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THIS ISSUE

Dear Reader,

Welcome to yet another issue of King's leading STEM magazine. This issue includes articles on the topics of Genetics, Immunology, Neuroscience, Technology, and Physics.

This issue brings an exciting update! For the first time in more than 1 year, we are organising an official magazine launch social (print copies have been ordered). By popular demand, we will give authors and editors the chance to connect with fellow ScienceMind-ers via 5-minute presentations of their work. Anyone can attend! Save the date on Nov 30th, 6.30-7.30 pm, Guy's Campus.

In the months following our Summer issue, ScienceMind has kept busy. Just last week, some of you joined us for a Careers Panel with Roche. Representatives from the pharmaceutical industry giant talked about their experience in transitioning from university to BioPharma, whilst the attendees asked burning questions. The panel took place both on Guy's Campus and on Instagram Live, making it the first-ever hybrid event in ScienceMind history!

And next time you have a spare minute, do yourself a favour and tune in to the revived ScienceMind Podcast! Having wrapped up our collaboration with KCL iGEM, the (newly expanded!) team has exciting new content planned, including a brand-new series on Student Life.

To stay in the know on all our initiatives, sign up for our newsletter, follow us on social media, or check for regular updates on the brand-new ScienceMind Website (we're recruiting for Web Designers, by the way!).

If this is your first time reading our magazine...

ScienceMind is the award-winning, student-led science magazine of King's College London. We report the latest findings in STEM to students and the wider community. We showcase and develop the written and oral communication skills of students interested in STEM by concisely explaining complex scientific concepts in the form of lay articles and by conducting interviews. Authors can also broaden their knowledge by writing articles for different sectors.

Articles have difficulty levels. There's something for everyone!
Shallow dive: Secondary school level
Treading water: A-level to undergraduate level
Deep dive: Final year undergraduate, postgraduate, professor level

ScienceMind is ever growing, join the new age of science media.

Kind regards,

Olivera Mitevska

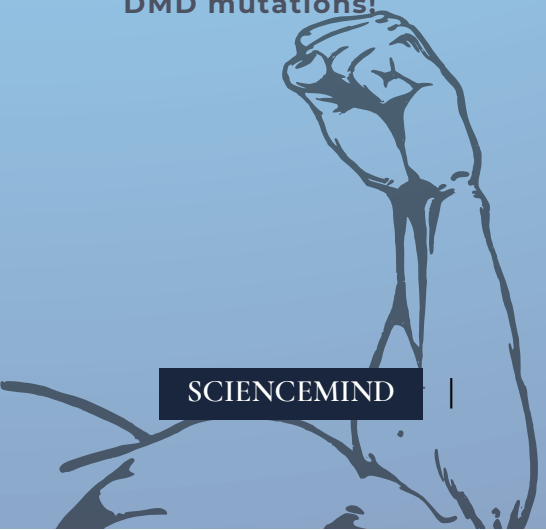
Editor-in-Chief
Olivera Mitevska

CRISPR/Cas9 For Duchenne Muscular Dystrophy

WRITTEN BY ADVAITA SETH
EDITED BY AJDA PRISTAVEC
DESIGNED BY ASHNA SURANA

The **clustered regularly interspaced palindromic repeats (CRISPR)/Caspase-9 system** is one of the **hottest topics** in science at the moment.

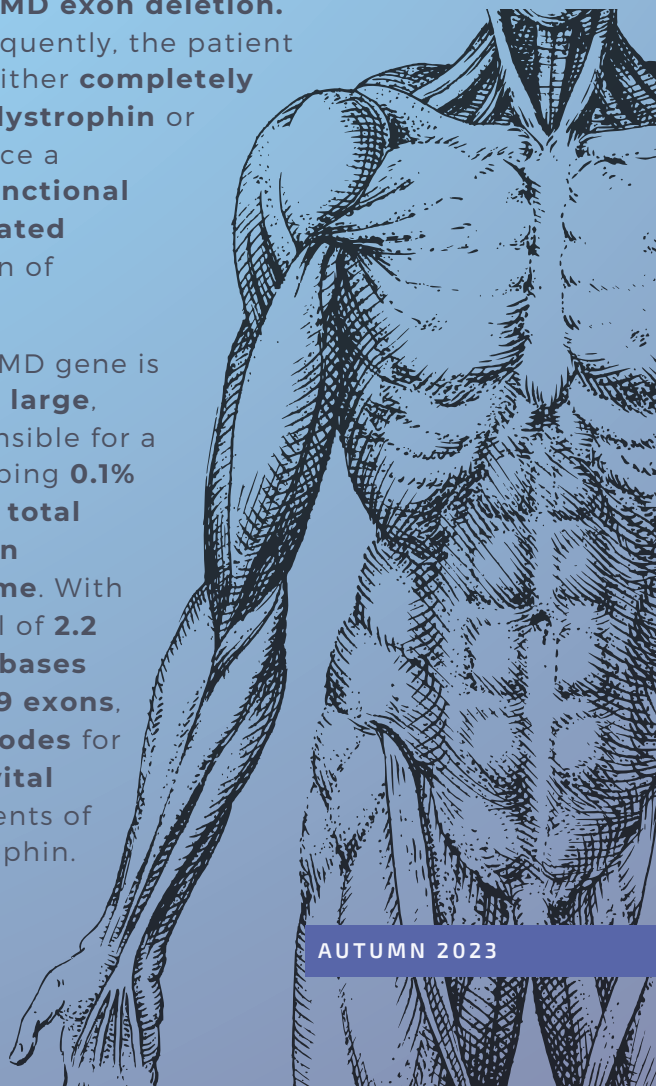
In recent years, interest in **CRISPR/Cas9** has skyrocketed with the aim to integrate it into the **development** of **countless therapeutics**. Its ability to introduce changes into the genome is **unparalleled** by any other method of **gene editing** especially in terms of **precision**, **speed** and **cost-effectiveness** [1]. Therefore, it underlines enormous potential to touch patient lives by **treating** several conditions, one of which is **Duchenne Muscular Dystrophy (DMD)**. DMD is a **neuromuscular X-linked disorder** attributed to **exon deletions** or **point mutations** which **plummet** the expression of the **vital protein dystrophin**. It is characterized by **clinical manifestations** such as early onset of **cardiomyopathy** and **severe muscle wasting** [2]. **Progressive muscle degeneration** in DMD means that patients' quality of life is **drastically affected** by **immobility.** Thus far, it has **no cure** and can only be treated with **corticosteroids** for symptomatic relief [3]. CRISPR/Cas9 may change that, with its **great potential** to **permanently repair DMD mutations!**



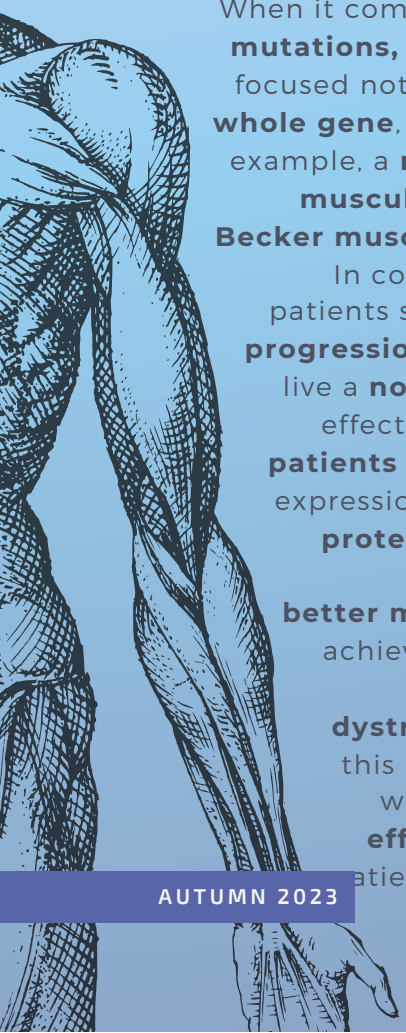
Understanding The Pathophysiology Of DMD

Dystrophin is an **essential protein**, as it is an integral part of the **dystrophin-glycoprotein complex** which links the **extracellular matrix** to the **actin cytoskeleton** [3]. Without dystrophin, the cell membrane is rendered **unstable**, leading to **frail myofibers** and therefore **muscle degeneration** upon contraction. Since DMD is an **X-linked disorder,** it predominantly **affects males**. A mutation in the DMD gene, most likely an **exon deletion,** leads to the **absence** of the protein **dystrophin** under the patient's **sarcolemma**. This is because a **premature stop codon** or a shift in the **open reading frame (ORF)** may be generated as a result of a **DMD exon deletion.** Subsequently, the patient may either **completely lack dystrophin** or produce a **malfunctional truncated** version of it [3].

The DMD gene is rather **large**, responsible for a whopping **0.1%** of the **total human genome**. With a total of **2.2 megabases** and **79 exons**, it **encodes** for **four vital** segments of dystrophin.



The **actin-binding amino terminal domain**, **ABD1**, binds the skeletal muscle's **contractile apparatus** to **dystrophin**. The second segment, the **rod domain**, is made of **spectrin-like repeats** which **interact** with **microtubules** and the membrane. Next up, the **cysteine-rich domain** helps to **maintain dystrophin** under the sarcolemma. Finally, the **carboxy terminal domain** is responsible for **protein-protein interactions** of dystrophin [4]. It is important to note that all of these **dystrophin segments** are **integral** to maintaining membrane stability and therefore **defects** in them would **orchestrate muscle degeneration.** Out of all **79 exons** in the **DMD gene**, researchers have deemed **exons 2-10** and **45-55** the **'mutational hotspots**'. From these, **exon 51, exon 53, exon 43, exon 44 and exon 45** are most frequently found to be **mutated** in DMD patients[3]. Therefore, CRISPR/Cas9 research for DMD is typically focused around **understanding mutations** in these regions and designing a way to **repair them.**



When it comes to **addressing** these **mutations,** researchers have often focused not only on **restoring the whole gene**, but also **parts** of it. For example, a **mild or benign form** of **muscular dystrophy** is called **Becker muscular dystrophy (BMD)** In comparison to DMD, BMD patients suffer far **slower diseas progression** and often manage to live a **normal lifespan**. Thus, an effective way to r**elieve DMD patients** may be to strive for the expression of a **semi-functional protein**. Research has shown that **better muscle function** can be achieved with even just a **4% increase** in **functional dystrophin levels** [5]. While this isn't a complete fix, it would **mirror the milder effects of BMD** and allow atients a far **better quality of life**.

Exploiting CRISPR/Cas9 To Repair Mutant DMD Genes

Moving on to understanding the **use of CRISPR/Cas9** as a **therapeutic**, there are **two main molecules** that **underpin** the **CRISPR-Cas9 system - sgRNA (single guide RNA) and Cas9 (CRISPR-associated endonuclease).** The **Cas9 enzyme** essentially acts as **scissors**, **cutting DNA strands** at a **specific location**. In order to cut at the **desired point** in the genome**, sgRNA leads Cas9** to it. Consisting of a **long RNA scaffold** and a **pre-designed RNA sequence (20 bases)**, sgRNA can lure Cas9 to a **precise genomic location**. Its RNA scaffold **binds** to the DNA, while its **pre-designed sequence** also uses **base pairing** to **chaperone Cas9** to the cut site [6]. Once Cas9 generates a **double-stranded break (DSB)** in the DNA, the mutation can be **repaired** either by **homology-directed repair (HDR)** or **non-homologous end joining (NHEJ).**

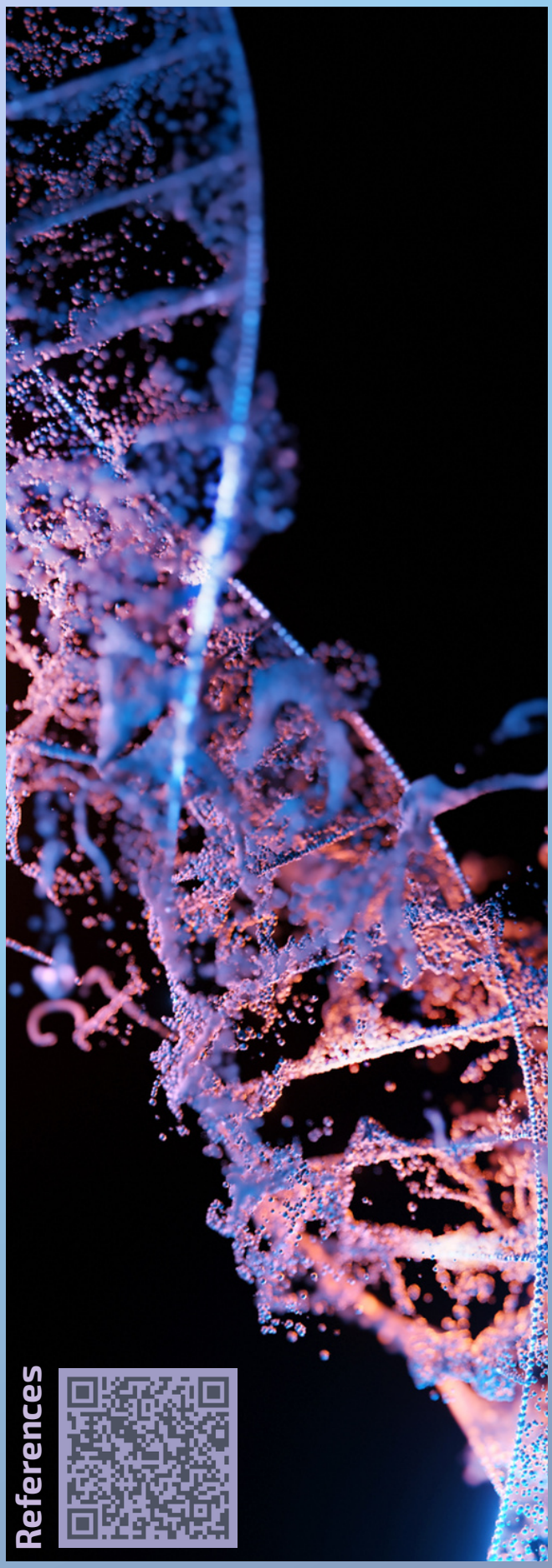
HDR is generally regarded as **superior** and **more precise,** as it utilizes an **exogenous DNA template (single-stranded oligodeoxynucleotides/ ssODNs)** to achieve **accurate editing** [7]. To treat DMD, HDR has the potential to **induce expression** of **full-length dystrophin** molecules by **"knocking in"** the **exon** that was deleted by the mutation. However, **NHEJ** is **heavily favored** over HDR in the context of DMD for two reasons. Firstly, only a **limited length of ssODNs** can be **delivered,** making **large exon deletions difficult to repair**. Secondly, HDR **cannot** effectively **repair mutations** in **post-mitotic cells** such as **myofibers** [3].

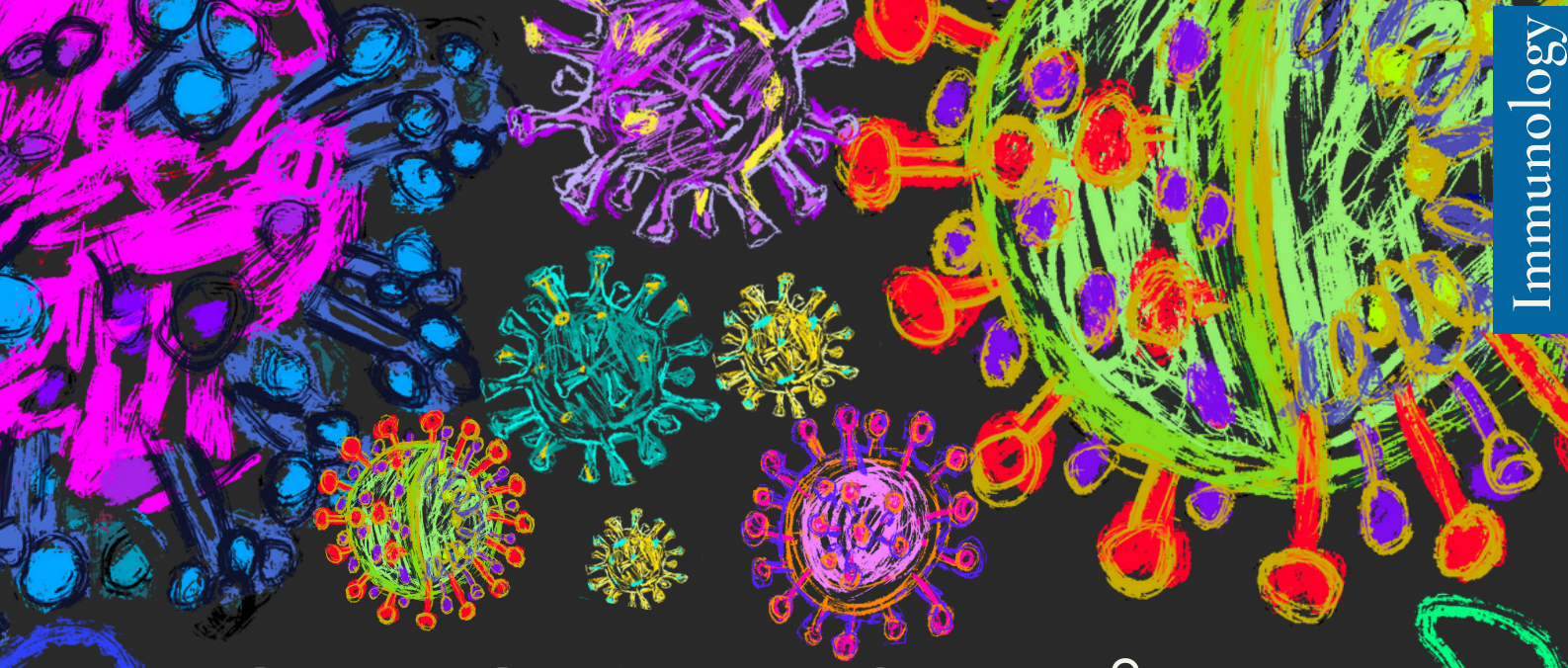
As for NHEJ, it can only **make insertions** or **deletions (indels)** at **DSBs** and therefore i**mprove dystrophin expression** by either **exon skipping**, **exon reframing** or **exon deletion mechanisms**. The exon skipping pathway **restores the (ORF)** for dystrophin by **hindering an exon splice site**. In doing so, exons may be **skipped** during **RNA splicing** and result in **expression of dystrophin.**

Research in the past few years has shown that around **80% of DMD patients** may benefit from this approach [5]. Comparatively, the **exon deletion pathway** is different to this. When a **mutation shifts** the **ORF** outside the reading frame, an **exon deletion** may help **bring it back** within the reading frame. Its drawback is that it may cause **truncated dystrophin proteins** which are only **semi-functional**. However, the **exon deletion** method may benefit an even **larger population of DMD** patients as compared to **exon skipping** [3]. Lastly, the **exon reframing method** creates **small indels** in order to **reframe the ORF** so that it is **read correctly**. While this can potentially **restore dystrophin expression,** there is only a mere **1 in 3 chance** that the reading frame will be correctly restored [5]. All in all, there are **many ways** to **repair DMD mutations,** but the **choice of method** depends on the **patient's profile.**

Conclusion

CRISPR/Cas9 proposes the possibility to **revolutionize** the **treatment of DMD**, moving beyond just **alleviating symptoms** to actually **restoring muscle function**. However, there is yet work to be done in order to **fine-tune CRISPR/Cas9** as a **therapy for DMD**. One of the main **challenges** in this regard are **delivery strategies** using **AAV (adeno-associated viral) vectors**, as they can hold a maximum of around **4.7kb of genetic material**. Furthermore, Cas9 enzymes may **trigger** an **immune response** due to their **bacterial origin**, or **off-target mutagenesis** may occur if the **sgRNA design** matches the DNA at an **undesired location** [3]. Despite this, progress is being made by **numerous academic labs** and **pharmaceutical companies.** Recently, **NS Pharma's candidate NS-089/NCNP-02** held its **first human clinical trial** using the NHEJ exon skipping method at **exon 44** and demonstrated **increase in dystrophin** and **motor function** [8]. All in all, the future of CRISPR/Cas9 for DMD **sparks hope** for **countless patients worldwide**, returning them the gift to movement!





SARS-CoV-2 variants and their impact on the pandemic

WRITTEN BY HAY YEE YUEN, HARMONY
EDITED BY NIKITA KATHURIA
DESIGNED BY YUSRA-AINA CHOUDHURY

TREADING WATERS

The **SARS-CoV-2 virus** gave rise to the COVID-19 pandemic that lasted for over 3 years. During this pandemic, several SARS-CoV-2 variants are derived with some detrimental effects that initiate more waves of the pandemic. It is clearly evident that recently a new variant of the SARS-CoV-2 virus was discovered, concerns are raised on the severity of this variant and actions are taken to minimise the impact of this variant to the society.

Timeline of SARS-CoV-2

Different variants have emerged at times and locations during the pandemic, these variants show differences due to the mutations of the amino acid sequences on the spike protein of the virus. (Zhou & Wang, 2021)

As shown in Figure 1, spike proteins (S) are present. It has a role in delivering the RNA viral genome into host cells for infection. (Agarwal et al., 2020)

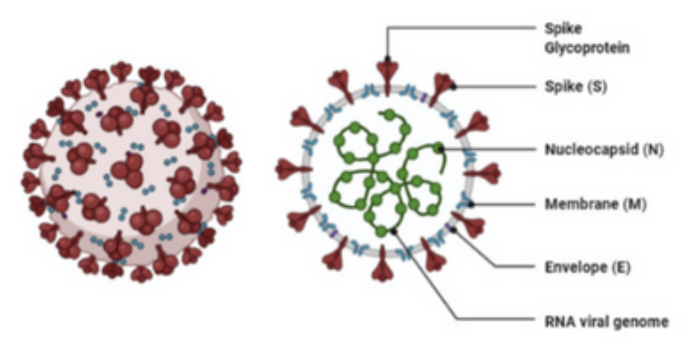


Figure 1. Diagram of the basic structure of the SARS-CoV-2 virus This diagram shows the cross section structure of the SARS-CoV-2 virus.

Five major variants are identified during the pandemic, including Alpha, Beta, Gamma, and Delta. These detected variants are known as the **variants of concern (VOC).** These names are designated by WHO. Additionally, due to the high rates of mutations of the VOC, **lineages** are also allocated to each of the variants. (Islam et al., 2022, Cojocaru et al., 2022)

WHO allocated name	Lineage	First detected location	Time of first detection
Alpha	B.1.1.7	United Kingdom	November 2020
Beta	B.1.351	South Africa	December 2020
Gamma	P.1	Brazil/Japan	Late 2020
Delta	B.1.617.2	India	Late 2020
Omicron	B.1.1.529	Multiple countries	November 2021

Table 1. Table showing basic information of the variants This table briefly shows each variants' WHO name and their lineage and the location of where the variant is first detected (Cojocaru et al., 2022)

Structural differences of VOC

With the VOC emerging, scientists dedicated their research onto their **mutations** on the amino acids on the spike proteins of the coronavirus. There are two subunits in each spike protein that are known as the S1 and S2 subunit. According to **Figure.2b,** the S1 subunit mainly consists of a **receptor binding domain (RBD)** that facilitates the binding of the spike protein to the host cell. After the S1 subunit attaches to the host cell, the S2 subunit will be responsible to transmit the RNA material from the virus to the host cell. In the S2 subunit there are mainly two domains, known as the **heptad repeat 1 & 2 (HR1 & HR2) domains.**

(Huang et al., 2020) HR1 & HR2 facilitates the transmission of genetic material into host cell by increasing the proximity of the viral and cellular membranes. (Xia et al., 2020) On the other hand, according to **Figure. 2a**, there are mutations of the amino acid sequence in the alpha, beta, and delta variants and are highlighted in red. These mutations lead to some observable effects on the virus. (Zhou & Wang, 2021) Also seen in Figure. 2a, the mutations in the spike proteins are mainly deletion and substitution of amino acids. There are also other sequences that is known as **open reading frames (ORF)**, they are non-structural parts of the virus with some deletion mutations in different variants. (Tsai et al., 2020)

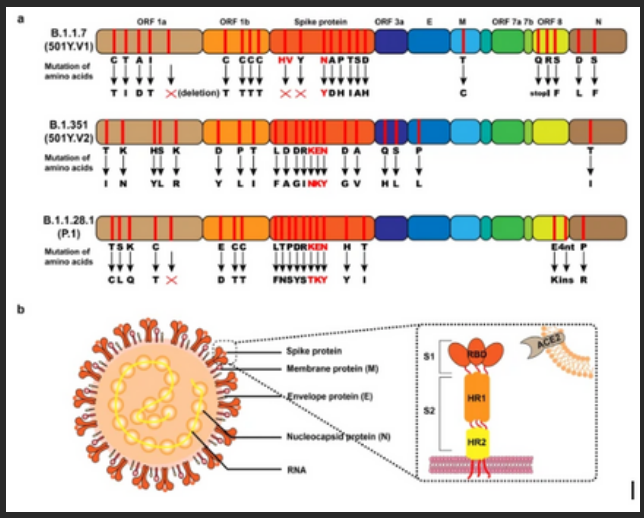


Figure 2. Diagram showing structure of virus (a) shows the mutation of the amino acid sequence within the spike protein and ORF of different covid variants (b) shows the basic structure of the spike protein. (Zhou & Wang, 2021)

Observable clinical differences of VOC

According to research, all strains are shown to have a **higher transmissibility** in comparison to past strains. on the other hand, study shows that the Alpha and the Gamma variants have **more virulence** than other strains (i.e. **more lethal**). (Otto et al., 2021, Duong, 2021) With the theory of **natural selection**, gene sequences evolve to be more advantageous. Population of variants or strains that do not have a high enough transmissibility will decline. Therefore, higher transmissibility will be the occurrence of mutations of the SARS-CoV-2. (Markov et al., 2023).

There is an increase in the difficulty to control the pandemic due to the increase in cases as new variants emerge. Therefore, **more doses of vaccinations** for each individual are required to reduce the number of Covid cases. (NHS, 2023) It can be concluded that the presence of variants increases the number of covid outbreaks and **extends the time of the pandemic**, where vaccine advancements and awareness towards safety measures of COVID are required to be taken to successfully terminate this Covid-19 pandemic.

In conclusion, the presence of the new types of variants has a negative impact on the progress of terminating the pandemic. Although the pandemic has ended, it is still important to understand the differences in the variants for a better development in science research.

References

Neurobiological basis of Psychedelics & their clinical uses

SHALLOW DIVE

WRITTEN BY ANUM WASEEM
EDITED BY SOFIAT ONAFUWA
DESIGNED BY TIFFANY KOH YU XUAN

Introduction

The word Psychedelics was coined by Humphry Osmond in the 1950s, inspired by the Greek word 'manifesting'. True to its name, psychedelics are chemical compounds that can affect an individual's psyche by invoking hallucinations. Consumption of psychedelics stimulates feelings of spirituality and creativity and alters the emotional states of an individual due to the activation of 5-HT receptors (Doblin et al., 2019). Psychedelics can be found naturally in fungi and plants and can be synthetically manufactured, namely 3,4-methylenedioxymethamphetamine (MDMA) and Lysergic acid diethylamide (LSD) discovered by Anton Kolloisch and Albert Hofmann in 1912 and 1943, respectively (Kelmendi et al., 2022). This article aims to review the neurobiological action of psychedelics and their therapeutic and clinical use. It concludes with current ongoing research on psychedelics as a psychotherapy at King's College London (KCL).

Neurobiological Action of Psychedelics

Psychedelics achieve their profound effects on neuronal activity due to their physical characteristics of being small and hydrophobic which allows them to cross the Blood Brain Barrier (BBB) (Kwan et al., 2022). Psychedelics primarily act on 5-HT2A receptors present in the Thalamus, Raphe Nuclei, and Adrenergic receptors present in the Hypothalamus (Figure 1). The primary mechanism by which psychedelics induce their effects is through binding to the GPCR 5-HT2A receptor. This allows the G-alpha subunit of the receptor to dissociate from the heterotrimeric complex and carry out a cascade of downstream reactions which has two effects; release of Ca^{2+} ions from the ER into cytoplasm and increasing transcription of genes involved in neural plasticity, such as c-fos, Arc and Egr2 (Figure 2) (Kwan et al., 2022). The liberation of Ca^{2+} increases calmodulin-dependent kinase (CaMKII) activity. This is a protein kinase that plays a significant role in learning, memory, and synaptic plasticity (de Vos et al., 2021). Furthermore, the release of Ca^{+} ions can also contribute to the increased release of NTs such as glutamate and dopamine in the synaptic cleft, which could explain the enhanced cognitive function and feelings of euphoria after psychedelic consumption (de Vos et al., 2021).

Effect of Psychedelics on neuronal activity

Consistent use of psychedelics induces long-term effects in the prefrontal cortex through increased proliferation of dendrites, resulting in increased dendritic density which occurs as little as 24 hours after the initial dose of psilocybin and lasts for up to one month (Healy, 2021). However, the effect of psychedelics in vivo is more difficult to comprehend due to the multiple cortical circuits present which have heterogenous responses to increase in 5-HT concentration. This theory is supported by a study done by Kwan and colleagues (2022) involving the administration of LSD which resulted in varied rates of neuronal firing across the frontal cortical neurons.

Psychedelics have a pronounced effect on the firing of the dorsal raphe nuclei, which is also the largest site for serotonergic neurons. In a longitudinal study spanning 20 years, George Aghajaman et al. (1979) showed that administration of LSD in rats led to the termination of neuronal firing in the dorsal raphe nuclei, which only returned to baseline after 20 minutes. Due to this, and multiple other studies, it was thought that the raphe nuclei action is thus responsible for the effects invoked by psychedelics (Aghajama et al., 1979; Arce & Winkelman, 2021; Bălăeţ, 2022).

However, further studies done in animals show that the administration of LSD does not consistently align with behaviour changes. Thus, for now, there is little clarity on which brain region and circuitry are responsible for inducing the effects of psychedelics, but it is confirmed that there is an alteration in synaptic transmission occurring in the prefrontal cortex, dorsal raphe, hippocampus, locus coeruleus, and visual cortex (de Vos et al., 2021).

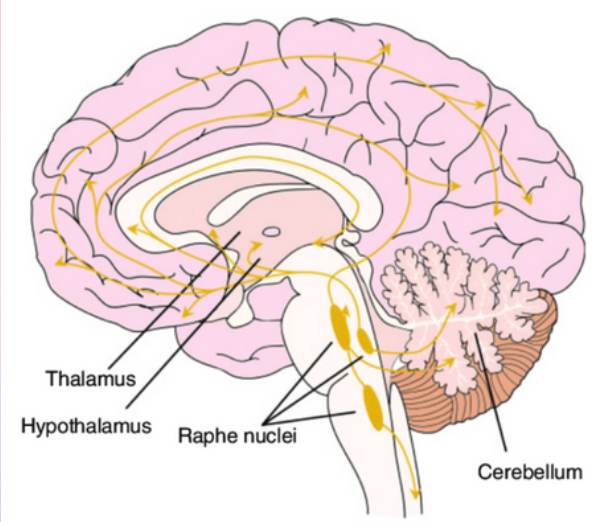


Figure 1. Labelled image of a midsagittal section of the brain. The serotonergic pathways are shown in yellow with the Thalamus, Hypothalamus, Raphe Nuclei, and Cerebellum labelled. Taken from Deen et al. (2017).

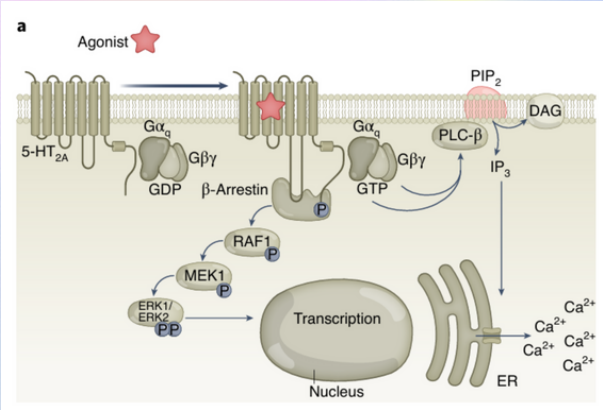


Figure 2. Downstream action of psychedelics. Psychedelics activate Gq-like G-proteins which allows hydrolysis of Phosphatidylinositol-4,5-bisphosphate (PIP2). This activates the secondary messengers Diacylglycerol (DAG) and Inositol trisphosphate (IP3), which activate Protein Kinase C (PKC) resulting in the liberation of Ca2+ ions from the Endoplasmic Reticulum. Taken from Kwan et al. (2022).

History of Psychedelics

Psychedelics as a therapeutic option were explored extensively during the 1950s and 1960s in the United States. Classic psychedelics such as LSD and Psilocybin were administered to patients with mental health disorders such as anxiety and depression which led to an improvement in their conditions (Vollenweider & Preller, 2020). Research on psychedelics was halted in the mid-1960s in the US when LSD was categorised as a Schedule 1 drug resulting in the termination of clinical trials. However, during the 1990s, the perception of psychedelics began to change, thanks to the advancement of imaging techniques which allowed empirical and analytical evidence for the therapeutic usage of psychedelics (Doblin et al., 2019).

Therapeutic Basis of Psychedelics

Psychedelics can be used in major depression disorders (MDD) to regulate mood and reduce the processing of negative emotions (Barrett et al., 2020). This may allow patients to reflect on their memories and surroundings in a less negative light during therapeutic sessions. The use of psychedelics to help process emotions has been extensively studied, and it has been shown that LSD and psilocybin decrease negative facial expressions in participants; both psychedelics also reduce the association of neutral expressions with fearful ones and LSD has been shown to reduce neuronal firing in response to negative stimuli which is associated with an increase in a positive mood (Vollenweider & Preller, 2020). These changes are particularly evident in participants who show resistance to conventional treatment of depression. It must be noted that the aforementioned reduced amygdala activity, which results in positive effects on emotional recognition and processing in patients with depression, lasted for only about one week after psilocybin and LSD administration (Vollenweider & Preller, 2020; Barrett et al., 2020). This indicates that for longer-lasting effects for the treatment of depression using psychedelics, regular administration might be required.

Current Research at KCL and Conclusion

Current research in psychedelics includes the work of Dr. James Rucker of IoPPN who is a pioneer for psychedelic research and is the project leader for the Psychoactive Trials Group at the Centre for Affective Disorders at KCL. In partnership with COMPASS in 2022, Dr. Rucker's team carried out a Phase 1, randomised, placebo-controlled trial which involved the administration of 10mg or 25mg dose of psilocybin to healthy participants (Rucker et al., 2022). It was concluded that both doses have no short or long-term detrimental effects on healthy participants (Rucker et al., 2022).

To conclude, this article aimed to provide a brief overview of psychedelic action and therapeutic abilities. The neurobiological basis of psychedelic action was discussed, along with its effects on a variety of brain regions. Further discussion on the history of psychedelics and their present usage as therapeutics for mental disorders took place. Future research in the field of psychedelics may focus on the development of psychedelics-based therapies to treat mental health disorders as well as making such therapies accessible to the general population.

References

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Beyond the Cycle: Can the menstrual cycle impact cognition?

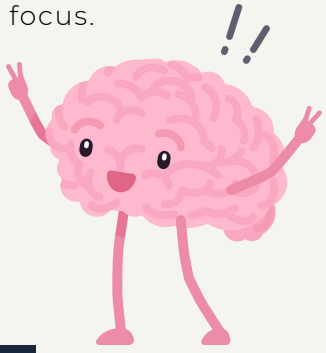
WRITTEN BY MAITHILI PITTEA
EDITED BY AALIYAH ADESIDA
DESIGNED BY HELENA BRADBURY

Whether or not you menstruate yourself, you likely know someone who does. It could be a family member, a friend or maybe a co-worker.

You also likely know that menstrual cycles come with a wide range of symptoms that can occur at different phases of the cycle. **But did you know that the menstrual cycle could potentially have an effect on the brain?**

An elderly coworker recently remarked to me that when she was menstruating, she found it more challenging to park her car when driving, describing herself as 'almost clumsy'. As a neuroscience student, this piqued my interest. It led me to wonder: **Could this issue with a normal task be due to the presence of other symptoms affecting her cognition (such as pain or nausea) or could it be the sign of something deeper at work?**

A quick survey of my friends also yielded similar statements. One remarked that they would burn things in the kitchen more often when menstruating; another that they would have 'brain fog'; others also agreed that it was much harder to focus.



Whether or not this is due to a slight difference in brain function or from the distracting nature of side effects such as cramps or nausea, it was significant enough for one friend to make changes to their routine, minimising the possibility of any injury that they might come to. **So, can the menstrual cycle affect cognition?**

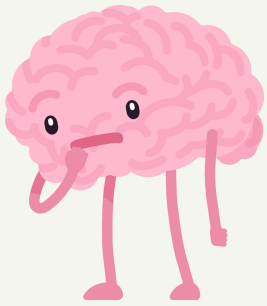
The driving factors of the menstrual cycle are sex steroid hormones such as estrogens and progesterone (as well as many others!). The rise and fall of the levels of different hormones signal to the body what it should be doing - for example, menstruating (bleeding) when it is time to shed the uterus lining of blood and the unfertilised egg.

Dozens of studies since the 1930s have explored the effects of sex steroid hormones on emotion, behaviour, and cognition. With respect to the cognitive field, the predominant hypothesis surrounds sexually dimorphic skills - these refer to skills that one sex allegedly can perform better at than the other. In this case, the idea is that when females are in the low estrogen phase of their cycle, they perform better at cognitive tasks that usually would favour males. Equally, the performance of skills that tend to favour women is improved with increased estrogen and/or progesterone. This hypothesis however, remains just that, a hypothesis, with insufficient evidence to prove it.

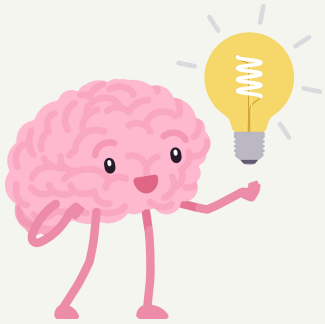
One example of a cognitive skill that is claimed to favour males is mental rotation, a visuospatial task where a subject has to mentally rotate shapes. The majority of studies which tried to replicate findings where females performed better at this skill are inconclusive with no clear findings. In parallel, many studies which attempted to show females with higher levels of estrogens and/or progesterone have no consistent pattern of findings, though this may be due to methodological problems rather than a lack of impact of sex hormones on cognition. Thus, there remains no conclusive evidence for the menstrual cycle's effect on sexually dimorphic tasks [1].

Moving onto a review by by Le et al. which focuses on cognition in females with premenstrual mood disorders. It discusses several preliminary studies which could indicate that those with premenstrual mood disorders might experience cognitive deficits given they have severe symptoms [2]. **This again raises the question, could the cognitive deficits be due to experiencing other distracting symptoms, or is there some more significant change in the brain?**

The studies examined by Le et al. all focus on different areas of cognition in varying phases of the cycle, and also have methodological problems, so we still have nothing conclusive. One thing to note, is that the Le et al. review does not disprove the possibility of altered cognitive functioning due to the menstrual cycle, but suggests that changes in cognition during the cycle are too subtle to detect and do not become clinically relevant until they present as severe symptoms.



So where does that leave us? With nothing conclusive but also without an outright refutal. Taking a closer look at the physiological effects that sex steroid hormones have on neurons might provide us with more promising evidence.



In rodents and non-human primates, progesterone and estradiol (an estrogen) have a regulatory effect on several very important processes including the maintenance of dendritic spines and spine density, synaptic sprouting and axon growth, and more [3]. The processes mentioned are all involved with the creation and maintenance of connections in the brain. Without these connections, there would be no cognition, no anything. Your brain simply would not work. It would be like a train with no tracks to use. Estradiol and progesterone levels increase eight and eighty times respectively over the course of a menstrual cycle [4] and since these hormones have an effect on connections in the brain, this research could hint at the menstrual cycle's effect on cognition.

Administering estradiol to an adult rat which has had its ovaries removed (and hence is unable to produce estrogens) increases synaptogenesis [5]. Synaptogenesis is the process of forming new synapses - the point between two neurons where information is transferred. It also increases dendritic spine density [6]. Dendritic spines are protrusions on a neuron which allow a neuron to 'connect' with another neuron via a synapse. Thus, estradiol encourages the formation of new connections in the brain.

Conversely, progesterone inhibits these processes. **Does this mean that the brain forms more connections when estrogen levels are at their highest? Should you be trying to study in that phase of your cycle?**

While this unfortunately remains unknown, a study by Zsido et al. published very recently aimed to explore the menstrual cycle's effect on memory and cognition using human participants.

One of the areas this study focused on was the hippocampus, an area of the brain involved in emotional regulation and cognition amongst other things. Areas within the medial temporal lobe (MTL) , which is involved with memory, were also looked at. Both the hippocampus and MTL are densely populated with estradiol and progesterone receptors which allow the hormones to affect the brain on a cellular level.

The study found that changes in volume for several subregions of the brain were associated with fluctuations in hormones over the menstrual cycle [3]. One particular region, the cornu ammonis 1 (CA1) increased in volume in association with increased levels of estradiol. Conversely, progesterone was negatively associated with volume of CA1. **The significance of this is that CA1 is critical for memory integration. What does this tell us?**

Well, it tells us that at certain points during the menstrual cycle, this crucial area undergoes changes in its plasticity - there are times when it might be able to form more connections and times where it may be forming fewer. **Is this because of sex steroid hormones?** We don't know that yet, but we do know there is a correlation.

If future research determines the relationship between them is causal, then the menstrual cycle could be directly or indirectly affecting memory and cognition. It could mean that at certain points of a cycle, one's memory might be better - or worse. It could change what we know about cognition, even how we approach cognition.

But, before we get ahead of ourselves, let's remember: even if the menstrual cycle does affect cognition, the changes may be too subtle to detect. Additionally, the brain has a tendency to try to compensate for any deficits, so although the brain may functionally work a little differently in certain phases of the cycle, we might perceive it as working the same.

So, what can we take away from all of this?

While so far we are unable to confirm anything, what we can say is, is that the impact of the menstrual cycle on cognition remains a complex and evolving area of study. Our knowledge of how the menstrual cycle affects the brain is steadily advancing, and with better technology we will hopefully be able to dive even deeper. Not only that, but this research could help create treatments for those who suffer from cognitive deficient due to their menstrual cycle. So, as we continue to explore this fascinating connection, the future holds the promise of unlocking new insights into cognition and the menstrual cycle.

REFERENCES:

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Changes that occur in the brain during learning

TREADING WATER

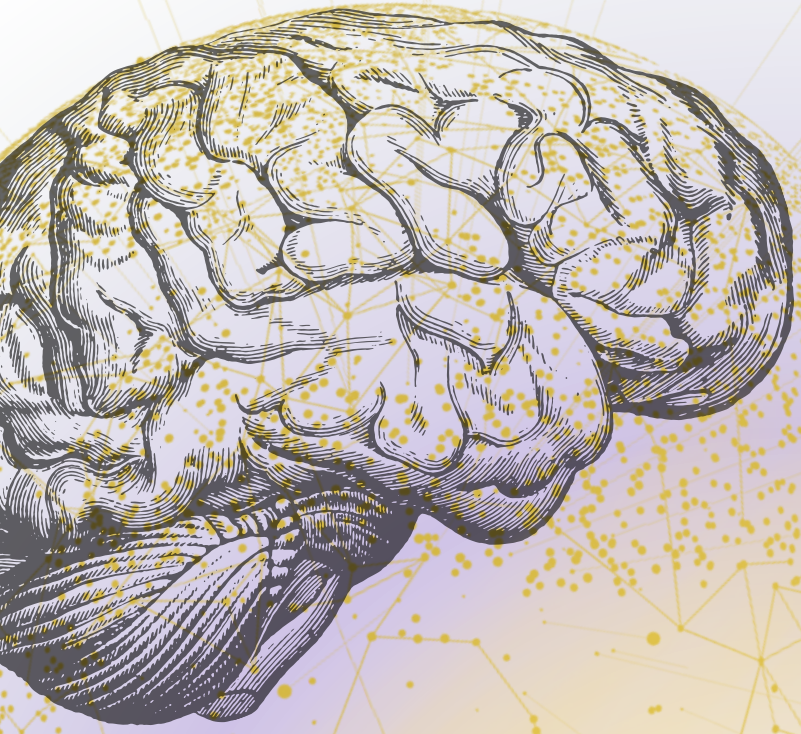
WRITTEN BY CHARLOTTE WILLI.
EDITED BY ARANII NAGARAJAH
DESIGNED BY LUCIA VILLANUEVA

"Neuroplasticity" is a term that was coined in the 1960s by Jerzy Konorski. This marked a significant shift from the earlier belief that the brain remains 'fixed' and unchanging after development or birth. Contrary to this prior notion, studies conducted for several decades have revealed that the brain is indeed "plastic" throughout one's entire life, constantly undergoing changes. These changes can occur in milliseconds, and a prominent mechanism driving these brain changes at any life stage is the process of learning and experiencing.

What changes does the brain undergo during learning?

Research in cognitive neuroscience has shown that learning causes physical structural changes in the brain. These changes are responsible for a functional reorganisation of the brain. There are two primary mechanisms through which the brain undergoes these physical changes: the formation of new connections and the reinforcement of existing connections.

When you learn **something new,** the brain forms **new connections** among synapses, and these new connections are associated with the process of learning. Conversely, when you practice a **task repeatedly,** the neuronal connections associated with that task are **reinforced**. This strengthening occurs because the brain recognizes the importance of solidifying connections required for frequently performed activities, such as the routine act of brushing your teeth. Another factor contributing to strengthened connections is the **influence of emotions.** If an experience is linked to a strong emotion, be it happiness or sadness, the brain prioritises strengthening this connection to aid in memory formation.This is why we may vividly remember significant life events, like our engagement, while forgetting routine specifics, such as what we had for dinner last Wednesday



The more you know the more you grow?

An illustration of the brain's structural changes resulting from learning can be seen in the context of language acquisition. A Swedish study (Mårtensson et al. 2012) conducted MRI scans to observe physical brain changes tied to specific areas. It involved young adult military recruits engaged in intensive language learning (Arabic, Russian, or Dari) compared to a control group consisting of medical and cognitive science students. The MRI scans revealed an expansion in the brain regions of group 1, while group 2, comprised of medical students, did not exhibit significant structural changes. However, this article focuses on changes in the brain during any type of learning, and certain aspects of the study warrant scrutiny. For instance, one may question what group 2 was studying, considering their medical background, which may have already influenced their brain structure.

Furthermore, distinguishing between studying and learning is essential, as students revising previously acquired knowledge might not exhibit substantial structural changes in the brain. In essence, this study underscores the significance of learning, even if the focus was primarily on language acquisition

Myelination as the main driver for learning?

More recent research has expanded our understanding of brain plasticity, indicating that neurons are not the sole neuronal cells exhibiting this characteristic. Oligodendrocytes, responsible for myelinating the brain's axons, have typically been associated with a primary function of generating myelin sheaths within the central nervous system. Astonishingly, one oligodendrocyte can myelinate up to 100 axons. Recent findings suggest a compelling connection between oligodendrocyte proliferation/distribution and myelination, and their influence on learning and memory, as well as the reciprocal impact of cognitive processes on these cells. This understanding has become particularly noteworthy in the context of conditions like multiple sclerosis, underscoring the pivotal role of oligodendrocytes and myelin. The ongoing degradation of myelin holds the potential for severe outcomes, including life-threatening consequences.

Firstly, it is important to discuss some background knowledge on how **myelination** occurs in infants. The human brain undergoes remarkable transformations during its developmental stages, and it's a known fact that full brain development continues until around the age of 25. We've already discussed the potential consequences of myelin loss. However, it's intriguing to note that a 6-month-old child possesses more **synapses** than an adult. This synapse abundance or synaptic loss overtime is not unhealthy. Between the ages of 2 and 10, an infant's brain experiences a phenomenon known as **pruning**. During development an overproduction of synapses takes place, creating more of them than necessary. Following this, pruning takes place: these "excess" synapses are selectively pruned, leaving behind only the strengthened connections.

It's during this process that myelination finally occurs, as myelinating axons with oligodendrocytes demands a significant amount of energy and only occurs when a connection is deemed vital.

A 2020 review (Xin & Chan, 2020) discussed a variety of rodent experiments that were conducted to analyse oligodendrocyte and myelin alterations following different experiences. These experiences encompassed **sensory changes**, such as sensory deprivation or increased sensory stimulation, social interaction effects (social isolation), motor learning (repeated motor training), spatial learning, and fear conditioning.The outcomes of these experiments revealed that the **impact of sensory deprivation** varied depending on whether it occurred during development or in adulthood.

However, it consistently led to lower rates of cortical-specific myelination. Increased sensory stimulation, through exposure to an enriched environment, resulted in higher numbers of **oligodendrocyte precursor cells (OPCs)**. Yet, after the cessation of stimulation, not all OPCs were able to fully integrate into the neural circuitry, though an overall increase in myelination was observed.

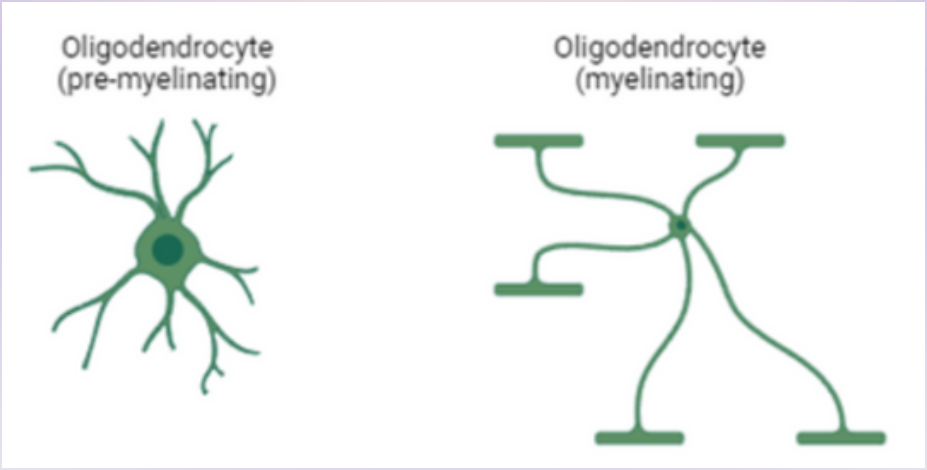


Figure 1: Visualisation of an oligodendrocyte, both pre-myelinating and as it is myelinating axons (Created with biorender.com).

Social isolation exhibited a decrease in myelin content but not in oligodendrocyte numbers, indicating that social isolation primarily **influences myelination** rather than oligodendrocyte differentiation. It's noteworthy that social isolation during adulthood might not have significant effects on myelination. In the context of repeated motor learning, rodents subjected to extended task training over multiple days showed increased OPCs and mature oligodendrocytes. These changes were particularly noticeable in regions of the brain associated with the specific task. **Spatial learning** led to a similar outcome, with an upsurge in OPCs observed in certain areas related to spatial learning. However, other regions crucial for spatial learning did not exhibit changes in OPC numbers. This suggests that learning-**induced OPC proliferation** and differentiation may occur at varying times and rates, depending on the specific brain region involved. Fear conditioning of rodents resulted in increased myelination in the prefrontal cortex, though these changes became apparent over a period of 7 to 14 days.

A common observation arising from these experiments is that oligodendrocyte plasticity primarily exerts its effects on brain regions associated with the specific type of learning undertaken. The studies collectively indicated an increase in oligodendrocyte precursor cells (OPCs), mature oligodendrocytes, and myelin in rodents engaged in various learning tasks

Notably, not all three of these factors were consistently present at the same time, suggesting that different tasks may necessitate distinct alterations in the brain, occurring at different paces and in different regions.

In conclusion, research has demonstrated the **brain is not a fixed structure.** It undergoes physical changes every time an individual learns something new or has a new experience. Recent studies have shed light on the essential functions of oligodendrocytes in the process of learning. Experiments conducted using rodent models have underscored the significance of oligodendrocytes and myelin in learning and memory. Moreover, individuals afflicted by neurological and psychiatric disorders that manifest anomalies in oligodendrocytes or myelin often exhibit cognitive symptoms, further reinforcing the critical role of these cellular elements.

Nonetheless, there appears to be no universal **mechanism of reorganisation.** Oligodendrocyte and myelin plasticity seem to be tailored to the specific neural circuitry and behaviours involved, leaving much yet to be unraveled about the complete understanding of how oligodendrocytes interact with neuronal circuits.

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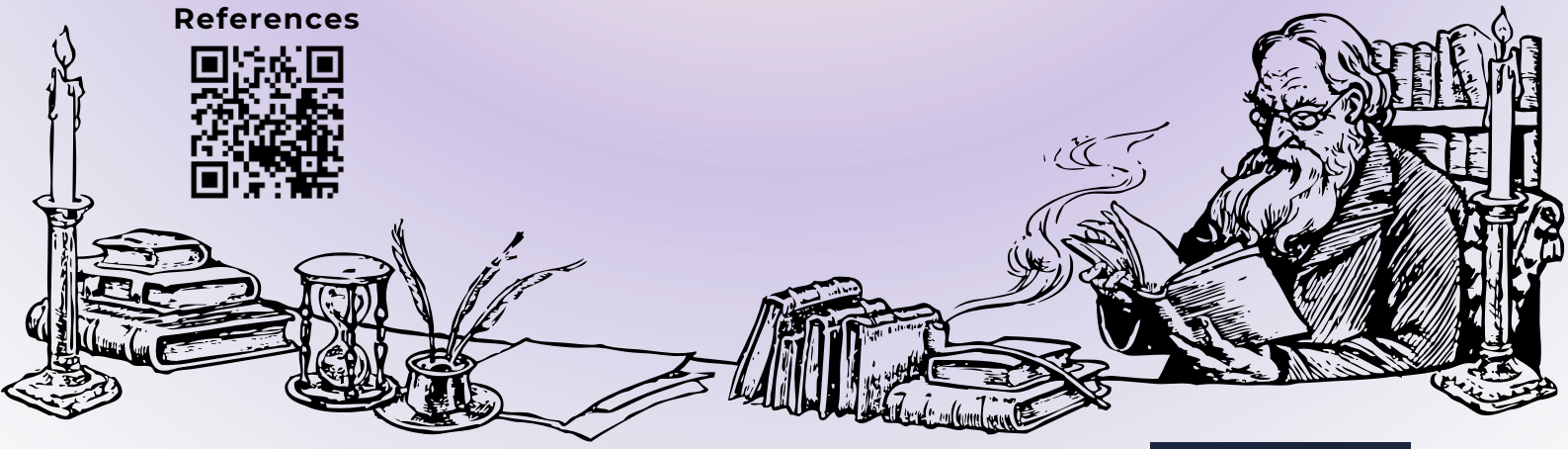


Cosmological Time Dilation

TREADING WATER
WRITTEN BY IDA ÅSLJUNG
EDITED BY SAMUEL GINZBURG
DESIGNED BY YASMIN MARZIAKHALL

Did time run slower

Over a century ago, Albert **Einstein** made the groundbreaking discovery that **time is relative.** This very moment in time, as you're reading this article, is therefore not universal, there is no absolute now that **pierces** through all the galaxies and **steadily** moves forward. In the realm of relativity, time is instead more like a **dynamic river**, flowing faster round certain creaks than others - slowing down in the presence of gravity and at **velocities** close to the speed of light. Recent research, published this July, seems to suggest that this cosmic river once flowed at a **much slower pace**, that **time itself is speeding up.**

Einstein's theory underpins this novel observation made by astronomers at the University of Sydney – Cosmological time dilation. They found that shortly after the Big Bang, around twelve billion years ago, time ran **five times slower** than it does today. This does not mean that if there existed a copy of earth back then, those humans would see rain falling in **slow motion** or that they would feel their hearts **beat five times slower.** However, if today, we could somehow look back into the past at this other earth, this is exactly what we would observe.

To properly understand cosmological time dilation and how scientists were able to observe it, let's first take a closer look at Einstein's two theories of relativity.

The theory of **special relativity**, postulated in 1905, was a monumental departure from the classical understanding of time and space, which was largely influenced by the ideas of **Isaac Newton**. This prevailing view, as described by Newton, held that time and space are **absolute, fixed entities.** A uniform river. Einstein's departure from this common view came from the realisation that the speed of light is the same to all observers, regardless of their motion, as implied by **Maxwell's** equations of electromagnetism. One of the primary **consequences** of this conclusion, is that there must be observers who don't agree on time-intervals, this is what is known as time dilation. For an object in motion, time passes by slower compared to an object at rest. This phenomenon is best exemplified by the famous **'twin paradox'** thought experiment. Imagine two identical twins, one of whom embarks on a high-speed rocket journey into outer space while the other remains on earth. The space-bound twin travels for one year at **99.99%** the speed of light before returning to Earth; upon landing, she finds that her twin has **grown old** and haggard, having aged 70 years, while she has only **aged one.**

in the early universe?

Ten years after publishing his paper on Special Relativity, Einstein published his General Theory of Relativity, adding gravity into the equations.

What he found was that gravity doesn't only pull bodies of mass together, it **curves space-time** and as a result of this time flows at a **slower pace** in the **presence** of **gravity**.

Once again, Einstein showed that Newton's uniform river of time is really a **dynamic and everchanging** one.

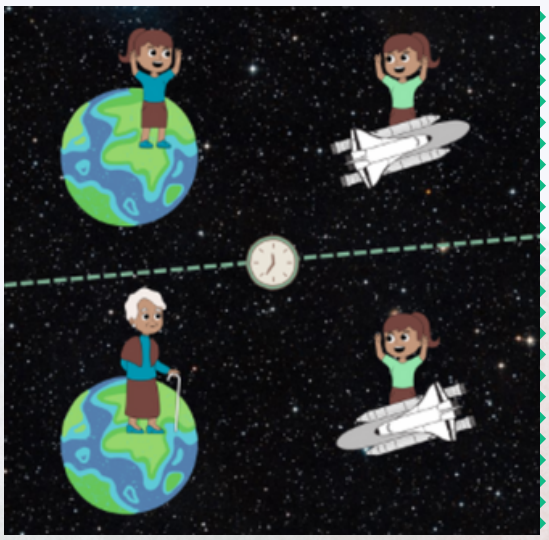
Although the movie Interstellar is mainly science fiction, it is therefore scientifically possible (spoiler alert) that for hour the crew spends on Miller's planet, seven years actually passes by on earth given that Miller's planet is big enough.

According to general relativity then, if one wishes to travel to the future all one must do is to spend some time near a large body of mass, such as on a massive planet or even more efficiently, close to a black hole, and voila, you've taken a faster root down the river. Although **time-travel** into the future is very much **possible** in accordance with the theories of relativity, the prospects of **travelling back** in time **don't** look as promising.

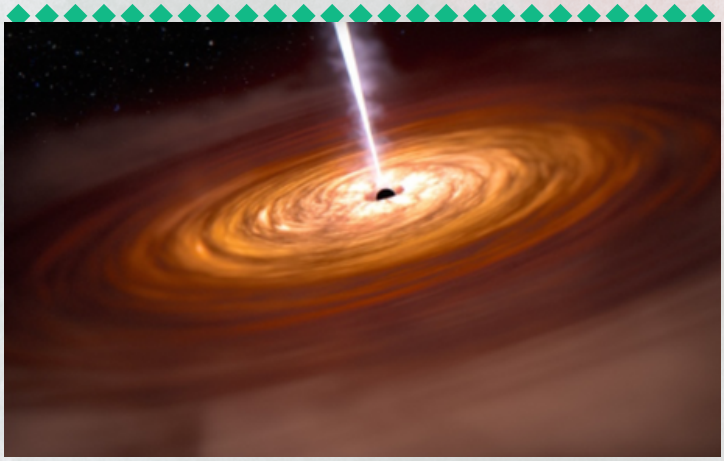
Luckily enough for astronomers however, there's another, rather simple way of peering into the past. In fact, since it takes time for light to travel from an object to our eyes, everywhere we look, we see the past. When you observe a tree 100 metres away, you see it at it was 333 nanoseconds ago and you see the moon.

Scientists are therefore able to look far back into the history of the universe by using powerful telescopes, such as the famous **James Webb Space Telescope**. The astronomers at the University of Sydney who published the study on cosmological time dilation in July this year were watching extremely luminous objects called **quasars**. Quasars, short for Quasi-Stellar Objects, are massive stellar nuclei powered by gases **spiralling** into **supermassive black holes** and releasing enormous amounts of radiant **energy** – which makes them **visible** billions of light years away.

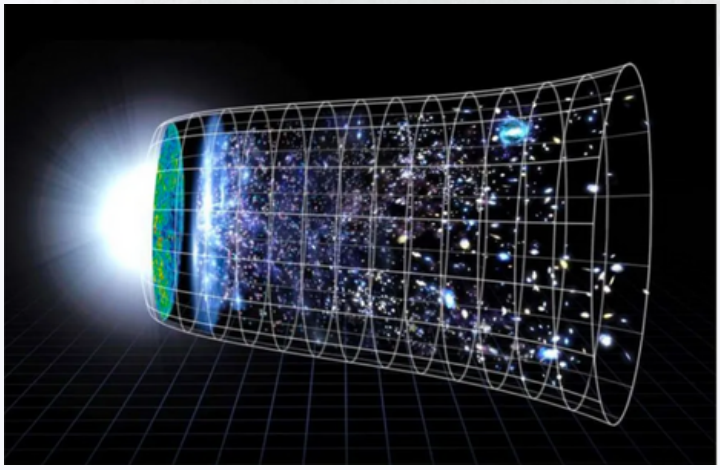
The astronomers at University of Sydney observed **190 quasars** at various distances from earth for **two decades**. Since the glow from quasars isn't steady, they were able to measure the relative time between the flickering as a function of distance. They found that quasars far away, hence further back in time, flickered slower than ones closer to earth, thus confirming Einstein's hundred-year-old prediction.



More precisely, they found that time appears to have passed at a rate five times slower than it does today. It is therefore the case that if there existed a copy of earth **twelve billion years ago**, and we had access to some science fiction telescope, we would see their rain falling in slow motion, their lives unfolding at a pace five times slower than **what we consider normal.**



Now does this mean that time itself is speeding up or could there be some other explanation for this observation? Well, a few articles following the publication in July suggest that time ran slower because the early universe was much denser and as we know from general relativity, **mass bends spacetime**. The more widespread conclusion, however, is that this is a result of **cosmological redshift**. The expansion of the universe means that distant galaxies and quasars are **receding at speed close to that of light.** Consequently, as their light traversers the cosmos it is stretched to **longer wavelengths – redshifted.** Not only are the wavelengths stretched towards the **red part of the spectrum**, but time itself is stretched. The light is in other words **dilated** and by the time it reaches earth what we see is **history unfold in slow motion.**



It is therefore not entirely clear whether this recent discovery means that the time of the universe is **actually speeding up or not,** frankly one could ask what that would even mean considering there is **no absolute**, universal time. Nevertheless, as Geraint Lewis, the lead author of the recent discovery at University of Sydney, concluded: "For decades **Isaac Newton** gave us this vision of a universe where space and time is **fixed**, and every clock across the universe ticks at exactly the same rate. Then **Einstein shattered this vision** by proposing that time is actually **rubbery and relative.** Now we've shown that **Einstein was, once again, correct**.".

References

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Connecting the Quantum Dots: The Science behind the Nobel Prize in Chemistry 2023

WRITTEN BY ISABELLA EWELL
EDITED BY SAMUEL GINZBURG
DESIGNED BY YASMIN MARZIAKHALL

TREADING WATER

On October 4th 2023, the Nobel Prize in Chemistry was awarded to Moungi Bawendi, Louis Brus and Alexei Ekimov for "the synthesis and discovery of quantum dots". Since quantum dots were first theorised in the **1970s,** there have been **few advances** with respect to the reproducible **synthesis** and applications of these **phenomenal nanoparticles** until now- changing the **field of nanoscience forever.**

What are quantum dots?

Chemistry is universally known as the study of electrons, something we have **accepted for centuries**. However, when groups of atoms approach the nanoscale (10-9 m), their electronic properties no longer behave in a **predictable** chemical manner.

Quantum dots (QDs) are clusters of **semiconductor crystals** made of only a few thousand **heavy atoms,** such as cadmium selenide (CdSe), zinc sulfide (ZnS) and, more recently, carbon-based quantum dots such as graphene nanostructures. Over the past five decades, we have only been able to **predict their behaviour**, but this year's

Figure 1: Quantum dots have the size relationship to a football as a football has to Earth.

Due to a phenomenon known as **quantum confinement,** a key characteristic of QDs is that their behaviour is no longer dictated by the number and properties of their electrons, but instead by their particle size. QDs are **so small** (1-10 nm) that the space available for their electrons to move in **rapidly shrinks**, causing them to **absorb and emit visible** light at **different wavelengths**.

As seen in Figure 2, the **smaller the size** of the quantum dot, the larger the energy **bandgap** between their low-energy **valence** bands and high-energy levels, known as **conduction bands**. These conduction bands are empty orbitals that electrons can occupy if provided with enough energy for excitation. The energy gap determines the **feasibility** of moving ground state (lowest energy) electrons into excited states (highest energy), thereby dictating how easily current can flow through the material. In a regular, or 'bulk,' semiconductor, such as arsenic or selenium, this bandgap is determined solely by their molecular structures.

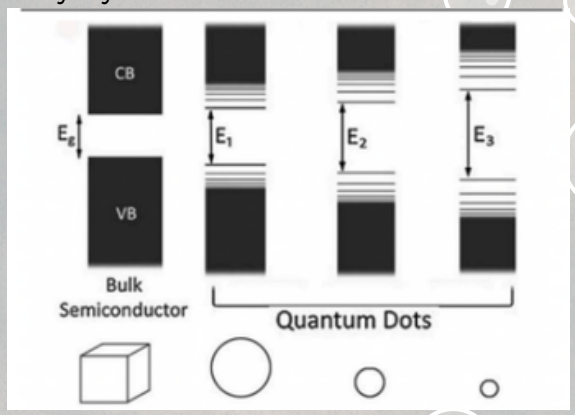

Figure 2: Size-dependent bandgap shown in bulk and quantum dot semiconductors.

Comparatively, the ability to finetune conductive properties based on molecular size using quantum dots affords scientists and engineers a much

greater level of control that we haven't previously been able to harness. Part of what makes this size-dependent control so revolutionary is that it can be visualised directly by simple **characterisation techniques**. Due to the ease of exciting electrons into the conduction bands of QD particles, they exhibit many types of **optical behaviour**, including **fluorescence** and **bioluminescence**. This allows them to be visualised by different tools such as fluorescence and laser scanning confocal microscopy, as well as more traditional techniques such as NMR and IR due to the ability of QDs to **interact with a wide range** of the electromagnetic spectrum.

Advancements in the synthesis of QDs

Quantum dots have been successfully synthesised since the late **1980s**, with the ultimate goal of making them at an industrial scale for a range of applications. However, this is only possible if the dots can be synthesised to produce shape and size uniformity in each QD- a feat for which **Bawendi is** attributed to overcoming by developing the **colloidal synthetic method.**

In Bawendi's scheme, semiconductor precursors are rapidly injected into extremely hot and vigorously stirring organic solvents, such as hexane or toluene. The hot solvent allows the **nucleation** of the particles to be controlled, to ensure their **miniature size.** Once the solvent begins to cool, the crystals **stop forming**. Reheating the reaction causes the crystals to grow once more; the **longer** the solvent is heated, the **larger** the crystals become. Controlling the temperature of the reaction in this way is **vital** for the formation of **uniformly-sized** quantum dots.

One of the more traditional methods of synthesising QDs was by **chemical vapour deposition,** where the crystals are deposited onto a solid substrate after volatile gaseous reagents **react together**. Although QDs synthesised by this method are generally uniform in size and exhibit sharp **phosphorescent peaks**, they are often larger (15 nm in diameter). While this method has proficient crystallinity for what is a chemically-challenging synthesis, the high diffusion rates can often lead to substrate degradation and the high temperatures make control of QD size and shape **more difficult.**

As we continue progressing the synthesis of QDs into the 21st century, it is vital that researchers **minimise** their environmental impact. One of the most promising methods of QD synthesis that takes this into account is **hydrothermal synthesis**, which offers a **more sustainable** alternative to both the high energy demands of the process and the use of **harmful solvents**. In this synthesis, bio-organic compounds can be used, such as **glucose,** acting as a carbon-based reagent. Similarly to Bawendi's synthesis, the sugar is heated to high temperatures but in an ionic solvent, such as KHNO3. The size and shape of the QDs is controlled by both **temperature** and the **salt concentration.**

What do quantum dots mean for our future?

The breadth of compounds and sizes available for creating quantum dots means their applications are equally broad, ranging from **high-resolution plasma screens,** to **revolutionising solar panel designs.** One of the most promising applications of quantum dots is in the field of biomedicine, where the structures have shown **great potential** in both **drug delivery** and **cellular imaging.**

Despite their miniscule size, the surfaces of QDs must be **engineered** in order to be taken up by cells- **vital** for their use in **biomedical imaging** and **targeted drug delivery**. **Coordinating ligands** have been used to facilitate the precipitation of QDs in their syntheses for **decades**. For instance, the use of **electrostatic ligands,** such as Na2S has accelerated the nucleation of QD crystals in organic solvents since the ligands render them insoluble due to the non-polar nature of the solvent environment. Remarkably, these ligands have also shown the **potential to minimise the size** of the QDs by nearly 5 nm.

While this has been phenomenal in developing synthetic strategies, more recent advancements have been made in engineering ligands that can facilitate the cellular uptake of QDs for biomedical applications, an **especially difficult** feat due to the two environments that must be taken into account: the **hydrophobic core** of cellular membranes, compared to the **aqueous solution** of the cytosol- both of which the QD must pass through.

One strategy for overcoming this **amphiphilic barrier** is the design of **charge-convertible ligands** derived from a widely-used anti-cancer drug: cis-platin. The coordination of pH-dependent ligands, such as the anionic polymer PEF-(PAH/DMMA) to generate cis-platin-based QDs has shown potential to **both image and treat cancer cells**. This is due to the ligands' charge-changing property, from a negative charge at physiological pH (pH 7.4) to a positive charge in a tumour environment, allowing the coordinated QD to both enter cancerous cells and to interact with the **negatively-charged** DNA backbone, triggering **cell death**. Additionally, due to their fluorescent properties the QDs can be visualised by multicolour bio-imaging such as fluorescence microscopy, which **assists in tracking the movement** and **mechanism** of QDs through cells.

An illuminating discovery

The **successful synthesis** and isolation of quantum dots has planted "seeds of nanoscience" that has **bridged the gap** between quantum mechanical theories of the past and the future of scientific technology.

As research into the creation and applications of quantum dots continues, researchers must be able to **elucidate** how their properties can best serve the needs of our society. A major consideration for the **industrial development** of QDs is how the reactions can be **scaled up in a sustainable and efficient way,** taking into account solvent effects and energy consumption. Equally, the development of carbon-based QDs has introduced novel imaging tools and drug delivery systems for biomedical scientists, but there are still concerns with respect to their **cytotoxicity** and **biocompatibility** in human cells which must be overcome in order for QD-based healthcare to become widely available.

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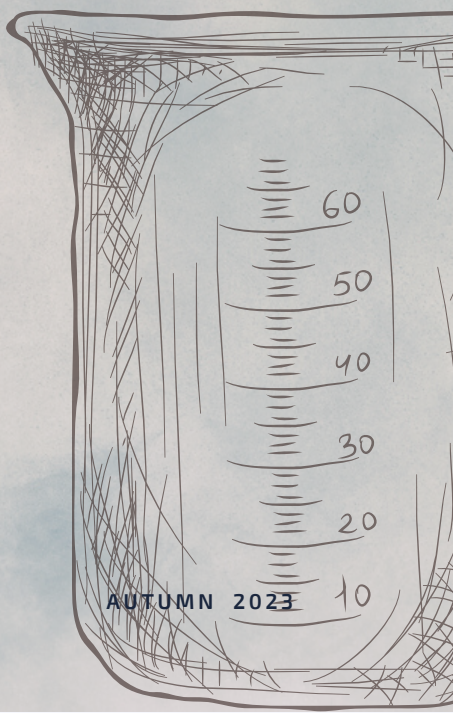

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How Google DeepMind's Artificial Intelligence is Transforming Retinal Healthcare

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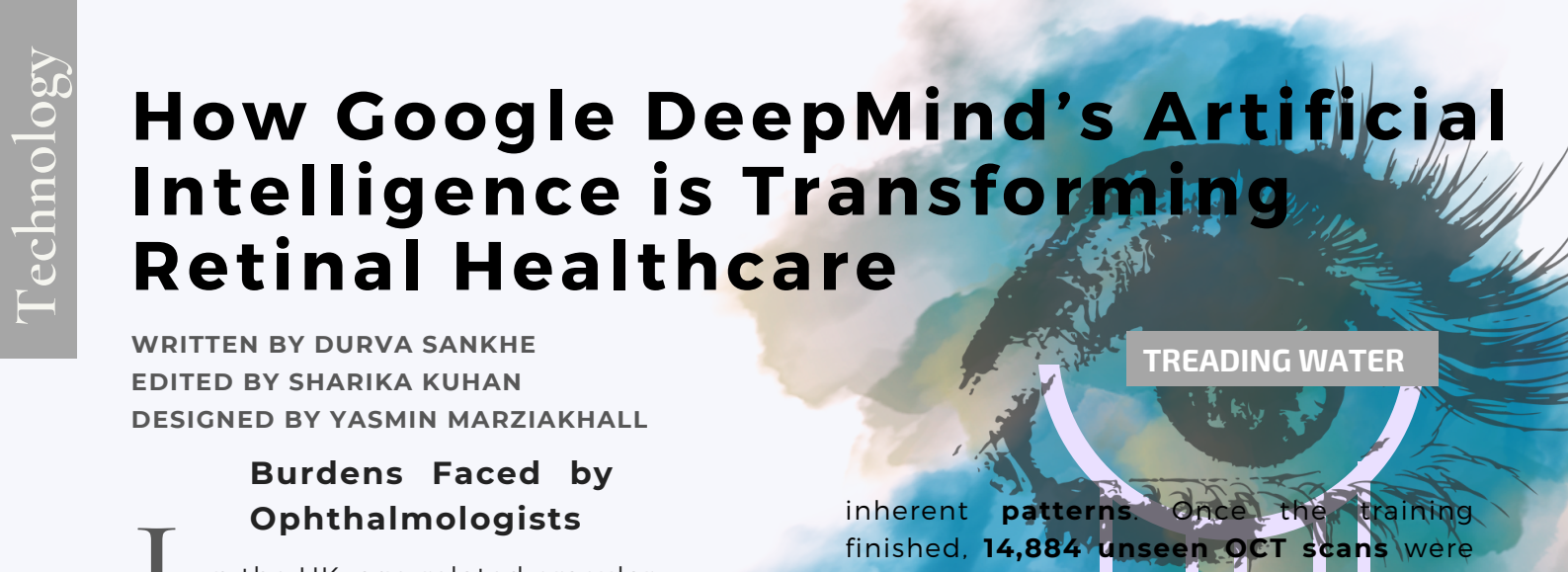

Burdens Faced by Ophthalmologists

In the UK, age-related oracular degeneration and diabetic retinopathy are the **leading causes of blindness** [1]. For such ocular morbidities, ophthalmologists require scans via digital fundus photography and optical coherence tomography (OCT) to diagnose and decide on appropriate treatment [2]. However, the process of analysing these scans is **time-intensive and complex,** which can result in delayed patient care. This warrants concern since a UK-based study discovered that patients are suffering **preventable vision loss** as a consequence of **delayed ophthalmic treatment**, indicating a **lack of capacity** within hospital eye services [3].

AI as a Diagnostic Tool

Intending to reduce the burden on ophthalmologists, researchers at Google DeepMind and Moorfields Eye Hospital formed a **partnership** concentrated on creating an **artificial intelligence (AI) tool** that could interpret OCT scans as accurately as humans, thus providing ophthalmologists **more time** to treat sight-threatening diseases **successfully** [4]. The diagnostic AI framework consisted of a combination of two deep learning networks- **image segmentation and classification** - in succession, as illustrated in Figure 1. The first half of the framework focused on the former network (image segmentation), which used a three-dimensional U-Net architecture to map the raw digital OCT scans into a tissue-segmentation map that delineated 15 retinal morphological features. In order to perform this mapping, the image segmentation network was trained. on 877 OCT scans and their manual segmentations with the expectation of recognising and learning the inherent **patterns**. Once the training finished, **14,884 unseen OCT scans** were passed through the trained image segmentation network and automatically segmented. These resulting tissue maps and the clinical labels (diagnosis and referral triage decision) formed the training set for the classification network [5].

The framework's performance was evaluated by a test dataset of 997 new patient scans (not in the training set) and their corresponding class label (final diagnosis and referral pathway). The **framework predicted a referral** for every patient in the test dataset, as did an independent cohort of eight clinicians composed of four retina specialists and four medical retina-trained optometrists. The clinicians provided two decisions: the first was based on analysing just the OCT scan, and the second was based on analysing the OCT scan, fundus image, and clinical notes. **Overall**, the framework demonstrated performance **on par or even superior to the experts.** For referral predictions, based solely on OCT scan alone, the framework performed the same as the two best retinal experts but was significantly better than the remaining retinal specialists and four optometrists. In contrast, when fundus image and clinical notes were provided to the clinicians alongside the OCT scan to make their referral prediction, their **performances improved,** yet only five of the experts matched the performance of the framework, and the remaining three **comparatively underperformed [**5]

Potential Future Work

In the future, researchers could conduct a randomised controlled trial to gather

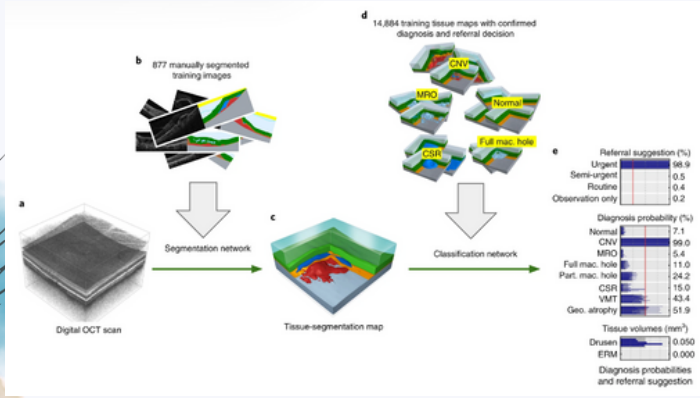

Figure 1: AI Framework; a Raw retinal OCT scan (6 × 6 × 2.3 mm³ around the macula). b, Deep segmentation network, trained with manually segmented OCT scans. c, Resulting tissue segmentation map. d, Deep classification network, trained with tissue maps with confirmed diagnoses and optimal referral decisions. e, Predicted diagnosis probabilities and referral suggestions. [5]

evidence about the **efficacy** of the developed diagnostic AI framework. Additionally, the output of this framework can be **further optimised** and **fine-tuned** in order to minimise various types of diagnostic errors, thereby improving its accuracy and reliability [5]. Currently, this diagnostic AI framework is directed towards the clinical treatment pathway. However, it has the potential to be implemented in the clinical training domain to teach healthcare professionals to an expert level since it already produces **visualisable** segmentations of OCT scans and matches clinician performance when predicting diagnoses and referrals for large volumes of imaging data [5]. Lastly, although this framework consists of two network stages, future work could focus on utilising the segmentation network and its output to **quantify retinal morphologies** and derive measurements of pathologies [5].

Academic Criticism

Although the developed diagnostic AI system has shown great success, the technology is still in the **preliminary stage** and needs to undergo **rigorous clinical trials** before deployment in clinical settings. For this reason, there have been no public and clinician responses to the the creation of the AI tool. That being said, researchers have expressed **concerns** about so-called "digital pioneers" like DeepMind

This scepticism has arisen due to the **controversy** surrounding the **company's app**, made in collaboration with the **Royal Free Hospital**, which alerted clinicians of patients at **risk of acute kidney injury**. Essentially, millions of **confidential** patient medical records were transferred from Royal Free Hospital and into the hands of Deep Mind **without informing patients** nor obtaining consent, as well as no prior consultation with relevant regulatory bodies. Thus, **breaching the UK Data Protection Act** [6].

From the research partnership with Moorfield's Eye Hospital, the developed **AI algorithm** and extracted knowledge will belong **exclusively** to DeepMind. Although they **published the scientific results** of their research study, DeepMind's researchers stated that they were unable to release the full algorithm code as it utilised **"proprietary components"**, thereby rendering it inaccessible to the general public. The inability to view or modify this code not only produces a lack of transparency between the creators and the consumers but **limits** the progression of research in the healthcare domain [6].

Conclusion

In conclusion, the creation of this diagnostic AI framework automates the otherwise complex and time-intensive process of analysing OCT scans faced by ophthalmologists as well as performing **on par and at times better** than experts, therefore highlighting the **utmost utility** of this technology. Furthermore, the various future works extending from this research partnership open the doors to further collaborative opportunities, continued development, and innovation. Nevertheless, it is **imperative** to emphasise that collaborations between healthcare institutes and tech enterprises uphold the protection of patients and their health data, to maintain **trust and confidentiality.**

References


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