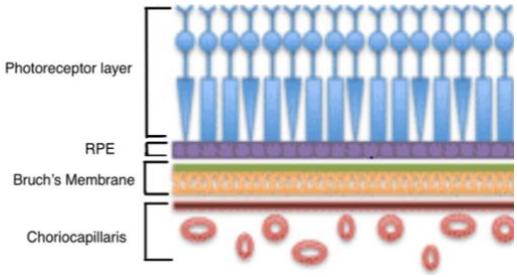
Hannah Xing, Question 3, Medicine. Word Count: 2,323

Looking to the future. Will stem cell therapies be outpaced by machine-brain interfaces for the treatment of retinal disease?

Introduction:
Currently, there is no comprehensive cure for retinal diseases, however they are one of the leading causes of sight loss globally[1]. These diseases often lead to irreversible sight loss or blindness, which can be linked to the development of feelings such as anxiety, self-isolation and reduced quality of life. The main types of retinal disease include: glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy, which affect around 280 million people worldwide[2]. In the UK, the number of people living with sight loss is predicted to double by 2050 from 2 million to 4.1 million people[3].

The chance of having a retinal disease increases with age[4], and while it is not yet possible to completely treat these diseases, it is possible to slow the progression of the disease by taking vitamins or medication, non-invasive procedures on the eye or using electronic aids to gain greater independence of mobility. However, as the population of many countries are ageing[5], and life expectancy is predicted to increase across the world, it becomes increasingly important to develop more permanent treatments for sight loss, to reduce the social and economic loss for individuals suffering from blindness.

How the retina is damaged:
The retina is made up of many complex specialised cells, each vital to the function of the eye. They allow us to perceive the world around us by sending electrical signals to the brain via the optic nerve.



Retinal diseases usually affect neural cells within the eye, such as photoreceptors which process colour and light, retinal ganglion cells which relay information to the brain and the retinal pigment epithelium (RPE), which acts as a selective barrier and a regulator for light coming into the eye[6]. Damage to these cells will affect our vision greatly, and while retinal diseases can be due to a range of reasons, such as age, diet, exercise or genetic predisposition to the disease, the root cause of visual impairment is the loss or damage of retinal neurones which cannot proliferate naturally within the adult eye.[7] While the eye does contain retinal stem cells (known as Müller glial cells), they cannot replicate in humans and are currently being researched for their properties to regenerate retinal cells in fish[8].

Different types of treatment:
Retinal diseases have a wide range of aetiologies and thus affect many different types of cell, this means that developing a general treatment for each type of disease would be challenging due to the vast multitude of ways that the disease can be expressed. Therefore, there is a need for multiple different types of treatment. Stem cell therapy, gene therapy and optogenetics, which use biological procedures to help heal retinal cells, and brain machine interfaces, which uses technology to help bypass some of the systems in the eye to deliver an image directly to the brain are currently being researched for the treatment of retinal diseases[9].

Selecting a treatment:
Selecting a suitable treatment for a retinal diseases often depends on the progression and severity of the condition, as well as the types of cells affected by the disease. To better explain and compare the different types of treatment for retinal diseases, the following will briefly describe

two of the most common retinal diseases, that progress in similar ways, but have different outcomes.

Age-related macular degeneration (AMD) is present in around 200 million people worldwide. The progression of the condition is classified into early, intermediate and late stage AMD, however the condition does not often lead to complete sight loss. The disease presents itself as the thinning of Bruch's membrane and the deterioration of retinal pigment epithelial cells in the macula. Damage to the retinal epithelium can cause severe impairment to the function of the photoreceptors in the macula, as the macula has the highest concentration of photoreceptors, which process light and colour[9]. Most individuals with dry AMD (the most common form of the disease) have very few symptoms initially, which may then develop into more serious outcomes. This is different to wet AMD where severe sight loss can occur in days. Nevertheless, most patients with the condition lose their central vision as opposed to becoming completely blind.

Glaucoma also has few symptoms initially, but unlike other retinal diseases, it can lead to complete blindness in around 15% of the 80 million people who have the condition[10,4]. Like retinitis pigmentosa, and AMD, it can be hereditary, however, the cause of the blindness is believed to stem from pressure within the eye, due to a build up of vitreous fluid, which damages the optic nerve[12].The condition can be slowed with treatments such as eye drops and laser surgery, however these procedures cannot recover damaged retinal cells.

As shown by the two diseases above, working vision is achieved through the coordination of many different cells within the retina, therefore, different diseases will likely require different treatments as they affect different cells.

Stem cell therapy:
Stem cells are undifferentiated cells which have the ability to develop into a range of different cells and divide indefinitely[15] when placed under the right conditions. They can be programmed to develop into retinal cells and replace degraded cells within the retina. Injection or implantation of stem cells can also prevent the further deterioration of other retinal cells through the secretion of neurotrophic factors (for support, growth, differentiation and survival of neurones)[16], which means that the condition can be maintained and further progression of the diseases can be prevented for a short period of time.

There are two different categories of natural stem cells: embryonic stem cells, which are pluripotent and can divide into all 220 cells within the body, and adult stem cells, which are multipotent as they can only divide into limited types of cells[17]. However, in 2006, induced pluripotent cells were discovered[18], which meant that somatic cells (normal body cells) could become pluripotent stem cells through genetic reprogramming. This expanded the range of stem cells that could potentially be used to treat retinal diseases, providing a larger group of cells that could be researched and used in stem cell therapy. Recently, retinal stem cells called Müller glial cells have been researched for their property to differentiate into photoreceptors within the eye in fish and other amphibians.

Specifically, mesenchymal stem cells (MSCs) are a popular area of research due to the wide range of sources they can originate from, and the ability to differentiate into many different types of cell. They display the typical stem cells features, such as secretion of neurotrophic factors and self-renewal, however they can also inhibit inflammation in the eye[16]. Most stem cells that do not originate from the patient themselves are often allogenic and therefore there is the risk of

immune rejection. While the eye is considered to be an immune privileged area, as there are very few white blood cells to reduce the possibility of inflammation, this privilege is often compromised when the patient has a retinal disease[29]. Therefore, autologous stem cells such as MSCs and induced pluripotent stem cells could decrease the risk of rejection.

Stem cells can be delivered to the eye either via an intravitreal injection or by transplanting a graft onto the retinal layer. Intravitreal injects are noninvasive and do not require specialised tools, but the stem cells do not proliferate well when injected without a scaffold and often leak out of the eye with vitreous fluid[27]. However, developing a scaffold material that will integrate well with the retina is challenging. Nevertheless, in 2018, Moorfields Eye Hospital London transplanted a small patch of retinal pigment epithelium cells, grown from embryonic stem cells and mounted on a synthetic membrane into the retina of a patient with wet AMD. This surgery is currently being considered for wet and early-stage dry AMD and is one out of the many clinical trials that have taken place, where the patients with AMD have shown long term improvement in their sight[24].

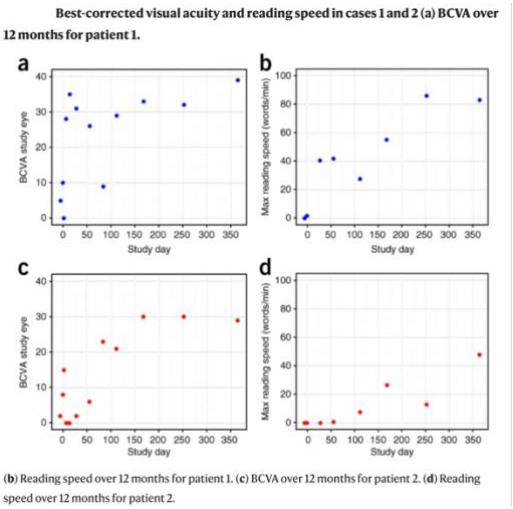


Fig 2. (da Cruz, L., Fynes, et. al, 2018)

Brain machine interfaces(BMIs)

Artistic interpretation of a retinal implant for AMD, Lucy Burscough, Central Manchester University Hospital NHS Foundation Trust

Unlike stem cell therapy brain machine interfaces cannot repair or replace any damaged cells within the retina. Instead they provide an alternate pathway for visual signals from the outside world to pass into the brain. Brain machine interfaces use bionic prosthesis implanted within the retina or directly onto the visual cortex to stimulate the remaining functional retinal cells to produce a basic pattern of light, for example using infrared signals to stimulate the remaining healthy photoreceptors using a camera-computer system and electrode array. This produces a phenomenon called phosphenes, which are flashes of light that can be perceived when the visual cortex is electrically stimulated[19]. Brain machine interfaces such as the Utah array bypass the eye entirely, therefore removing the need for a functioning optic nerve, allowing for a wider range of retinal diseases where there are very few functional retinal cells, or where the optic nerve has been irreversible damaged, such as in glaucoma, to be treated[20].

Currently, the standard number of electrodes in brain machine interfaces range from 60-100[21]. The Argus II implant, which has been approved for clinical trials in the UK contains 60 electrodes. This provides a very rudimentary image of flashing lights in a recognisable pattern, allowing patients to identify letters and boundaries between large objects. The interface requires hours of rehabilitation to use. The company have proposed increasing the electrode array to 240 electrodes in the future, however, this would still provide very rudimentary sight compared to the millions of retinal cells in a healthy eye.

Clinical trials for bionic prosthesis are limited to individuals who have ‘profound sight loss’ and are suffering from late stage retinitis pigmentosa. The conclusion of the trial conducted by NHS

England stated that the implantation of Argus II retinal prosthesis as a routine treatment was supported by sufficient evidence, however, all participants in the trial initially performed better with the prothesis in visual tests than without it. Of the 30 people part of the trial, 97% were able to do simple tasks and after 3 years, 65% of the 23 trial patients gave 'positive' or 'mildly positive' ratings for the implant[21].

Comparison of therapies:
Most retinal diseases are progressive, and symptoms such as sight loss or pain do not appear until the later stages of the disease, therefore treatments should be adaptive. Over time, the remaining healthy cells within the retina will also degrade. This would challenge the success of retinal prothesis in situations where the retina is still changing, as the visual ability of the patient may change and electrode implants cannot integrate naturally into the systems of the eye, and cannot adapt to changes in the microenvironment of the eye. On the other hand, stem cells are much more flexible and have been shown to be able to not only replace damaged cells but also maintain the surrounding cells[15]. Pre-clinical and clinical trials have shown that, with suitable conditions and reprogramming, stem cells can integrate well into the retinal layer when mounted on a scaffold within the eye.[24]

There are multiple different types of stem cells such as mesenchymal stem cells (MSCs), embryonic stem cells, retinal progenitor cells (RPE) and induced pluripotent cells (iPSCs), each with different properties. Stem cells are able to adapt to their environment and can proliferate due to having properties of self-renewal that allow it to multiply within the human body. Unfortunately, ability can cause the formation of teratomas, which are tumours that develop from injecting undifferentiated stem cells, however this side effect is mostly expressed in undifferentiated embryonic stem cells, and no tumour formation has been observed in embryonic stem cell or mesenchymal stem cell derived RPE cells [15,29].

Brain machine interfaces do not induce tumour formation, however, implantation of the device within the retina has been observed to cause inflammation and subsequent death of the surrounding retinal cells[15]. Therefore, brain machine interfaces are only suitable for people with severe and long term sight loss. Additionally, brain machine interfaces are also unable to self-regulate and renew itself, creating the need for specialist maintenance and upgrades. As the implant is a specialised device, few medical staff will understand how best to maintain them, therefore, a consistent and reliable source of help is required for patients with the implant. However, in 2020, Second Sight (the company that manufactures Argus II implants) became bankrupt, preventing individuals with the transplant from accessing information and specialist care, despite selling the technology and rehabilitation treatment in America for $497,000.

In conclusion:
Brain machine interfaces are not likely to outpace stem cell therapy, as they not suitable for people that have early retinal disease, do not appear to be able to reach the level of visual acuity that stem cells can and the companies that research and manufacture the implants do not appear to be economically sustainable. Stem cells, on the other hand, offer the opportunity to maintain the situation of retinal cells in the eye and prevent further degradation of retinal neurones, and is therefore more suitable for the majority of people who have early stage retinal diseases.

As most people with retinal diseases do not have severe sight loss from late stage retinal diseases, brain machine interfaces will not be their first treatment option, as there is the risk of the implants damaging their vision further. Nevertheless it provides hope and a chance for independence for

those who have been blind for a long period of time, or those who have late stage retinal diseases, with no other treatment options. For now, brain machine interfaces could provide an essential visual lifeline, however pixelated for those who cannot currently benefit from stem cell therapies.

More clinical trials must take place for both BMIs and stem cell therapy in order to create a safe and effective treatment, as most research uses pre-clinical animal trials. However, due to the increasing number of people in developed countries that will potentially develop retinal diseases such as AMD, there may be more urgency to develop a treatment which can adapt to the many different individuals with the disease, as each eye is different.

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