Visual neuroprosthesis: present and future perspectives

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The purpose of this study is to provide an overview of the replacements used in lost vision in the form of the bionic eye, to show their deficiencies and outline other possibilities for non-invasive stimulation of functional areas of the visual cortex.

The review highlights the damage not only to the primary altered cellular structures, but also to all other horizontally and vertically localised structures. Based on the results of a large number of functional magnetic resonance imaging and electrophysiological methods, the authors focus on the pathology of the entire visual pathway in pigmentary retinopathy (PR) and age-related macular degeneration (AMD). This study provides a recent overview of the possible systems used to replace lost vision. These range from stimulation with intraocular implants, through stimulation of the optic nerve and lateral geniculate nucleus to the visual cortex.

The second part deals with the design of image processing technology and its transformation into the form of transcranial stimulation of undamaged parts of the brain, which is protected by a patent.

This is comprehensive overview of the current possibilities of replacement of lost vision and a proposal for a new non-invasive methods of stimulation of functional neurons of the visual cortex.

Key words: functional magnetic resonance imaging, electrophysiological methods, pigmentary retinopathy, age-related macular degeneration, visual neuroprosthesis

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INTRODUCTION

Impaired vision and blindness remain major public health problems worldwide. The World Health Organization estimates that globally there are approximately 253 million visually impaired people: 36 million blind and 217 million had moderate to severe visual impairment in 2015 (ref.[1]).

Blindness caused by eye diseases is also a problem in Europe. According to Fernandez et al., approximately 140 000 blind people in industrial countries could benefit from a bionic eye[2].

The effort to create a visual neuroprosthesis using electronics to replace damaged vision is the logical outcome of the state of the art and will remain the only method of replacing lost vision until there is genetic manipulation.

MOST COMMON OPHTHALMOLOGICAL DISEASES FOR WHICH A BIONIC EYE IS INDICATED

Any retinal nerve cell lesion can damage not only cellular structures located horizontally, but also vertically in the visual pathway. Another important finding resulting from this information as well as from the visual pathway anatomy is that unilateral lesions also cause damage to the contralateral nerve structures[3].

Therefore, it is not possible to predict improvement of visual functions to usable values when implanting a visual neuroprosthesis. It is clear that, despite the damaged visual structures, a non-specific electrical stimulus can be transmitted to the brain, resulting in phosphene, or a flash perceived by the individual.

Because the bionic eye is most often indicated in patients with pigmentary retinopathy (PR) and age-related macular degeneration (AMD), we focus mainly on these two diagnostic groups. Damage of the photoreceptors occurs in both cases. A prerequisite for the effectiveness of the bionic eye is to maintain the integrity of the middle and internal retinal structures, the visual pathway, and the subcortical and cortical centres in the brain.

PR is a disease that primarily damages the rods and cones and the underlying retinal pigment epithelium. The inner nuclear and plexiform layers, ganglion cells and their fibres are subject to degeneration and are replaced by gliotic tissue. These changes may only be visible at a later stage of the disease[4].

Electrophysiological findings of vision show that not only rods but also macular retinal structures, including ganglion cells, are altered in the initial stages of PR. This also results in impairment of the visual nerve and visual cortex in the brain.

These findings of visual pathway damage were also verified by visual pathway tractography[5]. In a male aged 63 years with RP (VARE: 0.2, VALE: 0.3; perimeter indi-

cated a concentric narrowing of the visual fields to 10 or 5 °), when we used functional magnetic resonance imaging (fMRI) even with such "good" visual functions, we did not elicit any voxel activity of the visual cortex. The electrophysiological examination showed a mutually unfavourable response, both ERG and PERG and PVEP (ref.[3]).

Similarly, in a 38-year-old man with Usher syndrome (VARE: 0.5, VALE: 0.3; perimeter indicated a concentric narrowing of the visual fields to 10 or 5 °), we found a significant decrease in activity of fMRI of 950 voxels following right eye stimulation and 290 voxels following left eye stimulation. Values in healthy individuals are 9200 ± 2700 of activated voxels[6].

AMD is a disease that does not cause blindness in a patient, but significantly worsens his central visual acuity. In this disease, damage to the cones also leads to the loss of retinal ganglion cells. Retinal ganglion cell counts have been shown to be significantly lower in AMD than in control eyes. In the wet form of AMD, a 47% decrease in ganglion cells was observed[7].

The fact that even isolated central retinal lesions lead to damage to the visual cortex was demonstrated by fMRI in 10 patients with wet AMD. In this group, there was a significant decrease in voxel activity compared to the control group (P=0.024), Fig. 1 and 2 (ref.[6]).

From these case reports, it is clear that a retinal disorder at the level of photoreceptors (RP, AMD), leads to damage to the visual centres in the brain, most markedly in RP. This disease is most commonly indicated for implantation of the visual neuroprosthesis. Similar destruction occurs in hypertensive glaucoma, where primarily retinal ganglion cells are damaged[3].

VISUAL NEUROPROSTHESES – CURRENT SITUATION

Retinal stimulation

The first report in the literature of a retinal prosthesis was written by Australian engineer Graham Tassicker, who reported the implantation of a photovoltaic system into the suprachoroidal space of a blind volunteer, who perceived "uniform white light" after surgery[8].

Pioneers in the field of retinal prostheses include Alan and Vincent Chow (Optobionics), Eugene de Juan, Mark Humayun, Robert Greenberg, and Jim Weiland (Second Sight Medical Products), Joe Rizzo and John Wyatt (Boston Retinal Implant Project), Eberhart Zrenner (University of Tuebingen) and Rolf Eckmiller (University of Bonn). Their successes led to expanded efforts to develop retinal prostheses and the approval of three devices: Argus (Second Sight, USA), Alpha AMS (Retina Implant, Germany) and IRIS II (Pixium, France) (ref.[9]).

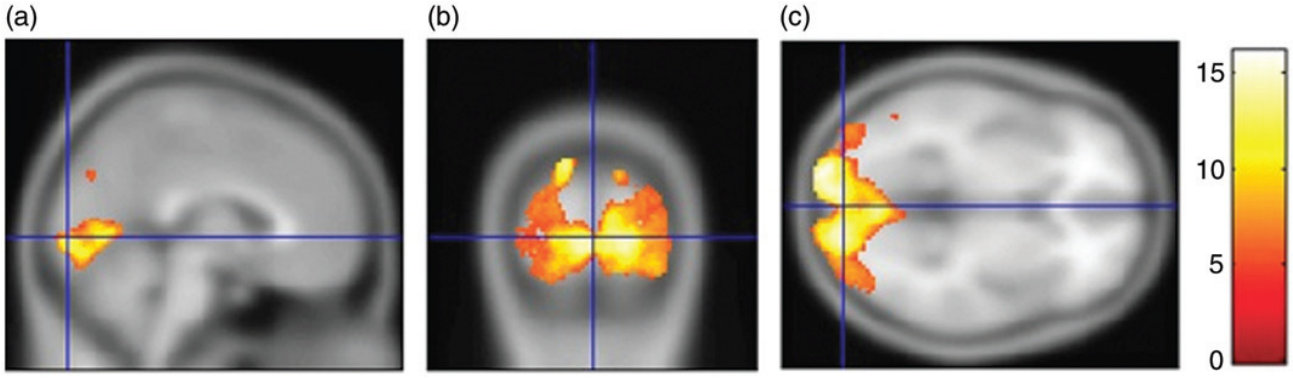

Fig. 1. Brain visual centre activity in a healthy 50-year-old woman. VARE: 1.0, VALE: 1.0 naturally. Sagittal (a), coronal (b) and transverse sections (c) show normal fMRI values of 6 815 voxels after simultaneous stimulation of both eyes (ref.[6]).

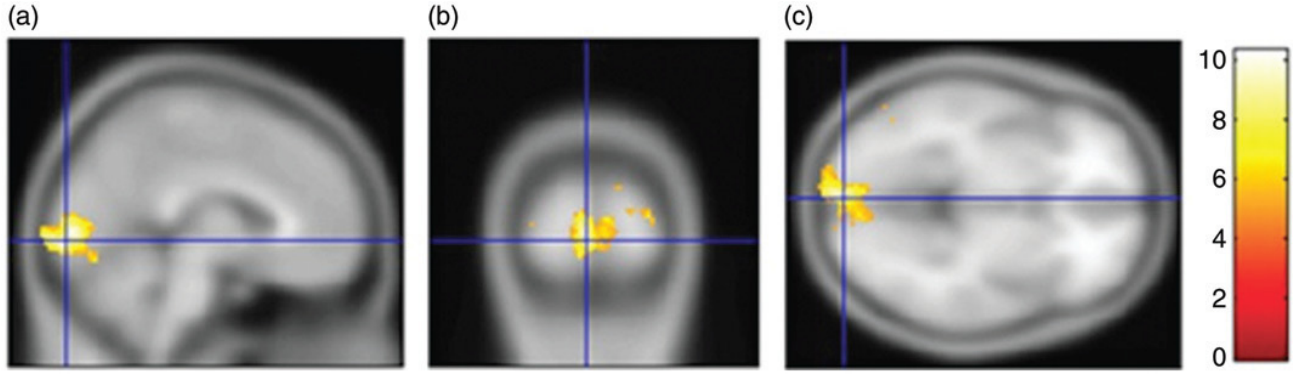

Fig. 2. Brain visual centre activity in a 54-year-old female patient with AMD, VARE: 0.04, VALE: 0.03. Sagittal (a), coronary (b) and transversal section (c) show a significant decrease of the fMRI activity (2 630 voxels, the usual correct threshold P=0.05 with a FWE correction). Both eyes were stimulated simultaneously (ref.[6]).

The system includes a small camera placed in the glasses, which transmits the captured information to the video chip. This video chip translates them into electrical voltage changes and transmits them to a retinal implant consisting of a certain number of electrodes to stimulate retinal cells.

This can be done through direct electrical stimulation of the retina or close to it[10-12].

Instead of a camera, photodiodes built directly into the microchip can also be used[13,14]. Even those require an external source of energy.

In photovoltaic implants, the image is projected on to the retina using incident light, where photodiodes convert the signal into electrical stimulation. The light source can either be natural light (i.e. an image that a person would normally see), or it can be modified and projected on to the retina using infrared wavelengths[14].

In the case of natural light, a direct power supply is required to convert the output signal from the photodiodes into a stimulus pulse. The photodiode system allows for a natural image. In contrast, with a camera-based system, there can be a significant mismatch, because the eye may point in a different direction than the head-mounted camera. This can lead to misdirection, with patients reaching the wrong positions to find an object. This is particularly important, because one of the potential risks of prosthesis implantation is restriction of the recipient's eye movements (either due to the presence of electronic components or due to limitation of extraocular muscle function after surgery) (ref.[9]).

The electrode microchip itself can be implanted epiretinally (on the retina), subretinally (under the retina) or suprachoroidally (above the choroid), or intrasclerally.

Epiretinal chips include the Argus II Retinal Prosthesis System. The chip consists of 60 microelectrodes that cover 20° of the field of view[15].

As of May 2019, this system is no longer in production and Second Sight Medical Products has shifted its focus to cortical implants (ORION). Other epiretinal systems include the Intelligent Retinal Implant System-IRIS II (Pixium Vision), which has also not been commercially produced as of 2018, and Epiret (Univ of Aachen). Future feasibility studies of EPI-RET3 have focused on the development of an exceptionally large electrode array for epiretinal stimulation (VLARS) that covers 37° of the visual field. However, no results from this group have been published since then[16].

The EPI-RET3 differed from the Argus and IRIS implants in that the internal components were completely intraocular. It consisted of a receiving coil and chip placed in an aphakic capsular bag, and a retinal stimulator connected directly to the epiretinal stimulation system. This technology eliminated the need for a physical transscleral cable and instead delivered power or data to the implant, via inductive connections, reducing the risk of complications. As with other epiretinal devices, the EPI-RET3 consisted of an external camera and a visual processor that wirelessly transmitted the calculated spatiotemporal pattern of stimulation pulses to an internal component[17].

These systems can theoretically be disadvantageous, because they exclude the processing of electrical voltage changes in bipolar, horizontal, amacrine and ganglion cells. We deliberately use the term "theoretically" because, as already mentioned, vertical damage occurs in photoreceptor lesions as well. Thus, the complex processing of electrical changes in the retina is insufficient in advanced dystrophies and degenerations.

These devices provide stimulation at the closest point to the target retinal ganglion cells, but there may be arcuate phosphene distortion due to direct stimulation of ganglion cell axons[9].

The **subretinal chip** is located between the pigment epithelium and the photoreceptors. These chips include the Boston Retinal Implant Project (BRIP). The BRIP device is similar in many ways to the Argus II implant design, but is implanted in the subretinal space to eliminate the need for device fixation and to minimise the gliosis that can occur with its intraocular implantation[18].

Others include Artificial silicon retina-ASR (Glen Ellyn, IL, USA) that used only ambient light. However, light was unable to generate sufficient voltage to directly stimulate a considerable number of neurons[19].

The company was dissolved in 2018 and no further published results from this group have been released[20].

Other subretinal implants include Alpha IMS and Alpha AMS (Retina Implant AG, Germany), which used photodiodes for stimulation. The company was dissolved in March 2019 (ref.[13]).

Currently, the Photovoltaic Retinal Implant (PRIMA) system, which was developed for patients with AMD, is used[14].

A report on the implantation in the first patient with AMD was published in January 2022 (ref.[21]).

The disadvantage of this system is that its implantation under the retina causes further iatrogenic damage to the retina. Therefore, the development of these systems was directed to suprachoroidal prostheses.

This localisation does not require transvitreal surgery and is therefore potentially less invasive and more easily accessible for possible repair or replacement. However, the suprachoroidal space is highly vascular and there is a significant risk of bleeding and fibrosis after implantation. In addition, due to the distance from the neurosensory retina, this embodiment appears to require more stimulus power to elicit visual sensations. The suprachoroidal location, by its distance from the retina, poses a risk of greater current propagation, thus reducing spatial resolution.

Suprachoroidal systems include GEN II (Bionic Vision Australia). Similarly to Alpha AMS and cochlear implants, this system involves dissection of the temporal muscle to connect the percutaneous connector to the bone. From there, the connecting wire is tunnelled into the orbit and into the suprachoroidal space[11,22].

Like other neuroprostheses, this device is tied to an external power source.

Another suprachoroidal system is the STS system, whose electrodes are implanted intrasclerally. The system

operates on a similar principle to the GEN II, except that the current STS consists of a "3D" (three-dimensional) array of 49 microelectrodes, with electrodes that protrude 0.3 mm from the array and are embedded in a 6×5 mm scleral pocket[12].

Considering that the average number of cones in the foveola is 199 000/mm^2 (ref.[23]) and the number of stimulating electrodes is from 49 for STS intrascleral systems (on an area of 5.7×4.6 mm) to 5 000 for ASR (on an area of 2 mm) subretinal systems, this is a negligible number compared to the number of photoreceptors[9].

However, it can be assumed that substantial improvements can be made over time and one can well imagine more powerful chips. In future, these may include processors that efficiently connect the appropriate electrical signals to the activated links, while the transmission of image information and power could be wireless.

Based on the pathology of individual retinal processes, it is not possible to deliver an adequate amount of action potentials to the visual cortex, even if the most powerful chips were used.

From a medical point of view, these systems have the limitation that once any neural disturbance in the visual analyser occurs after stabilisation of binocular function, the process is irreversible and progressive. As mentioned above, damage occurs not only to the primary structure but to the entire visual pathway, including the visual cortex of the brain. Therefore, stimulation on any of the structures implemented so far does not and cannot have the desired functional outcome, except for phosphenes. Another limitation is the indication of visual function pages. This means that there will certainly not be surgery for patients who have relatively good visual function.

Neural stimulation

Similarly, ganglion cell axons can be stimulated by electrodes placed in the cuff surrounding the optic nerve[24] or injected directly into the nerve itself[25,26].

The lateral geniculate nucleus (LGN) can also be stimulated and this stimulation can induce phosphenes[27,28].

Both optic nerve stimulation and CGL require challenging surgical intervention. Therefore, these interventions were abandoned.

The visual cortex was one of the first sites where possible visual prostheses were considered.

The first studies by the German ophthalmologist Foester in the 1930s confirmed that direct electrical stimulation of the visual cortex enabled a completely blind person to perceive light spots[29].

Subsequent work by Krause and Schum then showed that it can be induced even in people who have long-term vision loss. It was important that phosphenes from a fixed point on the cerebral cortex were localised to a corresponding point in the visual space and that phosphenes could be elicited even in a blind patient[30].

Thirty years later, Brindley and Lewi recorded similar findings by irritating the cerebral cortex[31]. Similar findings were also recorded by Dobelle and Mladejovsky[32].

The first visual cortical prosthesis was developed 30 years later[33].

However, these early cortical implants had poor resolution, were particularly challenging to operate, and often led to medical or psychological complications[34,35].

Also of significant importance in cortical neuroprostheses was the study by Piedade et al., who developed a wireless connection between an external camera, a processor, and an intracranial unit to stimulate cortical cells implanted as electrodes in the visual cortex[36].

As noted for retinal neuroprostheses, Second Sight Medical Products (Argus II) has developed the Orion cortical prosthesis. This is where the principle of wireless connection is used[36].

In 2020, the American neurosurgeon Pouratian reported on his first experience with implantation of the Orion cortical prosthesis. When examining stimulus paradigms, three out of the six patients experienced neurological problems. There were no system failures during the annual monitoring. All subjects perceived phosphenes during this time and reported functional improvements. Although this study included only a small number of patients, the results are encouraging. As the author himself states, "the prosthesis provides artificial vision but does not restore vision"[37].

The authors also published the functional results of the Orion system in another paper, where they were able to induce phosphenes of different geometric shapes (letters M, N, U, W, etc.) using electrodes implanted in various locations that dynamically stimulated the visual cortex[38].

The disadvantage of the Orion prosthesis is that it stimulates only a small part of the visual cortex (V1, V2).

The main visual decoding processes take place in the higher regions (V4 and V5) (ref.[39-41]).

Connections to V5 also come directly from the lateral geniculate body. That is, they avoid the V1 region[42,43].

Another disadvantage of the Orion prosthesis is that, due to the microchip placed intracranially, the patient cannot be examined by magnetic resonance imaging in indicated cases.

Systems using electrode installation in the cerebral cortex and its stimulation by electrical signals are based on the analogy with a cochlear endoprosthesis. The problem, however, is fundamental here. The transmission of sound replacement data requires (from a technical point of view) a relatively small amount of data (typically units up to tens of kB/s), brain stimulation is only at a single defined location in the auditory centre, and the number of electrodes is small. From the point of view of image processing, the logically assumed number of electrodes is several orders of magnitude higher. This, together with the need for surgery, brings about intolerable health risks, and moreover, with an uncertain outcome. Nevertheless, earlier experiments showed that this path leads to the implementation of possible simple images to date, in the form of phosphenes. However, it will still be necessary to

do a lot of work on the type of electrical signals and their possible modulation.

All these systems have one, quite major drawback. It is not possible to use the option of MRI examination. Examination with a strong magnetic field leads to damage to the stimulation device and thus the stimulated structure (eye, optic nerve, subcortical and cortical headquarters in the brain). In addition, if the electrodes are installed in the cerebral cortex, it can put the patient at serious risk.

Other valuable information for cortical stimulations is that the processing of image information does not occur only in a single, precisely defined, area of the brain, but according to the nature of the image scene, in various parts of the visual cortex.

For completeness, we also present a non-invasive option for stimulating the visual cortex in patients who had phosphenes induced into the visual cortex using focused ultrasound[44,45].

Similar experiments have been conducted with retinal stimulation[46.]

The disadvantages of these systems are the size of the modulation area, in the order of centimetres, and the temperature when focusing on a given area.

For the sake of completeness, let us also mention transcranial magnetic field stimulation (which is performed as a treatment method for epilepsy, Parkinson's disease, recurrent vascular events, etc.) (ref.[47,48]), and stimulation by alternating electric current[49].

Visual neuroprostheses and electronics options

From the above overview, it is clear that existing electronic vision replacement systems are implemented in two ways:

- Replacement of the retina, or those cells that are damaged, and subsequent connection to the existing nerve connections to the brain's vision centres.
- If the nerve connection between the eye and the brain is not functional, the replacement is solved by implanting electrodes into the cortex.

Stimulation of the cerebral cortex using radio waves

However, there is another option, which is the application of electromagnetic signals without surgical intervention. Since approximately 1969, attempts have been made to create a neural interface to create a brain-computer interface, with the aim of linking the brain to a computer and thus allowing the brain to control other devices (e.g. an artificial limb). In principle, the electroencephalogram signals Alpha (8–13 Hz), Beta (14–30 Hz), Theta (4–7.5 Hz) and Delta (0.5–4 Hz) are sensed. However, this process can also be reversed. Electromagnetic waves at an extremely low energy level, where higher power is not absorbed, can induce electrochemical changes in stimulated neurons. No harmful effects on DNA, cell membranes, enzymes or other parts of cells have yet been demonstrated[50].

For hygienic standards, the measure is usually the density of the incident power p [W/m^2], actual energy in the tissue (Specific Absorption Rate) [W/kg] or absorbed power per kg of tissue ARD (Absorption Rate Density) [W/m3] and the electric field strength E [V/m], as well as the magnetic field strength: H [A/m] and many other parameters[51].

It can be assumed that this stimulation will lead to neuroplasticity in the visual centres and improvement of the surrounding directly unstimulated areas of the visual cortex.

Use of this technology raises a number of questions:

- What radio frequencies can be used to stimulate the cerebral cortex?
- Is it advisable to use some type of modulation, and if so, which ones (analogue, digital, amplitude, frequency)?
- How are the areas in the brain, which are to be stimulated, selected and delineated?
- Should the stimulation be point or area? Actually 2D or 3D?
- Should one area or several cortical areas be stimulated at the same time?
- How is it determined (depending on the image) which area to stimulate?

On the contrary, some stimulation parameters are already clearly defined – the amount of stimulation energy must not exceed the value defined by the health standard[52,53].

Therefore, we designed and developed a completely new type of stimulation called:

"Unit for stimulating the cells of the visual cortex in severe visual disturbances."

In principle, this is a camera whose signal is processed (microprocessor-controlled video chip, possibly supported by artificial intelligence detecting the character of the image) in the form of a radio frequency and sent to the brain. The assembly is placed in a stabilised position relative to the brain. This position is defined and calibrated, using MRI and skull markers to determine the positions at which stimulation will occur.

For each potential patient, it will be necessary firstly to identify undamaged areas of the visual cortex, using fMRI (Fig. 1 and 2). It is possible that we will not prove them with the current methodology. However, this does not mean that the suprastriatic regions V4 and V5 will be non-functional in this case. In both cases, the most crucial step follows, and that is the direct transcranial transmission of image information to the brain (without implanted electrodes), using appropriate frequencies and appropriate modulation of stimulating neurons. A combination of signals from the entire electromagnetic spectrum is used for stimulation. In the first stage, frequencies of units up to hundreds of GHz are used. Finding the correct range and modulation is a priority part of implementation. The stimulation itself will be point-focused by the antenna assembly of the transmitter unit, so that it will be possible to shape it, sweep it, and focus the target area in both 2D and 3D.

On this basis, it will be possible to identify other possible parallel or superior relationships between the areas of the visual cortex, and also to stimulate these, or to use

even more complex images. The corresponding stimulation will be emitted by antennas. Here, phase-controlled antenna modules will be used, enabling, together with gyroscopic position stabilisation, precise signal routing. Position stabilisation also has a number of active and passive sensors, enabling the maintenance of antenna radiation even during head movements in space.

An important part is the possibility of communication of LAN and WAN modules with the control (tablet or mobile phone) and especially with the transmission of image information to a remote centre with powerful computing technology, enabling the determination of the nature of the scanned image and thus focusing stimulation on the correct areas of the brain. It can be assumed that, in the near future, parts of the determination of the character of the captured scene will probably take over the elements of artificial intelligence directly in the camera.

The new method of stimulation is already covered by valid national patent No. 309083 (Unit for non-invasive stimulation of cerebral cortex cells in severe visual disturbances) and utility model No. 34195 (A unit for stimulating the cells of the visual cortex in severe visual disturbances) – see www.upv.cz International Patent Application No. WO2021250596A1 (UNIT FOR NON-INVASIVE STIMULATION OF THE VISUAL CORTEX CELLS IN SEVERE VISUAL IMPAIRMENT) is at an advanced stage of patent prosecution – see https://worldwide.espacenet.com/.

CONCLUSION

The study provides a comprehensive overview of the current possibilities of replacement of lost vision and a proposal for a new non-invasive method of stimulation of neurons of the visual cortex.

Search strategy and selection criteria

The aim of the work was to create a complete review containing the issue of vision replacement according to the available literature material from the PubMed database.

Author contributions: JL: wrote the first part of the manuscript; JC: wrote the second part of the manuscript; JR, KH: performed the final revision of the manuscript. All authors participated in the overall editing and control of the manuscript. All authors participated in Patent No. 2020-337.

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