Review Article

A Review on Recent Advances in Vision Prostheses

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ABSTRACT

Vision Loss causes socioeconomic alterations in a number of individuals. Vision loss, or blindness in particular, incurs a large economic burden on the United States. Moreover, blindness and vision loss have several negative effects on its population, including economic instability, as well as psychological strain. Vision loss and blindness may result from damage to the retina, optic nerve, or genetic factors (defecting either) causing blindness at birth. Traditional treatments of vision loss may attempt repair to this damage through injections or surgery or prevent further damage to the region through applied medication but are limited in that several of these conditions progress quickly, irreversibly, and cannot be treated once the patient is completely blind. Therefore, treatments using electrical stimulation have been developed to restore vision in blind patients. Such methods include Intracortical, Retinal, Optic Nerve, and Lateral Geniculate Nucleus Prostheses. The Intracortical Vision Prosthesis (ICVP) is implanted on the visual cortex, the retinal prosthesis on the retina, the optic nerve prosthesis on the surface of the optic nerve, and the LGN prosthesis through Deep Brain stimulation. These mechanisms attempt phosphene (i.e., perceptions of light that imitate an image) production through electrical stimulation, but vary in image characteristics; they pose several challenges, such as the necessity to be both biocompatible and suitable for implantation without incurring damage. Moreover, socioeconomic effects of blindness also limit the ability to test and implement treatments. Overall, vision prostheses have become increasingly developed and sophisticated, and may, in the future, be utilized as a treatment for the common public.

Keywords: Bioengineering; Vision; Intracortical; Retinal; Prosthesis; Neurostimulation

INTRODUCTION

Vision loss (VL) may be a traumatic life event. The economic burden of vision loss in the United States is estimated to be $134.2 billion: $98.7 billion in direct costs and $35.5 billion in indirect costs. Those with VL incurred $16,838 per year in incremental economic burden [1]. VL patients are reported to experience stages of grief such as “denial” and “acceptance”. The overall effects on the mental health of these patients include depression, anxiety, and the worsening of their VL as a result of these factors as well as stress; it is reported that approximately half become clinically depressed as a result of VL. Some individuals with VL are reported to experience a positive impact; however, the majority of VL patients experience extremely negative emotions and some form of psychological stress [2, 3]. Many of said patients experience to some extent a negative effect on

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their interactions with others and interference with their career/career goals, more specifically a negative effect on self-perception as well as decreased social functioning [4]. Vision loss has several causes, including congenital defects (birth defects) and/or genetic disorders, age-related diseases, as well as injury. Age-related diseases and infections are among the most common and have the greatest severity and socioeconomic impact among individuals. Several forms of VL eventually result in blindness and cannot be completely treated or cured. Such forms of VL may be sudden, progress in slow succession, or worsen very quickly [5].

THE NEUROSCIENCE OF VISION

The perception of images requires the passage of electrical signals to the visual cortex to gain the characteristics of distance, color, texture, as well as object recognition. The visual cortex is therefore connected to the retina. The visual cortex is divided into five regions, ranging from V1 to V5, located both on the unfolded and folded visual cortices. 30% of the brain's neurons are located in the visual cortices. As the region increases in its corresponding number, it becomes furthermore anterior in the brain with respect to V1, as shown in Figure 1. Depending on the aspect of vision that is processed (i.e., the region of the Visual Cortex that the signal must reach), its corresponding retinal ganglion cell travels through one of two distinct pathways, namely the ventral and dorsal pathways. The three retinal ganglion cells, magnocellular, parvocellular, and koniocellular each respond to an image as transmitted by cones and rods in the retina with varying saturating contrasts such that neighboring points in the image are processed by the retina and mapped onto neighboring points in the visual cortex. This process is termed "retinotopy". Magnocellular and Parvocellular (M & P) cells constitute the majority of retinal ganglion cells [6]. Each region corresponds to increasingly refined characteristics of vision. V1, the primary visual cortex, is located in the most posterior region of the brain and surrounds the calcarine fissure; it controls the most fundamental aspects of vision processing such as the position or orientation of an object and its edges [6]. V1 neurons are subdivided into "blob" and "interblob" regions; "blob" regions consist of neurons that selectively process color, whereas "interblob" regions consist of neurons that selectively process orientation. Similarly, V2 contains regions known as "stripes" and "interstripes" that selectively process aspects of vision such as color and orientation. V2 interstripe regions in particular process shapes, similar to "neural compartments" present in V4. V2 thin stripe regions, in contrast, selectively process surface features as do certain neural compartments in V4. Excluding V1 and V2, the majority of vision is sent through mixed signals from the ventral and dorsal pathways. The dorsal pathway (or the dorsal stream) is constituted of predominantly magnocellular retinal ganglion cells and flows through V1, V2, and V5. V5 in particular processes space, movement, and action. The areas that are located

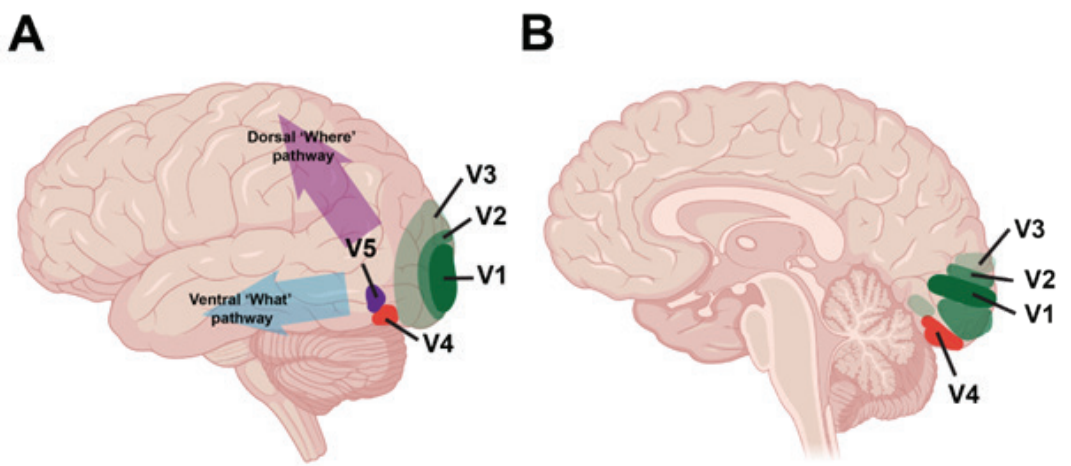

Figure 1. The Vision Cortices, Ventral, and Dorsal Streams with respect to the brain (A), The Vision Cortices from the interior of the brain (B).

in ventral (parvocellular dominated) pathways process object recognition, more specifically V3, V3A, and V4. Unlike V1, V2, and V3, V5 (the Middle temporal lobe) and V4 are not situated as a band surrounding the other regions and instead are located separately as a relatively minuscule area in the parietal cortex and directly below V1, respectively. Generally, all areas that are located in the path of parvocellular-dominated-ventral pathways process surface features and edges, whereas those connected to magnocellular-dominated dorsal pathways process aspects of vision such as motion and more refined spatial characteristics [6].

CAUSES FOR VISION LOSS

Vision loss (VL) commonly results from glaucoma, age-related macular degeneration (AMD), cataracts, diabetic retinopathy, uncorrected refractive error, and in some cases, physical injuries or prolonged, direct exposure to bright light [7, 8]. Injuries leading to vision loss most likely fall under the category of traumatic brain injuries and cause impaired visual perception [9]. Moreover, exposure to ionizing radiation results in a quick progression to complete blindness, not only distorting spatial and color aspects but also entirely destroying the perception of light [10]. Glaucoma, an irreversible type of vision loss, is described as a form of optic neuropathy involving the degeneration of ganglion cells and consequently damage to the optic nerve head. More specifically, glaucoma results from high pressure in the anterior chamber from the drainage of blood vessels. However, it is often initially asymptomatic, and therefore, its diagnosis is delayed, resulting in a lessened likelihood of recovery [11, 12]. Cataracts are a leading cause of treatable VL. Unlike other forms of VL, cataract is the clouding of the crystalline portion of the eye, caused by not genetic or age-related factors, but instead external factors such as the presence of certain polymers/sugars [13]. Finally, uncorrected refractive error is the second leading cause of blindness but is largely preventable/treatable by wearing eye-glasses [14]; it is characterized by “blurriness”, or a low-accuracy (below 50%) image presented after refraction, such as myopia(nearsightedness) and hyperopia(farsightedness). Macular Degeneration is also nearly irreversible, and the third leading cause of VL. It is characterized by two different forms, wet and dry, involving abnormal blood drainage from the retina and the accumulation of drusen (i.e., deposits of lipids & proteins), respectively. Dry forms of AMD are also caused by age-related thinning of the macula. Similar to glaucoma, Macular Degeneration develops asymptomatically and progresses in mild stages [15]. It is estimated that about 65% of VL/blindness is treatable and/or preventable, caused by ailments such as cataracts and Dry AMD. Out of all blindness, about 35% is accounted for by cataracts, 6% by macular degeneration, and 23% by uncorrected refractive error. Moreover, uncorrected refractive error accounts for about 54% of moderate to severe vision loss (MSVL) [10]. While several forms of VL/blindness, such as glaucoma (damaging the optic nerve rather than structures of the eye, more specifically the retina) are difficult to treat, the most common causes of VL (i.e., uncorrected refractive error and cataracts) are currently treated by traditional methods.

TRADITIONAL TREATMENTS

Overall, invasive treatments such as surgery, medication, laser therapy, and stem cell therapy are utilized to address long-term, more deeply rooted conditions such as glaucoma to correct or target certain physiology of the retina, the anterior chamber, and the optic nerve. In contrast, visual aids are most commonly used to treat uncorrected refractive error, which is not necessarily as progressive as AMD and glaucoma.

Surgery

Surgery is used to treat conditions such as glaucoma, cataracts, and retinal detachment. In the case of glaucoma, trabeculectomy, used to lower the pressure of the anterior chamber in order to decrease the damage to the optic nerve head [16, 17]. A similar procedure is performed to address cataracts; however, surgery is only performed for extremely late-stage, severe cataract conditions (Figure 2). The most commonly performed cataract surgery (extracapsular extraction or phacoemulsification) involves either the repositioning of the lens to an obscure location or the mechanized decomposition of this lens, to be disposed of through natural blood drainage systems [18]. However, both of these surgeries involve risks such as the rupture of a capsule within the eye, leading to retinal detachment [19]. Surgical treatments for retinal detachments include scleral buckling (involving a mechanical restriction of the sclera), pars plana vitrectomy (PPV), and pneumatic retinopexy. The three retinal detachment treatments are equally common, although vary in usage across regions of the United States. However, PPV is becoming increasingly common due to its relative success over scleral bucking, although it is largely more expensive than scleral buckling and is associated with a relatively greater risk of forming cataracts [20]. Other surgical

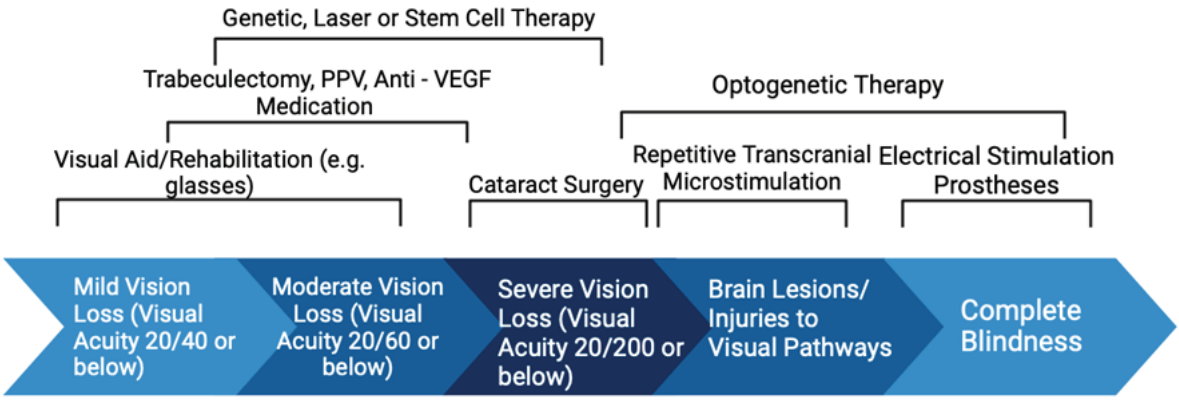

Figure 2. Treatment ranges for VL depending on varying VL severity. Note that repetitive Transcranial Microstimulation is unique to treating lesions, and does not require a damage – free visual cortex or optic nerve.

procedures may be performed depending on the condition and its severity; however, the above methods are the most commonly performed.

Medication

Medication is the most commonly used approach to address VL in the case of glaucoma and macular degeneration. However, as both of these conditions are irreversible, existing medications only slow the progression of the conditions rather than ameliorate their severity. Anti-inflammatory drugs are used to slow the accumulation of drusen in the case of Dry AMD through the breaking down of acids that contribute to drusen formation. Anti-VEGF medications/antibodies are injected to mildly improve vision in the cases of early (dry) AMD by improving the permeability of retinal cells [21]. Treatment through the injection of anti-VEGF antibodies generally requires repeated monthly injections in one or both eyes. However, slow-release anti-VEGF medications are currently in the process of development in order to decrease the frequency of injections [22]. Similar to invasive surgical methods, "eye drops" are utilized to reduce intraocular pressure (i.e., the pressure of the anterior chamber).

Laser Therapy

Laser therapy is used along with medication before attempting invasive surgical methods to address vision loss such as Dry AMD and glaucoma. Two methods of laser therapies are utilized-photocoagulation and prophylactic laser therapy. In the case of Dry AMD, laser therapy is used to simply burn the drusen, but must be performed periodically to prevent the progression of the condition to late-stage AMD [21]. In the case of glaucoma, laser therapy is used to aid fluid drainage from the eye to decrease intraocular pressure and therefore damage to the optic nerve. Similar to laser therapy for macular degeneration, this treatment must also be performed periodically in order to prevent severe damage to the optic nerve head [23].

Gene Therapy

Gene Therapy, as opposed to laser therapy and surgery, is a more modern approach to addressing vision loss. It is commonly used to treat glaucoma by targeting intraocular pressure through the application of interfering RNA over a long period of time. Another method of gene therapy to address glaucoma is through applying RNA to conceal or hinder the expression of inherently problematic genes that are already present in the patient. Angiogenic proteins are carried through a vector, namely an adeno-associated virus (AAV), in the case of age-related macular degeneration to target retinal cells in a similar way to anti-VEGF or anti-inflammatory medications, and the previously dysfunctional cells are eventually restored. Furthermore, in the cases of other diabetic retinopathy, gene therapy is likely more advantageous compared to the application of anti-VEGF medications due to the necessity of repeated medication, as opposed to a shorter treatment period presented by gene therapy [24].

Stem Cell Therapy

Stem cell therapy is primarily used to treat degenerative vision loss conditions such as diabetic retinopathy,

retinitis pigmentosa, and dry macular degeneration (currently, there are few to no solutions to wet macular degeneration). It utilizes adipose(lipid)- derived stem cells to regenerate lost or damaged cells/neurons in order to prevent the progressive thinning of the sclera (in the case of dry macular degeneration). Other currently explored treatments include embryonic – induced stem cells, endogenous retinal stem cells, as well as adult non-retinal stem cells have been explored. Non-retinal derived adult stem cells (most likely patient derived) include neural stem cells, bone marrow stem cells, and dental pulp stem cells. Stem cell therapy acts through the secretion of injection of proteins, which engages the corresponding receptors, resulting in a neurotrophic effect and the activation or disinhibition of neurons and/or photoreceptors, leading to restored visual function [25]. Conversely, however, stem cell therapy also possesses the risk of causing further vision loss (more specifically, retinal atrophy) [26]. Moreover, the retina is a less ideal environment for the growth and regeneration of stem cells, especially in the case of diabetic retinopathy. As a result, stem cell therapy is currently limited in the matter of blindness relating to damage to the optic nerve/neurons for this reason. [27] In general, stem cell therapy is currently the least developed area of treatment for VL. While it may have greater potential after further research, other methods of treatment are associated with fewer risks overall.

Visual Aid and Rehabilitation

Visual aids are most commonly used for uncorrected refractive error, more specifically hyperopia and myopia. Such magnification and rehabilitation tools are limited to visual therapy (involving the repeated action of focusing on a certain point) and physical aids such as eyeglasses and are therefore obscure when addressing glaucoma and forms of extreme VL. All visual aids are either worn or held by the user as an extra lens to aid in magnification or correct abnormal refraction. Rehabilitation is characterized by therapy intended to allow a patient to regain control over vision. Methods of rehabilitation therapy include eccentric fixation, in which a patient repeatedly follows a pattern of vision [28]. As a result, visual aids and therapy are only applicable in early-stage AMD and mild vision loss.

NEUROSTIMULATION BASED TREATMENTS

However, for many cases of irreversible, late-stage VL none of the traditional treatment options are valid. Therefore, electrical stimulation of the neural elements that are involved in processing visual information was developed. Neurostimulation-based treatments use electrodes that are currently wirelessly interfaced with the central and peripheral nervous systems. By electrically stimulating neurons, the cell membranes are chemically depolarized, and cause a functional response in the targeted tissue, eliciting phosphenes. To prevent damage to tissue in the brain, the current is applied biphasically (i.e., in a series of alternating cathodic and anodic phases). Parameters of neurostimulation are as follows; anodic and cathodic current (unit in amperes) may range from 1 μA to 10 mA; the duration of cathodic half - phase is typically 50 μs to 4 ms, whereas the duration of anodic half – phase for 50 μs to 10 ms, with a 0 – 1 ms interphase dwell (i.e, the resting period between the application of cathodic and anodic currents). Commonly used metals used for implanting in the visual cortex include tantalum oxide, titanium nitride, iridium oxide, and platinum alloys. The electrical stimulation results in the production of phosphenes in the visual cortex, creating visual perception in the patient [29].

Retinal Stimulation

Retinal stimulation is aimed at treating retina-damaging conditions, more specifically, forms of retinal degeneration such as dry AMD and retinal pigmentosa. In the cases of other VL causes, retinal stimulation is attempted to develop neuroprotective characteristics in the retina which effectively slows the progression of VL [30]. Two approaches to retinal stimulation have been investigated: the first by directly utilizing electrical stimulation to produce phosphenes in the retina, and the second by utilizing non-neural stimulation-based approaches such as gene therapy to familiarize retinal cells with electrical stimulation. Retinal Stimulation erupted upon the discovery of neural stimulation along with intracortical stimulation. The first trial of such retinal stimulation was through raw transcranial stimulation performed by French physician Charles Le Roy, which produced flashes of light (phosphenes) with no specific pattern or image recognition. Retinal stimulation was initially attempted much before intra-cortical stimulation before the refinement of invasive stimulation approaches. After the refinement of the fabrication of microelectronics and surgical techniques, several categories of retinal prostheses were subsequently developed.

The Argus II Retinal System is the most widely used retinal prosthesis system and was the first to obtain FDA approval (in the year 2011) [30, 31]. Unlike epiretinal prostheses, this retinal system involves both implanted

and external components. The Argus II Retinal System is unique in that it requires the patient to wear eyeglasses attached to a camera, which is then connected to a video processor, also worn externally. The receiving antenna and other electronics are secured through a procedure known as scleral buckling (additionally used as a surgical approach to retinal detachment) to the sclera, whereas an array of electrodes is inserted into the eye and secured to the macula. When the external camera captures images, it is subsequently received by the antenna in terms of brightness value and is then converted to current amplitudes in order to activate retinal neurons and thus be perceived as an image. In contrast to the simpler epiretinal prosthesis, the Argus II is largely more accurate as of present; however, due to the information processing in terms of "brightness", it does not produce colored perceptions and as a result, its user may only perceive black and white images. Currently, the Argus II system contains a moderate percentage of failure within 5 years of implantation, where the root cause is unknown [32].

Epiretinal prostheses involve the placement of a microelectrode array on the surface of the retina. This approach is the least complex to perform on a patient in the context of vision prosthesis and therefore is easily accomplished. The device is placed within the vitreous cavity, i.e., between the lens and the retina. The electrical stimulation is applied to retinal ganglion cells. However, due to the proximity of the electrical stimulation to axonal nerve fibers, extra stimulation may occur leading to the production of unnecessary phosphenes and therefore muddling the intended perception [33]. As a result, epiretinal prosthesis may be less desirable in both cases of complete blindness and severe VL, in that although they provide an opportunity to improve vision, they may also result in unrealistic or obfuscated images that do not resemble the intended image [33].

Subretinal prostheses, unlike Epiretinal prostheses and Argus II, do not rely on externally worn devices to translate images to brightness values. Subretinal prostheses attempt to imitate the function of photoreceptors through the implantation of a microphotodiode array (MPDA) between the retinal epithelium and bipolar cell layer. The microphotodiodes serve as solar cells and therefore also as powering mechanism for the subretinal prosthesis. Subretinal prostheses are advantageous in that they are nearer in proximity to the visual pathway (bipolar cell layer) and therefore require less current to generate visual percepts. A clinical trial performed by Zrenner et al. (2007) concluded the main function of subretinal prostheses to replace lost photoreceptors [34]. Generally, the success of subretinal prostheses is attributed to the presence of surviving retinal neurons despite photoreceptor degeneration. However, subretinal prostheses are limited by the availability of subretinal space for the implantation of electronics as well as the risk of thermal injury to neurons, caused by the proximity of the prosthesis to the retina. In a more recent clinical trial conducted by Muqit et al. (2023), a maximum visual acuity of 20/438 was achieved [35].

Although Retinal prostheses have emerged in several areas, many clinical trials have not ultimately ended successfully, and therefore a relatively smaller number of patients have received retinal prosthetic implants as opposed to intracortical visual implants. However, retinal prostheses, if successful, provides more coordinated prosthetic vision as a result of the stimulation of exterior bipolar cells.

Intracortical Stimulation

The concept of the intracortical visual prosthesis emerged along with the retinal prosthesis based upon the idea of electrically stimulating neurons. An array of electrodes provides the patient with electrical stimulation to the visual cortex, producing phosphenes or "dots of light". Generally, each electrode possesses its own threshold. However, Intracortical visual prostheses involve the stimulation of the visual cortex rather than retinal neurons, which (initially) required a more invasive implantation approach. Moreover, it relies on the inherent production of phosphenes in the visual cortex as a result of neuronal stimulation, rather than the enhancement of the retina. The earliest clinical trials of intracortical visual prostheses (ICVP) were designed to be stationary. The patient received several wires connecting the visual cortex to an array of electrodes, utilizing a belt-worn camera for a similar image processing method to the Argus II Retinal System. This trial was first performed by Dobelle et al. (1967) and shortly progressed to a microcontroller that was surgically implanted in the visual cortex itself [36]. Following the refinement of electrical fabrications and surgical methods, ICVPs were similarly refined to include signal processors to reduce power consumption and weight of the device. However, the discovered approach of raw phosphene production does not account for several spatial components that are inherently processed by neurons in the V1 region. While this may be rectified in animal testing through the tuning of cortical neurons, it is largely more complicated and untested in the case of humans [37]. Schmidt et al. (1996) subsequently conducted a trial in which 38 electrodes

were implanted in the visual cortex of a blind patient for a period of 4 months. The resultant phosphenes did not flicker and indicated that the stimulation currents and distance between stimulation electrodes could be manipulated to produce colors, variations in phosphene sizes, resolution, and duration, and resemble spatial characteristics, such as collinearity and coplanarity [38]. The latter two characteristics were further manipulated through asynchronous and synchronous stimulation of electrodes in more recent clinical trials (Moleirinho et al. in 2021). It was then concluded that asynchronous and synchronous stimulation create different perceptual effects, whereas asynchronous stimulation may decrease accurate visual perception due to issues such as phosphene fading. Alternatively, phosphenes may be manipulated to resolve issues with phosphene fading and improve image perception [39].

More specifically, when the stimulation currents neared either the lower or higher electrode thresholds, they gained hues of red, purple, yellow, and blue. Furthermore, the utilization of pauses between long periods of stimulation resulted in a longer duration of visual percepts following stimulation for up to 6 minutes after stimulation was terminated [40]. A clinical trial performed by Troyk et al. (2005) indicates the ability to input all devices in the visual cortex and the eye, ridding the patient of the wired connections. A wireless approach of ICVP was subsequently developed to increase the portability and reduce the risk of implantation through invasive brain surgery [41]. More specifically, intracortical electrodes penetrate about 1.5 mm into the cortical surface of the brain, more specifically V1, the primary visual cortex [42,43]. Before the discovery of safety concerns, biphasic currents, namely anodic-first and cathodic-first were initially utilized interchangeably; however, cathodic-first stimulation is now more commonly utilized as anodic-first stimulation requires a higher amplitude to effectively stimulate neurons as well as for physiological reasons [44].

For the majority of clinical trials, measurements and other data have been collected through patient questioning; consequently, qualitative results are likely to be solely based upon patient descriptions and therefore may not be completely accurate. Other methods of testing have been progressively developed. The phosphene mapping method was developed by Mladejovsky et al. (1976), in which the patient controls a "joystick" to indicate a possibility of 16 different directions in total, which is subsequently mapped on a polar quadrant coordinate system [39]. However, this may also lack accuracy to a certain degree as a result of the reliance on input from the patients themselves. Furthermore, through this method, the phosphenes appear densely clustered and do not provide data viable for thorough analysis. A more recent clinical trial performed by Troyk et al. in 2022 reveals the development of a more sophisticated approach to phosphene mapping for data collection. The patient is shown a reference phosphene and subsequently asked to draw a vector between the reference phosphene and its paired phosphene. Due to the proximity between certain reference phosphenes and the pair, a triangular method of mapping was applied in which the presumed vector was drawn and compared to the patient-drawn version in order to measure its accuracy [45]. Moreover, this trial also furthers the development of ICVPs towards human and animal testing.

The phosphenes produced from this most recent human clinical trial were bluish-white, orange, red, or iridescent. Rings and bright/dark dots were also perceived in this trial. The participant was able to discriminate horizontal and vertical lines, indicating the device's ability to generate a greater range of characteristics in prosthetic vision [45].

Optic Nerve Stimulation (ONS)

Unlike intracortical and retinal stimulation, ONS relies on the stimulation of the optic nerve in order to produce visual percepts. The first clinical trial to attempt an optic nerve prosthesis was performed by Veraart et al. (1998) [46]. This trial utilized several subcutaneous wires connected to an external electrode, rather than the wireless electrode arrays utilized in the ICVP project. The majority of optic nerve prostheses employ the use of a spiral nerve cuff electrode. The electrode cuff is surgically implanted onto the external surface of the optic nerve using the Pterional Transsylvian approach without penetrating its sheath, therefore relying predominantly on retinotopic organization within the optic nerve [47]. The most recent forms of optic nerve prostheses implant several electrodes on the optic nerve (Figure 3). Optic Nerve Stimulation, in addition to creating visual percepts, also institutes the revival of retinal ganglion cells [47].

The optic nerve constitutes the entire visual field in one region, that can be accessed surgically with relative ease. However, this also presents a problem in that its surgical manipulation requires the dissection of the dura, which contains the risk of interrupting blood flow to the optic nerve, thus furthering vision loss rather than improving vision. Moreover, the macular fibers lie within the optic nerve rather than on its surface, resulting in greater distance from the cuff electrodes to cells requiring stimulation when compared to retinal and intra-cortical vision prostheses [48].

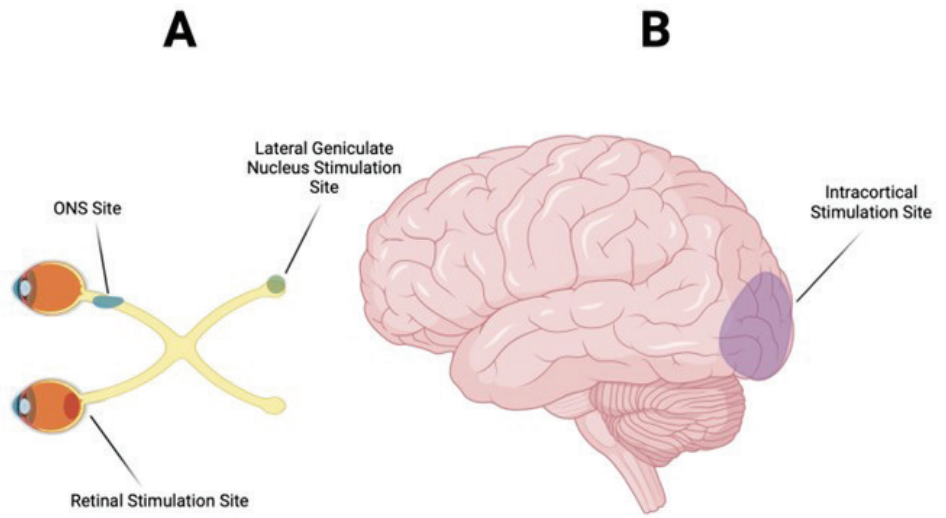

Figure 3. The stimulation sites for the Lateral Geniculate Nucleus, Optic Nerve, and Retinal prostheses (A) and Intracortical vision prostheses(B) with respect to the brain, the eye, and the optic nerve. (Note: The Optic Chiasm is shown separately from the brain in order to better visualize the LGN and Optic Nerve sites.)

In the trial by Veraart et al. (1998), a patient diagnosed with retinitis pigmentosa was implanted with an Optic Nerve Prosthesis consisting of four spiral nerve cuff electrodes. This trial attempted the recognition of 45 distinct geometrical patterns that consisted of the arrangements of two or more straight lines. Similar to the Argus II Retinal System, optic nerve prostheses utilize an externally worn camera to transmit the image. The trial yielded pattern recognition with 63% accuracy (determined through previously discussed methods of phosphene mapping and collection of results). The produced phosphenes varied widely in color or occasionally appeared without color against a colored background and arranged rows or clusters [48].

Lateral Geniculate Nucleus (LGN) Stimulation

LGN Stimulation utilizes the stimulation of the LGN and is often paired with optogenetic stimulation. Similar to the Optic Nerve, the LGN is compact and orderly, allowing for access to a large visual field in a relatively small area. Moreover, the LGN is the synapses point for approximately 90% of retinal ganglion cells [49]. A clinical trial investigating the retinotopic organization of the LGN was performed by Schneider et al. (2004) and identified that, unlike the retina, the visual field is evenly distributed in terms of density, resulting in the ability to utilize lower-density membrane electrode assemblies (MEAs), thus reducing tissue damage [50]. However, LGN prostheses, and Thalamic prostheses, in general, require a greater number of electrodes to reach a similar sophistication and image resolution as other vision prostheses due to the LGN's relatively unexposed position in the brain [48, 50]. The first clinical trial to attempt visual perception through the LGN was performed by Pezander & Eskander et al. (2009) and attempted electrical stimulation through the utilization of a high-density MEA from a microwire bundle inserted through a cannula. As the electrodes approach the LGN, the microwires exit the cannula and probe the tissue in discrete locations [49]. In more developed clinical trials, deep brain stimulation (DBS) is achieved in order to minimize the invasiveness of implantation. Kyada et al. performed the most recent trial for LGN stimulation in 2017 and utilized bilateral electrodes as in DBS therapy [51]. The resultant phosphenes were mapped on a computer screen and achieved a maximum visual accuracy of 20/240 [49, 51].

OPTOGENETIC THERAPY

Genetic therapy may be used for VL patients in early stages but cannot generally treat patients once VL progresses to complete blindness. Optogenetic Therapy may be utilized to treat patients who have bare or no light perception, as in neurostimulation-based treatments. Similar to electrical stimulation-based vision prostheses, optogenetic therapy stimulates retinal ganglion cells;

however, in the place of electrical stimulation, light-sensitive proteins are utilized through intravitreal injection to confer light-sensitivity to otherwise non-light-sensitive neurons (inherently present in a blind patient). It may also be applied to the LGN in place of electrical stimulation. Optogenetic therapy does not rely on the production of phosphenes but rather the development and restoration of vision through the continual treatment of said light-sensitive proteins [52]. More recent clinical trials of optogenetic therapy indicate the ability to "reprogram" ganglion and photoreceptors to become light sensitive; successfully injected proteins include ChR2 (a light-sensitive ion channel) and Halorhodopsin, carried by an AAV, a viral vector. As in all forms of electrical-stimulation-based vision prostheses, optogenetic therapy may be paired with an external vision device such as a camera in order to process otherwise invisible infrared light, which is necessary for optogenes to be successful [52, 53].

CHALLENGES OF VISION RESEARCH

Both the eye and the optic nerve are extremely complex to access surgically as well as manipulate to create the desired results. Many clinical trials of ICVP, retinal prostheses, optic nerve prostheses, and genetic therapies fail for this reason. The methodology of implantation for ICVPs and retinal prostheses are largely invasive, posing the risk of damaged brain tissue from not only surgery but originally from the electrical stimulation. In several cases, unwanted phosphenes may be inadvertently generated, or, in the case of genetic therapy, the majority of the eye is not a suitable area for the insertion and/or growth of novel genes, which may instead cause further VL or worsen the ability to perceive light.

Reporting Perceptions in Animal Studies

Animal testing is commonly utilized in vision research in order to determine the safety and side effects caused by such interventions. However, this process is often challenging as unlike human clinical trials, the participant lacks the ability to verbally describe the qualitative results. Animals that undergo this process are often strictly trained to respond to phosphene production through certain behaviors or are merely observed to behave in a certain manner based upon the qualities of phosphenes produced [54]. Moreover, the structure of animal eyes varies greatly from that of humans, which may skew the relative success of visual rehabilitation when compared to humans.

In general, different species (namely rats, sheep, rabbits, dogs, cats, and other miscellaneous rodents) are utilized for testing in the development of retinal prostheses, each for a different cause of VL. This is mainly due to, once more, the differing eye structure that may resemble a diseased or dysfunctional human eye. More specifically, in-vivo animal testing through rats is utilized when considering VL from photoreceptor degeneration. However, due to the size of a rat eye, the traditional methods of retinotomy are not possible. Similarly, in the case of rabbits, the retinal prostheses cannot be inserted through pars-plana sclerotomy; furthermore, rabbits do not possess a macula. However, rabbits are utilized extensively when considering glaucoma and overall, are used to assess the feasibility and compatibility of the prosthesis model [52]. Overall, although animal testing is necessary and provides insight into certain characteristics of visual perception, doing so may be inaccurate or difficult to translate to the human eye as a result of its distinguished features.

Verification and Quantification of Visual Percepts

As previously stated, results from vision research are assessed by the patient. Moreover, for several clinical trials, it is necessary for the patient to have acquired blindness, as in the clinical trials performed by Troyk et al. in 2022. This is a result of the necessity to hold pre - VL vision as a reference point in order to make adequate observations of the visual percepts produced. However, such visual percepts may pale in comparison to pre-blindness vision due to the complex spatial characteristics, resulting in underwhelming percepts as described by the patient. Although more quantitative methods of phosphene mapping have been developed and utilized (mainly in the trials by Troyk et al. in 2022), this by itself is unlikely to provide a thorough quantitative or qualitative assessment of visual percepts. Consequently, the exclusion criteria for many vision research clinical trials contain the expectation to return to pre-blindness vision through the clinical trial process.

Difficult Surgical Accessibility

The majority of the visual cortex is located in the posterior region of the brain. The primary visual cortex, V1, is located near the calcarine fissure, a fold in the brain tissue. This results in much difficulty in the surgical implantation of the device, which is located primarily in V1, the region that controls many spatial characteristics of visual perception. The occipital lobe itself is located in close proximity to the divide between the two hemispheres of the brain [55].

Difficulty of Color Production in Visual Percepts

The production of color through neural stimulation is extremely rare. As previously discussed, the production of colored phosphenes is likely to occur when the electrode is stimulated at a current near its threshold. However, this method requires an extreme level of precision. Moreover, many other spatial features of vision that are normally processed and created by the Visual cortex are also difficult to achieve through vision prosthesis. In the case of retinal prostheses, the majority of any visual percepts or images are black-and-white, as the images are transmitted as brightness values, resulting in the exclusion of color from the prosthetic vision [31,54].

Lengthy Mapping Sessions Tailored to Patient

In order to begin the production of phosphenes, a reference, or a phosphene map must be developed in order to improve or predict the phosphene pattern that would arise from stimulation. As previously stated, visual percepts are likely to vary depending on the patient as well as the amplitude current of stimulation, resulting in the need to test a number of times in order to determine the correct frequency and amplitude of stimulation; consequently, pattern recognition is likely to occur towards the end of a mapping session. Furthermore, pre-test phosphene maps are often idealized in that they may not accurately portray the participant or patient's true perception [56].

Vision Research Yields High Costs

The cost of treatment through Intracortical visual prostheses may range from 54,000 US dollars to 200,000 US dollars, while the most reliable genetic therapy may cost up to 850,000 US dollars [57]. While several patients participating in clinical trials do so for either altruistic reasons or the hope of restoring vision, this cost is currently unsustainable for the majority of VL patients. As previously mentioned, VL may contain several socio-economic effects on the patient that may severely hinder the patient's income and thus hinder the patient's ability to pay for treatment through ICVP, retinal prostheses, and/or genetic therapy. Currently, it is unlikely that ICVPs and the majority of retinal prostheses would be covered by insurance companies due to the lack of governmental clearance as well as the continuing clinical trials and reiteration.

Difficulties Finding Study Participants

The majority of vision research clinical trials contain extremely specific inclusion and exclusion criteria, limiting the type and severity of VL, as well as its duration. For example, several clinical trials attempt to exclude patients who cannot adjust to chronic blindness and subsequently experience extreme negative psychological effects or a decline in cognitive ability. The study populous is further limited by the intent and expectations of study participants, thus leaving a scarce number of eligible participants. However, it is unlikely for a great number of these eligible candidates to agree to the surgical implantation process, involving risks such as slow recovery from surgery and the application of anesthesia. The latter is significant in the process of vision research as it may heavily hinder the patient's ability to quantify or describe visual percepts as a result of the lack of awareness of anesthetics. More specifically, the three stages of recovery from anesthesia may vary among patients; however, the last stage, long-term recovery, may last up to days and affect overall awareness and coordination [58].

Psychological Limitations: Social Stigma. While a large number of VL patients may have severely negative psychological impacts as a result of blindness, those who adjust to the condition of blindness are more than likely to become acquainted with this disability. It is identified that about 81% of affirmers of adjustment to blindness view blindness as a part of their identity, rather than as a deficiency, and did in fact not wish to cure their blindness. Moreover, they view this identity as a path of independence; so attempting to cure or alter this identity would be unnecessary. More specifically, patients of complete blindness are reported to feel that their disability is not from blindness itself, but rather the unwillingness to adapt. Among completely blind individuals, 10 out of 11 are reported to have attended a form of blind school, in which their initially negative perception of blindness was eventually altered to be viewed neutrally or positively. Furthermore, the interaction of blind individuals with equally blind peers is reported to further affect the perception of blindness in this manner [59, 60]. As a result of the presence of certain inclusion criteria for many clinical trials/treatments, including positive adjustment to blindness as well as the lack of negative psychological effects, willing participants are scarce for this reason; more specifically, individuals who have well adjusted to blindness are likely to have perceived this condition as a part of their identity and therefore neglect to attempt treatment. In the case of the trial performed by Troyk et al. in 2022 among others, the individual was required to have a history of visual rehabilitation in order to decrease the likelihood of negative social interactions in response to attempting visual rehabilitation through ICVP/retinal prostheses.

Psychological Limitations: patients require a strong

Support Network. The exclusion criteria on the majority of ICVP/retinal prostheses clinical trials include a lack of support network or a general lack of support. Out of the 10 trials listed in Table 1, 7 clinical trials possessed this criteria. Negative psychological effects of VL may otherwise hinder the individual's thorough and accurate participation in the trial, and worsen these psychological effects following the surgical implantation and testing of the device.

Psychological Limitations: patient must adjust well to blindness. Individuals born blind are often not eligible for clinical trials as a result of their inability to identify, distinguish, and describe light perception. Moreover, such individuals, as a result of being fully adjusted/positively perceiving blindness, avoid attempting visual rehabilitation. A large portion of blind individuals, in addition to attending a school for the blind, also undergo "sleepshade" training, in which they develop an optimal use of residual vision as well as the ability to perform activities despite the lack of vision. However, despite the large percentage of blind patients that undergo this training, a vast amount still experiences the negative psychological effects of blindness. Participating in clinical trials or receiving treatment through either ICVP or retinal prostheses may worsen these effects, as the presence of underwhelming percepts may either create or destroy hopes of returning to pre-VL vision [61].

Challenges of electrical stimulation (ICVP, Optic Nerve, LGN, & Retinal)

Developing adequate electrical stimulation devices poses not only biological but also technological challenges. In order to prevent damage to tissue and increase the practical aspect of the device, electrodes must be ideally comparable in size to a neuron or optical cell. In addition, the mechanisms of the electrode/device must ideally match the mechanisms of the home site cell in order to stabilize the device and reduce side effects after implantation (including immune responses to foreign materials). As a result, this places heavy restrictions on both the impedance of the device and the charge capacity. Consequently, the charge capacity cannot be exceeded at the risk of further damaging the brain tissue. However, over time, a consistent usage of certain metals has been developed in order to make the production of this technology more feasible. Biological challenges of developing both intracortical and retinal prostheses include the distinguished physiological differences between animal implants and those in humans. As previously stated, both the eye and visual perception mechanisms vary greatly in rodents or mammals that are implanted with vision prostheses; although many models may work well in animal trials, they may subsequently fail in human testing. Furthermore, the lack of neuroplasticity as well as the presence of viable cells in the visual pathway may also impact the efficacy of the implant and cause variability in the stimulation required to create successful image or pattern recognition [61]. In the case of LGN prostheses, certain causes of vision loss such as glaucoma may affect the size and functionality of the LGN, lowering the efficacy of treatment through LGN stimulation [48].

Challenges of genetic therapy

Genetic therapy for treating vision loss attempts to insert novel RNA into the retina in order to reduce intraocular pressure to prevent damage to the optic nerve, or reduce retinal degeneration. Certain methods of genetic therapy including optogenetic therapy, utilize a viral vector (AAV) as a carrier of novel proteins in order to target retinal degeneration However, this method is prone to auto-immune responses or inflammatory reactions in the eye, more specifically uveitis, which may severely worsen vision loss and cause temporary blindness [63]. Optogenetic therapy, like all forms of genetic therapy, must be applied in moderate doses in order to reduce adverse immune responses to the application of opsins [51]. For optogenetic therapy in particular, the working wavelength required for optogenes falls outside of the human physiological range; more specifically, in order for optogenetic proteins to be successful in conferring light sensitivity, they must be sensitive to infrared wavelengths [52, 64]. This intensity of light may also be toxic to the retina, causing further damage.

Neuroplasticity

The success of neurostimulation-based treatments relies heavily upon the physiological state of the targeted region as well as surrounding regions that may otherwise disrupt the production of phosphenes or, in the case of optogenetic therapy, inhibit vision restoration. Such regions include the optic nerve, the visual cortex, and the LGN. Clinical trials have been established to target VL patients affected by brain injury, as shown in Table 1; a clinical trial utilized repetitive transcranial micro-stimulation (rTMS) to target vision loss from lesions (# NCT04021160). Apart from lesions, the brain of a VL patient may also be affected by neural rewiring, caused by the absence of a useful visual input. In conditions such as retinitis pigmentosa, this change first occurs in the retina and subsequently in the visual cortices. As a result, while electrical stimulation or genetic therapy delivered by vision prostheses may produce visual percepts or restore

Table 1. Recent clinical trials

Clinical Trial #	Start Date	End Date	Intervention	Condition(s)	Region of Treatment/ Surgical Procedure	Inclusion Criteria: VL Severity	Location
NCT01603576	2012	2014	Suprachoroidal Retnal Prosthesis	Retinis Pigmentosa, Choroideremia	Suprachoroidal Pocket	History of useful vision (10 years), no light perception	Canberra/ East Melbourne, Australia
NCT02747589	2016	2025	Intracortical Visual Prosthesis (ICVP)	Acquired Blindness	Visual Cortex	History of Useful Vision, Bare/no Light Perception	Los Angeles, California
NCT03344848	2017	2024	Orion Cortical Visual Prosthesis	Acquired Blindness	Occipital Lobe, medial surface	Less than 5 degrees of visual acuity	Los Angeles, California/ Houston, Texas
NCT04021160	2018	2019	rTMS (repetitive transcranial magnetic stimulation)	Visual Fields Hemianopsia	Perilesional Area	Blindness resulting from lesions in visual cortex	Cairo, Egypt
NCT03418116	2018	2021	Retinal Prosthesis - Argus II Retinal System	Retinitis Pigmentosa	Parafovea	Previous history of Vision, severe blindness, No Optic Nerve Damage	Aachen, Germany
NCT03392324	2018	2025	Subretinal Prosthesis - PRIMA	Dry AMD	Retina	Visual Acuity of 20/400 or Worse, Bare Light Perception	Palo Alto, California Miami, Florida / Pittsburgh, Pennsylvania
NCT02983370	2019	2024	CORTIVIS Intra-Cortical Visual Prosthesis (ICVP)	Blindness	Minicraniotomy	Greater than 12 years of blindness	Elche, Alicante, Spain
NCT04634383	2020	2023	Intra-Cortical Visual Prosthesis (ICVP)	Acquired Blindness, Photoreceptor Degeneration, Ocular Injury	Visual Cortex	History of Uncorrected or Corrected Vision for at least 10 years of life, No Light/Bare light perception	Chicago, Illinois
NCT04295304	2020	2023	NR600 Retinal System	Retinitis Pigmentosa, Retinal Degeneration	Surface of Retina	History of Useful Vision, Bare Light Perception	Ghent Belgium, Tel Aviv Israel
NCT06117332	2023	2027	AI-Powered Vision Prosthesis	Acquired Blindness	Visual Cortex	Already received vision prosthesis implant (retinal or ICVP)	Santa Barbara, California/ Ann Arbor, Michigan

vision in surviving neurons or retinal ganglion cells, respectively, it may not contain the same effect on non-surviving counterparts due to the death of photoreceptors, altering neural behaviors [65].

RECENT ADVANCES IN TECHNOLOGY

In recent years, novel technology has been developed that affects the power consumption, size, and convenience of electronics. In the context of vision prosthesis research, this allows for not only safer implantation but also reduces the invasiveness and damage to the brain tissue from large electronics. These advances allow for neural prostheses to become more biologically compatible and therefore increase the likelihood of producing visual percepts.

Flexible Electrodes

The development of flexible electrodes is largely compatible with retinal prostheses. As previously stated, metals utilized in flexible electrodes must be biologically compatible with tissue and must imitate the stretching of human tissue. Therefore, viable flexible electrodes must not only be flexible but also successfully endure stretching ranging to a 10% strain [66]. Inorganic compounds that may otherwise be utilized in electrodes such as Silicon and Silicon dioxide cannot sustain long-term usage and are biochemically incompatible. Electrodes composed of Silver Chloride easily become volatile and therefore are prone to signal degradation; all of these materials, as a result of their incompatibility with either brain or retinal tissue, are prone to causing allergies and immune responses upon implantation [67, 68]. It is thus necessary to utilize materials for flexible electrodes that may create a minimal FBR and undergo less strain when stretched over long periods of time. In the case of intracortical vision prosthesis (requiring implantation in the brain), electrodes must sustain the expansion and contraction of the brain synchronized with the cardiac cycle. Flexible electrodes using gold metallization have been developed, as well as carbon fibers to the extent that maintains feasible conduction of electricity. Electrodes that are based upon gold metallization must necessarily include adhesion using other metals such as Titanium or Chromium [69]. More specifically, conductive polymers allow for both the conduction of electricity but also ionic conduction. Consequently, Fiber-like materials (including those composed of carbon fiber) designs are often insulated with conductive polymers. The development of such flexible electrodes is likely to and has provided a greater signal duration, resulting in more consistent visual percepts [70, 71]. Currently, materials utilized for insulating flexible electrodes include parylene N, parylene C, and polystyrene sulfonate [72, 73]. The challenges of utilizing flexible electrodes include changes in physical properties over long periods of time as the electrodes undergo strain. Electrodes that are composed of polymers such as PDMS or parylene have a lower tensile strength (i.e. They are prone to damage upon incurring strain) and therefore must be dimensioned in order to prevent damage upon insertion into brain tissue [74].

Wireless Floating Microelectrode Arrays (WFMA)

The recent advancement of Wireless Floating Microelectrode Arrays (WFMA) eliminates the presence of percutaneous wires exiting the brain and moreover contributes to the reduction in the necessity for more invasive implantation. WFMAs used in neural prostheses generally each contain up to 16 electrodes and are able to interface to stimulation commands wirelessly [68]. In the case of neural prostheses, WFMAs are implanted into the occipital lobe. In clinical trials by Troyk et al. (2006-ongoing), the WFMA consists of a ceramic substrate platform on which the electrodes are situated. The WFMA provides a wireless connection between the microelectrodes (within the body of the WFMA), more specifically the ASIC and micro coil, and the external wireless stimulator module [75]. Unlike previous attempts of stimulation, the electronics within a WFMA allow each electrode to interface to an individual electrode driver so that the stimulation parameters can be adjusted.

Smaller Electronics utilizing Smaller ASICS

In addition to less invasive and more efficient technology, the general size of transistors continues to decrease, resulting in similarly smaller electronics. As in the advancement of neural prostheses from its first attempt (Brindley & Lewin), which involved highly invasive surgery as well as several externally connected wires, to the most advanced wireless prostheses (that largely utilizes WFMAs), the continuing reduction in electronic size would have a similarly beneficial effect; Moore's law professes that the number of transistors in any given circuit will double over a span of two years, while its individual price will halve [76]. As previously stated, the decreasing size and the simultaneous increase in efficiency provide an opportunity for less invasive neural prostheses as well as enhanced power; transistor efficiency subsequently translates to ASIC efficiency. An ASIC allows for wireless communication with WFMA, contributing to the function of a neural prosthesis [77]. In addition to efficiency, smaller

electronics allow for designing neural interfaces that are smaller in size and subsequently result in a reduced foreign body response (FBR).

CONCLUSION

Currently, retinal prostheses have reached the greatest extent of governmental clearance, including FDA approval. However, as the electrical components of intra-cortical vision prostheses develop, it is likely that both intra-cortical and retinal prostheses hold a promising future. More specifically, in several cases of irreversible, complete blindness caused by Macular Degeneration and Glaucoma, neural prostheses, with continuing innovation, provides a method of prosthetic vision. Both Optic Nerve and LGN Prostheses have not reached human testing through clinical trials; LGN prostheses in particular has reached testing in macaques. Thus, further research and development is necessary in order to establish governmental clearance for both Optic Nerve and LGN prostheses. In addition, the increasing reduction of prices of electronic components including WFMAs and ASICs may result in greater accessibility to neural prostheses; although such treatments are extremely costly as of now, it is likely that upon increased testing in human participants and governmental clearances, this may be alleviated. Although several previous trials have been executed in animals, only one human participant has been implanted with the most recent version of the ICVP (by Troyk et al. in 2024). In the case of gene therapy, more sophistication of techniques is necessary in order to eliminate the risks associated with inserting RNA into the site of therapy; currently, genetic therapy is associated with the risk of losing vision and has been shown to be no less extreme in the matter of costs, and the only FDA – approved gene therapy applicable to vision loss is Luxturna, a variation of ocular gene therapy. All intervention options (namely, intracortical prostheses, retinal prostheses, and genetic therapy) currently contain various side effects including mild damage to brain tissue, ameliorated by minimally invasive devices such as the WFMA in the case of ICVP. The WFMA in particular allows for the execution of intracortical stimulation without percutaneous wires. Overall, intracortical prostheses, due to the most recent advancements, may hold funding priority.

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REFERENCES

1. Rein DB, Wittenborn JS, Zhang P, Sublett F, Lamuda PA, Lundeen EA & Saaddine J. The economic burden of vision loss and blindness in the United States. Ophthalmology. 2022; 129 (4): 369-378.
2. Boagy H, Jolly J & Ferrey A. Psychological impact of vision loss. Journal of Mental Health and Clinical Psychology. 2022; 6 (3): 25–31.
3. Cimarolli VR, Casten RJ, Rovner BW, Heyl V, Sörensen S,& Horowitz A. Anxiety and depression in patients with advanced macular degeneration: current perspectives. Clinical ophthalmology (Auckland, N.Z.). 2015; 10: 55–63. https://doi.org/10.2147/OPTH.S80489
4. Brody BL, Gamst AC, Williams RA, Smith AR, Lau PW, Dolnak D, Rapaport MH, Kaplan RM & Brown SI. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. Ophthalmology. 2001; 108 (10): 1893–1901. https://doi.org/10.1016/s0161-6420(01)00754-0
5. Thurston M, Thurston A & McLeod J. Socio-emotional effects of the transition from sight to blindness. British Journal of Visual Impairment. 2010; 28 (2): 90–112. https://doi.org/10.1177/0264619609359304
6. Kafaligonul H. Vision: a systems neuroscience perspective. 2014.
7. Yacoub E. Contextual feedback to superficial layers of V1. Current Biology. 2015; 25 (20): 2690–2695.
8. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, ... & Taylor HR. Causes of vision loss worldwide, 1990–2010: a systematic analysis. The lancet global health. 2013; 1 (6): e339–e349.
9. Aldrees S & Micieli JA. Catastrophic vision loss from radiation-induced optic neuropathy. BMJ Case Reports CP. 2020; 13 (2): e233706.
10. Das M, Tang X, Mohapatra SS & Mohapatra S. Vision impairment after traumatic brain injury: present knowledge and future directions. Reviews in the Neurosciences. 2019; 30 (3): 305–315.
11. Weinreb RN, Aung T & Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014; 311 (18): 1901–1911. https://doi.org/10.1001/jama.2014.3192
12. Coleman HR, Chan CC, Ferris FL, 3rd, & Chew EY. Age-related macular degeneration. Lancet (London, England). 2008; 372 (9652): 1835–1845. https://doi.org/10.1016/S01406736(08)61759-6
13. Cheng H. Causes of cataract. BMJ (Clinical research ed.), 1989; 298 (6686): 1470–1471. https://doi.org/10.1136/bmj.298.6686.1470
14. Naidoo KS, Leasher J, Bourne RR, Flaxman SR, Jonas JB, Keeffe J, ... & Resnikoff S. Global vision impairment and blindness due to uncorrected refractive error, 1990–2010. Optometry and Vision Science. 2016; 93 (3): 227–234.

15. Honavar SG. The burden of uncorrected refractive error. Indian journal of ophthalmology. 2019; 67 (5): 577–578. https://doi.org/10.4103/ijo.IJO_762_19
16. Conlon R, Saheb H & Ahmed IIK. Glaucoma treatment trends: a review. Canadian Journal of Ophthalmology. 2017; 52 (1): 114–124.
17. Watson PG, Jakeman C, Ozturk M, Barnett MF, Barnett F & Khaw K. The complications of trabeculectomy (a 20-year follow-up). Eye. 1990; 4 (3): 425–438.
18. Allen D & Vasavada A. Cataract and surgery for cataract. BMJ (Clinical research ed.). 2006; 333 (7559); 128–132. https://doi.org/10.1136/bmj.333.7559.128
19. Chan E, Mahroo OA & Spalton DJ. Complications of cataract surgery.Clinical and Experimental Optometry. 2010; 93 (6): 379–389.
20. Schwartz SG, Flynn Jr, HW & Mieler WF. Update on retinal detachment surgery. Current Opinion in Ophthalmology. 2013; 24 (3): 255–261.
21. Cho YK, Park DH & Jeon IC. Medication trends for age-related macular degeneration. International journal of molecular sciences. 2021; 22 (21): 11837.
22. A Journey of STAR-DDS: Anti-VEGF Drug Delivery System for the Eye | NYU Tandon School of Engineering. (n.d.). Retrieved March 23, 2024, from engineering.nyu.edu website:
23. Lusthaus J & Goldberg I. Current management of glaucoma. Medical Journal of Australia. 2019; 210 (4): 180–187.
24. Lee JH, Wang JH, Chen J, Li F, Edwards TL, Hewitt AW & Liu GS. Gene therapy for visual loss: Opportunities and concerns. Progress in retinal and eye research. 2019; 68: 31–53.
25. Mead B, Berry M, Logan A, Scott RA, Leadbeater W & Scheven BA. Stem cell treatment of degenerative eye disease. Stem cell research. 2015; 14 (3): 243–257.
26. Kuriyan AE, Albini TA, Townsend JH, Rodriguez M, Pandya HK, Leonard RE, ... & Goldberg JL. Vision loss after intravitreal injection of autologous "stem cells" for AMD. New England Journal of Medicine. 2017; 376 (11): 1047–1053.
27. Li XJ, Li CY, Bai D & Leng Y. Insights into stem cell therapy for diabetic retinopathy: a bibliometric and visual analysis. Neural regeneration research. 2021; 16 (1): 172–178. https://doi.org/10.4103/1673-5374.286974
28. Trauzettel-Klosinski S. Current methods of visual rehabilitation. Deutsches Arzteblatt international. 2011; 108 (51-52): 871–878. https://doi.org/10.3238/arztebl.2011.0871.
29. Cogan SF. (2017, September). Neural Stimulation and Recording Electrodes. In Electrochemical Society Meeting Abstracts 232 (No. 55, pp. 2294–2294). The Electrochemical Society, Inc..
30. Gonzalez Calle A, Paknahad J, Pollalis D, Kosta P, Thomas B, Tew BY, ... & Humayun M. An extraocular electrical stimulation approach to slow down the progression of retinal degeneration in an animal model. Scientific reports. 2023; 13 (1): 15924.
31. da Cruz L, Dorn JD, Humayun MS, Dagnelie G, Handa J, Barale PO, ... & Argus II Study Group. Five-year safety and performance results from the Argus II retinal prosthesis system clinical trial. Ophthalmology. 2016; 123 (10): 2248–2254.
32. Bloch E, Luo Y & da Cruz L. Advances in retinal prosthesis systems. Therapeutic advances in ophthalmology. 2019; 11: 2515841418817501.
33. Banarji A, Gurunadh VS, Patyal S, Ahluwalia TS, Vats DP & Bhadauria M. Visual prosthesis: Artificial vision. Medical Journal Armed Forces India. 2009; 65 (4): 348–352.
34. Muqit MMK, Le Mer Y, de Koo LO, Holz FG, Sahel JA & Palanker D. Prosthetic Visual Acuity with the PRIMA Subretinal Microchip in Patients with Atrophic Age-Related Macular Degeneration at 4 Years Follow-up. Ophthalmology Science. 2024; 4 (5): 100510.
35. Troyk PR, Bradley D, Bak M, Cogan S, Erickson R, Hu Z, ... & Towle V. (2006, January). Intracortical visual prosthesis research-approach and progress. In 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference (pp. 7376-7379). IEEE.
36. Kaskhedikar GP, Hu Z, Dagnelie G & Troyk PR. (2013, November). Proposed Intracortical vision prosthesis system for phosphene mapping and psychophysical studies. In 2013 6th International IEEE/EMBS Conference on Neural Engineering (NER) (pp. 880-882). IEEE.
37. Schmidt EM, Bak MJ, Hambrecht FT, Kufta CV, O'rourke DK & Vallabhanath P. Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. Brain. 1996; 119 (2): 507–522.
38. Fernández E & Normann RA. CORTIVIS approach for an intracortical visual prostheses. Artificial vision: A clinical guide. 2017: 191–201.
39. Moleirinho S, Whalen AJ, Fried SI & Pezaris JS. The impact of synchronous versus asynchronous electrical stimulation in artificial vision. Journal of Neural Engineering. 2021; 18 (5): 051001.
40. Christie BP, Ashmont KR, House PA & Greger B. Approaches to a cortical vision prosthesis: implications of electrode size and placement. Journal of neural engineering. 2016; 13 (2): 025003.
41. Kirsch AD, Hassin-Baer S, Matthies C, Volkmann J & Steigerwald F. Anodic versus cathodic neurostimulation of the subthalamic nucleus: a randomized-controlled study of acute clinical effects. Parkinsonism & related disorders. 2018; 55: 61–67.
42. Kerkhoff G. Neurovisual rehabilitation: recent developments and future directions. Journal of Neurology, Neurosurgery & Psychiatry. 2000; 68 (6): 691–706.
43. Dagnelie G, Jiang A, Sadeghi R, Barry MP, Stipp K, Towle

VL & Troyk PR. Constructing a phosphene map for the inaugural recipient of the intracortical visual prosthesis (ICVP). Investigative Ophthalmology & Visual Science. 2023; 64 (8): 55205520.
44. Barry MP, Sadeghi R, Towle VL, Stipp K, Grant P, Lane FJ., ... & Troyk PR. Contributed Session III: Characteristics of electrically-induced visual percepts in the first human with the Intracortical Visual Prosthesis. Journal of Vision. 2023; 23 (11): 35–35.
45. Wang HZ & Wong YT. A novel simulation paradigm utilising MRI-derived phosphene maps for cortical prosthetic vision. Journal of Neural Engineering. 2023; 20 (4): 046027.
46. Delbeke J, Oozeer M & Veraart C. Position, size and luminosity of phosphenes generated by direct optic nerve stimulation. Vision research. 2003; 43 (9): 1091–1102.
47. Veraart C, Wanet Defalque MC, Gérard B, Vanlierde A & Delbeke J. Pattern recognition with the optic nerve visual prosthesis. Artificial organs. 2003; 27 (11): 9961004.
48. Bertschinger DR, Beknazar E, Simonutti M, Safran AB, Sahel JA, Rosolen SG, ... & Salzmann J. A review of in vivo animal studies in retinal prosthesis research. Graefe's Archive for Clinical and Experimental Ophthalmology. 2008; 246: 1505–1517.
49. Farnum A & Pelled G. New vision for visual prostheses. Frontiers in neuroscience. 2020; 14: 512184.
50. Schneider KA & Kastner S. Effects of sustained spatial attention in the human lateral geniculate nucleus and superior colliculus. Journal of Neuroscience. 2009; 29 (6): 17841795.
51. Kyada MJ, Killian NJ & Pezaris JS. Thalamic Visual Prosthesis Project.Artificial Vision: A Clinical Guide. 2017; 177-189.
52. Cehajic-Kapetanovic J, Singh MS, Zrenner E & MacLaren RE. Bioengineering strategies for restoring vision. Nature biomedical engineering. 2023; 7 (4): 387–404.
53. Montazeri L, El Zarif N, Trenholm S & Sawan M. Optogenetic stimulation for restoring vision to patients suffering from retinal degenerative diseases : current strategies and future directions. IEEE transactions on biomedical circuits and systems. 2019; 13 (6): 1792–1807.
54. Lee WC, Bonin V, Reed M, Graham BJ, Hood G, Glattfelder K & Reid RC. Anatomy and function of an excitatory network in the visual cortex. Nature. 2016; 532 (7599): 370–374. https://doi.org/10.1038/nature17192.
55. Troyk MJ. Preparation for implantation of an intracortical visual prosthesis in a human: Working towards saturation. Illinois Institute of Technology. 2017.
56. Darrow JJ. Luxturna: FDA documents reveal the value of a costly gene therapy. Drug Discov Today. 2019 Apr; 24 (4): 949–954. doi: 10.1016/j.drudis.2019.01.019. Epub 2019 Jan 31. PMID: 30711576.
57. Winter JO, Cogan SF & Rizzo JF. Retinal prostheses: current challenge sand future outlook. Journal of Biomaterials Science, Polymer Edition. 2007; 18 (8): 1031–1055.
58. Misal US, Joshi SA & Shaikh MM. Delayed recovery from anesthesia: A postgraduate educational review. Anesthesia Essays and Researches. 2016; 10 (2): 164–172.
59. Darrow JJ. Luxturna: FDA documents reveal the value of a costly gene therapy. Drug Discov Today. 2019 Apr; 24 (4): 949–954. doi: 10.1016/j.drudis.2019.01.019. Epub 2019 Jan 31. PMID: 30711576.
60. Yılmaz E. The phenomenon of disability perception in blindness. 2015.
61. Tunde-Ayinmode MF, Akande TM & Ademola-Popoola DS. Psychologica land social adjustment to blindness: Understanding from two groups of blind people in Ilorin, Nigeria. Annals of African medicine. 2011; 10 (2).
62. Salisbury JM & NOMC N. On the duration of sleepshade training in the adjustment to blindness. 2017.
63. Yiu GC, Khanani AM & Pepple KL. Current challenges in gene therapy trials. Retinal Physician. 2023.
64. Shen Y, Campbell RE, Côté DC & Paquet ME. Challenges for therapeutic applications of opsin-based optogenetic tools in humans. Frontiers in neural circuits. 2020; 14: 542693.
65. Caravaca-Rodriguez D, Gaytan SP, Suaning GJ & Barriga-Rivera A. Implications of neural plasticity in retinal prosthesis. Investigative ophthalmology & visual science. 2022; 63 (11): 11.
66. YH Liu, et al. "Assembly Development of a Highly Flexible and Biocompatible Optoelectronic Neural Stimulator for Implantable Retinal Prosthesis," 2021 IEEE 71st Electronic Components and Technology Conference (ECTC), San Diego, CA, USA, 2021, pp. 15381543, doi: 10.1109/ECTC32696.2021.00244.
67. Xiao Y, Wang M, Li Y, Sun Z, Liu Z, He L & Liu R. High-Adhesive Flexible Electrodes and Their Manufacture: A Review. Micromachines. 2021; 12 (12): 1505. https://doi.org/10.3390/mi12121505
68. Troyk PR & ILLINOIS INST OF TECH CHICAGO. Preparation for the Implantation of an Intracortical Visual Prosthesis in a Human. 2013.
69. Schiavone G, Kang X, Fallegger F, Gandar J, Courtine G & Lacour SP. Guidelines to study and develop soft electrode systems for neural stimulation. Neuron. 2020; 108 (2): 238–258.
70. Lacour SP, Courtine G & Guck J. Materials and technologies for soft implantable neuroprostheses. Nature Reviews Materials. 2016; 1 (10): 1–14.
71. Blau A. Prospects for neuroprosthetics: Flexible microelectrode arrays with polymer conductors. Applied Biomedical Engineering. 2011; 83-122.
72. Cho Y, Park S, Lee J & Yu KJ. Emerging materials and technologies with applications in flexible neural implants:

a comprehensive review of current issues with neural devices. Advanced Materials. 2021; 33 (47): 2005786.
73. Hou W, Liao Q, Xie S, Song Y & Qin L. Prospects and challenges of flexible stretchable electrodes for electronics. Coatings. 2022; 12 (5): 558.
74. Wester BA, Lee RH & LaPlaca MC. Development and characterization ofin vivo flexible electrodes compatible with large tissue displacements. Journal of neural engineering. 2009; 6 (2): 024002.
75. Troyk P, et al. "In-vivo tests of a 16-channel implantable wireless neural stimulator," 2015 7th International IEEE/EMBS Conference on Neural Engineering (NER), Montpellier, France. 2015; pp.474–477, doi: 10.1109/NER.2015.7146662.
76. Schaller RR. Moore's law: past, present and future. IEEE spectrum. 1997; 34 (6): 52–59.
77. Wu F, Tian H, Shen Y, et al. Vertical MoS2 transistors with sub-1-nm gate lengths. Nature. 2022; 603: 259–264.