ScienceMind

NOVEMBER 2021

KING'S College LONDON

STAFF

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THIS ISSUE

Dear Reader,

Welcome to the November 2021 issue of Science Mind, where you will find articles written in the topics of Genetics, Sports Science, Biochemistry, Immunology, Pharmaceuticals, Virology, Psychiatry and Neuroscience. I hope you enjoy reading this issue as much as we enjoyed creating it. Other references can be found in the code below.

Science Mind is the award-nominated, student-led science magazine of King's College London, which focuses on reporting recent findings in the main branches of science to students and the wider community. We aim to showcase and develop the written and oral communication skills of students interested in research by concisely explaining complex scientific concepts in the form of lay articles and conducting interviews. Authors can also broaden their knowledge by writing articles for different sectors between issues.

Each new issue features an interview with a King's College London researcher to discuss their current research and how they were introduced to their field, providing valuable networking opportunities.

Yours faithfully,

The Deputy Editor-in-Chief
Rosa Tsucala

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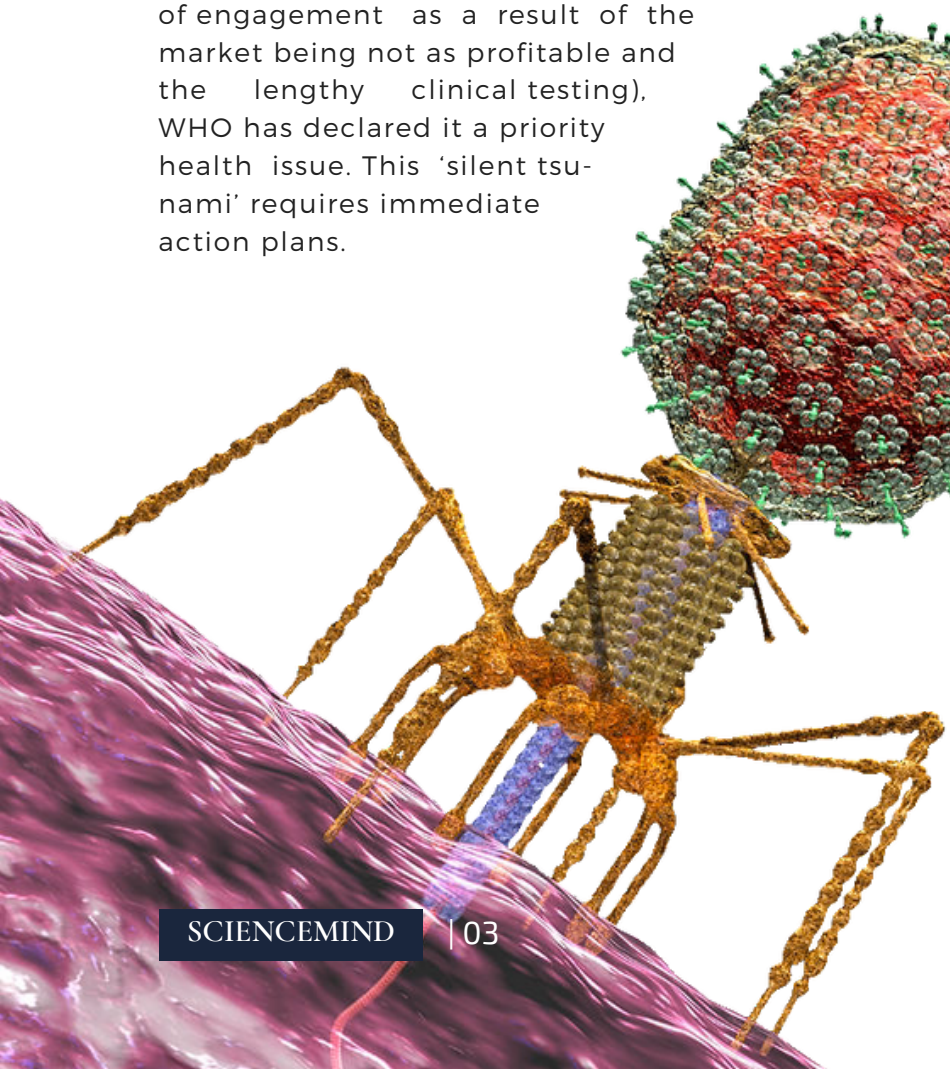
DEEP DIVE

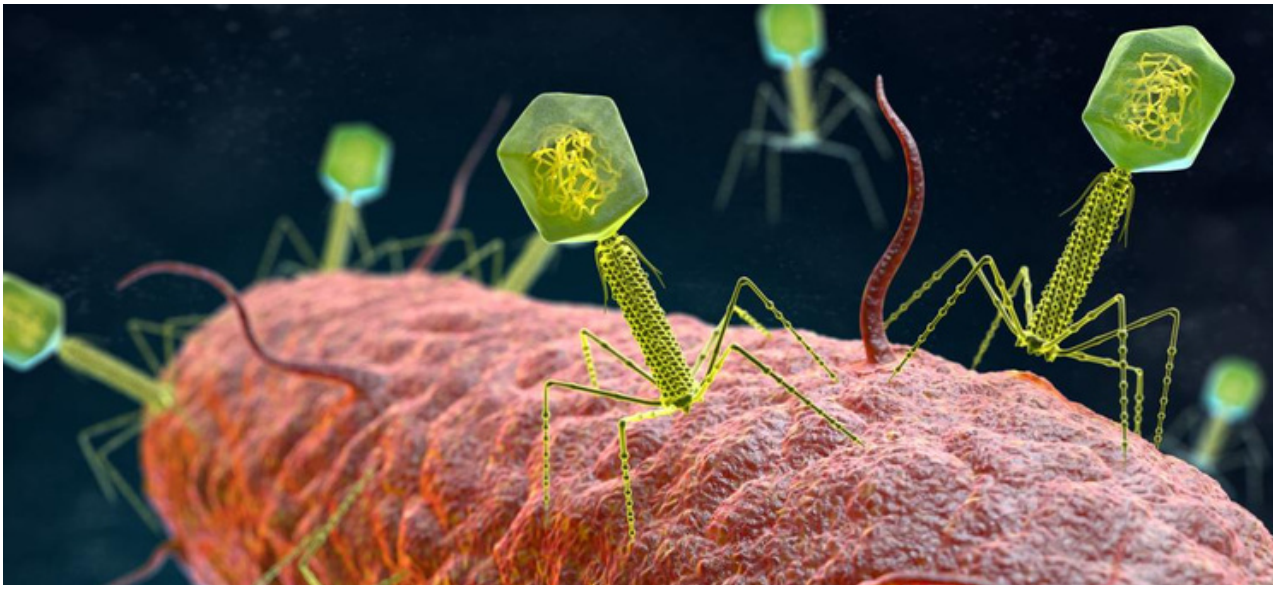
Phage Theory: Combatting Antibiotic Resistance Using Viruses

WRITTEN BY CANSU OZDEMIR | EDITED BY DRSHIKA MEHTANI | DESIGNED BY TAMARA YAP

Antibiotic resistance is a global threat to humanity, with common infections such as pneumonia and gonorrhoea becoming more difficult to treat as resistance continues to rise. Currently, disease-resistant illness takes over 700,000 lives each year but estimates show figures threatening to increase to 10 million deaths a year if no action is taken by 2050. With the last original class of antibiotics having been discovered in the 1980s (mainly due to both lack of engagement as a result of the market being not as profitable and the lengthy clinical testing), WHO has declared it a priority health issue. This 'silent tsunami' requires immediate action plans.



Bacteriophages, also commonly referred to as phages, are viruses that infect bacteria and are the most abundant organisms, with an estimated 10^31 particles on Earth. **Phage therapy** consists of viruses that are used to treat bacterial infections and is a current hopeful therapy to combat further resistance. The mechanism of phages is similar to that of a virus, as it binds to a specific receptor on the cell surface of the bacteria, inserts its genetic material into the cell where it then replicates and reassembles into its progeny. It goes on to follow one of two life cycles: lytic or lysogenic. **Lytic** phages are able to take over the machinery of the bacterium and make phage components, with the cell then undergoing lysis to release their own progeny. The **lysogenic** cycle results in the incorporation of the phage into the host's



genome using phage-encoded integrases (now labelled as a prophage). The **prophage** undergoes proliferation and the virus is able to reproduce in the offspring.

In theory, all bacteria can undergo lysis by either one bacteriophage, or by using a cocktail of phages to attack, thus they have the biological ability to be more effective than any antibiotic treatment. Their application in therapy is specific to which bacteria they are infecting, so spare collateral damage to the commensal microbiome of the patient, a current issue with broad-spectrum antibiotics, so can reduce the side effects that are experienced with antibiotic use such as nausea, abdominal pain and diarrhoea. The high specificity of phages benefit the issue at hand: even when bacteria do become resistant to a particular phage, this usually makes it more susceptible to antibiotics, so phage therapy could go hand in hand with current antibiotics to prolong their lifespan and reduce the rate of resistance. Research is being carried out for the opportunities that **CRISPR** (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing can bring to phage therapy, with the creation of a bioengineered phage to disrupt antibiotic-resistant genes and kill resistant plasmids. This sort of intervention would be invaluable to hospital settings and reduce the risk of contracting hospital-acquired infections such as MRSA and C.diff. Phages against disease-causing bacteria are quickly discovered due to their abundance and alongside their low production and purification costs, they have low costs relative to antibiotic use.

Whilst there are many positives for phage theory, there are also a handful of disadvantages that could hinder its progress in development. There could be reduced benefit due to the response of the immune system: as bacteriophages and their progeny are **non-self antigens**, they could be recognised by the immune

system and induce harmful responses, leading to the release of endotoxins; the introduction of inflammatory cascades and potential multiple organ failure. Identifying the appropriate therapeutic phage could be time-consuming and the risk of phages contributing to the development of antibiotic resistance through horizontal genetic exchange

Currently, whilst there are no approved phage therapies being used in humans, there has been use within the food industry with commercial phage preparations for taming bacterial pathogens against Salmonella spp., Listeria monocytogens, MRSA and E.Coli to name a few, and has been approved by the FDA to be a safe practice. There are currently many promising clinical trials taking place in humans, ranging from treatments for burn injuries infected by E.Coli and Pseudomonas aeruginosa, UTI and prosthetic joint infections..

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UK Disability History Month

18 November - 18 December

"My illness contributes to diversity by giving me an advantage and a perspective that's vital to the scientific community. That background and knowledge should be celebrated and cherished, not ignored. We must ignite discussions on the value of disability in the sciences."

Erica Avery

PhD, Johns Hopkins University
Fibromyalgia Syndrome

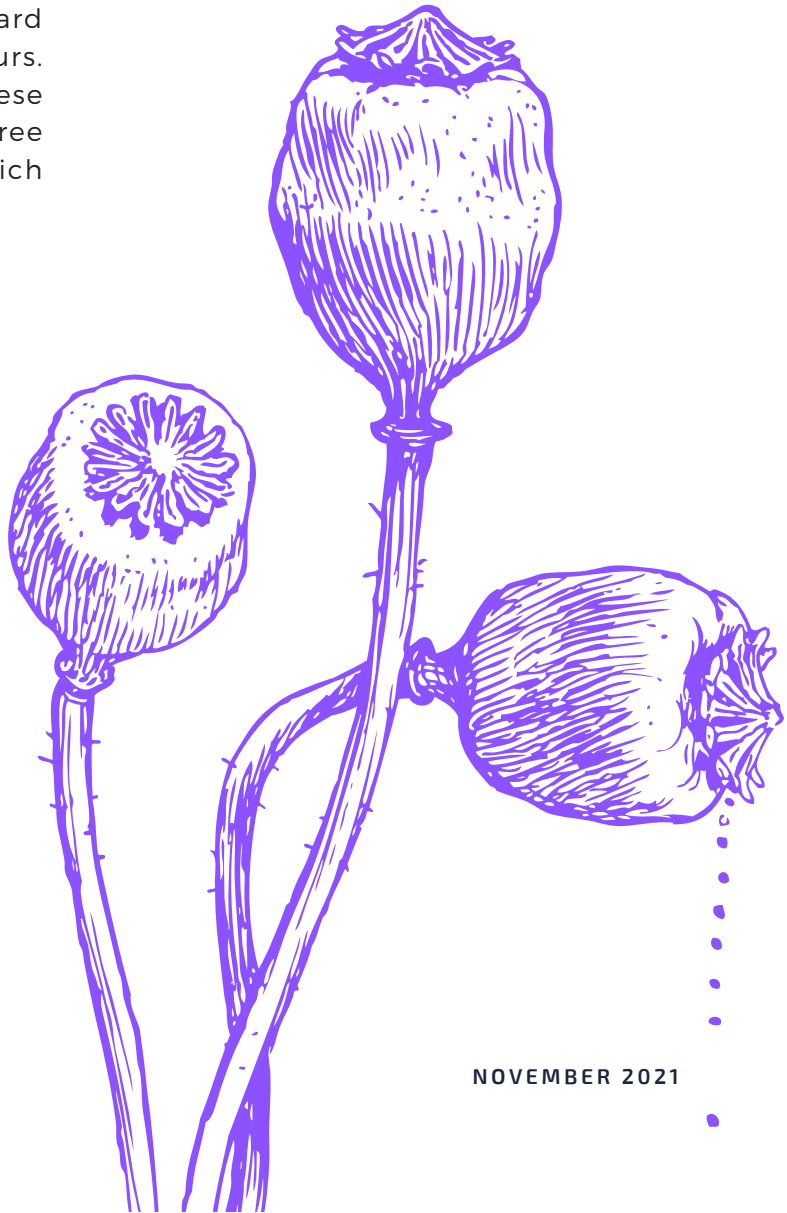
DEEP DIVE

Effects of Opioids on the Brain

WRITTEN BY CEREN YALCIN | EDITED BY ANAS SALEEM | DESIGNED BY TAMARA YAP

Opioids are naturally found in the seedpods of the **opium poppy plant** and have an astoundingly long-standing past in the history of humanity, considering that the early opioid use dates back to 5,000 years ago in Mesopotamia. Opioids were considered as 'the plant of joy' as they were said to generate a euphoric feeling (Smith & Passik, 2008, p. 4). At the present time, opioids are being utilised in medications to treat severe pain and are classified as prototypical analgesics, antitussives, and antidiarrheal drugs (KuKanich & Wiese, 2017). In addition to opioid consumption being highly addictive, it also has side effects including insomnia, constipation, nausea, shallow breathing, slowed heart rate, and loss of consciousness (Pathan & Williams, 2012).

Opioids administer pain control, reward mechanisms, and addictive behaviours. The underlying mechanism in which these processes occur is associated with three main **G protein-coupled receptors** which are: mu, delta, and kappa.



1- Mu Opioid (MOP) Receptors

Experiments conducted using mu-receptor knockout mice showed an increase in sensitivity to painful stimuli, a decrease in reward to non-opioid drugs of abuse an altered emotional response. Also, the feeling of euphoria, as well as the development of addictive behaviours are induced by the activation MOP receptors (European college of

Neuropsychopharmacology, 2017). Furthermore, major side effects regarding MOP receptors consist of respiratory depression and inhibited gastrointestinal tract secretions and peristalsis (McDonald & Lambert, 2005). Therefore, we can conclude that these receptors mediate both therapeutic and adverse effects.

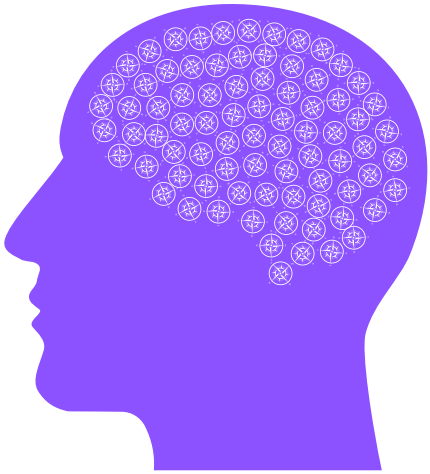
2- Delta Opioid (DOP) Receptors

Studies demonstrated an alteration in emotional reactivity in mutant mice lacking delta receptors mainly related to increased anxiety levels and depressive behaviours which make DOP receptors convenient substances for chronic pain treatment as well as providing anxiolytic and antidepressant-like effects (Quirion et al., 2020).

3- Kappa Opioid (KOP) Receptors

In another research, KOP receptor deficient mice established an increased response to visceral pain stimulus which implies the association of peripheral receptors rather than central receptors (Black & Travethick, 1998). However, unlike MOP and DOP receptors, KOP receptors were reported to cause unwanted effects such as dysphoria and stress.

Opioid receptors are spread across the brain, spinal cord, and peripheral nociceptors and they are detected at the presynaptic and postsynaptic sites of ascending pain transmission system of the dorsal horn of spinal cord, brain stem, thalamus, and the



cortex. These receptors can be activated by either endogenous peptides such as enkephalins, dynorphins and endorphin; or exogenous alkaloid opiates which can be exemplified with morphine as a prototype.

The mechanism by which the opioids work is carried out by the **attachment of opioids and opioid receptors.** Opioid receptors consist of extracellular, transmembrane regions linking to G-proteins, in this sense, opioid receptor activation induces a signal through Potassium ion channels and protein kinase C enzyme systems in cytosol and cell membrane which causes reduced action potential duration and neurotransmitter release. The binding results in cellular hyperpolarisation and inhibits the transport of information sent from the body to the brain regarding pain. Binding takes place between the three types of opioid receptors and their precursors (endogenous or exogenous as they were stated before (Law & Loh, n.d.). For example, pro-enkephalin binds to the DOP receptor, pro-dynorphin binds to the KOP receptor to establish their aforementioned effects (Pathan & Williams, 2012).

THREADING WATER

The Myth of Sex Differences in Human Brains

WRITTEN BY JANINE (WAI NG)
EDITED BY OLIVERA MITEVSKA
DESIGNED BY CELESTE COCKMARTIN

Other than **sex reproductive differences** (genitalia), human bodies are considered to share a lot of physiological similarities. However, there have been **controversies** in sex-specific characteristics in human brains over the decades. Some argue that the difference exists due to differences in biological mechanisms of the brain such as brain diseases observed in clinical cases. On the other hand, some believe that the variations developed owing to **environmental influences**, rather than the brain itself. In fact, some physiological differentiation may stem from subtle anatomical variance, but there is not always a correlation.

Before looking into the complexity of sex and neuroscience, it is crucial to understand some of the **terminologies**. Sex is referred to the chromosomal composition of a person. The sex spectrum is more sophisticated than we think but the ideas in this article will be based on **XX** and **XY** and focused on cisgenders, referring to the gender that is assigned at birth.

The assumption, or the classical view, of the suggested sex differences could be the action of **sex steroid hormones**. At first, it was believed that the presence of testosterone is the stimulus for differentiation into a male brain whereas the absence of testosterone leads to female brain development. Yet, future study shows that **oestrogen**, instead of solely testosterone, can be one of the essential elements for the differentiation of the partial sexually dimorphic brain regions such as the central nervous system (Hutchison et al., 1999).

In recent decades, studies speculate that the observations could be due to the distinct chromosomal composition. (Arnold, 2004) In general, males possess one X chromosome and one Y chromosome while females have two X chromosomes. Some genes on Y chromosomes, which are absent in females, may play a role in **non-gonadal cells**. This induces sex differences in cognition and brain physiology since infancy.

To validate the idea, the direct actions of sex chromosome genes on the brain have to be **isolated** from the indirect actions that are brought by gonadal secretions. However, it is **difficult** to develop a practical method to test the hypothesis on humans so it remains to be elucidated.

The differences between sexes can also be observed in the overall **composition** of the brain. Females have a higher proportion of grey matter in some regions of the cerebral cortex than males (den Braber, Anouk et al., 2011). The left hippocampus and amygdala of men tend to have a higher density. The former is involved in memory while the latter is responsible for memory formation, as well as emotion (Ruigrok et al., 2014).

Some physiological differences between the sexes are also revealed. The variance in the patterns or levels of brain activity is demonstrated using **PET imaging**. It is reported that the blood flow rate during a cascade of cognitive tasks was higher in female populations by measuring cerebral blood flow (Espisto et al. 1996) though the conclusion was not based on any anatomical difference. Nevertheless, a study related to glucose metabolism **failed** to present differences in overall glucose utilisation (Azari et al. 1992).

Building a clearer understanding of sex differences in brain organisations allows us to further explore sex-related behaviour, cognition and risk for psychiatric diseases. For instance, it is claimed that Alzheimer's disease and some depressive disorders are more prevalent in women. **More research** is required to clarify the relationship between anatomical distinctions and sex differentiation in human brains.

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SHALLOW DIVE

Has Society Built Psychiatry?

The Tale of Medicalisation

WRITTEN BY REBECCA HAMMERSLEY
EDITED BY ANASTASIIA TARASENKO
DESIGNED BY DORIS YU

In our current society mental ill health is treated with a concoction of drugs to allow the sufferers to conform to modern society living. But we can ask the question of **is this medicalisation necessary**? Is the reliance on drugs based on a purely biological need or has it come about as a result of our societal conformance?

First, we must look into **diagnosis**. Statistical manuals such as the **DSM** and **ICD** have been defining and classifying mental and behavioural disorders for many years, their purpose is to aid clinical diagnosis thus reducing the disease burden of mental disorders. Over the many years these manuals have been updated to ensure accuracy, disorders have been added and removed as have diagnostic symptoms. However, seemingly the main focus of diagnosis is the **deviation from the statistical norm**, this is when certain behaviours are labelled as wrong or as a sign of disease when they are abnormal in the current society. This causes disease to be **shaped by society and the current societal climate**.

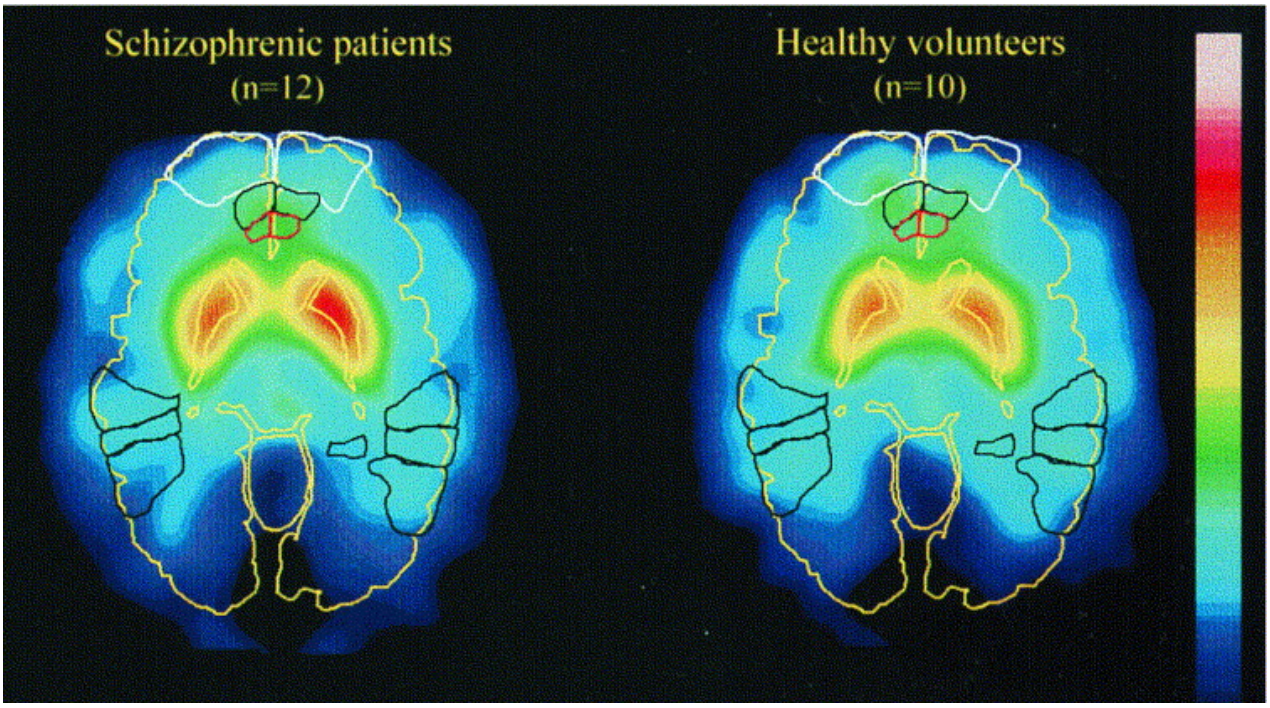


Figure 1. PET scans of the difference in dopamine activity between healthy volunteers and schizophrenic patients. The results of this study showed that the schizophrenic patients had increased dopamine activity in the prefrontal cortex and striatum. (Taken from Lindström et al., 1999)

For example, **homosexuality** was once listed as a mental health disorder in these manuals as this lifestyle did not fit into society at the time, whereas now homosexuality is widely accepted and is no longer clinically seen as a mental health disorder. In this example **all that has changed between these time periods is society**.

Many other disorders are placed in the DSM and IDC as mental health issues as the sufferers are not able to function in our high stress society, but does this make them mentally ill or is the issue our society? If our modern lifestyle was not as high demand would any of these conditions be defined?

This argument can be completely contradicted by our **improvement in modern technology**.

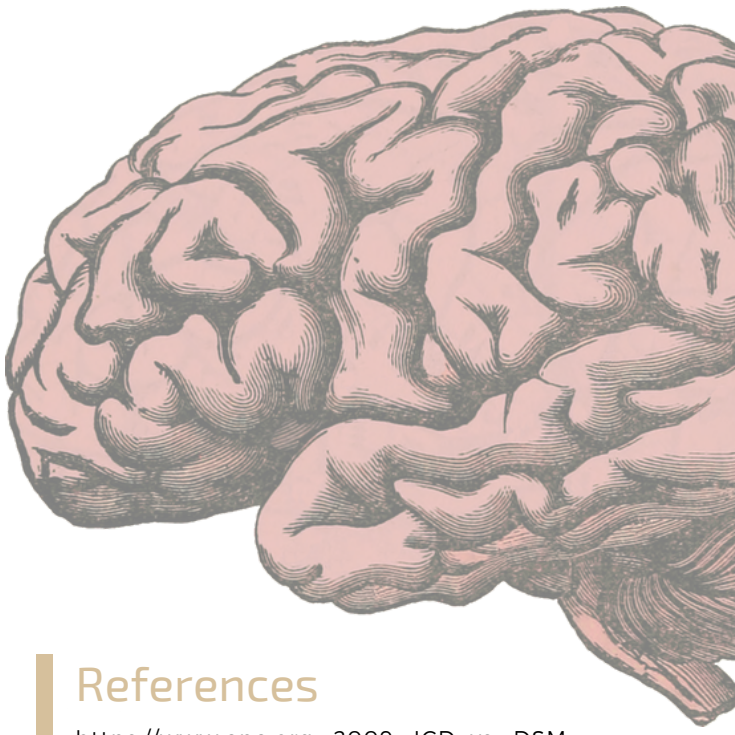
The improvement of brain scanning techniques has allowed us to see **changes in brain chemistry and structure** that could be responsible for causing this abnormality in behaviour.

For example, the research into **schizophrenia** suggested that it is linked to the levels of specific neurotransmitters, dopamine and glutamate for example, in the brain. Studies have found that positive symptoms of schizophrenia are linked to hyperactivity of the dopamine D2 receptor in the subcortical and limbic brain regions. Also, negative symptoms of schizophrenia have been linked to changes in activity at dopaminergic receptors; hypo-functionality of the dopamine D1 receptors in the prefrontal cortex has been linked to these negative symptoms.

Research such as this leads us to believe that these disorders are solely biological but, this is not the case. Schizophrenia is **strongly linked** to **living in urbanised areas** and being of a **low socioeconomic class**, these social factors cannot be explained biologically, feeding into the ongoing debate of nature or nurture.

For many years the debate of **nature or nurture** has been rife. Biological factors such as genetics predispose some to a certain disease but that disease might not become apparent if they do not meet the environmental triggers and vice versa. Meaning in order to answer this question the **interaction between our human biology** and **how and where we live our day to day lives** must be understood and interpreted to see the effect on our health.

Some biological factors are worsened by environmental factors allowing nature and nurture to go hand in hand, but this isn't always the case. Physical brain damage is not involved with the environmental or social factors and it could be argued that eating disorders would not be present if our society didn't focus on and stigmatise body images.



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UK Disability History Month

18 November - 18 December

"I believe it's (autism) why I am so precise, thorough, and logical, which are all excellent traits for a scientist. I make connections that the neurotypical brain might not be able to. It gives me a different insight into my work."

"Science really suits a lot of neurodivergent people. With the right support and adjustments, we can really thrive, and bring something unique to the table."

Daisy Shearer

PhD, University of Surrey
Autism

SHALLOW DIVE

THE PSYCHEDELIC RENAISSANCE

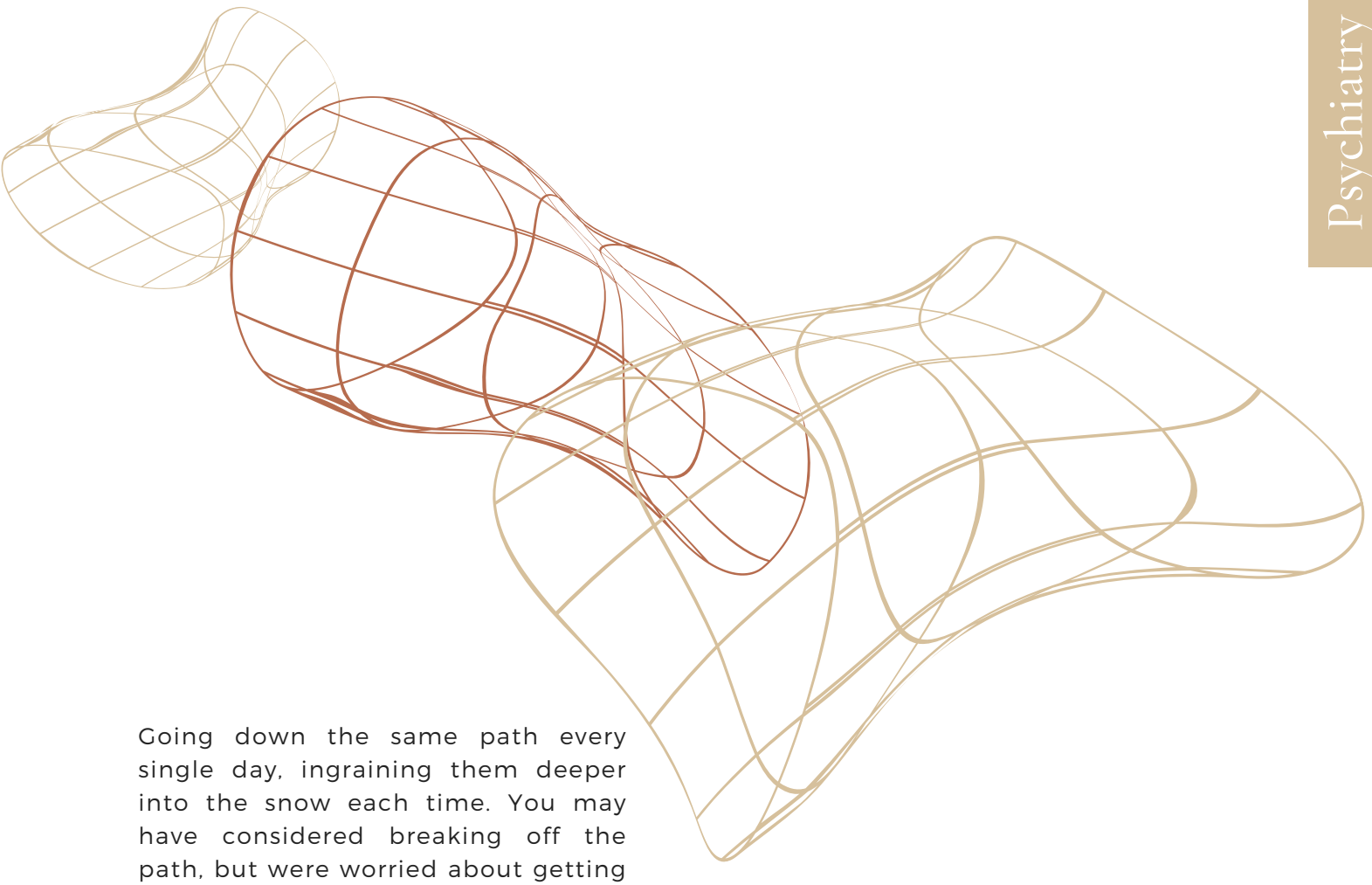
WRITTEN BY ALEX EPSHTEIN
EDITED BY MUKA OFOMATA
DESIGNED BY EMILY KOSTINA

It has been a long standing dogma in neuroscience that psychedelics have the potential for treatment of depression, anxiety, trauma and addiction, as well as many other mental disorders. Michael Pollan stated in an interview: '...for most of the 1950s and early 1960s, many in the psychiatric establishment regarded LSD and psilocybin as '**wonder drugs**'. So why haven't these drugs been accepted into the psychiatric community? Due to the surge of hallucinogen drug usage during the 1960s, stories surrounding 'bad trips' and psychotic breaks surfaced, which gave way to 'moral panic'. However, due to the rise in mental health awareness, the pendulum is swinging back as new government-funded research centres open to re-evaluate the advantages of these drugs as a tool in the treatment of various psychiatric conditions.

In order to classify as a 'psychedelic' a drug must have the power to alter thoughts and sensory perceptions. For example, well-known drugs, such as ***Lysergic acid diethylamide*** (LSD) or 'magic mushrooms' which contain psilocybin, an active ingredient that can often results in visual hallucinations at high doses.

Other properties/effects of psychedelic drugs include (primarily) elevation of the user's mood, by acting on serotonin receptors, such as 'ecstasy'; while others may act as anaesthetics or depressants, like ketamine, both of which have been recorded to put users into 'dreamlike' states. Some of these substances have been used in traditional healing methods in some cultures for centuries. An example of this would be **ayahuasca**, found in the jungles of South America. So what do psychedelics actually do?

Imagine you live on the top of a mountain, where each day you have to ski down a slope to get to town. You have lived there all your life and you follow the tracks you created for yourself when you were a child.



Going down the same path every single day, ingraining them deeper into the snow each time. You may have considered breaking off the path, but were worried about getting lost, not finding your way back (or maybe you were just) scared to venture into something unknown.

Overnight there was a blizzard, one which has blown away your previous tracks, blanketing them in an invisibility cloak. The routes you knew so well – carved for yourself in childhood, are now but a blank surface. This freshly fallen snow forces you to make new tracks above your old ones, giving you potential to explore paths you have never thought of or taken before.

This analogy refers to a process called '**neuroplasticity**', where the tracks represent neurons and the formation of new connections between them, and the invisibility cloak being effect of the drug on the individual's brain.

Psychedelic drugs act as a catalyst for neuroplasticity, putting patients into a resting or transient state, where they are more susceptive to processing things such as memory, trauma and emotions in a way the had never previously done, allowing them to 're-emerge with a new perspective on them that is freeing and healing'. This is the basis of psychedelic-assisted therapy.

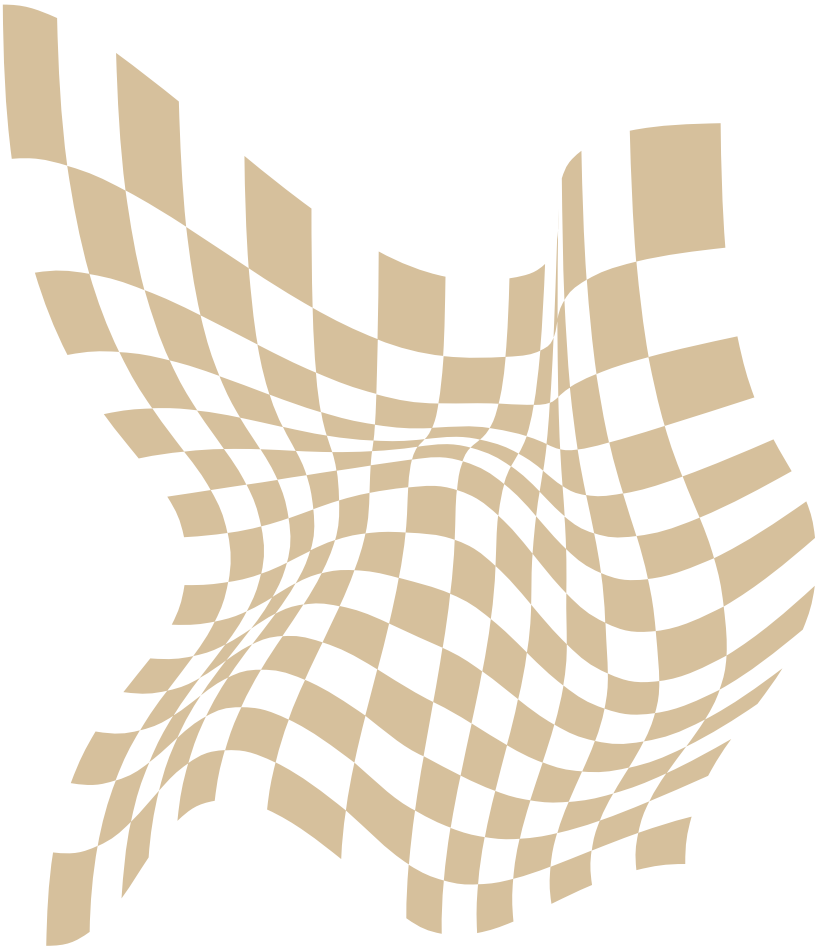
After conducting, and passing, multiple phase two trials, **MDMA**, commonly known as ecstasy – has produced promising results in the treatment of severe and moderate PTSD. The results suggested that 'ecstasy' can reduce symptoms for up to 4 years.

Researchers have also recently completed a phase 3 trial, which involved the first test for psychedelic-assisted therapy. The outcome being that 67% of patients with severe PTSD no longer qualified for a PTSD diagnosis post-therapy, while 88% of patients with moderate PTSD displayed reduced symptoms. The trial sponsor, the Multidisciplinary Association for Psychedelic Studies (MAPS), says these results could make/pave the way for Food and Drug Administration (FDA) approval by 2023.

Another example of a psychedelic drug and its medicinal uses is **ketamine**. 'K' is among one of the most-studied psychedelic drugs in psychological therapy. In low doses, trials have shown it to produce positive effects in the treatment of depression, although its effects are relatively short-lived. This research has led to the development of a drug called '**Spravato**', a nasal spray that delivers the active ketamine ingredient., used for treatments of some forms of depression and as an anesthesia.

Psilocybin, the active compound responsible for hallucinogenic symptoms in 'magic mushrooms' and LSD have both shown promising results in the treatment of depression and anxiety in people living with terminal illnesses, as well as other mental illness, such as OCD, addiction and treatment-resistant depression.

However, when taken unsupervised, these drugs could have multiple adverse effects.



For example, MDMA and psilocybin can increase blood pressure, heart rate and body temperature. As well as this, it has been reported that psychedelics can increase the risk of psychosis in patients with psychotic disorders.

Although more psychedelic-specific research centres have started to open, in order for these trials to continue there still remains a large amount of decriminalisation that needs to be done to de-stigmatise these drugs as purely harmful substances. Once this is tackled, the door will open for more research resulting in outcomes we can not even fathom, where the true power that psychedelics hold over psychiatry will be revealed.

UK Disability History Month

18 November - 18 December

"I feel that if young people identify as having these differences, they can start making career choices based on their strengths. Good scientists are innovative and creative, and that's how people would describe me, and I believe that that is down to my neurodiversity. I definitely see it as a strength and not a disability."

Sara Rankin

Professor, Imperial College London
Dyslexia and Dyspraxia

THREADING WATER

TILAPIA SKIN TREATMENT: A MODERN TREATMENT FOR BURNS

WRITTEN BY NEGAR MOUSAZADEH
EDITED BY ANASTASIIA TARASENKO
DESIGNED BY SAMARA SINGH

Burns are damages to the tissues that come in different levels of severity and can be **caused by heat, chemicals, electricity, etc**. Most of the major burns including third and fourth degree burns lead to death but even the moderate and minor ones can eventually be fatal if not treated including conditions involving acute infection. Residents of the low- and middle-income countries have been stated to be the primary burn victims, with around **180 000 deaths** annually in a report by WHO.

As the majority of these injured parties could not afford costly medication, scientists started to look for an affordable substitute treatment that can be as effective and convenient. Brazil is one of the first countries that have taken the initiative to combat this problem and has found an alternative solution.

They are using the skin of **Nile tilapia fish** to treat up to second-degree burns, including damages that extend into deep dermis.

However, the tilapia skin has to go through different stages of sterilization and microbiological tests for bacteria and fungi before direct application on the skin. From one of the first experiments on rats, doctors realised that tilapia collagen fibers increase the **speed of healing** in skin damage by promoting cell adhesion, proliferation and differentiation.

For further trials, they decided to try it on human skin by directly wrapping it around the burnt area without using any creams and protecting it with a bandage which can be removed about 10 days after first application, when the tilapia skin has dried out and can be peeled away easily.

This method has been introduced as a **prospective xenograft** compared to alternative xenografts and allografts, due to containing a high amount of collagen type I and III(which can be found in humans), suggesting morphological similarity of human skin to that of Nile tilapia, and having a non-infectious microbiota. The

collagen in tilapia has been suggested to **promote epidermal growth factor expression**, leading to an increase in fibroblasts and keratinocytes of skin tissue, which puts this treatment in a forward line compared to other substitutes.
Using tilapia skin also has some advantages compared to other alternative methods such as sulfur sulfadiazine which is used vastly for treating burns. Although sulfur sulfadiazine is a 2-weeks treatment, the wounds need to be cleaned and the bandages have to be changed every one or two days. Also, the patients have to use antibacterial soap and/or take anaesthetic baths to avoid unpleasant odor from the wounds while on the other hand, there is no need to change tilapia treatment after the first application. Further advantages of tilapia skin over the alternative methods of gauze include longer hydration of the graft and its soothing properties, leading to reduction of healing to several days and thus, **minimising the intake of additional painkillers** to be able to withstand the pain throughout the healing process.

In addition to the advantages mentioned, this method is nature-inspired, has a very simple application process and is more **cost-effective** for both the patient and the hospital and reduces the workload of the healthcare staff, benefitting both sides of the party. Despite all the advantages it encloses, the treatment is still under phase II and phase III of controlled trials with medics assessing the safety of its therapeutic use in the future, hoping it would help many burn victims all over the world.

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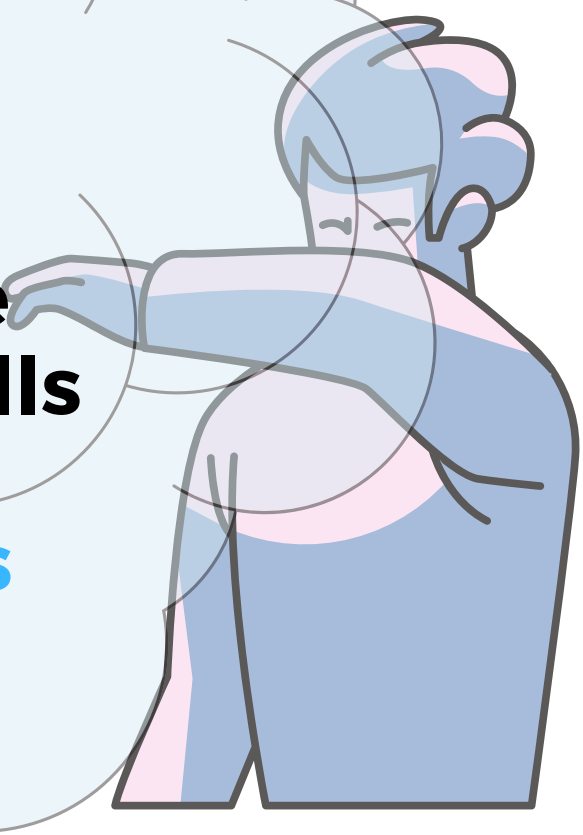
THREADING WATER

How E-cigarette Vapours Damage Vital Immune Cells and Increase Our Risk of Infections



WRITTEN BY CHELSEA BLAIR
EDITED BY DRSHIKA MEHTANI
DESIGNED BY VIRGINIA BALDI

There's no denying that vaping is hugely popular in today's society: sweet candy-flavoured vapour wafts the air and trickles down the throat of an estimated **55 million users** daily, the majority of which are aged **18-29** years old (World Health Organisations, 2021). Nonetheless, e-cigarettes only rose to popularity in the early 2000s, their long-term health effects still remain widely unknown.

Although vaping is advertised as the "safer alternative" to the conventional cigarette due its fewer chemical constituents (9 to 450 times less dosed), and while advertised as the "safer" alternative, new evidence is showing that the aromas and e-liquids inhaled can exert **toxic effects on the immune system.**

Immune gene alterations

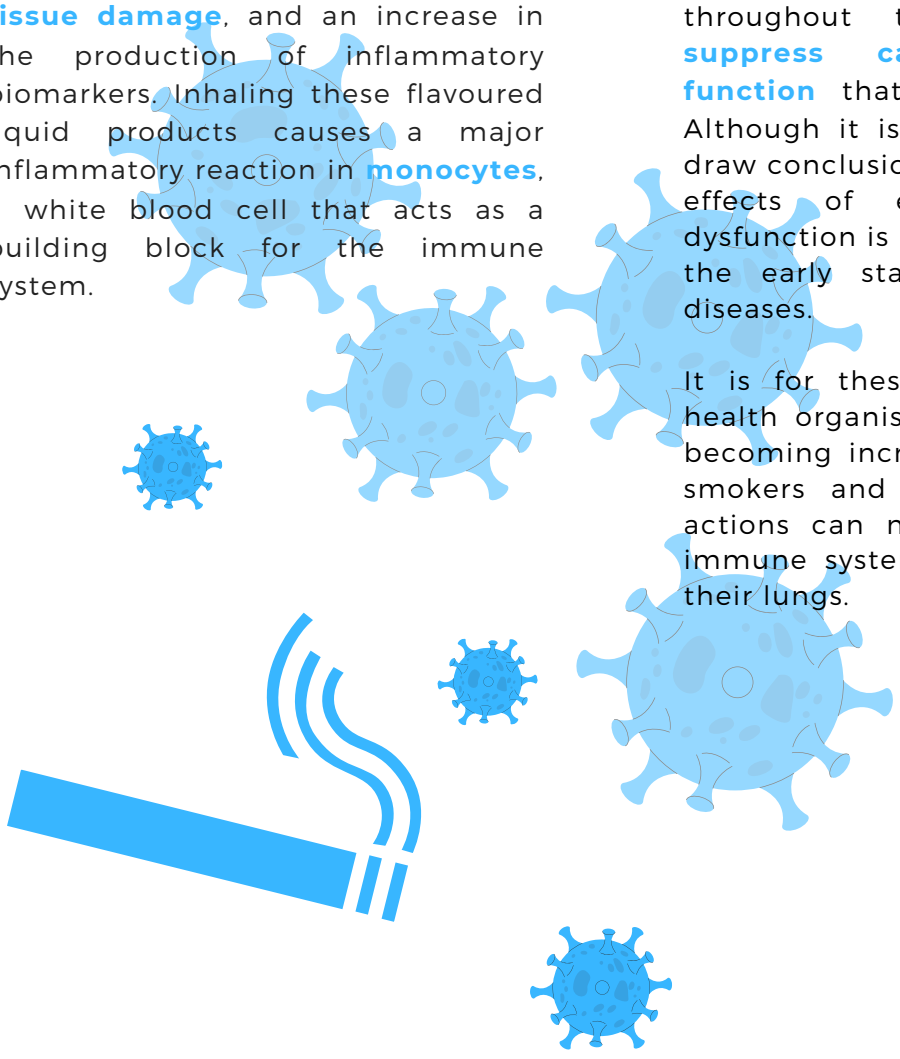
Toxicologists from the University of North Carolina recently reported in the American Journal of Physiology that e-cigarette vapours have the ability to **modify our immunity genes** at a **faster** and greater pace than **tobacco**. This physiological phenomena was discovered in vitro, where it has been claimed that the vapours can affect around **358 genes** (six times more than tobacco) that are involved in the immune defence of the upper respiratory tract.

Their study consisted of an analysis on the nicotine quantities in blood and urine samples of smokers, vapers and non-users, analysing the expression of epithelial immune-response genes. Their observations concluded that tobacco reduced the expression of 53 major immune genes, whereas e-cigarettes reduced the expression of the latter and an **additional 305 genes** involved in our immunity.

Harmless labels hiding dangerous chemicals?

On today's market, unregulated vape products are made attractive with decorative names to appeal to a younger audience. Many of these flavoured chemicals have shown to cause **significant cell death,** with 'cinnamon', 'vanilla' and 'buttered popcorn' being harmful examples. These proved to be the **most toxic** as they include higher doses of **diacetyl**, a chemical food additive used to offer candy and fruit-like flavours.

Additionally, an exposure to a multitude of flavours induces higher levels of **oxidative stress,** an imbalance between oxygen species and antioxidant defence mechanisms. This in turn leads to **tissue damage**, and an increase in the production of inflammatory biomarkers. Inhaling these flavoured liquid products causes a major inflammatory reaction in **monocytes**, a white blood cell that acts as a building block for the immune system.



COVID-19 and vaping

Recent studies show that smokers and vapers alike are at an **increased risk of severe illness** when affected by **COVID-19**. Being the virus attacks the lungs, behaviours weakening the latter are dangerous, hence why health officials are warning against the use of e-cigarettes in the context of the coronavirus pandemic. Exposure to **aerosol** from e-cigarettes can have negative effects on various types of lung cells, including those involved in the maintenance of normal, healthy lung function.

The aerosol deriving from e-cigarettes **inhibits** and **kills** several types of lung immune cells, compromising the lung's ability to fight off infections. Moreover, **nicotine**, an essential component of e-cigarette aerosol, suppresses immune function throughout the body and can **suppress cardiovascular tissue function** that controls blood flow. Although it is currently too early to draw conclusions about the long-term effects of e-cigarette use, this dysfunction is most commonly seen in the early stages of cardiovascular diseases.

It is for these reasons that public health organisations and experts are becoming increasingly concerned for smokers and vapers alike as their actions can negatively impact their immune system and the integrity of their lungs.

The body's pathway to recovery

Quitting vaping not only improves **lung function**, **immune response** and **cardiovascular health**, but puts former users in a better position to fight serious infections like COVID-19. Within **two weeks** of quitting, lung function improves: cilia, hair-like protrusions that protect the lungs, grow back and return to a normal level of activity, which facilitates the fight against infection. Many vapers start to notice a decrease of their respiratory symptoms such as cough and shortness of breath within **a month** of quitting. Further, the immune inflammation deriving from e-cigarettes decreases, the number of white blood cells returns to normal and immune function improves. This implies a **decrease in respiratory infection rates,** including pneumonia and bronchitis, and other vitals such as heart disease, heart rate and blood pressure.

To close, although the full effects brought by e-cigarettes has yet to be defined, regulating the former from a health policy perspective is crucial for youths and adults alike so as to properly **avoid suppressing vital genes, proteins** and **antibodies** involved in our body's natural immune response.

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UK Disability History Month

18 November - 18 December

“It (being a research technician in parasitology at the University of Oxford) was the first time I was taken seriously, my opinion counted and I was interested in the research.”

“Hold on to your willpower to power through the hurdles, and most importantly don’t be afraid to speak up about what you can or can’t hear or do. There are ways to make it easier.”

Clare Halliday

PhD, Oxford Brookes University
Deaf

SHALLOW DIVE

TO BE OR NOT TO BE?

How Our Immune System Might be Controlling Our Social Behaviour

WRITTEN BY MAHTA HAGHIGHAT GHAHFAROK | EDITED BY ANDREA MAZGALEVA | DESIGNED BY SAMARA SINGH

We like to think we have been the privileged species from the dawn of time; that through a divine spark, we could dominate our environment and the lesser mammals.

But it has not always been like that, at least not at first. We were simply another smart, social animal trying to survive in the wild. A truly unique trait of the human species is the ability to collectively create and believe fiction, and create large- and small-scale flexible cooperation systems accordingly. Which implies that our **unique social behavior is the heart of human civilization.**

Collective social behavior, creativity and intra-human cooperation are recognized for their importance. What has gone unnoticed until recent scientific ventures, is the cooperation between the human species and pathogens. Social behavior is, of course, in the interest of pathogens, as it allows them to spread. Researchers suggest that they could have directly affected the development of our social behavior, allowing us to create and engage in the social structures necessary for the survival of the species.

All of this while developing ways for our immune system to **protect us from the diseases** that accompany those interactions.

Researchers have also found mechanisms that highlight a **relationship between social dysfunction and immune dysfunction**.

The more we are discovering, the more we are recognizing that the mind and the body are not separate. The brain is not the ivory tower that sends orders to a mindless body that just does as it is told. The body talks to the brain, too. In fact, a group of scientists have recently discovered a particular **two-way connection between the brain and the immune system.**

One that could have far-reaching implications. Considering the immune system surveys and conserves what the body is, and what it is not made of. That was in 2015. Now, in 2021, a new study has shown that the immune system's connections with the central nervous system may affect, even control, how human beings behave socially, form social connections and cooperate on a large scale (Saad and Prochaska 2021).

The key is a mere molecule called **interferon-gamma**, produced and secreted by T-cells. T-cells are one of the immune system cells that are activated when encountered by what they recognize as non-self. They are responsible for recognizing anything in the body that does not match the body's identity code.

Present in the lymphatic vessels and important for draining fluid as well as immune cells from the cerebrospinal fluid, T-cells emit interferon-gamma into the brain. Once there, **interferon-gamma inhibits neurons in the prefrontal cortex**. The prefrontal cortex modulates cognitive control, by such means influencing **attention, impulse inhibition, prospective memory, and cognitive flexibility**. Without interferon-gamma, that region can become overactive. Subsequently, when the prefrontal cortex becomes overactive, much like mice who were the subjects of these experiments, human beings become asocial.

"It's extremely critical for an organism to be social for the survival of the species. It's important for foraging, sexual reproduction, gathering, hunting, etc" said Anthony J. Filiano, PhD, the lead author of the study. "So the hypothesis is that when organisms come together, you have a higher propensity to spread infection. So you need to be social, but in doing so you have a higher chance of spreading pathogens. The idea is that **interferon gamma, in evolution, has enabled a more efficient pathway to both boost social behavior while boosting an anti-pathogen response.**"

Blocking the molecule normally produced by the immune system in response to bacteria, viruses or parasites using genetic modification made the prefrontal cortex of the mice brain hyperactive, causing the mice to become less social. Restoring the molecule reestablishes the brain connectivity and behavior to normal levels which highlights that the **immune molecule plays a "profound role in maintaining proper social function.**" ("Shocking New Role Found for the Immune System: Controlling Social Interaction: It's of 'Profound' Importance to Proper Social Functioning, Researchers Determine," n.d.)

"Immune molecules are actually defining how the brain is functioning. So, what is the overall impact of the immune system on our brain development and function?" Kipnis said - PhD, chairman of University of Virginia School of Medicine's Department of Neuroscience.

"I think the philosophical aspects of this work are very interesting, but it also has potentially very important clinical implications."

What is more, the researchers also noted that a malfunctioning immune system may be responsible for "social deficits in numerous neurological and psychiatric disorders." (Devlin 2017) Exactly what this might mean for autism and other specific conditions, however, would require further investigation. It is unlikely for anyone molecule to be responsible for disease or to be the key to a cure, the researchers believe; instead, the causes are likely to be much more complex.

Consider the immune system, as a system in the body that determines what is "self" and what is "non-self". Hence, it identifies which structures/living forms to attack and which to protect within the body to maintain the integrity of biological identity.

Furthermore, the discovery that the immune system and possibly germs can control our interactions raises many exciting avenues for scientists to explore, both in terms of battling neurological disorders and understanding human behaviour. ("Shocking New Role Found for the Immune System: Controlling Social Interaction: It's of 'Profound' Importance to Proper Social Functioning, Researchers Determine," n.d.).

The immune system has also been shown to be able to affect behaviour, personality and social interaction without the interference of any external pathogen, such as the auto-immune activity observed in schizophrenia.

Auto-immune activity is also associated with behavior, or rather behavioral and psychiatric abnormalities and ultimately disease. It's been shown that in **schizophrenic patients, a normal function carried by the immune system appears to become more aggressive** (Figure 1), targeting the body's own critical brain tissue, leading to a loss of vital neuronal connections. Synaptic pruning is a natural, indeed essential, process that occurs in the brain between early childhood and adulthood. During synaptic pruning, the brain eliminates extra synapses with the expectation to remove unnecessary neuronal structures from the brain as the human brain develops.

In order to accommodate the need to understand more complex structures, the brain evolves to become much more pertinent. The simple associations formed at childhood are thought to be replaced by complex structures. Aggressive pruning, and inflammation it may result in, is observed in the frontal cortex and the auditory regions, potentially providing an explanation for patients reporting hearing voices. The **frontal cortex indirectly controls levels of dopamine** (also known as the "feel-good" hormone) in the brain. The elevated release of dopamine is thought to cause delusions and paranoia, common in people with schizophrenic tendencies (Devlin 2017).

Considering unique social and behavioral structures in human species being the factor that has

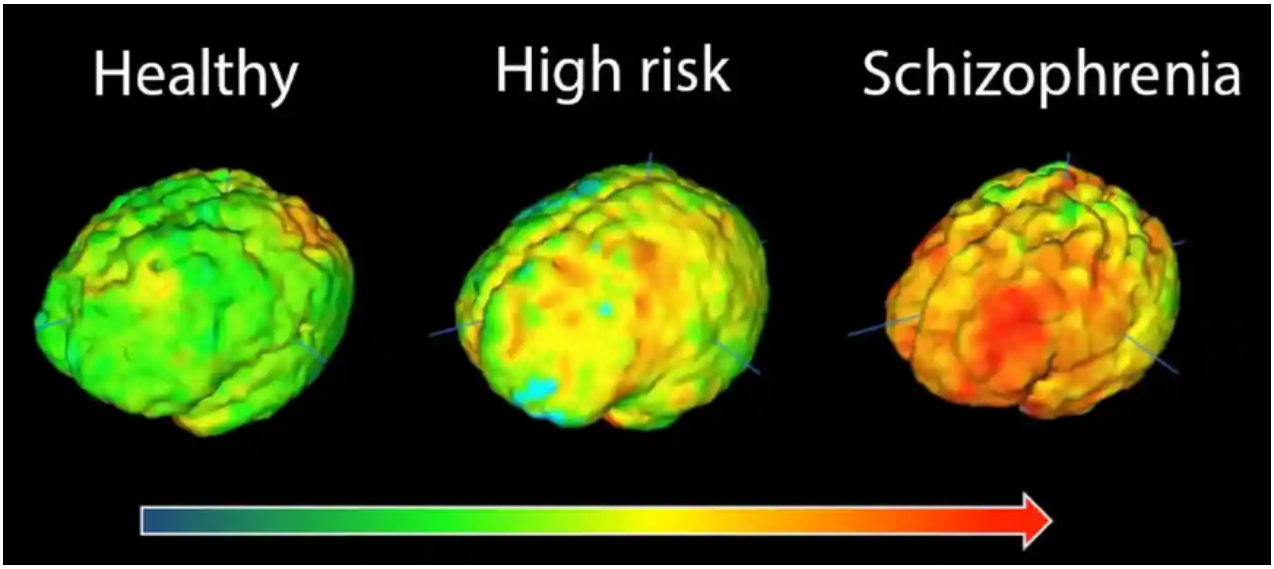

Figure 1. Levels of microglial activity in the brain

crowned them the dominant species on earth, perhaps we must consider Jonathan Kipnis's thought: "It's crazy, but perhaps we are just multicellular battlefields for two ancient forces: pathogens and the immune system.

Part of our personality may actually be dictated by the immune system." (Umer 2018) ("Shocking New Role Found for the Immune System: Controlling Social Interaction: It's of 'Profound' Importance to Proper Social Functioning, Researchers Determine," n.d.)

In conclusion, unraveling the link between social behavior and immune signaling is a fundamental challenge, one that is far too important to be left unaccepted. Not only is that to advance our understanding of collective and individual human health and development, but also to **design comprehensive pharmaco-behavioural therapeutic approaches** to combat neural disorders and disease as well as the worldwide epidemic of mental health.

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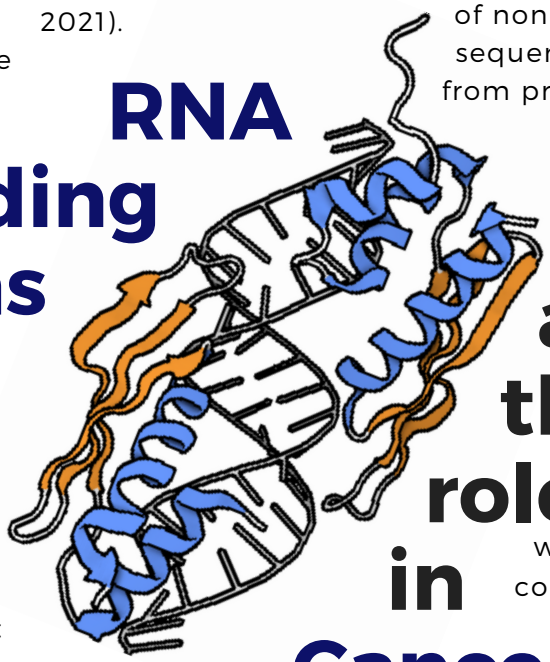
DEEP DIVE

WRITTEN BY ALEXI MERY
EDITED BY COURTNEY WEIR
DESIGNED BY WINNIE LIU

RNA Binding Proteins and their roles in Cancer



RNA binding proteins (RBP) have seen their importance increase massively over the last two decades. This is due to the discovery that **splicing, RNA localisation and the modulation of RNA stability** are vital for cellular health and all these processes are important in determining a cell's behaviour (Kelaini et al., 2021). Moreover, in recent years there are several diseases now shown to be caused by the malfunction of these processes, from cancers to neurodegenerative diseases. In the 1960s, Francis Crick famously described the 'Central Dogma' of molecular biology, which is the idea that DNA codes for messenger RNA (mRNA), which then codes for proteins. However, the oversimplification of this idea has been made increasingly evident, especially through the discovery of **noncoding RNAs** such as miRNA, snoRNA and siRNAs. To date, over 1914 RBPS have been discovered in the human genome (Qin et al., 2020).

These RBPs have now been shown to be responsible for a plethora of cellular effects, regulating processes such as splicing, which is the removal of non-coding regulatory sequences called introns from pre-mRNA, and RNA localization. It is therefore not surprising that these extremely important proteins, when **deregulated**, could lead to serious diseases such as cancers.

The first example of an RBP being linked to cancer is **TRBP** and it's important for **RNA interference** (RNAi). RNAi is used by cells to stabilise their genomes. In particular, RNA interference can help protect cells from viruses by degrading viral RNA (Obbard et al., 2008). RNAi can work in two ways, either by **preventing the mRNA from being translated**, or by destroying it completely.

The type of non-coding RNA responsible for degrading mRNA or blocking its synthesis is **miRNA or microRNA**. Its precursor, pri-miRNA, is synthesized from DNA as a result of RNA polymerase. This pri-miRNA is modified in the nucleus to form a pre-miRNA molecule which is then shipped out of the cell where it **binds to Dicer and TRBP** (see figure 1). TRBP is needed to increase Dicer protein's affinity to RNA and to increase its cleavage accuracy (Fareh et al., 2016). Dicer will then induce the formation of a complex with another protein called Argonaute. The resulting complex is called **RISC (RNA induced silencing complex)** and it is responsible for degrading or inhibiting the translation of mRNA (Setten et al., 2019). It is important to note that without TRBP, the RISC complex cannot be formed properly (Fareh et al., 2016).

Interestingly, mutations in TRBP can lead to increased miRNA degradation which therefore leads to less mRNA degradation. Hence, this can lead to **reduced regulation of key proteins needed to suppress cell growth and division in cancerous cells**. Thus, it is quite common to see reduced TRBP expression in cancerous cells for example, reducing the amount of protein regulation. In fact, when TRBP encoding genes are reactivated in cancerous cells, cell proliferation is slowed once again (Shuibin and Richard, 2015). TRBP deregulation seems to be particularly important in breast and colorectal cancer (Qin et al., 2020). Recently, the molecule **enoxacin** was shown to bind to TRBP and thus to increase miRNA production. This might therefore lead to the development of new drugs based on this molecule in the future (Felicetti et al., 2020).

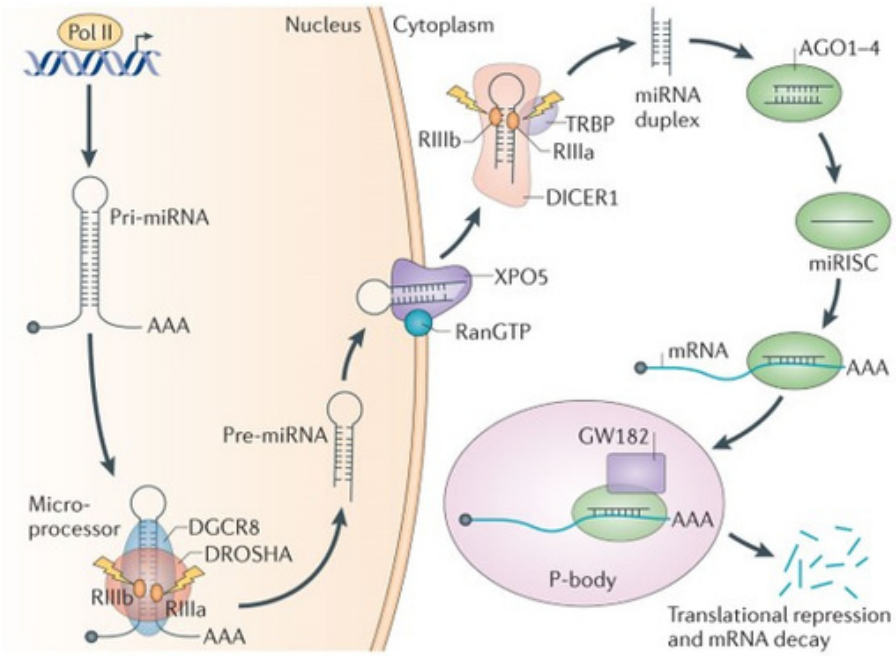


Figure 1. Diagram showing how miRNA silencing works A precursor form of miRNA is transcribed in the nucleus by RNA polymerase II and is then cleaved by proteins called microprocessors (DROSHA and DGCR8). The resulting molecule, called pre-miRNA, is transported out of the nucleus via exportin 5. Once in the cytoplasm, pre-miRNA binds to DICER1 and TRBP to form the RNA induced Silencing complex (RISC) which will bind to mRNA. (Taken from Lin & Gregory, 2015)

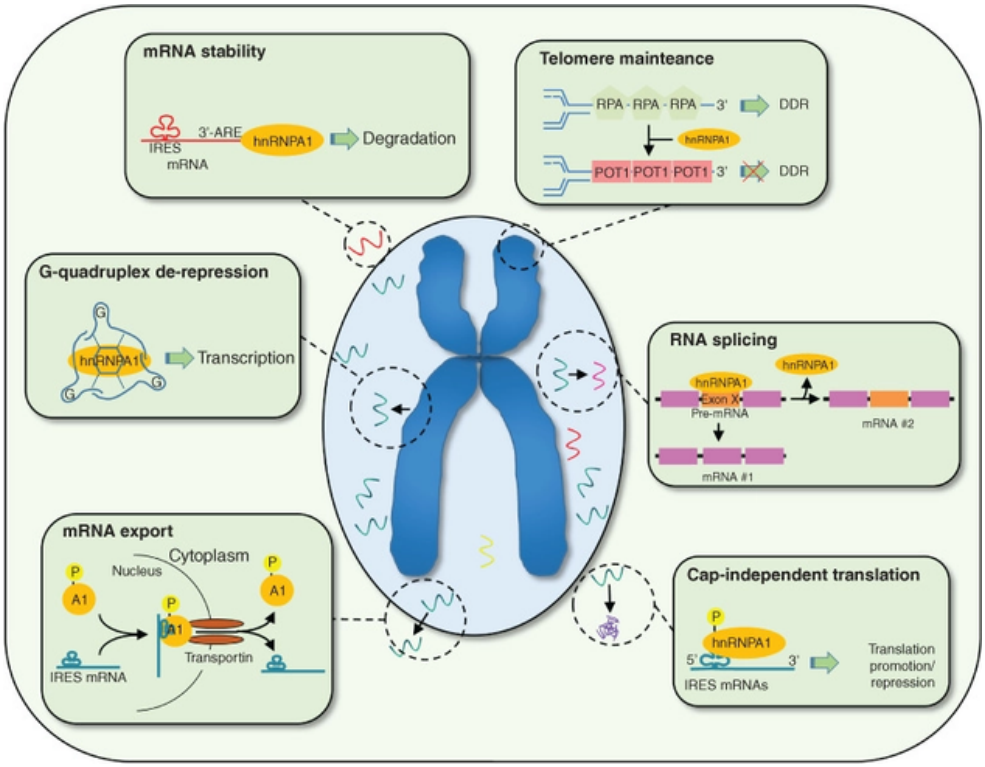


Figure 2. The roles of hnRNP A1 in tumour progression hnRNP A1 has a plethora of cellular functions, from RNA splicing, through to mRNA export and telomere maintenance. (taken from Roy et al., 2017).

A second example of RBP deregulation linked to cancer progression is the protein **hnRNP (Heterogeneous nuclear ribonucleoprotein) A1**. This protein is important for both splicing regulation and RNA stabilization and deregulation of these two proteins can lead both to cancer and to neurodegenerative diseases such as Alzheimer's disease (Geuens et al., 2016). In particular, hnRNP A1 has been shown to be associated with quite a large variety of cancers and is massively upregulated in lung tumour cells for instance. hnRNP A1 has therefore been **associated with tumour growth** (Geuens et al., 2016).

The reason why hnRNP A1 has a role in cancers is that when deregulated, it leads to splicing of key parts of proteins, a phenomenon known as **exon skipping**, and this can lead to that **protein being truncated** (Geuens et al., 2016). If this truncation happens in a protein which regulates cell growth for instance, this could lead to tumour formation. An example of an oncogene which is affected by hnRNP A1 deregulation is Kirsten rat sarcoma viral oncogene homolog (KRAS).

In conclusion, RNA binding proteins have been shown to be **associated with a variety of different cancers** throughout the body and their crucial contributions to proper protein expression are still being discovered today. To date, there are no drug treatments for cancer targeting RBPs but RBPs are **clearly attractive drug targets** and we can potentially expect to see drugs targeting these proteins appear in the near future.

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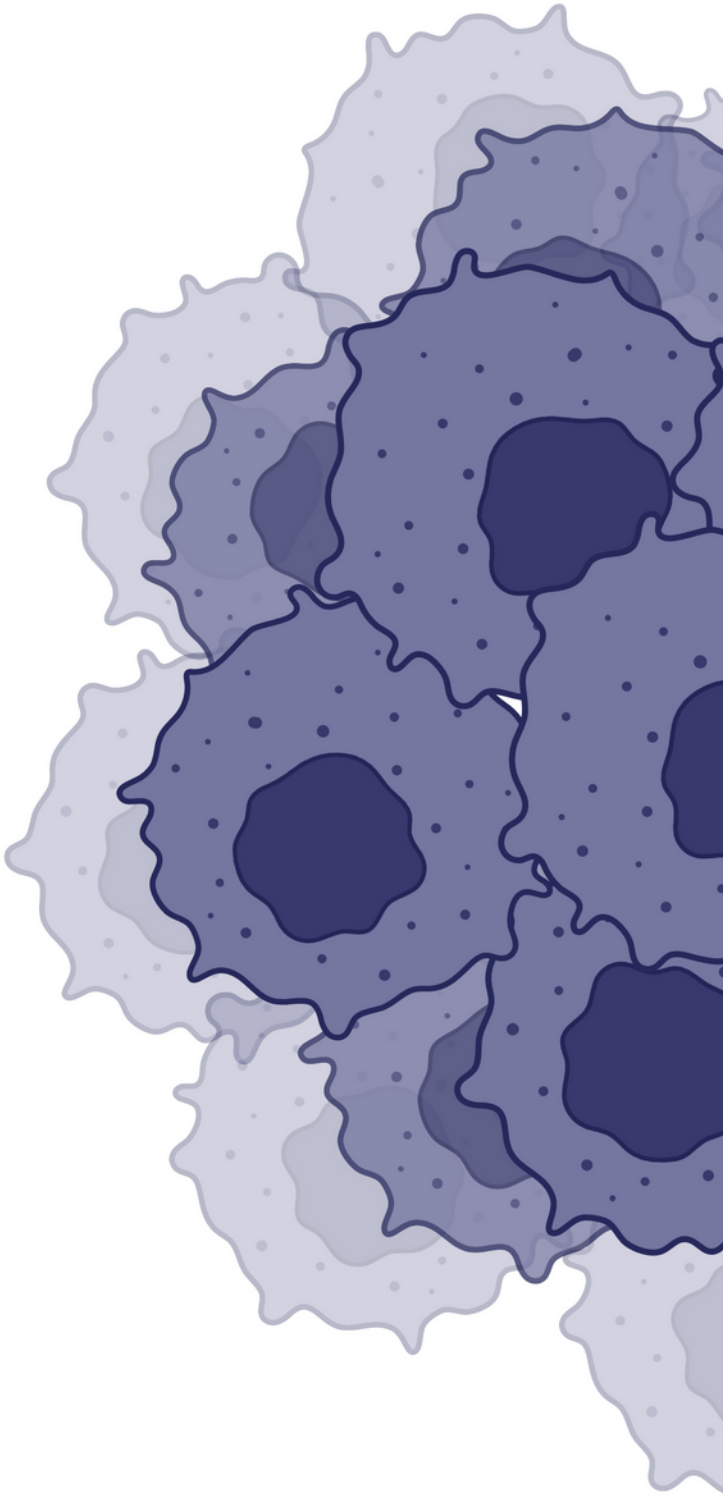


THREADING WATER

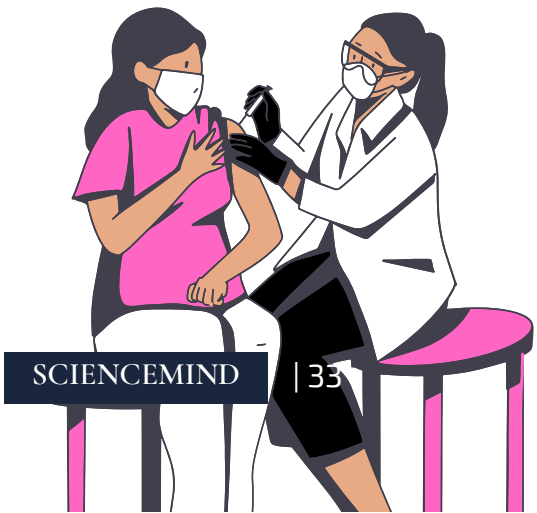
THE MISSING LINK TO THE LUPUS PUZZLE

WRITTEN BY ZAHRAA BHATTI | EDITED BY ANOUCHKA AZRIA | DESIGNED BY ZAHRAA BHATTI

Lupus is a chronic autoimmune disease in which the body's immune attacks its organs and tissues. The body produces **autoantibodies**, which inevitably leads to the destruction of healthy tissues. Symptoms of lupus include skin rashes, joint pain and fever.
There are four main types of lupus: neonatal, discoid, drug-induced, and **systemic lupus erythematosus** (SLE). SLE is the most common type of lupus, it affects approximately 0.02% to 0.15% of the population.

The exact mechanism of SLE is unknown, but it's thought that the deadly autoimmune disease is a result of presenting a T-lymphocyte to an antigen-presenting cell (APC). The receptor of the T-cell binds to the **major histocompatibility complex** (MHC) region of the APC. The MHC binds pathogen-derived peptide fragments and presents them onto the APC, where T-cells recognise them. The interaction between a T-cell receptor and the MHC leads to **inflammation** and the release of cytokines. B-cell stimulation can also occur, which leads to the production of autoantibodies.

Antinuclear antibodies (ANAs) are a type of autoantibody involved in SLE. The presence of large quantities of ANAs signals the body to begin attacking itself. SLE can be diagnosed by detecting ANAs via Fluorescent Antinuclear Antibody test (FANA). FANA involves fluorescently-labelling antibodies measuring the intensity of the fluorescence. Near to 95% of lupus patients are ANAs positive. Thus, detection of ANAs is an effective way of diagnosing SLE. However, 15% of those who test positive for ANAs are completely healthy. As a result, you can't just assume the ANAs positive person has lupus.



Patients of SLE report having red rashes on their face after sun exposure, known as the **"butterfly rash"** (figure 1). Other skin related conditions include alopecia (an autoimmune disease which causes hair loss) and Reynaud's phenomenon (decreased blood flow to fingers). SLE also causes inflammation of the musculoskeletal system, resulting in myalgia (muscle aches), arthralgia (joint stiffness), and arthritis.

Approximately 50% of lupus patients develop **lupus nephritis** (LN) (figure 2), which is the primary cause of mortality in SLE patients. LN is a type of kidney disease leading to inflammation of the kidneys resulting in renal failure. Early detection is crucial for patients with LN to ensure a better prognosis.

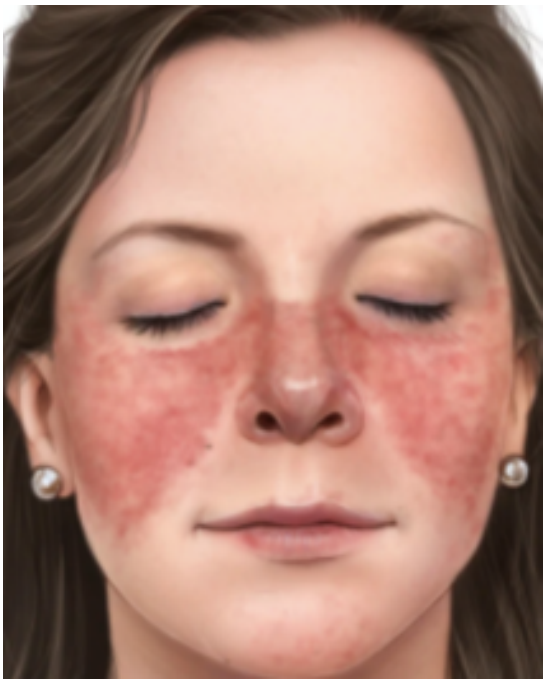


Figure 1. Image of lupus facial rash known as the "butterfly rash"

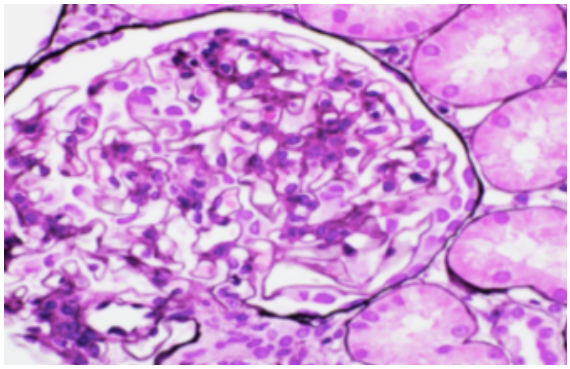


Figure 2. Histology of the glomerulus demonstrating lupus nephritis

Professor Roger Abramino Levy is a Global Medical Expert at GSK who is interested in learning more about SLE. He highlights how each individual reacts to SLE differently, thus diagnosing SLE patients is challenging. Lupus has a broad spectrum of clinical manifestations, so it's difficult to know what to look for and which treatments are effective. Genetics play a role in the development of the autoimmune disease. In comparison to the general population, first-degree relatives of SLE patients are substantially more likely to develop the disease.

On the other hand, Professor Levy researched lupus in identical twins and observed that, although living in the same environment, their lupus presentations were different to one another. Therefore, there's a missing element in determining the complete mechanism and causes of lupus. To overcome these challenges, scientists are currently working on biomarkers that can distinguish between different types of lupus symptoms and predict which treatments to use. For example, potential **biomarkers** associated with LN are currently being discovered.

IFI44, IFIT3, HERC5, RSAD2, and DDX60 are genes that could play an important role in the pathogenesis of LN. The discovery of biomarkers opens the door to **therapeutic intervention**, which could be a potential pharmaceutical breakthrough.

Current lupus treatments are used to alleviate the severity of the condition rather than cure it. **Non-steroidal anti-inflammatory drugs** (NSAIDS), antimalarial drugs, and corticosteroids are often used to treat the signs and symptoms of mild-to-moderate lupus. For instance, NSAIDS works by inhibiting the action of **cyclooxygenase enzymes**, thus preventing the production of prostaglandins. As a result, this drug has anti-inflammatory, analgesic, and antipyretic effects. High dose corticosteroids and **immunosuppressants** are administered to limit the disease from progressing and symptoms worsening. Immunosuppressants work by reducing the proliferation of T-cells and B-cells, thus reducing the production of autoantibodies. Furthermore, the use of stem-cell transplantation to transfer healthy cells into the body to help rebuild the immune system has piqued researchers' interest.

There are still many unresolved questions about lupus, but researchers are constantly identifying potential biomarkers and treatments to improve the quality of life and reduce the mortality rate for lupus patients.

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UK Disability History Month

18 November - 18 December

“It (car accident) was like Scrooge in 'A Christmas Carol', to see myself in death. The experience didn't feel scary or bad, and after the accident I became a different person. Before, I was trying to become number one in my field like everybody else. I was running full speed one way. Now I have a bigger purpose. It has let me see the wholeness of life."

Sang-Mook Lee

Associate Professor, Seoul National University
Quadriplegic

DEEP DIVE

MIGRAINE AND ITS PHARMACOTHERAPY

WRITTEN BY DRSHIKA MEHTANI | EDITED BY EMMA VON SETH | DESIGNED BY ZAHRAA BHATTI

A poet, Robert Staves, effectively sums up what a migraine attack feels like, using a rather unique analogy. He says, "Love is a universal migraine. A bright stain on the vision, blotting out reason." But what exactly is a migraine and how can one treat it? These **persistent headaches** are very common and can be triggered by a myriad of cues, such as stress, sleep disturbances and menstrual changes. Migraines affect more than 13% of adults (25-50 years of age) in the US alone and the direct and indirect costs associated with migraines have a significant impact on society worldwide. The **pharmacotherapy** of migraines is just as complex as the disorder itself and a definitive aetiology of the disease is not yet understood. Researchers have, however, been capable of understanding that the pathogenesis of migraines involves the **extracranial circulation**, and have been developing effective therapies for treating it.

Usually, a migraine attack consists of a unilateral headache that is accompanied by a cluster of other symptoms, such as nausea and photophobia. A migraine attack presents in four phases: premonitory, aura, headache, and postdrome.

Each of these phases have different symptoms associated with them and the attack can last anywhere from 4 to 72 hours. While the exact cause of migraines is unknown, current literature prominently highlights the changes in the sensitisation of the **trigeminovascular system**. Various inflammatory peptides such as calcitonin gene-related peptide (CGRP), substance P, neurokinin A and nitric oxide are released under the influence of several stimuli. These lead the trigeminovascular system to a state of **hyperexcitability** that induces migraine pain as well as several other symptoms associated with it, like nausea and visual problems. CGRP in particular has been shown to mediate many of these changes (Figure 1). While other neurotransmitters may be involved in the manifestation of migraines, the serotonergic (5-hydroxydopamine [5-HT]) system is likely to have significant contribution,

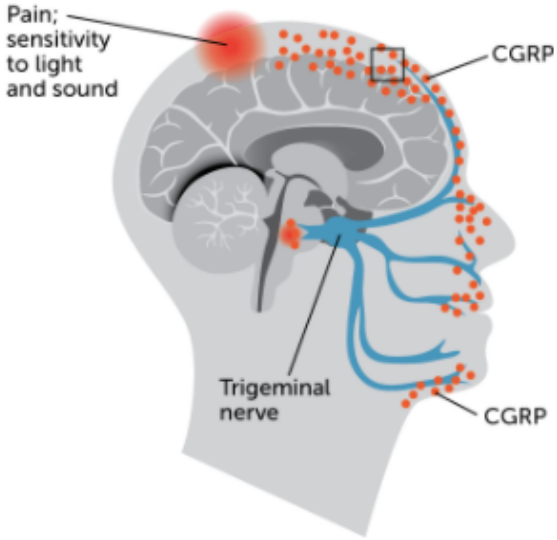

Figure 1. **CGRP release in the trigeminal system. CGRP is released at the trigeminal nerve**

where changes in 5-HT processing and breakdown have been recognised during a migraine attack. These suggest a central neurochemical imbalance due to the dysfunction of the serotonergic system and low levels of 5-HT seem to be activating the trigeminovascular system.

Migraines are also linked to a variety of other diseases such as depression, bipolar disease, irritable bowel syndrome and fibromyalgia. The manifestation of migraines varies from patient to patient, and individuals may present with either episodic or chronic migraines, as classified by the number of migraine occurrences per month. Episodic migraines have a migraine or headache presentation of less than fifteen days per month, while chronic migraines are diagnosed when at least eight of the now minimum fifteen days per month present as migraine days.

To differentiate between a migraine or a general headache, the International Classification of Headache Disorders (ICHD-3) has released guidelines that define migraines as headache attacks that last anywhere from 4 to 72 hours and are accompanied by nausea and/or photophobia. Migraines must also be accompanied by an aura, that is characterised by one or more reversible neurological deficits, of which one has a unilateral localisation.

To treat migraines effectively, two types of pharmacotherapies can be considered; **abortive or prophylactic therapies**. The therapeutic approach must be chosen with a careful evaluation of potential triggers of migraines. The sole use of abortive therapies in managing migraines acutely, is usually suitable for patients with fewer than two episodes of migraines per month. These include common drug classes such as **nonsteroidal anti-inflammatory drugs** (NSAIDs) and analgesics.

Analgesic agents, such as paracetamol or aspirin, may be used alone or in combination with NSAIDs to relieve a migraine attack. Several clinical trials have shown that these may also be used in combination with caffeine to increase absorption rates and potentiate drug activity. Opioid or barbiturate analgesics may also be used in the acute management of migraines, in combination with other therapies such as NSAIDs, but using these should be limited or avoided due to potential side effects or concerns with overuse.

New studies have shown the emergence of **opioid-induced hyperalgesia**, which may be unique to migraine patients. NSAIDs in combination with another drug class, triptans, have also been shown to be beneficial in the acute treatment of migraines. NSAID-induced gastrointestinal effects may be a cause of concern in patients that present with nausea, limiting their use.

Agonist activity at 5-HT receptors has also been shown to be beneficial in the treatment of migraines.

Two drug classes, the triptans (5-HT receptor agonists), of which sumatriptan is the most common, and the ergotamine derivatives, have shown significant efficacy in targeting 5-HT receptors. Triptans are more 5-HT selective than ergotamine derivatives and are a treatment of choice for many patients, but cannot be used for more than nine days per month, due to complications of possible drug-induced headaches.

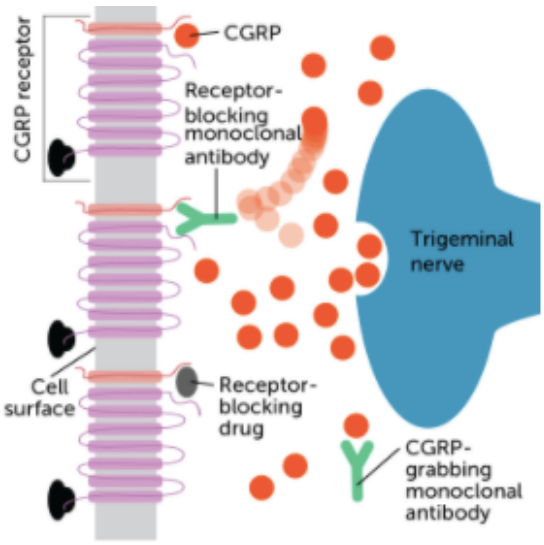

Figure 2. **Representation of the effects of CGRP antagonists (triptans) and monoclonal antibodies on either CGRP (nezumabs) or the CGRP receptor (numabs).**

As CGRP plays a prime role in the manifestation of migraines, CGRP antagonists called gepants have been developed, telgecepant being one of the first of these. These drugs have shown substantial benefits in relieving migraine attacks, but have been associated with hepatotoxicity. To combat this issue, and other adverse effects associated with gepants, monoclonal antibodies to target either CGRP (nezumabs) or the CGRP receptor (numabs) have been developed. These are beneficial, as they target the circulating CGRP to prevent migraines (Figure 2). **Monoclonal antibodies** do not cross the blood brain barrier, they target the trigeminal system, the dural vessels, which are not part of the blood brain barrier effectively. They are also advantageous, because several adverse effects associated with the other drugs, such as hepatotoxicity or cardiovascular problems, are negated.

When it comes to the prophylactic or preventative treatment of migraines, **beta-blockers** such as propranolol, tricyclic antidepressants such as desipramine, and anticonvulsant medications such as valproic acid and topiramate have been shown to be beneficial. Studies show that the use of anticonvulsant medications is the most effective of all available prophylactic treatments. A combination of different prophylactic drugs can be used, if patients benefit from monotherapy using one of the prophylactic drugs, and they are well tolerated.

While studies are still underway to understand the pathophysiology associated with migraines and there is significant ongoing research in the area, there are a myriad of treatment options available. Patient history, drug tolerance, side effects, external triggers and a lot of other factors must be taken into careful consideration when choosing a course of treatment. Moving forward, hopefully, researchers will have a stronger understanding of the disease and will be able to provide better solutions for this perilous headache that affects many individuals on a daily basis.

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DEEP DIVE

VITAMIN C PREVENTS ADAPTATION TO EXERCISE?

WRITTEN BY IRIS ZIELER
EDITED BY MAHTA HAGHIGHAT GHAHFAROK
DESIGNED BY ZAHRAA BHATTI

Vitamin C is one of the main **antioxidants** in our diet, along with Vitamin E.

These are predominantly found in our diet via sources such as citrus fruit, peppers, berries, broccoli, spinach, and collard greens. Antioxidants, and in this case vitamins, are micronutrients - essential **dietary elements** needed in small amounts - which act to neutralise **free radicals**.

Free radicals are inevitable chemical by-products of metabolic reactions. Their production is amplified by external factors such as smoking, air pollution, sunlight, but also exercise. Free radicals are very reactive, causing changes in DNA coding, potentiating the deposition of low-density lipoproteins (LDL) in arterial walls, and other destructive pathways which ultimately lead to oxidative stress that damages cells and may lead to chronic diseases.

LDL deposition is particularly concerning, as this may lead to plaque build-up, the driving factor of atherosclerosis and its resulting coronary artery disease. It is therefore paramount that our bodies receive and produce antioxidant mediators to neutralise these detrimental molecules.

Vitamin C, being one of the most potent antioxidants, became of particular interest in the fitness industry, as exercise has been shown to induce free radical production, putting athletes at higher risk of **oxidative stress**. What the industry fails to acknowledge however, is that oxidative stress is paramount for muscular adaptation to training stimuli.

In the short term, the increased oxidative stress induced by exercise and the subsequent release of free radicals leads to **muscle damage**, fatigue and a subsequent impairment of performance. The claims that antioxidant supplementation improves performance thus seem to make sense, as decreased muscle damage and fatigue enables the athlete to push harder during training.

The issue with this claim, however, is that muscle damage and fatigue are necessary for adaptation to training to occur.

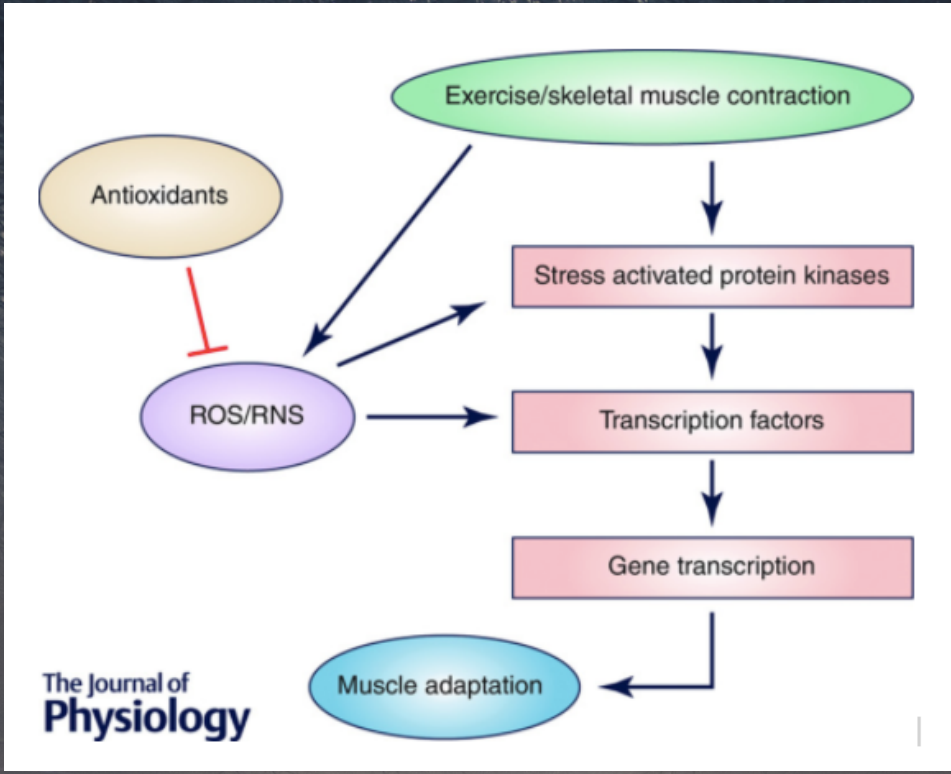

Figure 1. Simplified overview of the mechanism by which exercise, and its resulting reactive oxygen species (ROS) production, drives muscle adaptation. Vitamin C acts as an antioxidant by dissociating into ascorbate, which scavenges free reactive oxygen species, thereby protecting the body from oxidative stress.

In fact, while free radicals induce fatigue, they also act as signals to enhance protection against further physical stress. In other words, these molecules are a necessary product for our muscles to grow and become better suited to the exercise they are being exposed to.

This means that by attenuating the action of free radicals through neutralisation by antioxidant supplementation, athletes would be impairing their ability to adapt to the given training stimuli.

Furthermore, Higgins et al., showed that anabolic signalling was reduced when vitamin C was supplemented in the diet, suggesting a further reason for impairment of training adaptation.

With regards to myofibrillar muscle protein adaptations, a review by Martinez-Ferran et al., discovered a reduction in circulating creatine kinase (CK) post-exercise in chronic supplementation with vitamin C. CK is an indirect marker of muscle damage, further supporting that antioxidant supplementation protects muscle from oxidative stress.

As shown in the diagram, myofibrillar stress is necessary to induce adaptive pathways to the training stimulus.

Interestingly enough, antioxidant supplementation prior to exercise has been shown to reduce training-induced angiogenesis – a key component of mitochondrial muscle adaptation.

Angiogenesis is a mechanism by which oxygen delivery to working tissue is increased by vasodilation. This further suggests that antioxidant supplementation prevents the training-induced ROS regulation of blood flow.

ncreased oxygen delivery to tissues is necessary to maximise oxidative phosphorylation – they key pathway for ATP production in endurance training. Abundance of oxygen in the mitochondria acts as a stimulus for the TCA cycle intermediates to pass though the electron transport chain (ETC).

Hence, the greater the blood flow, the greater the oxygen delivery, the greater the potential of oxidative phosphorylation.

This signals the cells to increase the number and size of mitochondria to maximise its ATP-producing ability. Neutralising ROS hence inhibits this adaptive mechanism, preventing the athlete from progressing in their sport.

These findings underline the potential downside of trying to antagonise oxidative processes in our body, particularly for athletes looking to progress in their sport. While antioxidants have been shown to play a significant role in immune health, their effects on muscular adaptation call for different recommendations when focusing on performance optimization.

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UK Disability History Month

18 November - 18 December

“On the other hand, science is a very good area for disabled people because it goes on mainly in the mind. Of course, most kinds of experimental work are probably ruled out for most such people, but theoretical work is almost ideal. My disabilities have not been a significant handicap in my field, which is theoretical physics."

Stephen Hawking
Amyotrophic Lateral Sclerosis

THREADING WATER

DO LOW TEMPERATURE BATHS REALLY LEAD TO HIGH ATHLETIC PERFORMANCE?

WRITTEN BY ANMOYUL MOHON
EDITED BY MAHTA HAGHIGHAT GHAHFAROK
DESIGNED BY EMILY KOSTINA

Over the past decade, with the rising popularity of many sports across the globe, performance has become an obsession for many athletes as well as various sport federations dreaming to push the limit of human performance. As the way we practice some discipline evolves (disappearance of some weight lifting exercises , use of electronic sensors in taekwondo, use of VAR in football etc…) so does our training approach to competition in general.

While many people believe that progress is mainly made during training on the pitch or at the gym, a major part is played far from the main scene all the way at home such as good quality sleep , nutrition as well as other techniques to maximise our mental and physical recovery.

One of the techniques becoming more and more popular over this past decade is cold-water immersion (CWI) or also called cryotherapy. It is assumed that it will reduce inflammation and improve recovery by changing the way blood and other fluids flow through your body. Sitting in cold water, blood vessels constrict; when you get out, they dilate (or open back up). This process apparently helps to flush away metabolic waste post-workout. Despite the rapid rise in popularity, natural questions arise. Such as whether this approach is truly science based and proven to work.

Factors influencing recovery include sleep, mental fatigue/stress levels, nutrition, hydration, frequency and type of training loads, alcohol intake and methods of warm up pre exercise and cool down post exercise appropriately.

Suboptimal recovery usually leads to fatigue in the long term, reducing the quality of following training sessions and competitive performances while potentially inhibiting adaptive processes. There is currently an abundance of studies focused on the relationship between such recovery and CWI, and the potential post-exercise advantages/ impact it may present.

Currently, the possible **mechanisms** postulated (Lateef, Fatimah, 2010) for the use of cold water immersion therapy post exercise include :

1) With intense exercise, there will be some microtrauma and tears in the muscle fibres affected. This muscle damage will stimulate muscle cell activity (hypertrophy in the long term) and help in the repair and strengthening of the muscle. This is also thought to be the explanation for the delayed onset pain and soreness (delayed onset muscle soreness), which often presents 12–72 h post exercise.

2) The ice bath will cause constriction of blood vessels. This has been suggested as a mechanism that helps with the flushing of waste products, such as lactic acid, out of the affected tissue.

3) With the cold temperature, there will be a reduction of the metabolism and this can cause a slowing down of the physiological processes.

4) The cold temperature will reduce swelling and tissue breakdown.

5) Ice water immersion is also said to be able to shift lactic acid.

On the other hand, another study (Allan et al.2017) suggests that the possible mechanisms of action to be a mix of a reduced skeletal muscle temperature and reduced perception of pain via decreased nerve conduction velocity alongside temperature- and pressure-induced changes in blood flow. As a result, cold temperatures may help in workout recovery by lowering intramuscular temperature and metabolism, decreasing hypoxic stress and reactive oxygen species production (ROS).

It's worth noting that the phrases inflammation, oedema, and swelling are not synonymous terms. CWI, for example, may help with recovery in the initial period after intensive or muscle-damaging exercise by decreasing oedema and swelling without affecting inflammation. However, the effectiveness of CWI techniques in lowering the inflammatory response has lately been questioned. Although the inflammatory response and subsequent oxidative stress have been shown to be important in the cell signalling and remodelling processes involved in the post-exercise adaptive response of skeletal muscle. (Peake et al. 2015).

Indeed, cytokines and chemokines recruit inflammatory cells like neutrophils and macrophages to aid in the healing process. Despite this, the effect of CWI (cold water immersion) on the inflammatory response in human skeletal muscle has received little attention.

Many studies look at performance and subjective measurements as well as systemic inflammatory markers in the blood, but they don't look at muscle as a local secretory tissue that generates inflammatory cytokines, or myokines as they're now known. Although there is evidence from animal research that cryotherapy treatments can help reduce inflammation in muscle damage, there is still a lack of data from human experimentation.

In a recent well-designed study in The Journal of Physiology, Peake and colleagues (2017) used a number of local (gene expression of a muscle homogenate) and systemic (blood plasma/serum concentration) inflammatory markers to compare the effectiveness of CWI to an active recovery treatment, and to look at the inflammatory and cellular stress response after a bout of resistance exercise.

For this purpose, nine active young men completed a single-leg resistance exercise consisting of 45 deg leg press and knee extensions(6 sets of 8–12 repetitions), single-leg squats and walking lunges (3 sets of 12 repetitions), on alternate legs. The participants completed two trials separated by one weeks of the same resistance exercise regime and followed by either an active recovery period (10 min low-intensity self-selected cycling) or CWI (10 min at 10˚C).

Blood samples were taken Pre-exercise, immediately post-exercise, immediately post-recovery, and 30 minutes, 1, 2, 24, and 48 hours after exercise.

Muscle samples were taken from the vastus lateralis before and after exercise at 2, 24, and 48 hours. The exercise protocol successfully induced inflammation and a cellular stress response, as evidenced by increased numbers of neutrophils , macrophage, and gene expression of macrophage cell surface receptors 48 hours after exercise compared to pre-exercise.

Peake and colleagues also showed that, in comparison to the active recovery experiment, CWI had **no effect on inflammatory parameters** and cellular stress, which may come as a surprise given the traditional belief that CWI decreases inflammation.

As previously mentioned, much of the past research has focused on blood-based systemic inflammatory indicators. After a high-intensity sprint workout, White et al. (2014) compared four different CWI regimens (10 and 30 minutes at 10˚C and 20˚C) versus passive rest (12 maximal sprints of 120 m, performed every 3 min). CWI for 10 minutes did not significantly reduce plasma concentrations of inflammatory markers (IL6, IL8, myeloperoxidase) in any of the protocols; on the contrary, CWI for 30 minutes in both cold (10˚C) and cool (20˚C) temperatures exacerbated the response of IL8 and myeloperoxidase in the blood following exercise.

For generations, it has been assumed that the application of a cold stimulus reduces the post-exercise inflammatory cellular stress response, without sufficient data to support this theory.

Peake et al. (2017) were the first to show no difference in the post resistance-exercise inflammatory and cellular stress response in comparison to an active recovery in human skeletal muscle as work investigating inflammatory markers in the blood often shown little or no effect of CWI, normally in comparison with a passive control. These results, and the results from Peake and colleagues (2017), challenge the mainstream concept of recovery that has been commonplace for decades.

Accordingly, the disparity between beneficial reductions of inflammation in animal studies and the neutral results indicated by Peake et al. (2017) might be due to the level of muscle injury and inflammation. Further work is required to assess the relationship between post-exercise CWI and inflammatory cellular stress.

In addition, chronic CWI has been linked to a delay in the activation of critical proteins and satellite cells in skeletal muscle for up to two days following strength training (Roberts et al. 2015), with a decrease in inflammatory signalling being the likely culprit.

Despite this, some study (Peake et al 2017) pointed out that no changes in inflammatory markers in human skeletal muscle and blood were observed in their study, implying that a cold-induced reduction in the inflammatory response is unlikely to be a causative factor in the dampened adaptive response to resistance training (Roberts et al. 2015), as both studies use the same data.

Despite some of the contradictions with other studies , CWI may still be useful. If not for the benefits of greater functional recovery and improved subsequent performance, then for the reduction in delayed onset muscle soreness and the reported analgesic and placebo properties. Currently, further investigation is needed into the correct periodisation of CWI whilst recovery programmes require a more individualised approach: with a particular focus on the goals of the athlete, their training/competition schedule and the environment they are in.

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