Introduction

The selected telegraph article for group review claims the technique of genetically modifying neurons in the brain to become light sensitive can provide revolutionary treatments to control sleep disorders, epilepsy, psychiatric illnesses such as Alzheimer's disease, depression, bipolar, schizophrenia and Parkinson's disease. Other claims made are to create new memories, the ability to control behavior, the ability to alleviate pain and/or restore movement in spinal cord injuries and restore sight in the case of a
damaged retina. This paper investigates the technique of optogenetics and the current research to support the claims made in the article. This particular article appealed to the group because of the wide scope of new neuroscientific treatments potentially offered by optogenetics. Optogenetics is a technique that utilizes the principles of gene therapy to compensate for the loss of a function by targeting DNA. The process can be best broken down into 5 procedural steps as shown in figure 1.

**Genetic Construct (step 1)**
The process of the technique begins by piecing together a genetic construct comprising of a promoter sequence and a gene. Channelrhodopsin (ChR) or Halorhodopsin (NpHR) are two of the most commonly used genes in coding light-sensitive proteins into target cells. In the presence of blue light (wavelength 470 nm) ChR undergoes a change to allow the influx of sodium Na+ ions to depolarize the cell, effectively turning it on. Whereas in the case of NpHR the cell is effectively turned off by the presence of yellow light (wavelength 580 nm) in allowing chloride Cl- ions to hyperpolarize the cell. (Fig-2) (G,N. et al., 2013).

**Delivery of gene to target cell (step 2 and 3)**
There are three main methods for delivery of genes coding for light sensitive proteins into target cells. They consist of transfection, transgenic animal lines and the most popular method viral transduction. With the use of viral vectors precise cells can be targeted in using a specific promoter delivered by a location specific injection. (fig-3) (Tonnesen, 2013).

**Delivery of light to target cell (step 4 and 5)**
The delivery of light in vivo to stimulate the target cell is commonly done by a laser light coupled to optical fibres guided through a cannula to the transduced tissue. (fig-4) (Bernstein et al., 2013).

**Neuroscientific Context**

**Epilepsy Treatment**
Epilepsy is a chronic neurological disorder which is described as the onset of recurrent and unpredictable seizures which is triggered by the increase in electrical activity in the neurons of the brain. In most cases, the cause of epilepsy has not been identified but it has been associated with factors such as brain trauma, stroke, cancer, drug and alcohol misuse and high fever in children.
Temporal lobe epilepsy is one of the most common types of epilepsy affecting adults. Current treatments for temporal lobe epilepsy caused major concerns due to negative side effects and this is why it is important to consider other forms of treatment such as optogenetics. Armstrong and colleagues (2013) have suggested arresting the onset of spontaneous seizures using optogenetics in a mouse model having temporal lobe epilepsy. They discovered that optogenetics activates GABAergic cells in the hippocampus which prevents the occurrence of seizures due to the exposure of light. They pointed out that temporal lobe seizures can be detected and prevented by controlling specific populations of cells in a spatially constrained manner using this technique (Armstrong et al., 2013). Therefore clinical approaches for the treatment of epilepsy could be developed further using the concepts of optogenetics but the side effects of this treatment will be unknown till it has been tested on human epileptic brains.

**Treatment for Psychiatric illnesses**

**Alzheimer's Disease**
Alzheimer's Disease (AD) is a disease that occurs as a result of the deterioration of the brain. It is the most common form of memory loss in humans and occurs as a result of loss of synaptic activity in the brain. Optogenetics has enabled researchers to use light activation proteins such as photoactivatable Rac which can be activated in AD brains of animal models. These proteins help to trigger the reorganisation of actin in dendritic spines in AD brains preventing the loss of synapses. Zahedi and colleagues (2012) confirmed that this protein could help prevent the loss of synapses improving electrical impulse conduction in Alzheimer's brains bringing us closer to helping patients with Alzheimer's. This has not been tested on human AD brain.

**Depression and Bipolar disorder**
Depression is a mental disorder that is characterized by social withdrawal and low levels of pleasure seeking behaviour. Bipolar disorder is characterized by alternation between depression and mania. Research has shown that Depressive mice become resilient after optogenetics was used to control their midbrain dopamine neurons (Tye et al., 2012). This needs to be investigated in humans.

**Schizophrenia**
Schizophrenia is a mental disorder where one of the main concerns is errors in thinking and errors in prediction. When the brain predicts or expects a certain response to occur as a result of a particular stimulus and if this response is different to what was expected to happen a prediction error occurs. This type of error helps people learn and respond differently improving their learning. The release of dopamine is said to be involved in this process. This particular process of release of dopamine and learning of prediction errors is malfunctioned in a schizophrenic brain (Steinberg et al., 2013). Steinberg and colleagues (2013) discovered that when the dopamine neurons are stimulated at a particular time using optogenetic stimulation, the learning of the prediction errors could be altered with a long lasting effect on reward seeking behaviour thereby improving prediction error learning. This model has yet to be applied to a human Schizophrenic brain.

**Parkinson's disease**
Parkinson's disease is a degenerative disease of the central nervous system where a major implication is impaired motor functions. The Neural Circuits of the basal ganglia of the brain is important for motor action selection and motor planning. Kravitez and colleagues (2010) used the concept of optogenetics to excite and inhibit Basal ganglia pathways which increased or decreased freezing and locomotion. The application of optogenetics on mice with Parkinson's disease had salvaged deficits in their freezing and locomotive functions. This suggests that activation of the basal ganglia pathways using
optogenetics could directly enhance motor functions in brains with Parkinson's disease.

**Memory**

Consolidation of long-term memories involves the hippocampus and the neocortex in a two-step process. While the hippocampus is essential in initial memory formation, it is not used in recall after memories are consolidated. In particular the hippocampal CA1 excitatory neuron is theorised to have a role in remote memory. Goshen et al. (2011) optogenetically stimulated this neuron in mice. Green light - which is inhibitory - was continuously applied while the mice were fear conditioned. When later tested, the mice were shown to have a disrupted contextual fear memory. These same mice, when retrained without optogenetic interference displayed intact recall ability.

When these mice with normal fear responses were retested the next day with inhibitory green light, the mice again displayed impaired recall. It was concluded that immediate inhibition of hippocampal CA1 neurons was also able to modulate memory formation. This demonstrated that photoactivation of neurons is able to inhibit both acquisition and retrieval of contextual fear memories (Goshen et al., 2011).

Other studies suggest that fear memory recall is context specific where photoactivation of channelrhodopsin-2 in hippocampal dentate gyrus neurons, associated with fear conditioning, did not evoke freezing in mice if the training phase was completed in a different context to the test phase (Liu et al., 2012). Nonetheless, it is uncertain whether fear memory retrieval is context specific as observed by Liu et al. (2012) where freezing increased when this population of cells was stimulated in mice tested in a different context to the learning phase, indicating that fear memory was retained and learning was achieved.

**The ability to control behaviour**

Through optogenetic tools, selectively activating pathways to release specific neurotransmitters has allowed researchers to manipulate behaviour in animals (Stuber et al., 2012). Behaviour conditioning has been linked to the firing of ventral tegmental area (VTA) dopaminergic (DA) neurons, releasing dopamine in the nucleus accumbens (Tsai et al., 2009). A study by van Zessen et al. (2012) has found that VTA GABAergic inhibition of VTA DA neurons in a reward-seeking task was able to disrupt unconditioned behaviour i.e. consumption of the reward, sucrose. Not limited to behaviour conditioning, photostimulation of the ventromedial hypothalamus by Lin et al. (2011) has induced aggression in mice towards a multitude of subjects regardless of origin, including inanimate objects such as gloves. In addition, inhibition of VTA DA neurons in genetically modified mice through optogenetics caused behavioural changes. These mice exhibited depression-like symptoms (Tye et al., 2012). However, this was contradicted by Chaudhury et al. (2013), where persistent depression-like behaviour in mice was induced by the phasic stimulation of VTA DA neurons.

**Spinal cord injuries**

Nerves that control the upper body, neck, head and the diaphragm are contained within a cervical region of the spinal cord. Damage to this region leads to dysfunction of the diaphragmatic and respiratory motor activity because it causes paralysis of the muscles that are involved in breathing.
Alilain and Silver (2009) investigated whether optogenetics could restore function of diaphragmatic muscles needed for respiration in rats that had cervical spinal cord injury. They injected a modified Sindbis virus containing the gene which encoded the green fluorescent protein and channel rhodopsin in the motor neurons of the spinal cord. These motor neurons are involved in innervating the diaphragm that regulates breathing. Photostimulation of the motor neurons that had the injected virus induced a form of synaptic plasticity of crossed pathways in the cervical spinal region which had restored and generated respiratory function in the muscles of the diaphragm. They suggested that after further investigation in humans and with the correct manipulation of the spinal neuronal circuits, scientists may be able to recover lost functions such as bladder and bowel movement due to spinal cord injuries and even the possibility of walking again (Alilain and Sliver, 2009).

**Restore sight**

The retina contains light-sensitive proteins and given the nature of optogenetics i.e. photostimulation of proteins e.g. ChR2 and NpHR, many studies have explored whether optogenetics will be able to provide a solution to retinal diseases such as retinitis pigmentosa or photoreceptor degeneration. G et al. (2013) demonstrated that long-term stability of ChR2 expression was achieved in vivo, with restoration of photosensitivity in almost the whole lifespan (64 weeks) of murine models. Stimulation of transduced tissue using blue light mediated depolarization and subsequent action potential in retinal ON bipolar cells, generating visual signals sufficient for animals to perform optomotor tasks. However, there is little evidence to suggest that optogenetics would be able to regulate OFF bipolar cell response (Chen et al., 2012).

**Induce Sleep in Monkeys**

The article claims that researchers were able to send non-human primates to sleep using optogenetics, “hoping to develop this technique further for use in humans”. However, there is little evidence to suggest that monkeys can be sent to sleep using this method despite successful trials run on mice that changed their behaviour and sleeping patterns (see Memory and The Ability to Control Behaviour). On the other hand, in non-human primates studies, researchers have optogenetically stimulated the cortical neurons of monkeys. These monkeys were to complete a guided task which required them to make rapid eye movements. It was found that these saccades were slowed (Gerits et al., 2012; Cavanaugh et al., 2012).

**Critical Analysis**

The article was published on The Telegraph’s website and has some 8.7 million readers a month (Marshall, 2013; Telegraph Media Group 2013), ranking it in the top three most viewed British news websites. The author, Richard Gray, graduated from the University of Edinburgh with a BSc in Biochemistry (Gray, 2013) and was science correspondent at The Sunday Telegraph for six years when the article was published.

The innovative technology of optogenetics is introduced in the article to the general public and conveys many neuroscientific concepts quite clearly for people with little or no scientific background. The uses and treatments were not deeply discussed, with only general references to research institutes and no cited sources for each of the claims made. Even without specific references, the group was able to find reputable sources to give some merit to the promises of new treatments for epilepsy, several psychiatric illnesses, the ability to control behaviour, fear memory recall, treatments for spinal cord injury and
restoring sight. However, primate studies have proved more complex, and there is little evidence that
monkeys have been optogenetically put to sleep, but sleep pattern studies in mice provided some merit to
the claim.

The technology is presented in the article as significantly more developed, and more dangerous than
scientific literature would suggest. Gray's main concerns, while valid, play more on emotions than any
documented failings. Gray writes: “cells in the brain itself must be genetically altered... Such genetic
modification of human cells is still an emerging science and the long term effects are still largely
unknown.” It is framed as though there are effects from genetic modification are still waiting to be
discovered, whereas the literature would suggest the technique of genetic modification used in
optogenetics is a well documented process.

Gray continues with, “An implant must also be placed directly into the brain, requiring an operation, so
that it can deliver light to the brain cells using tiny optical fibres similar to those that carry broadband
signals around the UK.” He implies brain implants are a controversial technology, saying “Drawing on the
growing scientific knowledge of how our brains work, this opens up the ability to control behaviour –
something that will alarm the more paranoid free rights campaigners.” Again, the article says that “...they
have also turned mice into "light addicts"... Such technology, if it is ever used in humans, would give
doctors the potential to control people's behaviour...”

Essentially the arguments by Gray seem to sensationalise a fear that our brains can be overrun by men in
lab coats for whatever purposes they choose. The scientific evidence found by the group’s research
suggests the technology, if developed further, certainly can be capable of controlling the brain, however it
appears Grey is deliberately presenting optogenetics as highly controversial. Considering the ethical issues
of a technology in its infancy is important, but presenting these issues with a lack of evidence seems be a
ploy for controversy to gain a larger readership. Despite this, the article quite faithfully represents the
current state of optogenetics in an informative and engaging manner.

Appendix

Search Strategy

The search strategy employed by the group was for each group member to present three media articles that
related to the course content of Neuroscience Fundamentals in a group discussion. The group then
evaluated each of the articles put forward against a criteria of course relevance and the sensationalism of
the claims made in the media article. The optogenetics article met all these criteria overwhelmingly due to
the sheer number of proposed treatments attributed to the optogenetics technique. The references used for
the report were obtained from search engines such as google scholar and the library database, and it was
ensured by the group that most of these sources were peer reviewed and were from reputable journals
articles.
Review

The reviewer comments noted a particular disconnect in the subject flow and the language style between the main paper and the critical analysis. The group addressed the issue of subject flow by firstly summarising the merit of the claims made in the article as described in the group's research findings. This summary was then linked to a discussion of the sensational quotes made in the article and concluded with a critique of the neuroscientific information portrayed. The language was also changed to reflect the more factual and formal style presented in the main body of the paper. The group also adopted the suggestion to improve the banner of the wiki page to make it more eye catching and to also include some discussion to why the group chose this particular media item in the introduction. The overall grammar and spelling mistakes were also corrected as advised by the reviewers.

The reviewer comments that the group chose not to adopt was the addition of more figures throughout the main body of the paper. The group decided that the existing figures in the background information explained the optogenetics technique broadly enough to provide detail for the reader to understand the topics discussed. The group's main focus of the paper was to analyse the merit of the claims made in the article in a general description overview with cited references, it was decided that the inclusion of detailed figures would complicate the subject flow with unnecessary technical information. A suggestion to further explain the three methods for delivery of genes was also not adopted as the group agreed that the level of background information of the optogenetics technique was adequate to understand the main ideas presented in the main body of the paper. Critique in regard to the neuroscientific context being difficult to read due to the level of detail was taken as a comment. The group felt that the level of technical detail was sufficient for the aimed reader audience of neuroscience students expected to have a required knowledge of the neuroscientific concepts discussed in the paper. However, the group did condense some of the content with the intention of adhering to the word limit.

References


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