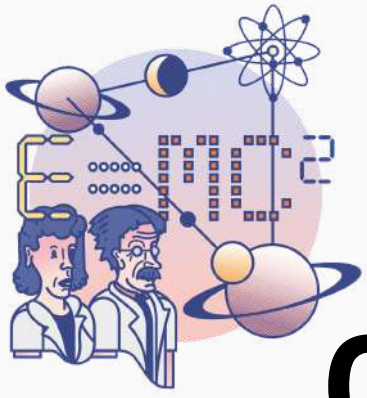
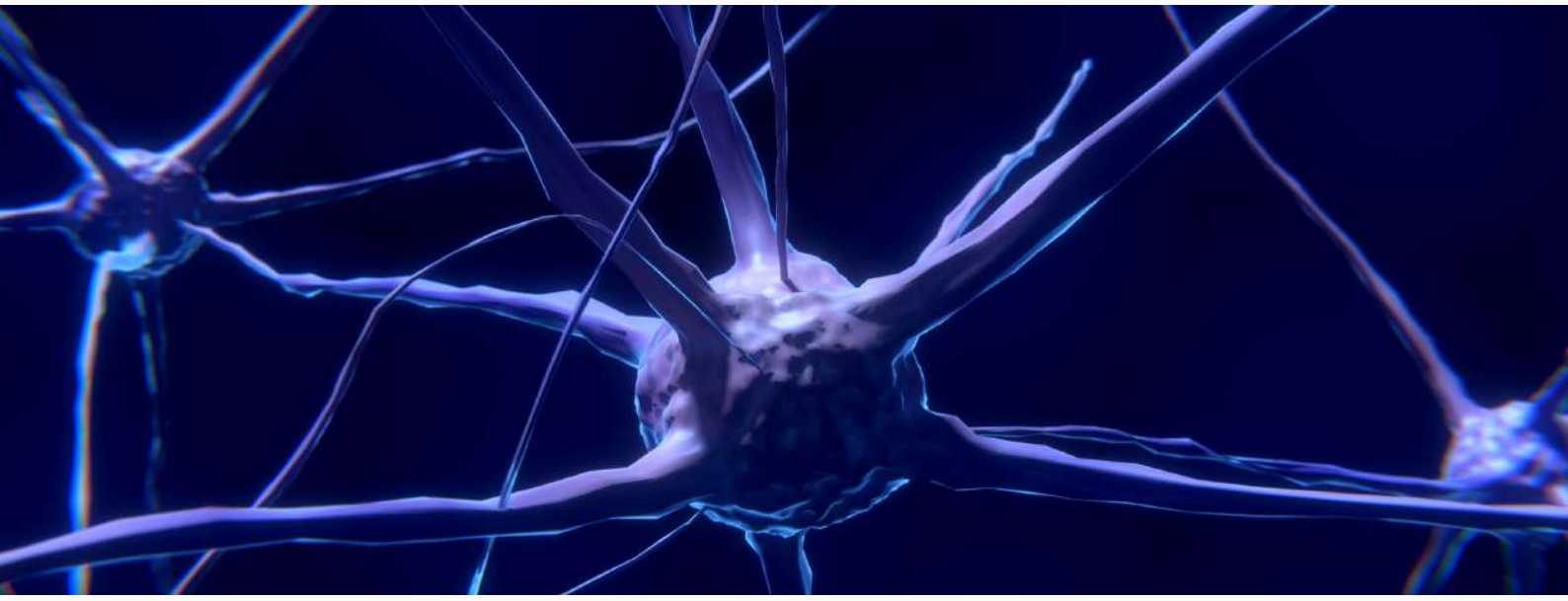


# Optogenetics Project

Yvie Firmin



SUPERVISED BY JAKE (MSC IN NEUROSCIENCE, OXFORD. EDITOR FOR CACTUS COMMUNICATIONS, EDITING SCIENTIFIC MANUSCRIPTS PRIOR TO PUBLICATION IN LEADING JOURNALS).

**Evaluate the therapeutic potential of optogenetics and discuss the ethical implications**

Optogenetics is a breakthrough neuromodulation technology in which individual neuron activity is controlled with light[1]. Despite its recency, much progress has been made in the investigation of potential brain stimulation treatments for various psychiatric disorders, and research has even reached a level of human clinical trials.

With the use of a viral vector, a neuron can be genetically modified to include a channelrhodopsin protein. Depending on the rhodopsin variation, different wavelengths of light can be used to manually control the movement of ions across phospholipid bilayers, and therefore manipulate membrane potential. The light can be targeted to a small area of the brain, and the expression of the opsin can be restricted to a population of cells which express a particular gene or genes. This results in unparalleled precision and will lead to not only a deeper understanding of individual neuron activity, but also contribute towards incredible treatments. It also allows us to measure brain activity using EEGs, which was previously unachievable whilst alternative electric forms of biological brain manipulation were performed due to electrical interference.

The potential for optogenetic treatments is expansive and broad, offering solutions to various conditions ranging over the scope of human neurological function. José-Alain Sahel and colleagues have already achieved partial recovery from complete blindness in human clinical testing of retinitis pigmentosa by injecting vector genomes (coding for ChrimsonR) intravitreally, and with the use of light-stimulating goggles[2]. Although this newfound vision will undoubtedly improve their quality of life, the resultant vision should aim to be of a higher resolution, as the picture produced is very low-resolution. Only the visual perception of a static diorama was measured, though in day-to-day life we are constantly moving and shifting, which means that how this current technology would function may be incompatible for a non-sedentary lifestyle. Though optogenetics has succeeded in enhancing and improving retinitis pigmentosa, a neurodegenerative condition, the technology is limited. It may not, for example, offer relief from brain damage or other neurodegenerative diseases such as Huntington's disease where necrotic tissue cannot be resuscitated.

Not only has optogenetics partially alleviated a neurodegenerative condition, it has also implanted false contextual fear memories in the brains of mice. Memory is thought to be encoded in a specific population of hippocampal neurons, and Xu Lui et al. have found that the re-excitation of engrams elicit conditioned behaviour learnt in these memories[3]. This potential manipulation of memory proves hopeful in severe PTSD and CPTSD treatments, by

inhibiting engrams associated with the traumatic memory as opposed to re-exciting them. PTSD is a psychological disorder with various clinically-approved ameliorating treatments such as cognitive behavioural therapy or ketamine therapy, yet it is lacking in a fully reliable solution that elicits minimal side effects. Optogenetics could provide a strong solution for the suffering caused by painful and traumatic memories through the inhibition of cell populations responsible for the memory. However, Xu Lui and colleagues have only researched procedural memory, and so the transfer of this technology may need to be adjusted to suit the more complex episodic memory implicated in PTSD. Testing true episodic memory also proves to be difficult in animal trials, as there is no mechanism to communicate subjective thoughts and ideas with rodents.

This technology may also be morally objectionable to some, as its development could consequently lead to malpractice. Regardless of the objectivity of science, a true state of pure unbiased action is unachievable for the living, thinking human. This is also applicable to doctors and researchers. If a patient's memory were being manipulated, the person administering the treatment would inevitably encode the memory according to their own perception. If a large chunk of memory were erased using optogenetics, in order to improve the quality of life of an individual with PTSD, a decision must be made whether to fabricate said memory in a positive light to avoid the loss of other attached memories that are vital to their everyday function and identity. Although they may need this treatment to prevent suicide or severe self-damaging behaviour, there comes a point at which their memories construct who they are and how they behave.

Akiko Hayashi-Takagi and colleagues used optogenetic engineering to shrink dendritic spines in the motor cortices of mice, therefore disrupting the acquired learning of a recent motor task[4]. The genetically modified fusion protein PaRac1 disrupts synaptic plasticity. Hayashi-Takagi et al. chose to shrink dendritic spine size as an independent variable, through which the results became observable in mice (anterograde alteration)[5]. Following the logic of their hypothesis, artificially enlarging dendritic spines should induce positive change in synaptic efficacy. As both long term memory and working memory are positively correlated with measures of intelligence, as is mental speed, future technology may be on its way to synthetically improve intelligence, which could potentially lead to innumerable good, or mass immorality. As this technology would be, in almost all cases, unnecessary and over-expensive, those with access to the initial technology would be the extremely wealthy. In the extremely unlikely case of widespread distribution, a vast and dystopian disparity would be created between the elite with access to phenomenal intelligence, and those without. Alternatively, the photoactivation of a developed genetic construct in dendritic

spines with intent to improve memory recall could be beneficial for those who suffer from amnesia or other conditions involving memory loss.

Schizophrenia is a chronic mental health disorder characterised in the DSM 5 by delusions, hallucinations, disorganised or incoherent speaking, catatonic behaviour and negative symptoms[6]. There are multiple treatment options for schizophrenia, predominantly including prescribed antipsychotics that block both dopamine and serotonin receptors. Despite their widespread usage, these medications induce severe side effects and have overall extreme negative feedback for something intended as a solution. As according to John Read and James Williams' 2019 international online study into the positive and negative effects of antipsychotic medication, 54% reported that their quality of life was made worse (as opposed to the 35% that reported improvement), 43% found the drugs unhelpful, and 70% had attempted to stop taking the drugs[7].

Optogenetics potentially offers an alternative and novel treatment: neocortical excitation/inhibition manipulation. Yizhar et al. have hypothesised that the behavioural deficits displayed in schizophrenia are caused by an imbalance of excitation/inhibition in neural microcircuitry[8]. There is a lack of understanding surrounding the physical substrates of many psychiatric disorders, however through the use of optogenetics, we can begin to understand and therefore progress towards suitable treatment. A potential treatment could involve the synthetic rebalance of the neural microcircuitry through silica-based fibre optics. Nonetheless, the nature of schizophrenia may mean that patients are resistant to such technologies. Paranoid schizophrenia, the most common variation, involves hallucinations, extreme suspicion, and distrust. The likelihood of a paranoid schizophrenic consenting to have fibres mechanically inserted into their skull is low, as the delusions that they experience would possibly lead them into a heightened emotional and aggressive state if they believed that the optogenetic technology was a part of a conspiracy.

The therapeutic potential of optogenetics is vast and optimistic, though limited to the analysis and manipulation of neurons and neuronal circuitries. Optogenetics is already offering partial recovery from complete blindness in patients with retinitis pigmentosa, alongside hopeful treatment for amnesia and memory loss, and possible schizophrenia mitigation. Despite its versatility in the different issues it may be able to solve, it is also a very expensive technology, and may lack time and cost efficiency. Biochemical methods such as certain drugs and pharmaceuticals are also very potent and should not be overlooked as a solution for psychological conditions.

## References:


1. Adamczyk AK, Zawadzki P. The Memory-Modifying Potential of Optogenetics and the Need for Neuroethics. *NanoEthics*. 2020;14(3):207-225. doi:10.1007/s11569-020-00377-1
2. Sahel JA, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. *Nat Med*. 2021;27(7):1223-1229. doi:10.1038/s41591-021-01351-4
3. Liu X, Ramirez S, Pang PT, et al. Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature*. 2012;484(7394):381-385. doi:10.1038/nature11028
4. Hayashi-Takagi A, Yagishita S, Nakamura M, et al. Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature*. 2015;525(7569):333-338. doi:10.1038/nature15257
5. Swann J. Labelling and optical erasure of synaptic memory traces in the motor cortex. Published online 2021.
6. Administration SA and MHS. Table 3.22, DSM-IV to DSM-5 Schizophrenia Comparison. Published June 2016. Accessed February 28, 2023. https://www.ncbi.nlm.nih.gov/books/NBK519704/table/ch3.t22/
7. Read J, Williams J. Positive and Negative Effects of Antipsychotic Medication: An International Online Survey of 832 Recipients. *Curr Drug Saf*. 2019;14(3):173-181. doi:10.2174/1574886314666190301152734
8. Yizhar O, Fenno LE, Prigge M, et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*. 2011;477(7363):171-178. doi:10.1038/nature10360