the device is placed on top of the retina and uses an array of electrodes fixed to the retina do deliver the electrical stimulants. The electrical stimulants are derived from an external camera that captures images which are converted to stimulations data and then wirelessly transmitted to the device in the eye [8]. The device then converts the stimulations data to the electric impulses delivered through the electrodes [8]. This is more or less the same process for subretinal implants, except they are instead placed in the location of deteriorating photoreceptors [5].

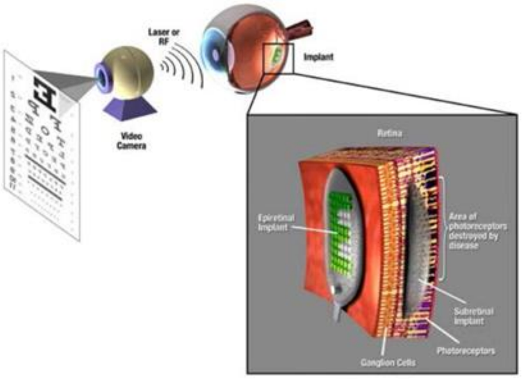

Figure 3: How Epiretinal Implants Work Conceptually

Image from Retinal Prosthesis [7]

Of the many designs for retinal neural protheses, the most prominent is the successor of the Argus I, the Argus II. As of 2013, the Argus II has received European and the United States' FDA approval [1]. The device consists of a camera and transmitter coil mounted on a pair of glasses that are then connected to an image processor and battery [1][5]. The implant component of the Argus II consists of a receiver and electrode array attached to the retina [1]. The Argus II illustrates the main advantages researchers have identified of eliciting electrical stimulation in retinal neurons compared to other parts of the visual pathway. The first being how retinal neurons are the first stop along the visual pathway and therefore eliciting a response here would provide the most natural propagation of signals throughout the rest of the visual pathway [1]. This thought also lends itself to the second advantage of having lower surgical risk with the implantation of electrodes [1].

The progress made in retinal neural prosthetics is vast compared to where it started, the Argus II is the perfect demonstration of this. However, all the systems previously described including the Argus II are susceptible to the same flaws, each one a substantial roadblock for retinal neural protheses to address the growing population of the visually impaired. The most prominent roadblock is unwanted electrochemical reactions that can occur during the delivery of the stimulus, which can lead to neuronal death [1]. This is due to retinal stimulation usually consisting of constant current pulses and the limited charge carrying capacity of the materials used in the electrodes [1]. As result many devices utilize biphasic pulses for a short duration to increase the longevity of the neural prosthetic [1]. This leads to the next primary issue which is the low resolution. All systems provide quite low resolution but in return provide a longer lasting product as many are advertised as lifetime systems. The Alpha-IMS is a retinal device that has the highest density of electrodes providing better resolution, however, only has a lifetime of less than a year [7].

Optical Nerves Protheses

Located in the back of the eye the primary job of the optic nerve is the transmitting of visual information received from the retina to the brain. Opposite to the wide surface area retina, the optic nerve that transmits information to the brain is quite narrow. Consisting of approximately 1.2 million axons densely consolidated into a 2mm diameter [10]. Therefore, it could be stated that the entire visual field captured by the retina is represented in such a small area along the visual pathway [3]. This also illustrates how the optic nerve as a structure is a vitally important aspect of the visual pathway that any damage sustained to it can likely cause blindness [11]. The densely packed neurons in the optic nerve preset researchers with a double-edged sword, as it is an appealing site for implementation of a visual prothesis that can be reached surgically, however, with inherent risk such as infection [10][9].

Excluding the surgical risk, the optic nerve is a primary location for visual prothesis because it eliminates many of the risks associated with a retinal prosthesis. The main detriment of a retinal prothesis is the unwanted electrochemical reactions caused by the abundance of electrode necessary to provide an image, however, it is possible to provide more meaningful visual stimulus is to the optic nerve with the same number of electrodes because of its high density [9]. The general operation of a visual neural prosthetic for the optic nerve is exactly like that of a retinal implant with the electrodes being the only critical difference. In order to take advantage of the density present within the optic nerve researchers have developed a method of using an electrode cuff that encapsulates the external surface of the optic nerve, similar to a Schwann cell around an axon [10][11]. This method was developed to limit additional surgical risk by penetrating the sheath of the optic nerve but as a result translation of signals rely on the principle of retinotopic organization [10].

Progress towards a commercial optic nerve protheses remain currently in development but noticeable strides have been made. All steaming from an article published in 2009 that demonstrated the results of a successful implementation of an optic nerve prothesis in a blind volunteer [10][11]. The study utilized a cuff consisting of four electrodes with 200 µm squared contacts [11]. After the patient underwent surgery and performance evaluations analysis of the system provided encouraging results eliciting various phosphene responses [11]. By adjusting various parameter such as the duration of pulses and the frequency of the pulses the volunteer was able to demonstrate pattern recognition and even interact with their environment by discriminating between and grasping different objects [9][10][11]. Systems that hope to implement the cuff of electrodes developed in this study plan to build off the existing devices created for retinal implants with the only substantial difference being the location of the electrodes.

Although studies have proven that optical nerve protheses are promising the technology has remined rather stagnant. This stagnation can be largely contributed to the researchers having to find the perfect balance between surgical risk and optimal performance. With the surgical implantation replacing the optic nerve the processing power becomes solely reliant on the prosthetic as the processing power of bipolar, amacrine, and horizontal cells contained in retinal ganglion cells is lost [10]. With the limited amount of phosphenes elicited the processing aspect of a prosthetic becomes more prominent requiring more significant studies to determine the minimal information requirement [9]. Specifically, a precise description of phosphene mapping and sizing in order to optimize the process [9]. This reliance on the prosthetics processing power is only augmented by the fact that the nerve fibers the electrodes what target lie directly in the center of the optic nerve. Therefore, the cuff electrodes are quite far away from the specific nerve fibers they are targeting as they rest along the outside of the nerve [10]. In order to work around this optic nerve implants could have their electrodes implanted further along the optic nerve, but this would drastically increase the surgical risk where any damage is likely permanent.

Lateral Geniculate Nucleus Protheses

The Lateral Geniculate Nucleus (LGN) located within the thalamus is the visual relay center where inputs are received from the optic nerve and then redirected to the visual cortex [3]. Compared to the optic nerve even more visual data is processed at this point in the visual pathway, as ninety percent of the retinal ganglion cells axon form synapses at the LGN [11]. The relay center devotes about sixty percent of its total volume to processing the central 3 degrees of the visual field providing a consistent spatial density independent of a person's visual field eccentricity [3][11]. Additionally, the LGN is a highly organized structure with the subdivisions of the neurons it contains actually being separable on a macroscopic scale [12]. These factors feed into many researchers believe that the LGN could support a wide visual field with better acuity than other approaches and even support artificial color vison [3]. However, the greatest benefit of a LGN prosthetic is that even if there is substantial damage to the eye or even deterioration of the optic nerve, this highly organized and powerful processing relay center remains mostly functional [12]. Therefore, the LGN has become a target for prosthetics to treat blindness stemming from diseases, trauma, and or enucleation [12].

There has been a plethora of methods proposed on how to implement an LGN prosthetic. Each one following a similar premise to that of both retinal prosthetics and optic nerve prosthetics with the main difference being the location at which the electrodes are placed. One proposed method was the utilization of surgical techniques from deep brain stimulation to place electrodes at the subthalamic nucleus and substantia nigra approximately ten millimeters away from the LGN [12]. The most prominent method utilizes high density multi electrode arrays as a microwire bundle that would be inserted with a cannula [11]. The microwires would spread outward from the cannula in penetrate the LGN at distinct locations [11]. A model that utilized a four hundred electrode implant was estimated to provide a maximum visual acuity of about 20/240 [11]. As of 2020, there has yet to be an LGN prosthetic implanted into humans, however, animal models have demonstrated the possible effectiveness with cortical responses and adequate resolution through object localization tasks [11].

Although LGN neural prosthetic have some very promising aspects, there are still some limitations and problems that researchers need to address as they further develop the technology. The benefit of the LGN is its location in the visual pathway, however, this also presents a disadvantage as it is located behind the optic chasm where the visual field becomes vertically segregated [12]. Therefore, the LGN on each side of the brain only accounts for one hemifield of the visual field [3][12]. This increases the surgical risk as any meaningful prosthetic would require two separate multi electrode arrays, one for each hemisphere of the brain [3]. Simultaneously the need for two different multi electrode arrays increases the possibility of any unwanted electrochemical reactions that could lead to neuronal death, which in this case would be particularly devastating as the LGN is located within the thalamus of the brain.

Cortical Protheses

Although it is the last location in the visual pathway, the visual cortex, was a relatively early target for visual prosthetics. The idea for these prosthetics originally began in the late 1960s by G.S. Brindley and W.S. Lewin who demonstrated that phosphenes could be produced by stimulating the area [3][10]. The primary visual cortex was targeted due to the large surface area that is easily accessible because it is located close to the surface of the occipital lobe and its ability to help those who suffer from most forms a visual impairment due to a wide variety of causes [3][11][12]. Additionally, researchers have a comprehensive knowledge on the representation of the primary visual cortex compared to almost any other brain areas.

However, this comprehensive knowledge presented researchers with many setbacks as the primary visual cortex has a complexity far more intricate than any other stage of the visual pathway [12]. The complexity of the primary visual cortex presents a few major setbacks to cortical prosthetics. Primarily, the organization of the visual primary cortex increases the number of computations necessary to transform any visual stimulus into signals that will stimulate phosphenes within the visual cortex [12]. A problem that is only exacerbated by the fact that a visual complication such as blindness may lead to the visual cortex reorganizing itself leading to further complications in decoding the produced phosphenes [3]. Also, the easily accessed surface on the occipital lobe is a benefit, however, most of the visual cortex lies deep within the calcarine fissure that inaccessible to cortical surface electrodes [10]. This limited accessibility causes many prosthetics to have a limited peripheral vision [11]. Lastly, the interhemispheric fissure provides an additional anatomical limitation as it makes stimulating 85% of layer four of the visual cortex much harder [11]. This is a vital limitation as layer four of the visual cortex is the layer that receives most of the signals created by the LGN.

No matter how substantial these setbacks were many previous and current researchers have pursed cortical prosthetics, leading to models such as the Utah electrode array and Illinois Intracortical Visual Prothesis [10]. The Utah device utilized platinum electrode tips connected to silicon spikes compared the Illinois device that used a common microelectrode array [10]. Currently, there are multiple devices in development, with some as the Orion Cortical Visual Prothesis System receiving FDA approval for clinical trials [3]. Other prosthetics such as the CORTIVITS device and NEUROPace RNS System are currently conducting clinical trials [3]. All of these devices have benefited from a plethora of advancements in technology and our understanding of the primary visual cortex. Specifically, the knowledge that spatial representation of the visual field is repeated multiple times in the visual cortex allowing for additional multi electrode arrays to be placed on its surface to compensate for inaccessible areas [11]. Other advancements in deep learning, pattern recognition, and microelectronic device fabrication have made cortical based visual prothesis more and more viable [3][11].

Future Possibilities:

All current visual neural prothesis have their different disadvantages, however, two primary issues are consistently present with each device. There is the surgical risk associated any implant and the possibility of unwanted electrochemical reactions. Unwanted electrochemical reactions are consistent issue due to the need for electrodes to cause electrical stimulation and the materials the electrodes are made of. Therefore, the future of visual neural protheses lies in the research and development of better biomaterials and new stimulation methods that can replicate the neural activity. Promising alternative for current electrode materials are conducting polymers, carbon nanotubes, nanocrystalline diamonds, optoelectronic silicon nanowires, and lining electrodes [1]. These are just five of the materials researchers are hoping to incorporate into future prosthetics, illustrating how the vast potential for improvement to any current devices could be. A potential augmented by the other possible methods for stimulation such as magnetic stimulation, nanoparticle-based stimulation, genetically encoded magnetic stimulation, and sensory substitution [11].

Discussion:

With the global rise in visual imparity showing no sign of slowing down visual neural prosthetics will become increasingly important. To this extent many visual prosthetics have already been developed, each primarily targeting a different step along the visual pathway. Primarily, retinal implants are farther along in development compared to prosthetics that attempt to replace the optic nerve, LGN, and primary visual cortex. However, retinal implants suffer from multiple disadvantages specifically its ability to provide a comprehensive replacement for vision especially in those who are severely impaired or blind. While the optic nerve, LGN, and primary visual cortex all boast advantage's that retinal implants cannot provide, they also are limited by the complexity of each region compared to retina. Therefore, the ideal visual implant will vary drastically based on the level of visual imparity. There are also problems that plague all visual prosthetics such as their surgical risk and need for electrodes that could lead to neuronal death if an unwanted electrochemical reaction were to occur. These disadvantages although substantial do not diminish the vast potential of visual neural prosthetics as new materials and methods are developed.

Definitions

Phosphene: an impression of light that occurs without light entering the eye and is usually caused by stimulation of the retina (as by pressure on the eyeball when the lid is closed) or by excitation of neurons in the visual system [13].

Enucleation: to remove without cutting into [13].

Cannula: a small tube for insertion into a body cavity or into a duct or vessel [13].

Interhemispheric Fissure: is the deep groove within the midline separating both cerebral hemispheres [14].

Calcarine Fissure is located on the medial surface of the occipital lobe and divides the visual cortex into two [15].

References

[1] Barriga-Rivera, A., Bareket, L., Goding, J., Aregueta-Robles, U. A., & Suaning, G. J. (2017). Visual Prosthesis: Interfacing Stimulating Electrodes with Retinal Neurons to Restore Vision. Frontiers in Neuroscience, 11. doi:10.3389/fnins.2017.00620

[2] Fernandez, E. (2018). Development of VISUAL neuroprostheses: Trends and challenges. Bioelectronic Medicine, 4(1). doi:10.1186/s42234-018-0013-8

[3] Mirochnik, R. M., & Pezaris, J. S. (2019). Contemporary approaches to visual prostheses. Military Medical Research, 6(1). doi:10.1186/s40779-019-0206-9

[4] Cross, J. (2006). MEDLINE, pubmed, PubMed Central, and the NLM. Editors' Bulletin, 2(1), 1-5. doi:10.1080/17521740701702115

[5] Mills, J. O., Jalil, A., & Stanga, P. E. (2017). Electronic retinal implants and artificial vision: Journey and present. Eye, 31(10), 1383-1398. doi:10.1038/eye.2017.65

[6] Ackland, P., Resnikoff, S., & Bourne, R. (2017). World blindness and visual impairment: despite many successes, the problem is growing. Community eye health, 30(100), 71–73.

[7] J. D. Weiland and M. S. Humayun, “Retinal Prosthesis,” IEEE Transactions on Biomedical Engineering, vol. 61, no. 5, pp. 1412–1424, 2014.

[8] M. Auffan, C. Santaella, A. Thiéry, C. Paillès, J. Rose, W. Achouak, A. Thill, A. Masion, M. Wiesner, J.-Y. Bottero, F. Mouchet, P. Landois, F. Bourdiol, I. Fourquaux, P. Puech, E. Flahaut, L. Gauthier, M. J. Rybak-Smith, Y. Song, M. J. Heller, D. Holmes, B. L. Webb, T. Sun, T. S. Mayer, J. S. Mayer, C. D. Keating, A. Ghosh, I. V. Pobelov, C. Li, T. Wandlowski, M. G. Helander, Z. Wang, Z.-H. Lu, F. Carpino, L. R. Gibson, D. A. Grismer, P. W. Bohn, N. Pala, M. Karabiyik, A. Porter, E. McGuire, G. Xie, A. Lopez-Bezanilla, S. Roche, E. Cruz-Silva, B. G. Sumpter, V. Meunier, M. J. Laudenslager, W. M. Sigmund, N. A. Hall, C. J. Kim, G. Wang, R. J. Greenberg, C. Mbanaso, G. Denbeaux, C. Coutris, and E. J. Joner, “Epiretinal Prosthesis,” Encyclopedia of Nanotechnology, pp. 789–797, 2012.

[9] Q. Ren, “Visual Prosthesis, Optic Nerve Approaches,” Encyclopedia of Computational Neuroscience, pp. 1–3, 2014.

[10] A. Banarji, V. S. Gurunadh, S. Patyal, T. S. Ahluwalia, D. P. Vats, and M. Bhadauria, “Visual Prosthesis: Artificial Vision,” Medical Journal Armed Forces India, vol. 65, no. 4, pp. 348–352, 2009.

[11] A. Farnum and G. Pelled, “New Vision for Visual Prostheses,” Frontiers in Neuroscience, vol. 14, 2020.

[12] J. S. Pezaris and E. N. Eskandar, “Getting signals into the brain: visual prosthetics through thalamic microstimulation,” Neurosurgical Focus, vol. 27, no. 1, 2009.

[13] Merriam-Webster's dictionary

[14] Sekhar LN, Fessler RG. Atlas of Neurosurgical Techniques. Thieme. (2011) ISBN:1604067705

[15] Waxman SG. Clinical neuroanatomy. McGraw-Hill Medical. (2003) ISBN:0071392386.