ROARING CUBS COLLECTIVE

Scientific Review

Summer 2024

LETTER FROM THE EDITOR

Dear Readers,

This is the third issue of the Roaring Cubs Collective Scientific Review, a publication featuring the sophisticated musings of a handful of brilliant high school students aiming to be the scientists who pave the way for our future.

RCC's STEM Research Scholars Program this summer featured an updated curriculum and a wider selection of exceptional research mentors from universities around the country. During the program, our students learned how to read, write, and understand scientific literature, while also gaining key networking skills en route to producing literature reviews on a topic of their interest. These research papers make up the entirety of this publication, endowing it with the powerful voices of young scientists.

What stands out most in this edition is the diligence and interest with which our students have engaged with current events, both within and outside the realm of science. This is most evident by the vastly insightful discussion of Artificial Intelligence within a variety of contexts and from varying perspectives, such as the use of AI to help surgeons in operating rooms, the security threats which implementing AI technology into healthcare databases could create, and the ethical challenges AI will present. Research is a field which requires scientists to be dynamic, and by tackling novel issues and technologies and discussing their future impacts, our students are well on their way to be successful as future researchers.

I must also take the time to thank our research mentors, a group of incredible undergraduate and postgraduate researchers from universities across the country, for volunteering their time and unwavering dedication to help educate our students. By sharing their own research experiences, while also providing 1-on-1 counseling to help students craft their own papers, they have enriched our program and our students' learning.

As you peruse the articles contained within, I hope you will enjoy them as much as we did, and distinguish within them the mark of intellectual curiosity unique to those aspiring to become the researchers of tomorrow. RCC is a small stepping stone within their greater journeys, and we cannot wait to see the brilliant things our students achieve in their own futures. Nothing brings us more pleasure than being able to support their dreams.

Sincerely,

Muhammad Sharjeel Ansari

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A Subtle Genetic Mutation to Combat Alzheimer's Disease

Sumaiya Amer

I. Introduction

The stimulation of a nerve cell's synergy in the human brain plays a crucial role in sending messages through chemical signals in our body. Within the functionality of nerve cells, many brain diseases prevent neurons from functioning simultaneously. In the case study of Alzheimer's disease, a form of Dementia, – nerve cells are damaged and cannot be repaired. As this disease progressively gets worse with age, symptoms can get worse throughout a person's lifetime until death. Researchers/doctors have declared that there is no cure for this lifelong disease. However, in recent case studies, it has been reported that there is a rare Genetic Mutation (Fibronectin 1 [*FN1*]) that can help fight off Alzheimer's disease and allow a person to live a healthy life.

II. Background

Alzheimer has been chronically known as a permanent disease that malfunctions a person's memory over their lifetime. During that time range, a single individual can forget most of their memory, finally decaying their last memory by forgetting their name. The overall phenomenon of the (Fibronectin 1 [*FN1*]) mutation was that it has cured many affected patients. The initial thought within all Neurologists and doctors was that this was one of the many diseases that cannot be cured. (NIMH, 2023). The damage of nerve cells are unable to be repaired, but many Genes that are in human DNA can chronically salvage many patients' lives. These Mutations hold the phenomenon of having people live a healthy life afterwards.

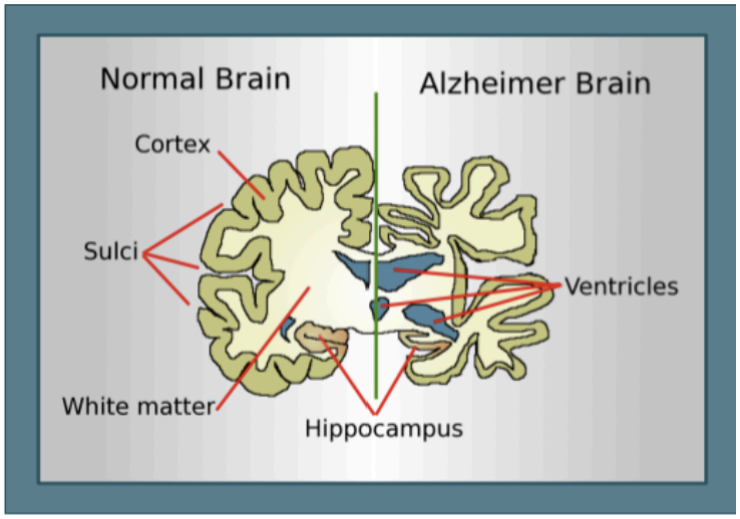

Figure 1: Comparing from a healthy, normal brain to an Alzheimer affected brain, much of the brain has diminished all around. Based on the microtubule. the Tau detaches and forms joining threads.

III. The functionality of the Fibronectin 1 Gene

The Gene variation of the Fibronectin 1 (*FN1*) insists that there is impairment between the cell and its proteins (NIMH, 2023). The function of the Fibronectin 1 (*FN1*) involves an interaction with the integrins, fibrins and collagens (matrix proteins and cellular ligands) Thompsay, H. (2023).. The correlation that this Gene has with curing Alzheimers is that cells have an opportunity to move around and expand. While expanding, to cover more space this can also help with differentiation and cell shape. Fibronectin is usually present in the blood-brain barrier in very minimal amounts, but it is increased in large amounts in brains with Alzheimer's disease. The variant identified in the fibronectin gene seems to protect against Alzheimer's disease by preventing the buildup of excess fibronectin at the blood-brain barrier (CUIMC, 2024). Accordingly, the amyloid plaques, initial thought, are to kill neurons and protein called tau which continues on progressively as the disease spreads throughout the brain— damaging more nerve cells (Reardon, S. 2023). The main purpose within his genetic variation is that, when there are damaged cells caused from Alzheimer's, there is a binding between the integrins, fibrins and collagens. Cells being repaired that were previously damaged from this disease.

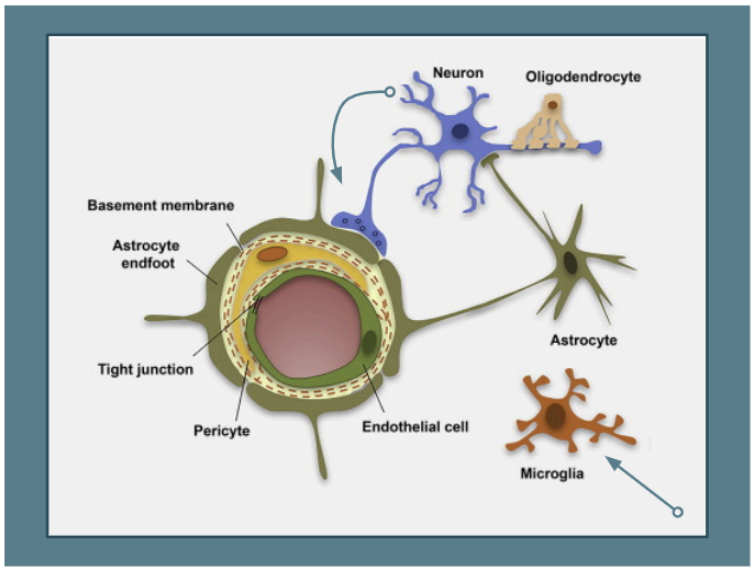

Figure 2: The blood brain barrier in which there is a secured layer of cells that protect any harm from reaching to the brain causing more damage to nerves. Cells are tightly packed and are linked to the microglia which alerts any neuronal injuries appearing.

IV. Stimulation of Nerve cells & Neurons in an Alzheimer brain

A neuron is a part of the nerve cell that stimulates sending signals in our body. This is the core sensory responsible for our muscles and sending messages throughout our body with nerves. It contains 3 different structures (cell body, dendrites and axon). All 3 are important structures of a neuron and hold a very key factor to nerves. (NIH, 2024). In an Alzheimer brain, when neurons are injured they

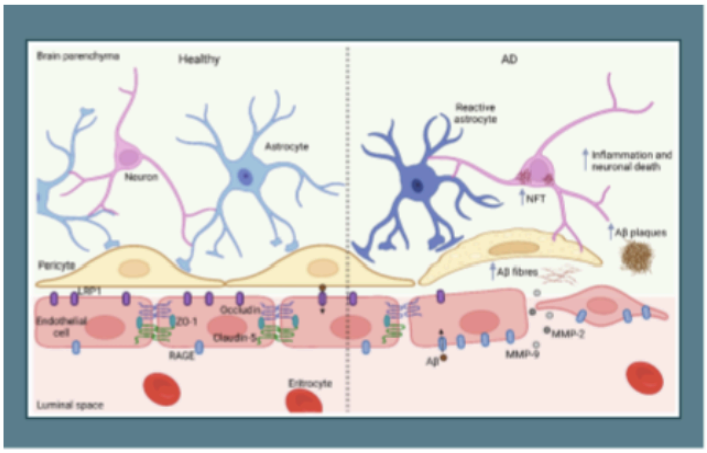

Figure 3: In a healthy condition, the leveling of blood vessels are low. While on the Alzheimer's condition, Amyloid is gradually being build up and the transport systems are being impaired.

stop functionally properly and cause issues within sending signals in our body. Going back to *figure 1,* much of the brain has diminished and shrinked all around. (Makin, S, 2023). When a patient reaches its final stages of this disease, the brain loses a lot of its value, and decays through the last stages. Cells start to decay and lose their function.

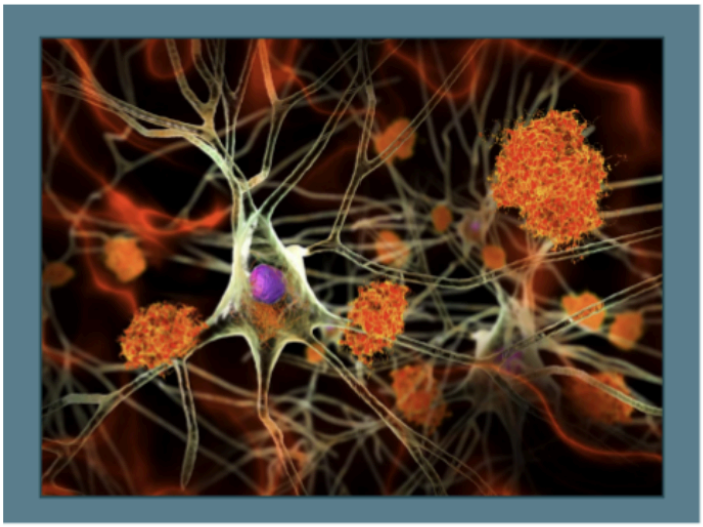

Figure 4: The intertwining of the nerve cells when the disease cells of Alzheimer's attacks all points of the cell.

V. Conclusion

The Fibronectin 1 (*FN1*) upholds many crucial benefits for patients affected with Alzheimers. The Mutation [Fibronectin 1(*FN1*)] has promising results that include curing a patient's disease and helping them maintain a healthy lifestyle after their treatment. However, there still is much more that must be investigated for future case studies, such as investigations regarding figuring out a solid cure for Alzheimer without this Genetic Mutation [Fibronectin 1(*FN1*)] or medicine.

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The Benefits of AI Devices in Healthcare

Amneek Brar

Introduction

Artificial intelligence has begun to shape the world in unbelievable ways. From everyday life to strategic concepts in medicine, subsets of AI have made life for all beings much less complicated. Furthermore, AI devices have allowed many hospital facilities as well as private companies to flourish due to the extensive demand of these devices. AI devices power every day life and are the foundation of keeping hospitals and institutions prestigious and competing with one another. In this research paper, specifically the benefits of AI in the medical field will be discussed. This paper will give an in depth tour of why AI devices are so essential in health care and how they have shaped society. The information will revolve around how these devices aid in diagnosing diseases, finding treatments and enhancing knowledge on incurable diseases through clinical trials and how AI has allowed for a skyrocket in patient care.

Diagnosing Diseases/Treatment Plans

Firstly, AI has truly impacted the healthcare field in aspects such as diagnosing diseases. It has been proven multiple times in various experiments that with the input of AI, diseases are caught much faster and provide more direct treatment plans as well. Firstly, an article published by Beckman institute consists of multiple scenarios in which AI devices have shown their superiority in the field of medicine by diagnosing tumors at exceptional rates. Specifically, the article states that “Their new model accurately identifies tumors and diseases in medical images and is programmed to explain each diagnosis with a visual map. The tool’s unique transparency allows doctors to easily follow its line of reasoning, double-check for accuracy, and explain the results to patients.” (Kurtzweil, 2024) This quote shows how significant this model is because in spite of decades of research and experiments to find the cure for cancer and find how to diagnose it faster, scientists were unable to get to this point. However, with this model, medicine will truly be transformed allowing for many more lives to be saved. With the application of this device, tumors are shown to be quickly diagnosed and treated in the most precise and effective way possible. Additionally, Shaheen exclaims in the article how the medical field had been destroyed after Covid and how healthcare professionals struggled to maintain a healthy lifestyle due to overtime because of short staff and the abundance of patients that had to be dealt with. Specifically, Shaheen includes that “AI should be a critical enabler of healthcare simplification and the development of intelligent care systems. The COVID-19 problem demonstrates how AI may be used for a variety of purposes, including diagnoses and treatment decision assistance, as well as contact tracing and the deployment of AI-driven technologies.” (Shaheen, 2021) This quote especially highlights how beneficial AI devices are in healthcare through the perspective

of deadly diseases. As stated before, Covid-19 had a tremendous role on the lives of people and these diseases further resulted in the loss of multiple lives. This deadly period of time had shown that in order to maintain stability in the healthcare field, physicians and medical professionals were unable to take this task upon themselves and needed aid immediately. As stated by Shaheen, these ai-driven devices can be a drastic change in the medical field for the better by allowing for diseases to be diagnosed at much faster rates. Lastly, the study provided by authors Lee and Yoon is exceptional at emphasizing how far AI devices have allowed for medicine to grow. Specifically, the implementation of the 3Billion device had been shown to be extremely helpful due to the rapid response provided by the device and the accurate diagnosing. In the article, the authors include that "3Billion, a bio-startup that provides DNA diagnosis services for rare diseases, reported that approximately 1200 patients have been diagnosed with rare diseases using AI. In suspected cases of the disease, 3Billion can test up to 7000 diseases at one time." This quote underlines how superior this device is at diagnosing rather than mankind. As stated in the quote, it is highlighting how this AI-driven device can test up to 7,000 diseases at one time. The statistics provided by this article also state that there are approximately 6,000-8,000 unknown diseases and over 400 million people suffer from these diseases. With the implementation of this device, so many people will be saved and can be warned and acknowledged of their health conditions. In conclusion, all the information above is truly significant as it shows how essential it is for AI-driven devices to be applied in the healthcare field. They have exceptional benefits and only of them being how efficient these devices are at diagnosing diseases and treating them.

AI Devices in Carrying Out Challenging tasks

Secondly, AI has also impacted the field of medicine in ways that allow for AI devices to carry out difficult tasks in all areas. Specifically, AI has truly impacted the surgical field of medicine as it has allowed for minimal mistakes and the most precision in all procedures. Firstly, AI-driven devices have shown to be extremely beneficial in minimizing mistakes by carrying out challenging tasks. Oftenly, many surgeons depend on these devices to get the best results possible and help save patients lives.

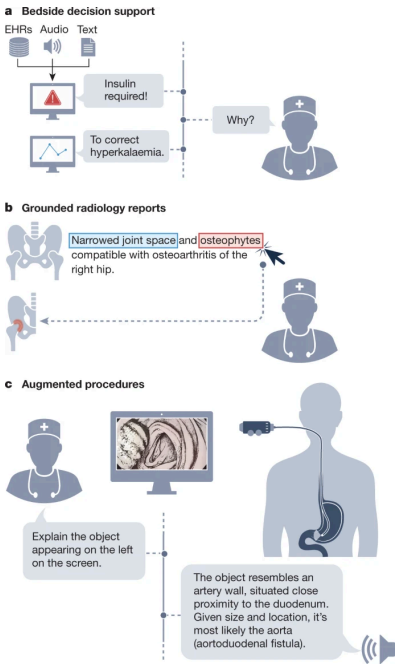

Figure 1: A walkthrough of how GMAI models were able to effectively work through procedures. Specifically, it states how anytime a surgeon needed a clear view or wanted to ensure with another set of eyes, they relied on the GMAI robot to tell them a detailed description of what the scenario was.

They state that "We anticipate a surgical GMAI model that can assist surgical teams with procedures: "We cannot find the intestinal rupture. Check whether we missed a view of any intestinal section in the visual feed of the last 15 minutes". (Moor et al., 2023). This quote is

extremely important as it shows how these GMAI models shaped the operation room by aiding surgeons. Furthermore, these devices help minimize error and ultimately help save patients lives by allowing for a much clearer view on the anatomy of a human. Furthermore, another study conducted by Bohr and Memarzedah proves the benefits of AI devices in surgery as well. For example, the article includes how computer vision allows for the input of clear images as well as interpretation of those images and videos by machines. This is known as image-guided surgery. Specifically, the article includes that "Video data is estimated to contain 25 times the amount of data from high-resolution diagnostic images such as CT and could thus provide a higher data value based on resolution over time. Video analysis is still premature but has great potential for clinical decision support. As an example, a video analysis of a laparoscopic procedure in real time has resulted in 92.8% accuracy in identification of all the steps of the procedure and surprisingly, the detection of missing or unexpected steps" (Bohr, Memarzedah, 2020) This quote is especially important as it provides a real life example in which these image-guided machines were shown to be far more successful in the operating room than the surgeons themselves. Ultimately, the implementation of these devices will allow for the utmost care and the best results for the patient. This will allow for an easy and speedy recovery which will ultimately impact the life of all.

AI Devices in Enhancing Patient Care

Additionally, AI has not only impacted procedures and diagnosing abilities but has truly shaped patient care. With AI, a patient's safety was put at the utmost and became a main priority. AI has further also allowed for patients to feel more welcomed in the difficult times they had been going through. A study conducted by Dave and Patel highlighted how significant AI application is in improving patient care. Firstly, a major concept is that AI devices allowed patients to receive care regardless of where they were. The article states that "Virtual consultations are another way in which AI is being used to improve the delivery of healthcare. By providing remote medical care, patients can receive medical treatment without having to travel to a healthcare facility. This can be especially beneficial for those who live in remote areas or who have mobility issues." (Dave, Patel, 2023). This quote represents how AI has impacted patient care because these devices allowed for people to get treatment regardless of how far they were from a doctor's office.

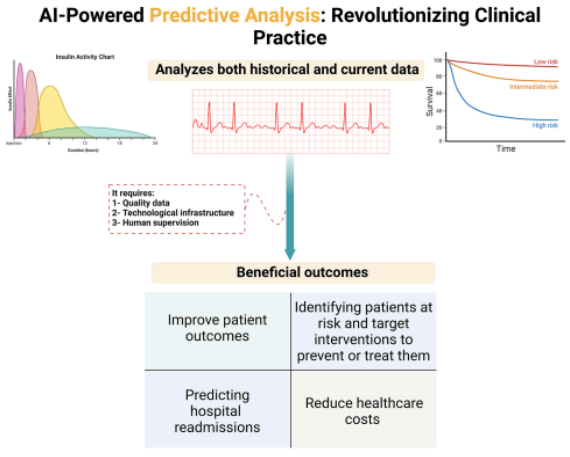

Figure 2: The image taken from "Revolutionizing healthcare: the role of artificial intelligence in clinical practice" is truly significant at showing the role of AI in healthcare, specifically patient care. The image specifically states how these algorithms were able to analyze a patient's current and prior data allowing for the best treatment.

Ultimately, this routine saved multiple lives and allowed for a more flexible healthcare system. Adding on, the same study also mentions how AI driven devices were used in medication management as well as patient transparency. The article mentions how with these devices, appropriate doses were ensured and reduced risks for adverse drug events. The article specifically states that “Finally, AI can increase transparency in healthcare by providing patients with more information about their health and the treatments they are receiving. This can empower patients to make informed decisions about their care and help to build trust between patients and healthcare providers.” (Dave, Patel, 2023) This quote proves how AI devices have shaped patient care by allowing patients to feel acknowledged and well informed about their health issues. This further aided in patients feeling more comfortable with their experience and no shame for sharing out. Secondly, this article also supports this claim as it provides multiple reasons how AI algorithms shaped patient care. The article shows that the GMAI models were not only beneficial for surgical purposes but also for patient care. The models stood as chatbots for patients that provide support and high quality care. This model can truly impact the healthcare system because hospital stays are a;ready extremely draining and difficult. Many struggle with loneliness as often they are stuck in the same room for extenuating periods of time and visiting hours are limited. However, with the implementation of these robots, this aspect can change and allow patients to feel more at home with the friendliness and the never ending support.

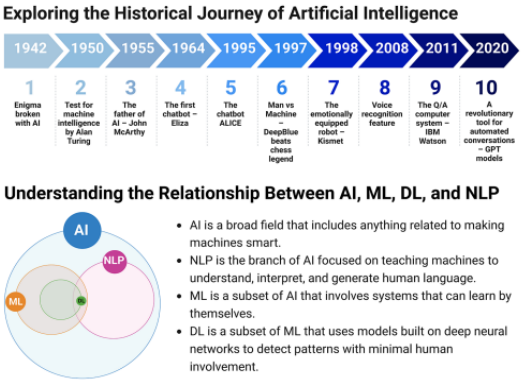

Figure 3: Historical progress in AI models. The figure also shows how NLP, a branch of AI, has the capabilities to understand, interpret and generate human language.

Conclusion

In conclusion, AI has been proven to be extremely beneficial countless times. Despite counterarguments highlighting how AI may destroy the concept of medicine, evidence refutes this claim multiple times and at the end of the argument, the implementation of AI devices is truly significant. Overall, the implementation of AI devices may completely shape the healthcare industry and ultimately improve all aspects of medicine. FRome patient care to physician care, these devices will take a more efficient role than mankind allowing the best possible care. As shown above, these devices can be trained to detect minor errors as well as avoid any possible mistakes and alert professionals if any life-threatening circumstance is bound to come. To wrap this up, the inclusion of AI devices in healthcare is extremely beneficial and therefore a positive step in the healthcare industry.

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The Economic and Political Impact of COVID-19 Vaccine Development

Rebecca Chen

Introduction

During the COVID-19 pandemic, world health and economy had a total turning point through that. Not only vaccine companies from Moderna and Comirnaty represent scientific causes, they can also represent as a catalyst for changing the global health political dynamics and health due to their overstimulated distribution and their production usages. This study will overlook the impactful display of how science takes part in strengthening social flexibility as it looks at the big impactful effects of the COVID-19 vaccine development on the political and economic sides. It also looks at the difficult social connections that have grown during the pandemic between scientific health, policies, and public opinions.

Advancements in Vaccine Development

The flow of developmental COVID-19 vaccines represents an extraordinary developmental achievement in modern medicine, created with innovative technologies and unprecedented collaborations globally to form this vaccine [2][3]. One piece of technology that really stood out behind this progress is the mRNA technology, which was utilized by companies like

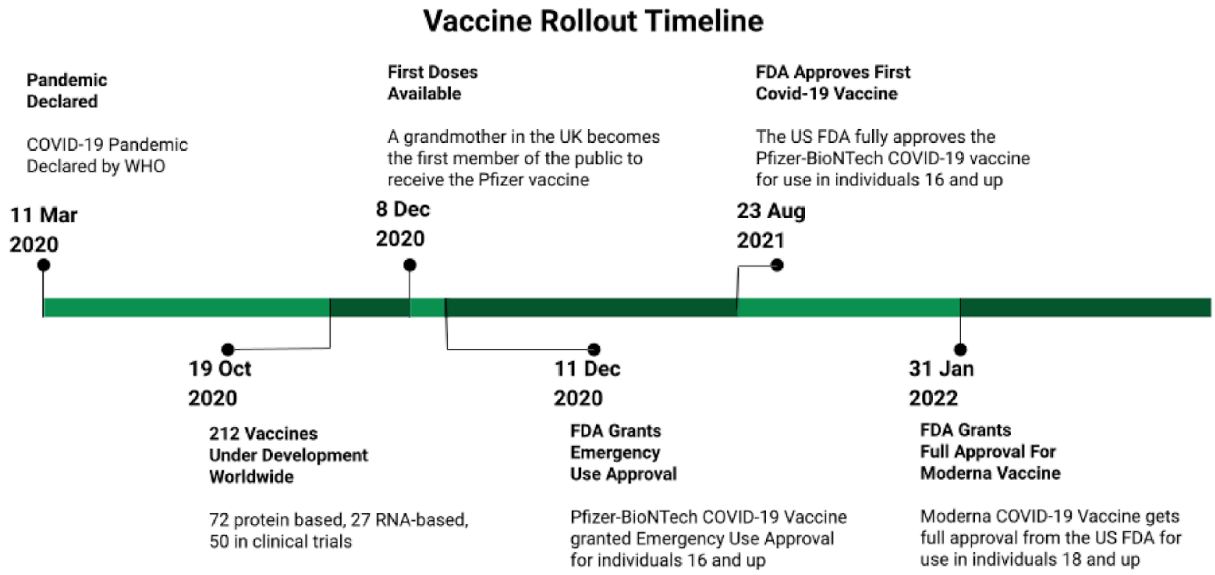

Figure 1: COVID-19 vaccine development: milestones, lessons and prospects. *A visual representation of the timeline for the development of major COVID-19 vaccines, illustrating the rapid pace from initial research to emergency use authorization.*

Pfizer-BioNTech to develop their different forms of vaccines in historic times [1][2]. The mRNA technology is used for the design and the production of the vaccines, allowing a faster response to emerging diseases [2]. The world-wide efforts to overthrow the COVID-19 was created by increased funding and international cooperation, which significantly increased vaccine development processes [3]. For example, research prior on mRNA technology sent a strong foundation, allowing scientists to overthrow and bypass some of the early stages of the vaccine development that was required [1]. To add on, the users of EUAs are prioritized by the swift deployment of these vaccines, combining everything from the original time for vaccine acceptance [2]. The combined collaboration and approach not only highlights the power of world-wide teamwork in public health crises but also sets a new precedent for how rapidly life-saving interventions can be developed and distributed in the future [2][3].

Economic Impact

The distribution of COVID-19 vaccines is increasingly influencing world-wide economic recovery, addressing the severe disruptions caused by the pandemic [4][5]. During Covid, lockdowns and restrictions have caused the spread of the virus to go down and this led to a significant spread of job losses, businesses closing down, and economic decrease, which created many challenges for the economy worldwide [4]. The distribution of vaccines has been spreading in the stabilized economy, as they have been able to reopen businesses and slowly return the

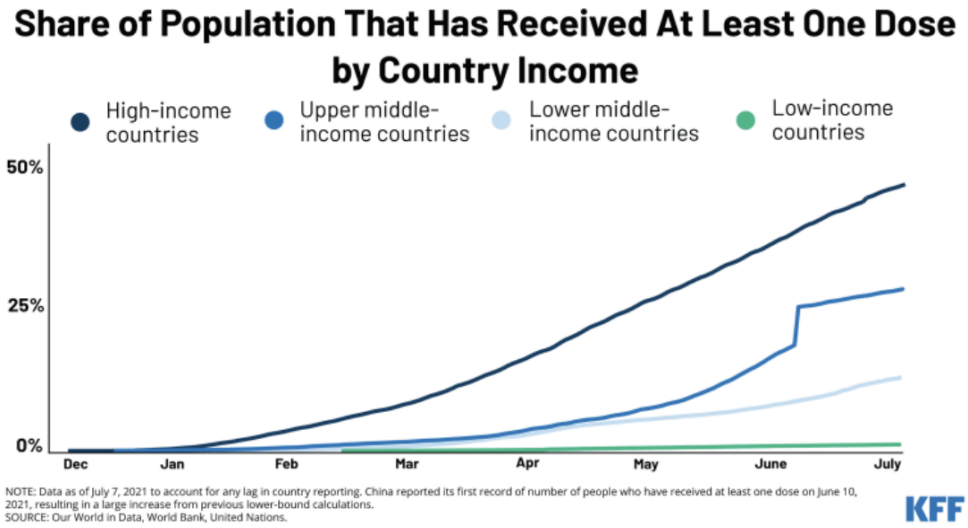

Figure 2: Share of Population That Has Received At Least One Dose by Country Income. *The KFF Graph shows the economic recovery trends in high-income versus low-income countries post-vaccine rollout, highlighting the disparity in economic stabilization.*

consumerism of confidence [4]. For example, countries with bigger vaccine rates have been through faster economic redemption, businesses have been freely more operative, and consumers feel safer engaging in activities [4]. However, this recovery was not fully back to normal. Disparities in vaccine access between high-income and low-income countries have exacerbated existing economic inequalities, leading to uneven recovery patterns across the globe [5]. While some nations are experiencing robust economic revival, others continue to struggle, highlighting the need for more equitable vaccine distribution to ensure a balanced global recovery [5].

Political Implications

The display of COVID-19 vaccines has been significantly binded to the connections of the political policies, making it turn into a shaped bond by the actions of the government and public opinion [6]. The distribution and creation of vaccines have not only reflected on influencing public health, but also become mainly important to political debates and even elections [6]. For example, the governments' pass of success or failure in distributing vaccines have often been a litmus test for public's opinion and trust, which affects the electoral outcomes and shapes voter perspectives [7]. The variety of approaches to vaccine requirements, distribution strategy planning, and public health separation have gone under the difficult combination of science, policies politically, and the public's perspective [8]. In some countries, the efficiency and transparency of vaccine distribution have strengthened public ability to have confidence and the leadership of political policies, while in others, have lost plenty of trust between the past years in America [7]. This intersection of health and politics has revealed the deep policies in the public and scientific efforts can influence each other in times of crisis, with governments being judged on their ability to navigate these challenges effectively [7][8].

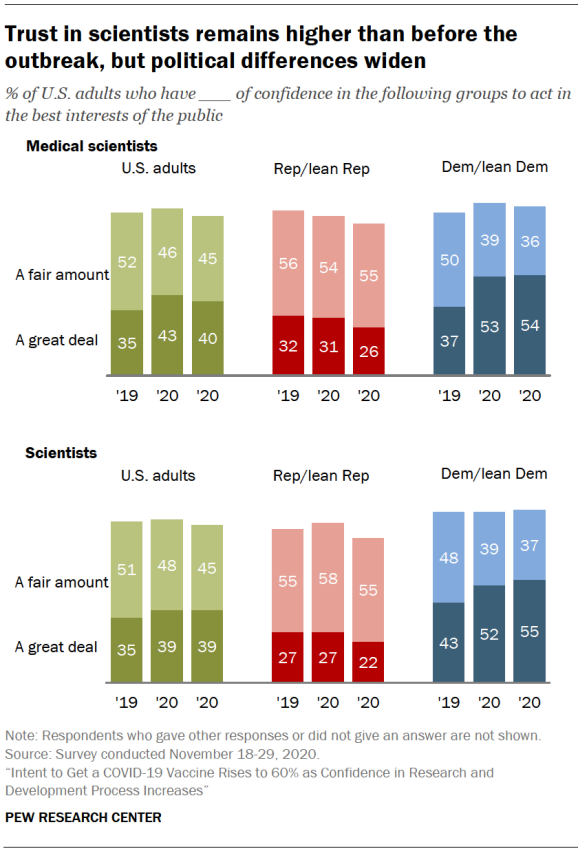

Figure 3: Public Trust in Government and Vaccine Distribution. *This Pew Research Center Chart depicts the correlation between public trust in government and the efficiency of vaccine distribution in various countries.*

Global Health Governance

The COVID-19 cause of everyone to undergo isolation during the pandemic have highlighted how important it is to be in global health governance. Companies like COVAX have been established to protect the insurance of access to vaccines across the world, aiming to make sure

that even the low-income people and countries will have the opportunities to secure the resources given in the medical field to prevent the spread of the virus. However, the difficulty during this distribution process is exposed with the crazy amount of flaws in current global health passions. Despite these goals, COVAX has been struggling to meet the demand, and vaccine distribution was insanely not equal for the longest time, with the wealthier countries and nations that have received vaccines mostly flowable than those in need. This disparity has sparked widespread calls for a change in new reforms in global health governance, pointing out the fact that they are in need for more robust systems that can better coordinate future pandemics and viruses from spreading so strongly. This pandemic has reflected the necessity for making sure there was a fair cause of access to medical resources, pointing out significant discussions on how to strengthen international businesses and corporations and improve the effectiveness of global health initiatives [9][10]

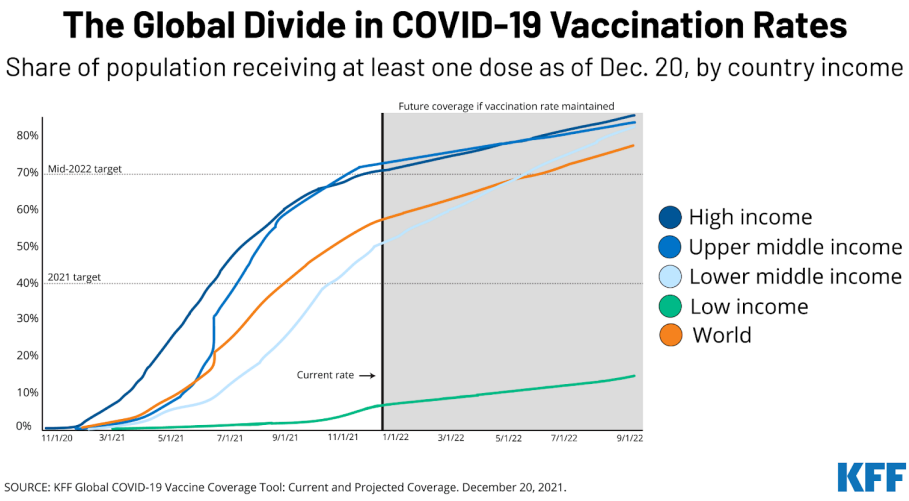

Figure 4: Vaccine Distribution and Global Health Governance. *This Diagram illustrates the structure and challenges of the COVAX initiative and its impact on global health governance.*

Conclusion

The creation of the COVID-19 vaccines and how the method of distribution them have significantly shaped both the economic increase and the political aspect of things [12]. While these vaccines have made such a huge impact on our society in making stable economies and opening up societies again, the disparities in vaccine access have prevented the way of things including having the deeper meaning of global inequalities[11]. Politically, the methods of vaccine distribution has become a huge factor in influencing the public trust and the legitimacy of governments, often swaying political debates and electoral results.

However, this experience of the pandemic has also reflected on the great limitations in global health governance, especially in making sure the access of vaccines was equal to medical resources. The distribution was greatly unequal and it has revealed the need for more effective strategies that can better address global health crises and create a readiness for future pandemics. To add on, it is greatly imperative to include the scientific innovations part of this COVID-19 vaccine plan, the economic stability, and political strategies more closely to enhance societies in resilience and to make sure that this crisis will reflect in future needs.

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How Illness Influences Cognitive Development: A Critical Factor In Lifelong Outcomes

Cassidy Chin

The study of viruses often focuses on their impact on the immune system and their origins. Still, the effects of viral infections on cognitive development during childhood are equally as crucial. Early-age illnesses can profoundly influence cognitive development and lead to impairments if not properly managed. This leads us to our everlasting question: what are the profound effects of early-age sickness on cognitive development? In the study, *Infections and brain development,* the correlation between maternal infections, such as influenza or herpes, as a fetus and an altered brain development is highlighted.[1] *Effects of poverty on interacting biological systems underlying child development - The Lancet Child & Adolescent* a real-world connection, showcasing external impacts[2]. Comparatively, *Researcher to decipher how viruses affect the developing brain with nearly $1M NIH award* implements the idea that not only is this topic one that has been briefly studied, but also one that is continuing to be studied.[3] *Podcast: The science behind vaccines and immunity, Viruses: What they are & how they work*, & *What is neurodevelopment?* were essential to understanding how viral infections affect brain development and function can shed light on long-term consequences and inform strategies for mitigating these effects. This review will briefly introduce neurodevelopment and how a virus works, followed by the effects of a virus on a fetus as well as a child and how this impacts cognitive development. [4], [5] & [6] were key contributors to the comprehension of the news and primary articles. Additionally, *Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (pandas)* gives us a synopsis of specific childhood illnesses[7]. [8], [9], [10], [11] & [12] were used for figures. This review will briefly introduce neurodevelopment and how a virus works, followed by the effects of a virus on a fetus as well as a child and how this impacts cognitive development.

What are the profound effects of early-age sickness on cognitive development? In order to fully comprehend what this question is asking, we must delve into how a virus works, the impact of viruses, and the infections that a virus may cause. Additionally, we must be able to understand the significance of early-age sickness and its correlation to cognitive development (see Figure 5). Cognitive development evolves from childhood to adulthood in distinct stages[6]. Children's brains are more sensitive and malleable due to their ongoing maturation, which affects their initial concrete thinking and gradual development of abstract reasoning. This sensitivity means that children might be more impacted by illnesses, as their developing brains are less resilient to disruptions. For instance, when a child suffers from a "...chronic illness or severe acute illnesses in children [it] can affect cognitive functions such as attention and memory. For instance, pediatric research has documented that conditions like pediatric autoimmune neuropsychiatric disorders can disrupt cognitive development and functioning in children."[7] A

virus works by invading a host by entering cells in the body. It then attaches to a cell's surface using specific proteins that bind to receptors on the host cell[5]. Once inside, the virus releases its genetic material (either DNA or RNA) into the host cell. The host cell's machinery then reads this viral genetic material and uses it to produce new viral particles. New viruses are assembled inside the host cell and eventually leave the cell, often destroying it in the process[4]. These new viruses then infect other cells, continuing the cycle of infection (see Figure 4). Though getting sick and becoming infected by a virus can have severe detrimental impacts on an adult and a child, children are biologically more vulnerable. Viral infections can impact critical periods of brain development, potentially affecting cognitive, emotional, and motor functions (see Figure 2). Particular infections in children can lead to acute conditions like encephalitis (inflammation of the brain), which can cause long-term cognitive and neurological deficits. Additionally, conditions like measles can also lead to subacute sclerosing panencephalitis (SSPE), a rare but severe complication. Children who live in poverty are the most vulnerable to being sick. This isn't directly impacted by poverty, but by the internal factors that lay within[2]. Mainly, those in poverty have less access to health care which shoots them into further risk. Not only are these few instances more likely to harm a child's cognitive development, but fetuses especially are even more vulnerable to these illnesses.

A fetus depends on their mother's health for essential nutrients, but in the case where the mother falls severely ill, the fetus may not receive the vital nutrients needed for optimal development. The fetus is put at immense risk when their mother gets sick, this is a result of many underlying factors. Not only can maternal illness lead to congenital issues or cognitive development, but it can also impact fetal health. Because of a maternal illness, the fetus is exposed to higher rates of complications at birth such as premature labor, low birth weight, and cognitive delays. Furthermore, infections are able to cross the placenta and directly affect the developing fetus. This process can cause inflammation, where inflammatory pathways are activated, causing the release of "various proinflammatory biomarkers and histological changes consistent with an infectious intrauterine environment (chorioamnionitis) or umbilical cord (funisitis). Elevations in inflammatory cytokines are correlated with cerebral palsy, schizophrenia, and autism"[1] (see Figure 1). It is essential for optimal health during pregnancy because it directly impacts the mother and the fetus. Though maternal illness may not cause the mother's cognitive abilities to falter, because the fetus is so vulnerable, it is more likely to be harmed by the illness. This topic is one that has been briefly studied, but also one that is continuing to be studied.[3]

The topic I am exploring delves into the profound effects of early-age sickness on brain development. By delving into this area, I aim to contribute new insights that could inform strategies for prevention, diagnosis, and treatment of developmental disorders associated with viral infections. The study of viruses often focuses on their impact on the immune system and their origins, but the effects of viral infections on cognitive development, particularly in early childhood, are also crucial. Early-age illnesses profoundly influence cognitive development and

may lead to cognitive impairments when not properly managed. My research focuses on the intersection of virology and neurodevelopment, aiming to uncover how viruses can hinder optimal brain growth in children. Understanding this topic holds immense potential to benefit countless individuals and families who have faced such challenges. Moreover, raising awareness about the impact of viruses on childhood brain development could empower caregivers and healthcare providers to mitigate and take proactive steps to safeguard children's neurological health. By studying these interactions, scientists hope to identify biomarkers or early indicators that could predict susceptibility to such developmental disruptions. Furthermore, my investigation seeks to highlight the importance of early detection and intervention strategies. By identifying children at higher risk or developing therapies that mitigate the neurological impacts of severe illnesses, we can potentially improve long-term outcomes for affected individuals. In order to truly prevent illnesses, it is vital to wash your hands before eating (see Figure 3). Ultimately, this exploration not only aims to elucidate the mechanisms underlying virus-induced developmental disruptions but also strives to pave the way for strategies to protect and support children's brain development effectively.

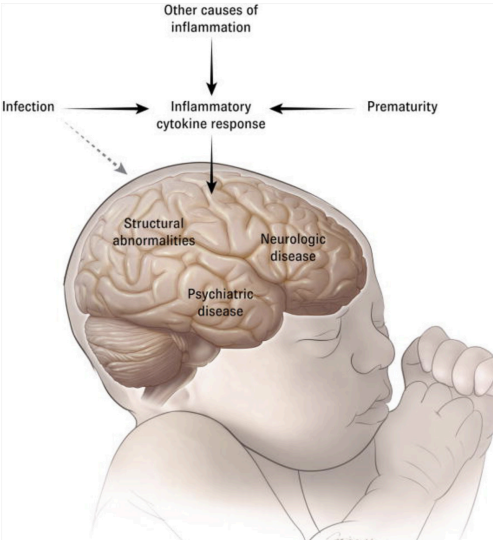

Figure 1: The fetal brain, which faces extreme vulnerability, is going through infection from maternal illness during crucial stages of illnesses[1]. Affects as severe as these can cause the fetus to have structural abnormalities, psychiatric disease, neurologic disease, and overall cognitive impairments.

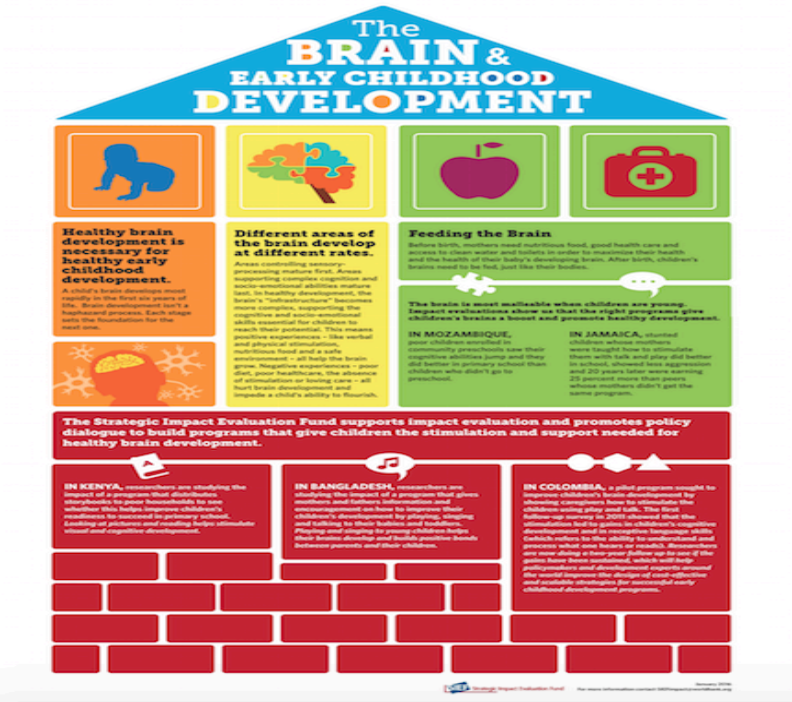

Figure 2: This chart highlights how optimal brain development in various places in the world will lead to healthy aging, in turn capturing cognitive reserve[11].

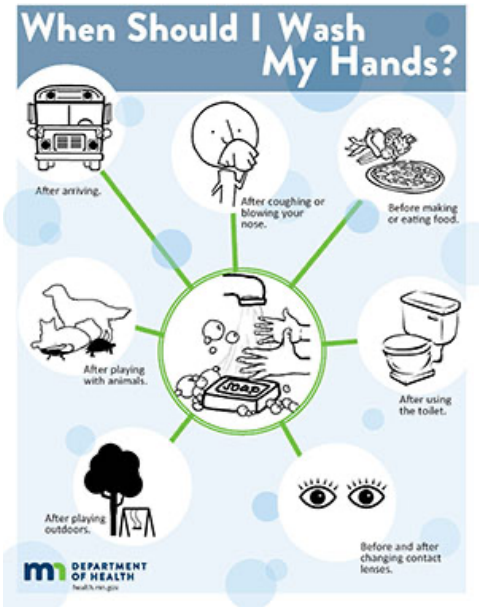

Figure 3: As preventative care for not falling ill, it is essential to wash our hands after our daily activities. Although it is especially important to promote cleanliness in the seven examples above, we must be aware of washing our hands everywhere we go[10].

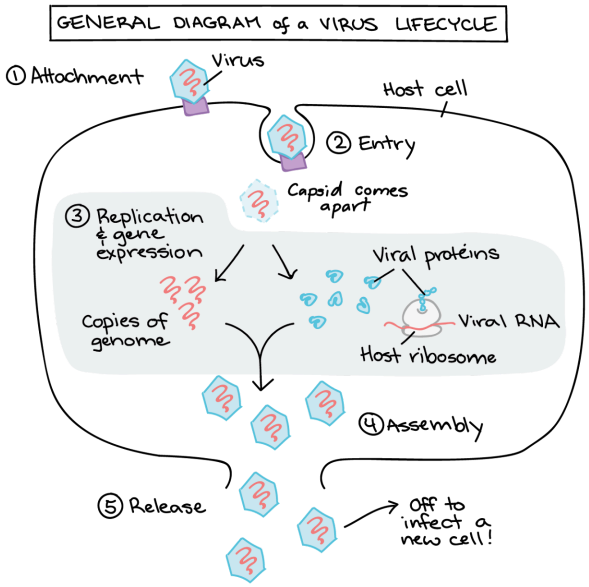

Figure 4: This diagram showcases what may happen in the case of a virus infecting the human body[11].

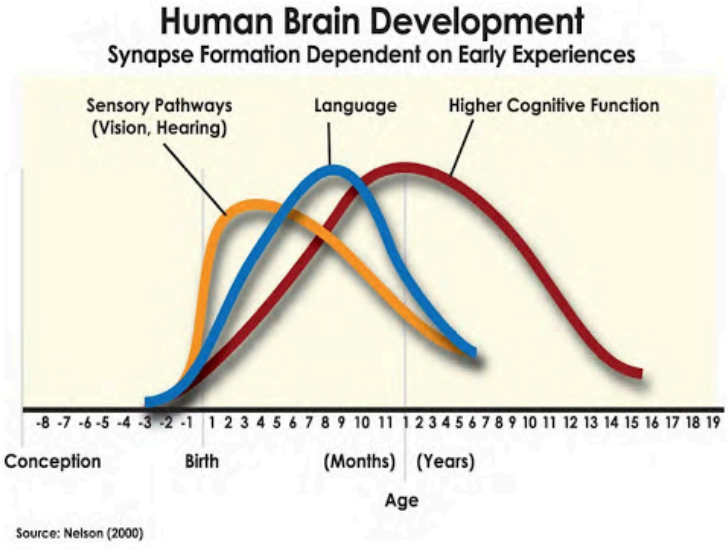

Figure 5: The first five years of a child's life is the most crucial to their cognitive development[9]. *Though one is able to perform with higher cognitive capabilities as they age, this may be hindered during childhood if a child faces cognitive impairment. One cause of this is severe illness.*

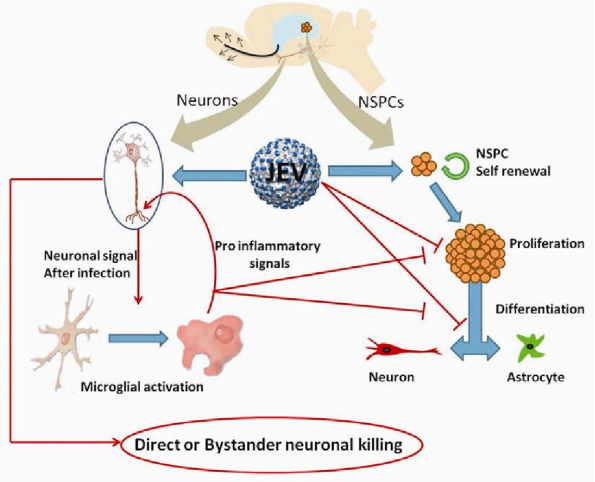

Figure 6: This is a brief introduction into how the Japanese Encephalitis Virus Infection[8], one of the many cognitive impairing illnesses, has an impact on brain development and repair.

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Improved Plasma Confinement Methods in Nuclear Fusion Reactors

Om Dagadgunde

Abstract

Ever since the dawn of mankind, humanity has constantly tested and used numerous sources of energy to fuel our ever-growing need. However, most of the energy we use is not sustainable and is finite. On the other hand, nuclear fusion is entirely sustainable and is an almost infinite source of clean energy that is lying untapped. However, the challenge of plasma confinement in nuclear fusion reactors poses a significant barrier for further advancement. The primary obstacles include turbulence-induced heat/energy loss, plasma instabilities, and the severe degradation of plasma-facing components due to extreme heats and pressures. To address these challenges, scientists are working on new methods and systems to improve plasma confinement in fusion reactors. Major strategies that are being implemented include better magnetic confinement technologies and systems to reduce error and the implementation of real-time computer and AI powered programs to monitor plasma performance. Furthermore, highly performing and advanced materials are being developed to withstand the grueling conditions inside of a fusion reactor. If the integration of these solutions is a success, then they will tremendously boost plasma confinement efficiency in fusion reactors leading to a cleaner and more sustainable world without the worries of energy.

Introduction

The plasma-facing components of nuclear fusion reactors must be able to withstand extreme temperatures and pressure loads. This poses critical challenges for engineers associated with plasma confinement in nuclear fusion reactors. Thus, by examining advanced techniques and confinement methods, confinement efficiency can significantly increase and provide a clear solution to achieve sustainable fusion energy. To note the different types of methods that are implemented in different reactors around the world. However, when comparing different methods, there can be several trade-offs, such as increasing magnetic fields, or increasing the size of the reactor itself. On the other hand, it is also worth mentioning that plasma-facing components in fusion reactors face extreme thermal and irradiation loads. Due to this, highly advanced and capable materials are needed to withstand these harsh conditions. Furthermore, analogous to both mentions, combining advanced confinement techniques with improved plasma stabilization methods is the best way to go for the future of fusion energy. In addition to this, if methods are properly implemented, the potential for nuclear fusion for power generation has no limit and is significantly better than traditional fission reactors or other clean energy methods on the market. Lastly, this paper will discuss the basics of nuclear fusion and plasma physics and then will move onto talking about critical challenges in plasma confinement and then close with

solutions to the problem.

Fusion Reactions

Nuclear fusion is the process where two light atomic nuclei merge together to form a much heavier nucleus. The most common element's isotopes that are needed for sustainable fusion reactions are the isotopes of Hydrogen. More specifically, Tritium (T) and Deuterium (D), these isotopes fuse during a fusion reaction and produce helium while releasing a gargantuan amount of energy. Hydrogen atom fusions are the most used because they have a low coulomb barrier and beneficial wave mechanical transmission factor (fraction of an incident's wave's amplitude, intensity, or power that is able to pass through a barrier). The reactions between T and D is able to be ignited at a temperature of 3107 K. On the other hand, the D and D reactions and the D+3He reactions ignite at a temperature of 3108 K. All of these reactions are the leading processes in which controlled and efficient nuclear fusion reactions can occur. Furthermore, even though lighter-than-iron atomic nuclei can experience fusion reactions, most elements won't fuse until they experience the immense pressure of a star. For instance, in a star, a process called stellar nucleosynthesis results in huge compositional changes over a huge span of time. The equation listed below represents this process where B= The binding energy, Z= Number of protons, N= Number of protons, M= Nucleons Mass (Z+N), c= The speed of light, and mp and mn= Mass of neutrons and protons.

$$B = (Zmp + Nmn - M)c^2$$

Moving on, fusion reactions have two main types of reactions, The first type being a reaction that conserves the amount of protons and neutrons while the second type has a conversion between protons and neutrons. The first type is the most commonly used type of fusion reaction used in modern nuclear fusion. Furthermore, energy can only be released in a fusion reaction if the total mass of the resultant particles is less than the mass of the initial reactants. The equation represented below depicts this process where Q= Energy quantity, m-letters represent mass of each particle, and c= The speed of light. In addition to this, if Q is positive, the reaction is exoergic, and if Q is negative, the reaction is endoergic (absorbs energy).

$$Q = (ml + m2 - m3 - m4)c^2$$

In addition to this, when a particle of one type passes through a collection of particles of the same or different type, there is a chance that they might interact. One of the ways these particles might interact is through scattering, scattering means that a particle changes direction and exchanges energy to undergo a fusion reaction. Furthermore, a cross section refers to the likelihood of particles interacting and thus by measuring all of these factors, we can determine the relative likelihood of one fusion reaction to occur versus another, including optimal

conditions needed for these reactions.

Plasma Physics

Plasma is often referred to as the "fourth" state of matter since it is a gas that has had most of its atoms ionized resulting in free electrons that can freely conduct charges. Due to these free electrons being able to conduct charges, plasma is the only state of matter in which self-sustaining nuclear fusion reactions can occur. Since plasma is a fully ionized gas, it has way more charged atoms than neutral gas atoms. Furthermore, if we take into account the fact that

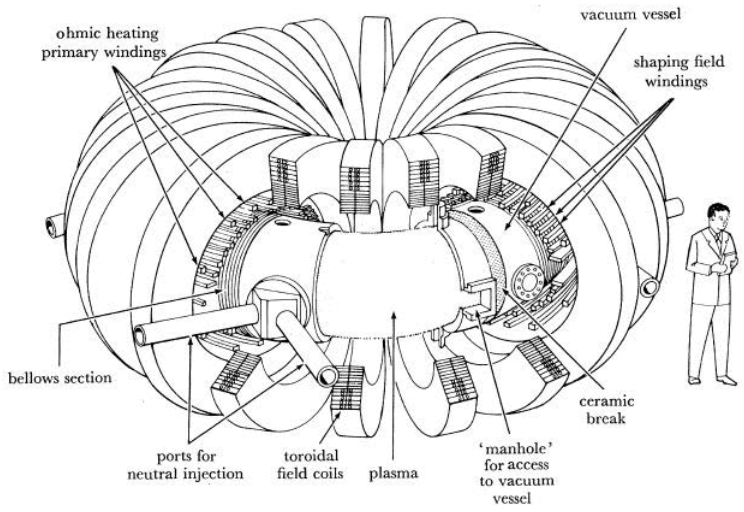

Fig. 1- A schematic showing the inside of a tokamak with essential parts labeled.

plasma particles have an energy distribution just like in any gas, we can use The Maxwell-Boltzmann distribution law to predict these energy distributions to predict an appropriate reaction- rate parameter. The Maxwell-Boltzmann distribution law states that the energy distribution of a plasma and the temperature of the plasma is equal to two-thirds of the average particle energy inside of the constant. For instance, the correlation between the average energy (E) and temperature (T) is listed below where k is the Boltzmann constant of 8.62 x 10-5 eV per Kelvin.

$$E=3kT/2$$

In addition to this, the intensity of nuclear fusion processes in plasma is found by averaging the product of the speed of the particle and the cross section (a particle's energy or speed) over a range of speeds that relate to a Maxwell-Boltzmann distribution. Thus, after averaging these results, a function (f(t)) is created that is only dependent on temperature. The below equation represents the rate of energy released in a given reaction between two species (a and b). In the below equation, n sub a and n sub b depict the density of each species in the plasma; U sub a and U sub b represent the energy released each time a and b undergo a fusion reaction; and P sub a and P sub b depict a parameter that takes into account the rate of a given reaction and the energy yield per reaction.

$$Pab = na(nb)(fab)(T)Uab$$

Moving on, reactions between T and D are the most important and widely used for controlled fusion reactions due to their cross sections being higher than other elements. Moreover, any plasma that contains D will automatically produce T and Helium-3 and the energy yield for a D and T reaction will be equal to 17.58 MeV.

Challenges Facing Nuclear Fusion Reactors

Numerous challenges lie in the way of sustainable fusion reactors to power the world, obstacles such as material challenges, thermal loads, and much more plague further achievements in fusion reactors. However, all of these problems can be linked to the issue of plasma confinement as a whole. If the issue of plasma confinement is solved, then practical fusion reactors can turn from a dream into reality. To commence, a significant issue that lies in the way for fusion reactors is the formation of plasma edges during high-confinement mode (H-mode). If the plasma edges are formed during the H-mode then, the pressure gradient increases at an alarming rate leading to the creation of a structure that resembles a series of steps. These edges can result in edge-localized models (ELMs). Thus, resulting in periodic bursts of particles and heat flux that damage plasma-facing components. The solution to the ELMs problem is crucial since they can lead to tremendous erosion and melting of the divertor plates (a component designed to manage byproducts and protect the reactor's interior). Furthermore, the lack of highly advanced materials that are capable of withstanding extreme temperature fluxes and pressures poses a significant threat towards future fusion development.

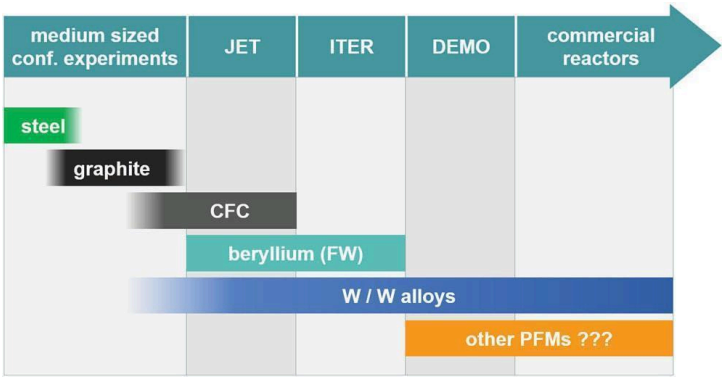

Fig. 2- Schematic summary of the implementation of new PFMs in magnetic confinement experiments.

High-energy neutrons produced during fusion reactions can lead to severe material degradation over a short span of time which leads to embrittlement and impurities within materials facing the plasma. The implantation of hydrogen into the surfaces of the plasma-facing walls, worsens this issue, leading to hydrogen embrittlement. This is a major cause in the reduction of tensile strength and ductility of plasma-facing components such as the divertor plates. However, this embrittlement is the most catastrophic for the structural integrity of the first wall and blanket modules of the reactor. The first wall and blanket modules are essential for maintaining the overall stability of the reactor. The extreme conditions inside of fusion

reactors which include temperatures reaching over a l00 million degrees celsius and immense pressure stresses, further adds to the problem. Due to these conditions, tile detachment and thermal fatigue of materials is a major problem in fusion reactors. These problems ultimately lead to thermal expansion of components and cause shocks that compromise the structural integrity of the reactor.

Tungsten as plasma-facing material	• Modification of grain structure ○ Grain deformation ○ Micro-/nanostructured grains (using RSUHP, SPMM, PIM/MIM processes) • Smart alloys ○ Re, La, Ta, K, Y_2O_3, TiC, Ti, Mo, ... (and oxygen- resistant alloys: Si, Cr, Zr, .. .) • Tungsten coatings ○ PVD, CVD, plasma spraying ○ Functionally graded layers
Tungsten as structural material	• Pseudo-ductile tungsten composites ○ Layered structures ○ Fiber-reinforced tungsten

[a]RSUHP, resistance sintering under ultrahigh pressure. SPMM, microstructural modification using superplasticity; PIM, power injection molding; MIM, metal injection molding.

Fig. 3- Different tungsten grades and alloys that have been developed and investigated thoroughly as plasma- facing and structural materials for next-step magnetic confinement experiments.

Even tough materials like tungsten which is commonly used in plasma-facing components, suffers from recrystallization and embrittlement leading to low effectiveness. In addition to these issues, the effects of irradiation, hydrogen, and helium on various components emphasizes the need for materials with enhanced radiation tolerance. For instance, helium which is produced as a byproduct of D and T fusion reactions, causes helium embrittlement which leads to the formation of bubbles within certain materials that leads to swelling and further degradation. Moving on, currentless plasma, ohmic heating, and auxiliary heating methods are some techniques that are used to achieve the extremely high temperatures needed for fusion reactions. On the other hand, they introduce a variety of challenges relating to plasma fueling and control of impurities. Ohmic heating relies on the resistance of plasma to electric currents becoming less effective at higher temperatures. This leads to the need for auxiliary heating methods such as neutral beam injection and radiofrequency heating. These methods are proven to be efficient, however, they require precise control systems to avoid the introduction of impurities that can cool the plasma. Moreover, energy losses and the high voltages required for these heating methods further complicate the design of reactors and introduce even more problems. For example, the high voltages needed for neutral beam injection, can lead to tremendous energy

losses through a process known as bremsstrahlung radiation. During bremsstrahlung radiation, electrons are rapidly decelerated by the electric field which emits X-rays leading to lower plasma efficiency. If all of the problems stated above are mended, then efficient and sustainable nuclear fusion energy can be a viable energy source for the future of humanity.

Solutions to the Plasma Confinement Problem

To address the monumental challenges facing nuclear fusion, it is important to implement advanced plasma confinement techniques such as the use of different confinement techniques, development of resistant materials through rigorous testing, and other plasma stabilization methods that have been and will need to be developed through constant trials and experiments. The two primary types of systems used in fusion reactors are tokamaks and stellarators. Tokamaks which are used in fusion reactors such as ITER, use a toroidal (donut-shaped) magnetic field to confine plasma to achieve temperatures that exceed 100 million degrees Celsius. The magnetic fields in tokamaks are generated by a mix of external coils and plasma currents. These then create a helical magnetic field that is able to firmly confine the plasma. On the other hand, this reliance on plasma currents can lead to instability and disruptions during the fusion reaction process. Moving on, stellarators such as the Wendelstein 7-X, implement a

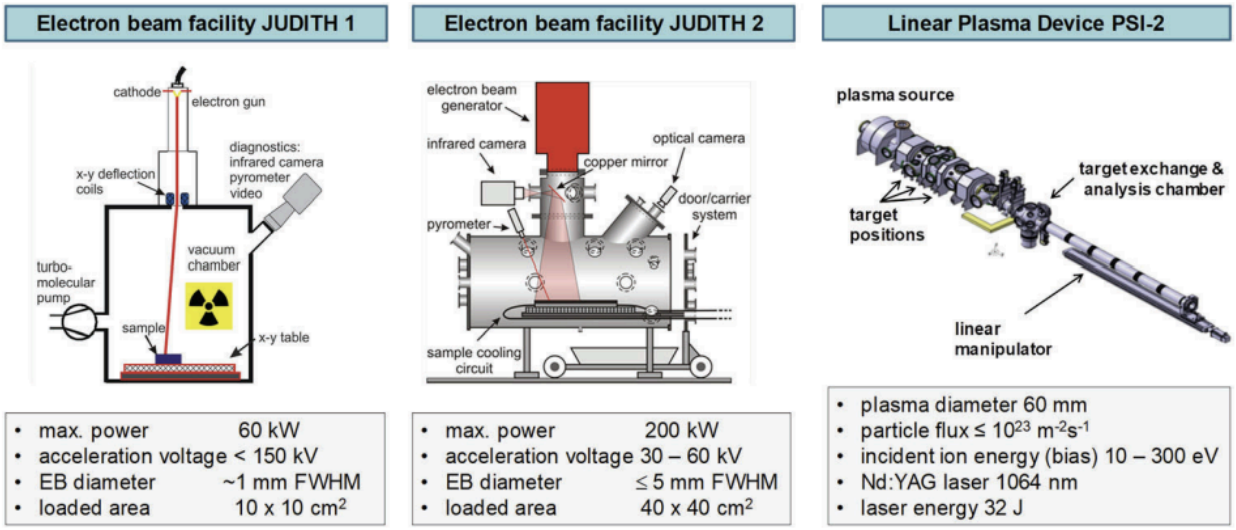

Fig. 4- Selected test facilities and layout parameters for high-heat-flux and plasma exposure of PFMs under fusion-relevant conditions.

continuous mode of operation without the need for a plasma current, thus reducing the risk of disruptions. Furthermore, stellarators use twisted magnetic coils to create a stable magnetic field that can confine plasma without the need for huge amounts of plasma. These magnetic confinement techniques are essential to contain the highly unstable and energetic plasma during fusion reactions. Innovations in these magnetic field technologies include the usage of

superconducting magnets that can generate stronger magnetic fields with lower energy consumption. In addition to this, superconducting magnets operate at extremely low temperatures, this allows them to carry huge amounts of current without any resistance. Thus, maintaining the high magnetic field needed to maintain and confine the plasma. Moreover, advanced materials such as carbon fiber composites and silicon carbide composites are created to withhold the grueling temperatures and pressures. These materials have been proven to offer excellent thermal shock resistance and low neutron activation, this makes them ideal materials for plasma facing components. For instance, carbon fiber composites can withstand temperatures of up to 3000 degrees Celsius with amazing thermal conductivity. Additionally, carbon fiber composites are being graphitized to further improve their thermal conductivity and shock resistance (graphitized means to heat the carbon fibers to extremely high temperatures).

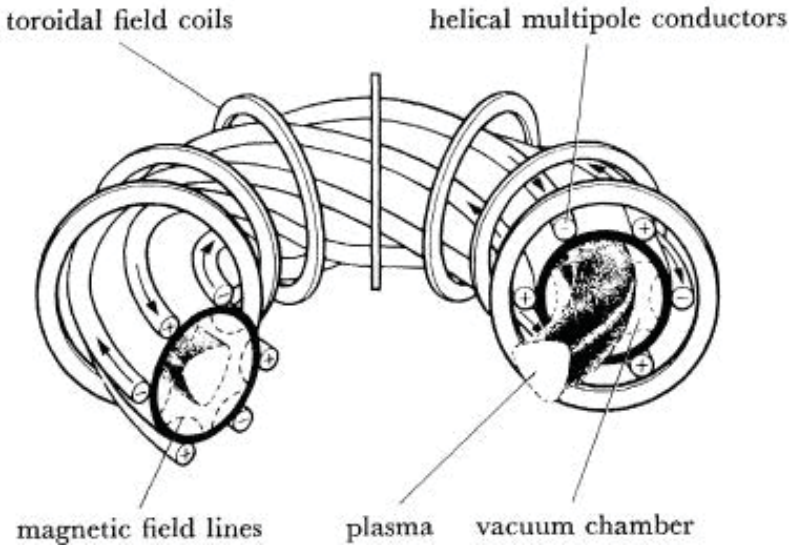

Fig. 5- A schematic showing the inside of a stellarator with crucial parts labeled.

Radiofrequency (RF) waves and neutral beam injections are also being used for heating the plasma and making the current flow smoothly. For example, RF waves include electron cyclotron and ion cyclotron waves that transfer energy to the plasma via resonating with the already occurring frequencies in the plasma. On the other hand, neutral beam injection involves injecting high energy atoms that are neutral to keep plasma temperatures at a constant high. The process involves accelerating ions to high amounts of energy and then neutralizing them before they enter the plasma via collisions. Moving on to divertor materials and designs, it is crucial for the divertor to be able to withstand harsh conditions since a diverter is essential for maintaining heat and particle fluxes at the plasma edge. A common material used for diverters is Tungsten since it has a high melting point and excellent thermal conductivity. Furthermore, plasma simulations and reactor component modeling systems can offer insight for optimizing the design of fusion reactors. These simulations will allow scientists to know about plasma behavior and how plasma interacts with materials in more depth and detail. Advanced diagnostic tools and real-time control systems are also used to monitor and maintain the stability of plasma. These systems incorporate AI and machine learning to predict and solve disruptions to ensure peak efficient plasma performance. In particular, these real-time systems can adjust magnetic fields and heating power strength in response to the changing nature of the plasma. In addition to this, the first wall

and blanket materials are designed to absorb intense amounts of heat and neutron flux much like the divertor. Tungsten and beryllium are most commonly used for the first wall materials and the blanket uses lithium to be able to breed/make tritium. On top of Tungsten's high melting point, it also has a low sputtering yield (this means it scatters particles less which improves plasma confinement). Additionally, beryllium has amazing thermal conductivity and low neutron activation which reduces radiation damage to the parts of the reactor. Lastly, moving onto manufacturing techniques like additive manufacturing (3D printing) and advanced joining techniques, allow engineers to create complex parts with high accuracy and efficiency.

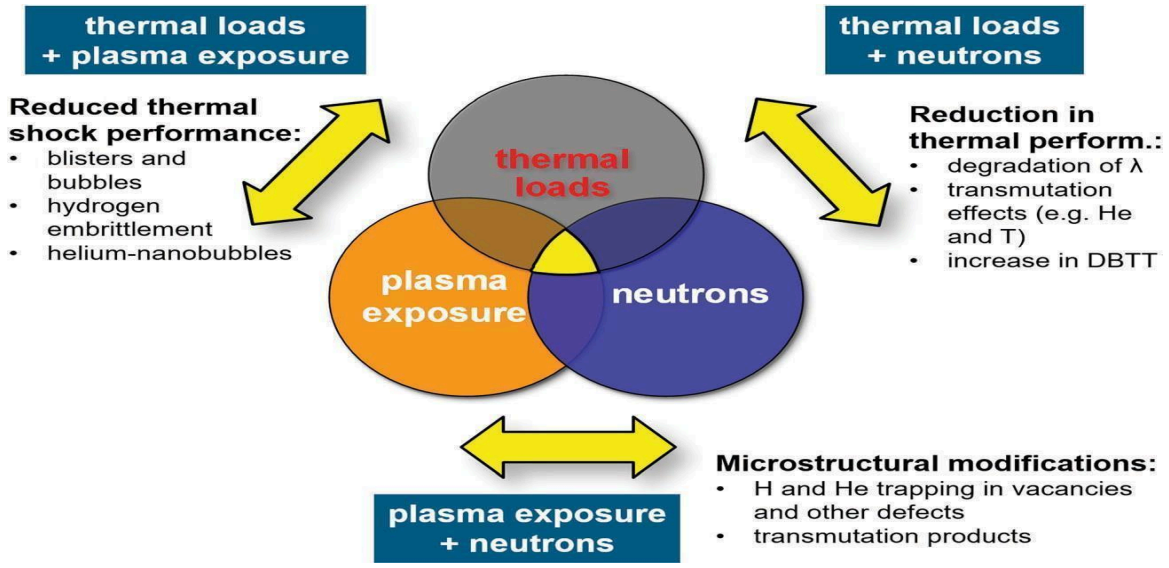

Fig. 6- A chart showing the transitions and descriptions of thermal loads, plasma exposure, and neutrons during a fusion reaction.

These methods allow for complex and intricate geometries with multiple materials to be produced. Advanced joining techniques on the other hand, use laser welding and diffusion bonding methods to assemble components in order to develop advanced materials for reactors.

Conclusion

Nuclear fusion possesses a gargantuan promise as a self-sustaining and unlimited source of energy. However, despite its incredible outlook, the path towards practical fusion reactors is scattered with tremendous obstacles. The main among these obstacles is achieving efficient and effective plasma confinement. Then, to narrow it down even more, challenges such as constraints that current materials pose to us, lack of proper plasma stabilization methods, and the tremendous temperatures and pressures caused by fusion reactors on components. Due to this, plasma confinement poses a significant hindrance with its instabilities and impurities that lead to

huge energy losses and extreme conditions are caused which leads to rapid degradation of materials that make up the critical components of the reactors. However, the path to effective nuclear fusion isn't all filled with potholes and troubles, there is some good news after all. Innovative solutions are constantly being explored such as improved magnetic field configurations and advanced plasma stabilization systems represent a bright hope in a dark situation. Furthermore, engineers are developing advanced and improved materials which are capable of enduring the extremely grueling conditions inside fusion reactors. On the other hand, nuclear fusion still faces limitations like any other major discovery in the history of mankind. These include the tremendous costs and complex systems of constructing a reactor and the huge amounts of time that is required for technological breakthroughs in the field of fusion energy. Nonetheless, with continued and eager research and development, which is combined with increased funding and the free exchange of research, could lead to practical fusion reactors which attract commercial investors. As the future approaches rapidly and the world's energy supplies dwindle, nuclear fusion offers a promising solution to the world's energy problems. Despite the challenges, nuclear fusion offers a way for the international community to come together and work on such a pressing issue to not just imagine but forge a future where fusion energy is in the center of global energy and a more clean and green future is present.

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Is AI Capable of Replacing STEM Careers?

Lianna Dessources

What is AI?

First coined in 1956 by John McCarthy, the term artificial intelligence is defined as the theory that computer systems can perform tasks believed to require human intelligence to complete. For more than half a century AI has been continuously developed and has even become a staple in the daily lives of many. AI's nearly 70 year history starts with the advent of the Turing Test. The Turing Test was created in the 1950s by Alan Turing to determine the level of human intelligence

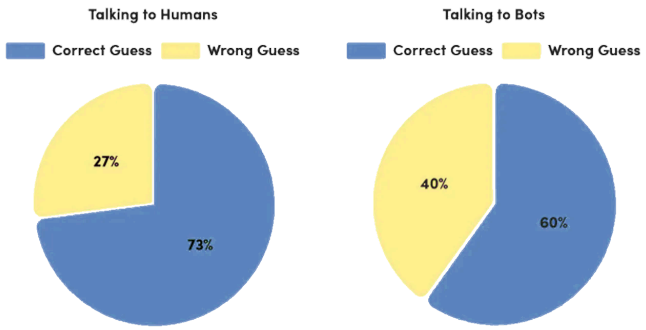

Figure 1: Effectiveness of AI at emulating human intelligence as depicted by people's guesses of whether they are in conversation with humans or bots as part of an experiment.

a computer algorithm possesses. While it can be used to see if one of today's AI algorithms can imitate human interaction, using the Turing Test it is impossible to see if the AI can truly understand what it is saying. Up until the 1970s, research on AI occurred, but from the 1970s to the 1980s there was a pause in research known as AI winter. After the AI winter, research and development of AI continued and many notable achievements in development occurred. In the late 1990s a chess bot beat a chess champion. In the 2010s Apple added Siri, an intelligent speech assistant, to Apple phones for the first time. The introduction to Siri was revolutionary and on most modern phones some sort of AI voice assistant can be found. AI has been widely implemented which led to many ethics guidelines to be put into place. In its vastly expanding abilities, AI has caused many to fear the possibility that it can replace their job. For many in STEM fields the use of AI has become a controversial topic, but should AI be considered a threat? While it may seem like AI can replace some careers in medical and technological fields, AI is incapable of doing so.

AI capabilities and ethics in the Medical Field

AI in Radiology

Radiology is one of the many medical fields that has been implementing AI. There are a variety of different types of radiologists such as diagnostic radiologists, radiation oncologists, and interventional radiologists. They all use radiation to perform their duties, for example diagnostic radiologists use radiation to take photographs of a patient's interior tissue in order to

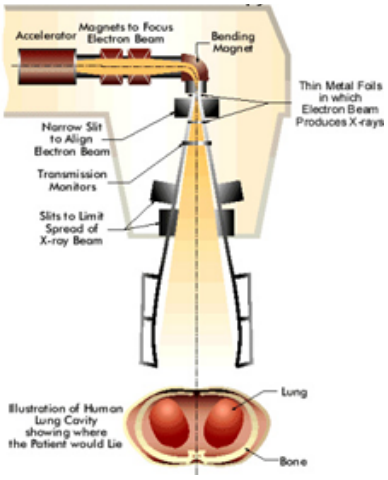

Figure 2: Schematic diagram of a typical medical accelerator used in cancer radiotherapy

diagnose them. The process of taking photographs of interior tissue is known as medical imaging. Diagnostic radiologists must analyze images and determine if there is an issue with the patient. Using machine learning AI is also capable of doing their exact job, which causes many to ask “should we use AI instead of diagnostic radiologists?” Emily Ambinder, an assistant professor specializing in diagnostic radiology at John Hopkins states that AI does not run autonomously and radiologists will continue to review all cases and findings. AI very much acts as a tool used to make more accurate diagnosis. Unlike trained human professionals, AI when only fed a specific demographic will be less accurate at identifying issues in people that fall outside its fed data. This bias that AI may contain can become very deadly when not looked over. While AI can be an amazing tool for assisting medical professionals in diagnosis, it cannot replace the career of diagnostic radiology.

AI is viewed as a great tool that can greatly assist radiologists in diagnosis and treatment. However it is not as ethical as it seems to be, in the mid 1980s a computer controlled radiation therapy machine known as the Therac-25 caused a series of radiation overdoses. The Therac-25 was primarily software based, and the software used while reused was not tested properly. This incident brings the question, can AI be trusted in being accurate in fields that determine if someone lives or dies? By only trusting the machine, multiple lives were lost, to avoid such tragedy to repeat itself AI can not be used to replace careers in the medical field.

AI capabilities and ethics in the Computer Science Field

Web development

From programming websites to designing them, web developers are an important part of how many see the world. While there are multiple types of web developers they all follow the same general process: planning, design, development, testing, deployment, and maintenance. AI is very versatile and has even found itself a place in web development. According to an article by They Make Design, AI is very useful in web design as it can quickly automate repetitive tasks. Web development involves a lot of coding and testing for bugs, AI allows for quick identification of bugs which lets web developers code more efficiently.

While AI is extremely useful in web development, it is incapable of replacing that career. It will and has however, changed the career vastly. An article from CMSWire calls "AI's capability to analyze vast amounts of user data and behavior" a "revolutionizing user experience (UX) design" (Clark). AI can be used to provide personalized content that can possibly increase user engagement and help the company that controls the website. Despite being able to provide personalized content through machine learning, AI is not able to replace web development careers due to its inability to do tasks that require human insight. In web development, AI will act as an assistant used to optimize the tasks of a developer.

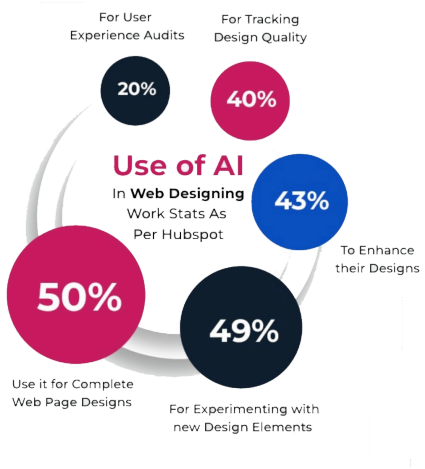

Figure 3: Use of AI in Web Designing

Information technology

Similarly, information technology or IT is a very large career field. The careers in this field involve implementation, support, maintenance, repair or protection of computer systems and data. One highly important area of IT is cybersecurity. In cybersecurity AI is used to aid with threat detection, and response time against cyber threats, and increasing human capabilities against more complex cyber attacks. AI can detect irregularities and possible weak points based on the information that is provided to them, that allows them to inform IT workers so they can fix the threat before it becomes an issue. In cyber security time is a very valuable thing, the quicker possible openings for threats can be fixed or the quicker cyber threats are dealt with the safer data is. AI is extremely useful in increasing the speeds of IT workers, protecting the valuable data found online. In late July 2024, there was a North Korean hacker that attempted to hack into NASA, hospitals, and healthcare providers to acquire data. This data is highly sensitive and it being provided to a country that the USA is not on extremely friendly terms with is a huge risk.

The faster that government cybersecurity officers solved the issue, the less data acquired by the hacker. When threats like this attack occur, IT workers using AI assistance to increase working speeds is extremely important. AI however, is not able to take cyber security jobs as it can easily be manipulated to miss possible openings when it has no supervision. AI is better off as an assistant for analyzing and combating threats in the cybersecurity field of IT.

Conclusion

Upon considering all these facts, the logical conclusion is AI is incapable of replacing careers in STEM. Initially thought of toward the end of the second world war, AI has been developed greatly and is now used in the daily life of many Americans. In today's workforce AI has been increasingly implemented but many fear that AI may replace their career. For careers in the STEM field like radiologists, web developers, and IT workers, using AI is not a risk to their livelihoods despite how much AI can do for their career. AI has greatly transformed STEM careers but it lacks the capability to fully complete essential tasks that human workers are able to do.

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Assessing Innovations in Glioblastoma Treatment

Sophie Dong

Introduction

Glioblastoma (GBM) is one of the most belligerent and treatment-resistant brain cancers, accounting for 50.1% of all tumors occurring in the brain (National Brain Tumor Society). Patients with newly diagnosed glioblastoma (ndGBM) can anticipate an average survival length of just 15 months while those with recurrent glioblastoma (rGBM) can expect only five to seven months (Odia et al., 2021). The cancer is estimated to claim over 10,000 lives per year in the U.S. alone (National Brain Tumor Society). Standard-of-care therapy mostly consists of surgery, radiotherapy, and chemotherapy (Ivy Brain Tumor Center). Despite extensive efforts over the decades to develop new and improved treatments, survival rates have barely changed (National Brain Tumor Society). However, there have been several recent innovations that show some promise for future treatment. This paper will examine three of these innovations – specifically focusing on the drug selinexor, focused ultrasound, and CAR-T cell therapy – including how they work, their advantages and limitations, and how they are revolutionizing GBM treatment methods. Glioblastoma is an extremely difficult cancer to treat, so it is imperative to continue researching and working towards improved treatment options for patients.

Selinexor

Selinexor is an oral medication that has demonstrated promise in treating rGBM. It belongs to a group of drugs called selective inhibitors of nuclear export (SINE). Selinexor functions by selectively inhibiting exportin-1 (XPO-1), a major exporter that transports proteins from the nucleus to the cytoplasm and is overexpressed in GBM. By inhibiting exportin-1, selinexor induces the nuclear retention of several tumor suppressor proteins, which leads to the rejuvenation of tumor suppressor activity (New York Presbyterian, 2022).

In 2022, researchers at Columbia University performed a clinical trial to examine the intratumoral penetration, safety, and effectiveness of selinexor in the treatment of rGBM. A total of seventy-six adults were accepted for the trial (Lassman et al., 2022). Patients were treated with only selinexor for over twelve months (Figure 1); and one patient was treated for over forty-two months (Figure 2) (New York Presbyterian, 2022). The study saw tumor alterations in certain patients and tumor reduction in 28% of the patients; this is a very positive result considering how difficult it is to treat GBM. At a weekly dose of 80 mg, researchers observed good intratumoral penetration and disease control. Side effects experienced from receiving the treatment included fatigue, nausea, decreased appetite, and low platelet counts. These adverse effects were manageable with dose reductions (Lassman et al., 2022).

In addition, other preclinical studies have shown encouraging results when selinexor is synergized with standard therapies such as radiation and temozolomide, a chemotherapy drug (Odia et al., 2021). Another study has shown that selinexor is effective in patients that were heavily pretreated for other cancers (Vergote et al., 2020).

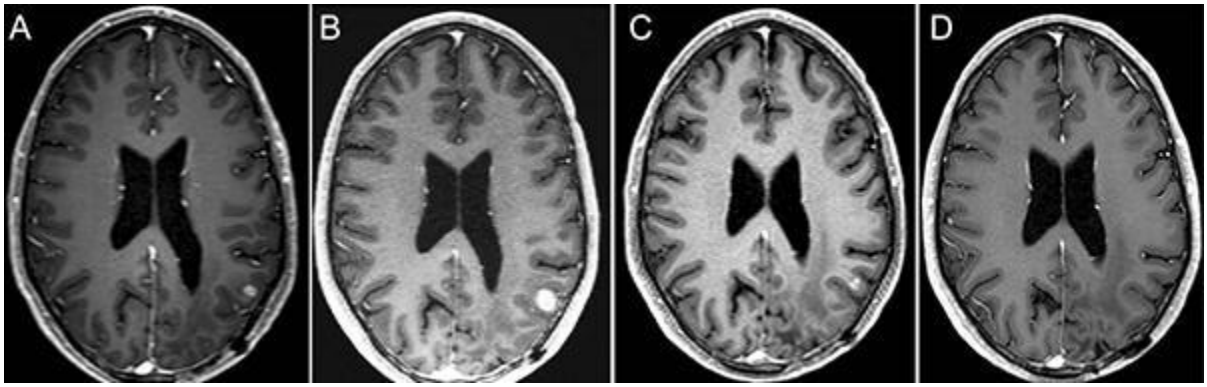


Figure 1: A 36-year-old patient with GBM treated with selinexor after treatment with radiotherapy and temozolomide. *Images taken throughout treatment are shown 7 weeks before selinexor (A), 1 week before selinexor (B), 16 weeks of treatment during a partial response(C), and 24 weeks of treatment for a complete response (D) which was confirmed after 32 weeks of treatment (not shown) (Source: New York Presbyterian, 2022).*

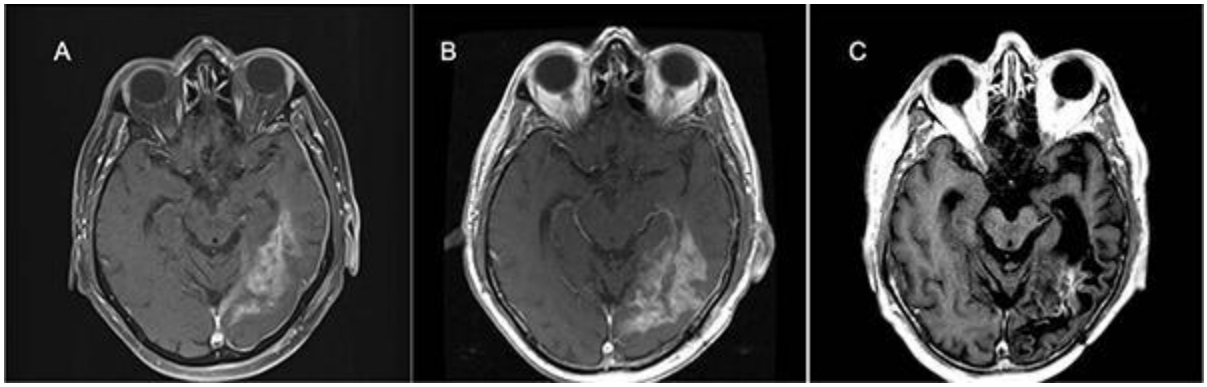


Figure 2: A 64-year-old patient with GBM treated with selinexor after treatment with radiotherapy, temozolomide, and an experimental AKT inhibitor combined with an mTOR inhibitor. *Images taken after subtotal resection of recurrent GBM (A), after further increase in tumor size after ~3 weeks (B), and after a durable partial response from ~73 weeks of receiving selinexor with a maximum tumor size reduction of 72 percent. Patient remained in a partial response after 42 months of selinexor when data collection ceased (Source: New York Presbyterian, 2022).*

Focused Ultrasound (FUS)

Glioblastoma presents very unique challenges for cancer researchers, and one of the most formidable impediments is the blood-brain barrier (BBB). This membrane is a structure of cells that shields the brain from harmful substances while allowing essential nutrients and other

necessary substances to pass. While this structure is helpful in protecting the brain from dangerous toxins and microbes within the bloodstream, it is also very effective in preventing most treatments from entering the brain. In fact, about 98% of small molecule drugs are thwarted by the BBB (Wu et al., 2020). This proves very troublesome for patients with brain cancers like GBM. One approach that is currently being studied to combat this issue is using focused ultrasound (FUS), as it can help open the BBB to increase drug delivery.

In 2023, scientists at Northwestern Medicine conducted a clinical trial where they implanted an ultrasound device to disrupt the BBB and deliver chemotherapy drugs. The two chemotherapy drugs used were paclitaxel and carboplatin; these two medications are not usually given to brain cancer patients due to their inability to pass the BBB. Some patients received six rounds of treatment, which supported that FUS is safe and well-tolerated. The results of the trial showed that drug concentrations increased by four to six times when FUS was used. This is a major increase and shows that FUS is a successful method to open the BBB. In addition, the BBB was restored to its original state within 30 to 60 minutes after ultrasound sonification, showing that the effects on the BBB are transient (Paul, 2023).

In 2020, a study was performed where mice were injected in the brain with a murine glioma cell line, a cell line taken from mice that is grown in laboratories and used to study brain tumors (Wei et al., 2020, National Cancer Institute). FUS and microbubbles were used to deliver a chemotherapy drug, etoposide, through the BBB. Microbubbles are tiny gas-filled microspheres encased in an organic shell that increase the permeability of the BBB by expanding and contracting in response to ultrasound, thus enhancing the drug delivery and therapeutic effects. In the end, the treatment managed to abate tumor growth by 45% and the median overall survival was lengthened by 6 days. The MRI scans from the trial showed significant BBB opening (see Figure 3). Furthermore, the ratio of the brain tumor to medication increased by 3.5 times (see Figure 4), and the medication concentration in the tumor tissue grew by eight times when compared to treatment without FUS (see Figure 5) (Wei et al., 2020).

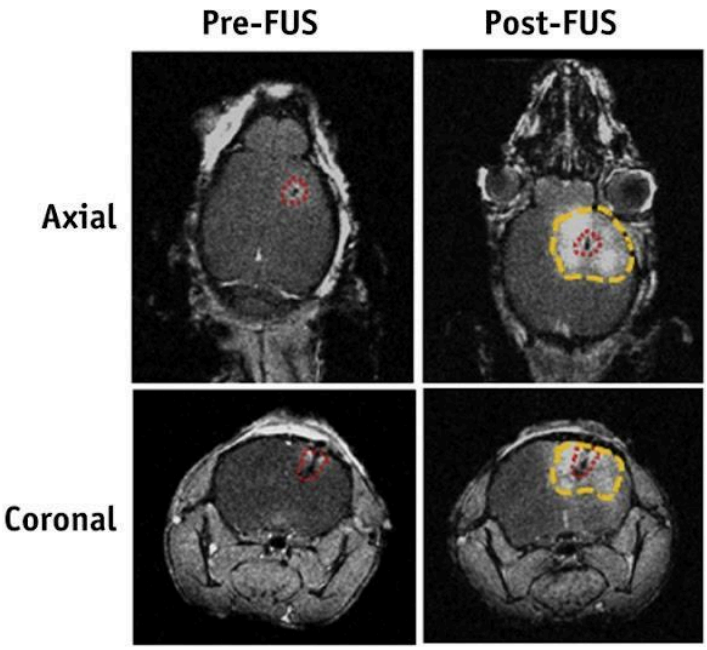
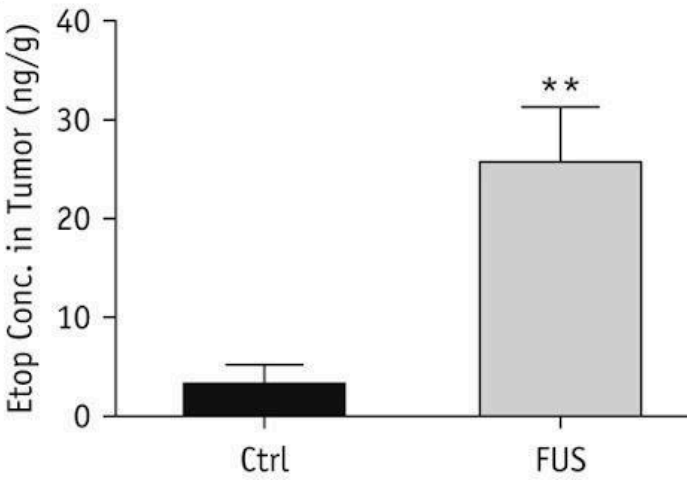


Figure 3: MRI brain scans of BBB opening before and after FUS sonification. *GBM tumor-bearing mice received FUS and etoposide. Images were taken from the axial and coronal views of the brain; Red dotted line indicates tumor; Yellow dotted line indicates BBB opening (Source: Wei et al., 2020).*

Figure 4: Tumor-to-Serum ratio (%) results in control vs. FUS sonification treatment. *GBM tumor-bearing mice received FUS and etoposide, a drug. Tumor-to-medication ratio increased by 3.5-fold (Source: Wei et al., 2020).*



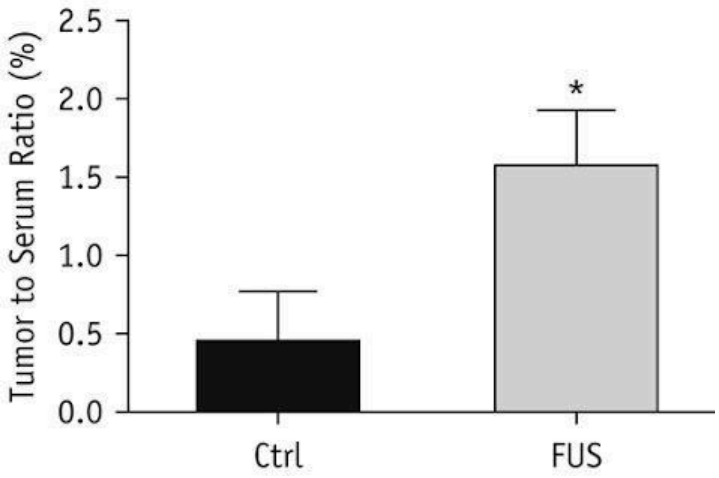


Figure 5: Etoposide concentration results in control vs. FUS sonification treatment (ng/g). *GBM tumor-bearing mice received FUS and the drug, etoposide. Etoposide concentration increased by 8-fold (Source: Wei et al., 2020).*

FUS has both advantages and disadvantages. It enhances drug delivery and is noninvasive as it does not involve making incisions or cuts that risk infection. It is able to reach the intended target without causing much harm to the surrounding tissue and can be repeatedly used as a treatment method (Focused Ultrasound Foundation, 2024). However, there are some potential disadvantages. Any damage to brain tissue is always a concern since it is irreversible, and opening the protective BBB is a risk for infections and pathogens. Ultimately, FUS is emerging as a propitious way to increase drug delivery through the BBB.

CAR-T Cell Therapy

Another potential therapy being developed to treat GBM is chimeric antigen receptor T-cell therapy, also known as CAR-T cell therapy. It is a form of immunotherapy that collects and genetically engineers a patient's white T-cells to target antigens on tumor cells (Luksik et al., 2023). Trials using this therapy have shown energizing results so far. One instance is a trial done by researchers at the Perelman School of Medicine at UPenn and Penn Medicine's Abramson Cancer Center. The main goal of their trial was to assess the efficacy of dual-target therapy, a treatment involving the use of CAR-T cells to target two tumor-related proteins instead of one. The altered T-cells were delivered through the spinal fluid of six patients with rGBM to locate the epidermal growth factor receptor, a protein estimated to appear in 50-60% of all GBMs, and interleukin-13 receptor alpha 2 (IL13Rα2), a protein present in 50-75% of GBMs. MRI scans were taken 24 to 48 hours after the patients received the treatment, and they showed decreased

tumor size for all six patients (see Figure 6). However, a concern with using CAR-T cell therapy is neurotoxicity, which is when a toxic substance enters the brain, disrupts the nervous system, and kills neurons. The neurotoxicity in the six patients was significant but managed and monitored with care (Bagley et al., 2024).

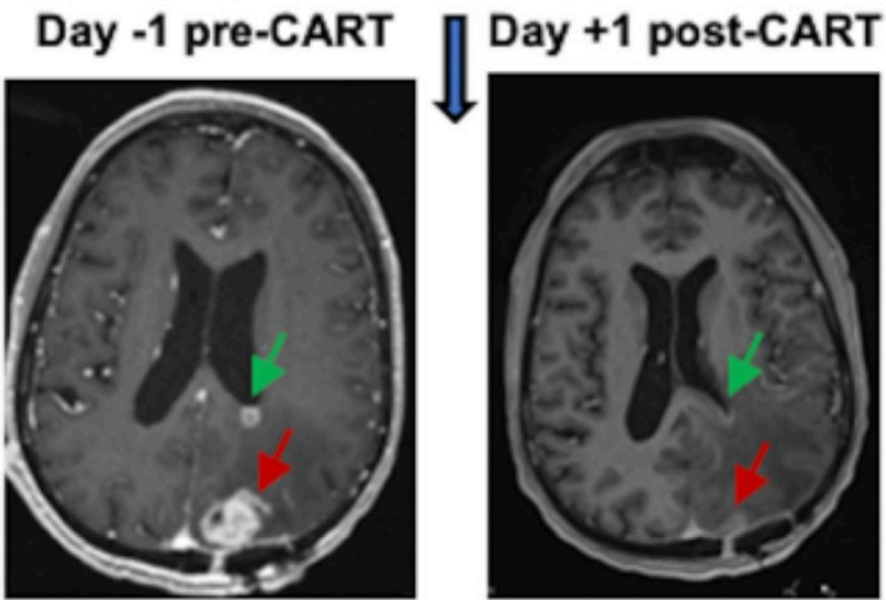


Figure 6: MRI scans of patients treated with CAR-T cell therapy. *Images taken one day before CAR-T cell therapy and one day after CAR-T cell therapy. Red and green arrows indicate the tumor. There is evident tumor reduction (Source: Penn Medicine, 2024).*

CAR-T cells have unique characteristics that make this therapy well suited for GBM. One advantage of using this therapy is better BBB penetration; CAR-T cells are able to pass through the barrier easier than most other treatment substances by utilizing immune cell trafficking. Another major benefit is that CAR-T cell therapy can directly kill the tumor cells once attached to the tumor cell's receptor. Therefore, it does not rely on the body's immune system that is already severely repressed by GBM. CAR-T cells also show some promise in eliminating cancer stem cells, cancer cells that can self-renew, reinstitute, and redevelop the diminished cancer cells (Luksik et al., 2023). This is a great potential benefit since cancer stem cells can cause tumor relapse.

However, there are many drawbacks and areas to improve if CAR-T cell therapy will be used on GBM patients, including antigen escape. Tumors can eventually lose their expression of some antigens, effectively making them undetectable to the genetically engineered CAR-T cells (Luksik et al., 2023). Tumor heterogeneity of GBM is another challenge. Genetic alterations between the cancer cells make them distinct from one another, so not all cells in GBM are the same or possess the same antigens that the CAR-T cells are programmed to attack. Therefore, cancer cells can evade and block the CAR-T cells (Penn Medicine, 2024). Lastly, immune

exhaustion can occur when prolonged exposure to antigens wears out the T-cells, making them less effective (Luksik et al., 2023).

Fortunately, potential solutions to these issues are being actively studied. For example, to combat antigen escape, scientists are working on engineering CAR-T cells to have multiple receptors or multiple antigen-bonding domains (Luksik et al., 2023). Combining CAR-T cell therapy with radiotherapy, chemotherapy, and FUS is also being researched to improve antigen availability (Luksik et al., 2023). The use of oncolytic viruses is also being combined with CAR-T cell therapy. These viruses can infect and kill tumor cells without harming healthy cells. They may also force tumor cells to release tumor-associated antigens (TAAs) to assist the CAR-T cells (Luksik et al., 2023). While there are still some drawbacks to using CAR-T cell therapy to treat GBM, scientists are currently working to address these issues, making it a promising future treatment option.

Conclusion

Glioblastoma remains a destructive brain cancer with very few effective treatments. Advancements like selinexor, focused ultrasound, and CAR-T cell therapy provide a hopeful direction for cancer researchers to eventually develop a strong treatment regimen for glioblastoma. Each innovation has their own advantages and limitations, but with more time and research, these new treatment strategies can be refined (Table 1). Furthermore, these treatments could potentially be combined in the future to create an effective treatment plan for patients. Glioblastoma is an extremely malignant tumor, making it crucial to continually enhance treatments to improve patient survival rates.

Treatment	Advantages	Disadvantages/Limitations
Selinexor	• Shows promise on patients with rGBM • Demonstrated encouraging intratumoral penetration • 28% of patients experienced tumor reduction • Demonstrated encouraging results when combined other therapies	• Not much study on patients with newly diagnosed GBM • Side effects (fatigue, nausea, smaller appetite, etc.)
Focused Ultrasound (FUS)	• Improved BBB penetration • Can be combined with other therapies to enhance their effects • Noninvasive • Can be repeated • Can reach desired target w/o damaging tissue	• Potential risk when protective BBB is opened • Potential damage to healthy tissue
CAR-T cell therapy	• Better BBB penetration that other treatments • Kills tumor cells with precision while reducing collateral damage • Does not rely on the body's immune system • Shows promise in killing cancer stem cells • Demonstrated encouraging results when combined with other therapies	• Antigen escape • Inadequate tumor-specific antigen expression • Low mutational burden (LMB) • Molecular heterogeneity of GBM • Immune exhaustion • Neurotoxicity

Table 1: *Summary of Advantages & Disadvantages of New Treatment Strategies for GBM*

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How do Psychological Factors Including Stress, Environmental Influence, and Depression Contribute to the Progression of Cardiovascular Disease?

Annabelle Franklin

Introduction

Heart disease is the leading cause of death globally, with one person dying every 33 seconds from cardiovascular disease (CDC, 2024). Understanding the relationship between psychology and cardiology disease (CVD) is a major issue to examine. Studies have proven that common psychological factors such as anxiety, depression and stress are vital contributors to cardiovascular well-being (Rozanski et al., 2005). For example, stress increases blood pressure and inflammation, contributing to higher heart disease rates. Additionally, depression and anxiety are major factors in developing coronary artery disease (CAD) (Barefoot & Schroll, 1996).

The rise in recognition of psychological factors that affect cardiology disease rates emphasizes the critical importance of addressing this issue. Prioritizing psychological well-being, including fostering optimism and happiness, can lower cardiovascular risk and encourage a healthier lifestyle (Boehm & Kubzansky, 2012).Researchers are also increasingly advocating for psychological interventions for patients (Easton R., 2022).

This research paper evaluates the relationship between psychology and cardiology disease, reviews literature, endorses psychological interventions for patients. Acknowledging these connections is essential for strengthening patient care and improving heart health outcomes.

Impact of Psychological Stress on Cardiovascular Health

Psychological stress significantly impacts cardiovascular health by causing physiological changes such as increased blood pressure and inflammation. Stressors can be categorized into two different types: chronic and acute; both having a significant relationship to the heart.

Acute stress is what activates the body to respond, contributing to immediate physiological changes and exerting pressure on the cardiovascular system. Earthquakes are common examples of acute stress. During the Taiwan earthquake in 1999, patients experienced unexpected increases in heart rate, with some rates observed as high as 160 beats per minute (Rozanski et al., 2005). In contrast, a normal heart rate for adults typically ranges from 60 to 100 beats per minute. The dramatic and abrupt heart rate increase can strain the heart and blood vessels, leading to the cardiovascular system suddenly working harder to meet these increased

demands. This elevated heart rate can lead to complications such as arrhythmias and an increased risk of heart disease.

Repeated exposure to acute stress can cause the body to remain in a constant state of alert, putting extra pressure on the heart and blood vessels. This sustained high level of stress can strain the cardiovascular system, resulting in elevated blood pressure and a heightened risk of developing heart disease.

Chronic stress also contributes to the likelihood of developing heart disease. Chronic stress refers to prolonged stress experienced over an extended period, such as from job-related pressures, marital discord, or everyday hassles. Similar to acute stressors, chronic stressors cause a persistent increase in blood pressure and increasing cardiovascular risks. The INTERHEART study reports that employees with "permanent stress" from work or at home have 2.1 times the risk for developing myocardial infarction (MI), which is commonly known as a heart attack (Dimsdale, 2008) (Figure 1).

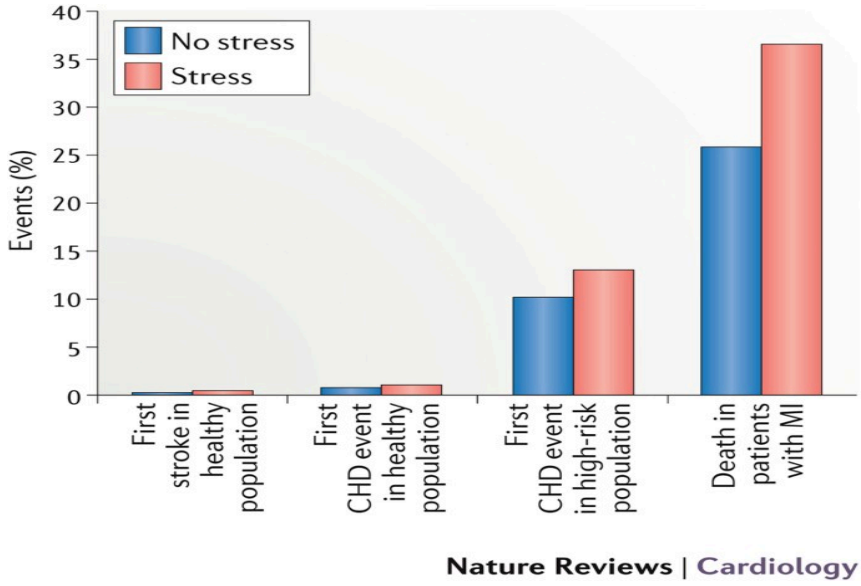

Figure 1: The Influence of Stress on Cardiovascular Event Rates in Various Populations
This figure illustrates the percentage of various cardiovascular events among populations under stress (red bars) versus no stress (blue bars). The events compared include the first stroke in a healthy population, the first coronary heart disease (CHD) event in a healthy population, the first CHD event in a high-risk population, and death in patients with myocardial infarction (MI). The data indicate that stress significantly increases the incidence of these events across all categories, with the most pronounced effect seen in the mortality rate among patients with MI. Figure received from (Kivimaki, 2017).

Another historical instance of chronic stress impacting lives is the siege of Leningrad, during World War II, when the city was surrounded by German and Finnish forces from 1941 to 1944, leading to prolonged stress, severe famine, and increased mortality and morbidity rates. Significantly, residents experienced an increase of blood pressure. Joel Dimsdale wrote in their research journal that "During the siege of Leningrad, BP increased dramatically. Even 50 years

later, survivors had increased BP and cardiovascular mortality compared with those not in the besieged city" (2009). This long-lasting impact emphasizes the effect chronic stress has on cardiovascular health.

Additionally, the Northridge earthquake in California in 1994 was a monumental event that vividly demonstrated the connection between acute stress and heart issues. On the day of the earthquake, there was a dramatic increase in sudden deaths attributed to atherosclerotic cardiovascular disease, with 24 fatalities recorded—a significant deviation from the daily average of 4.6 deaths in the preceding week. This increase highlights the vulnerability of the cardiovascular system to extreme stress, particularly in the context of natural disasters (Figure 2).

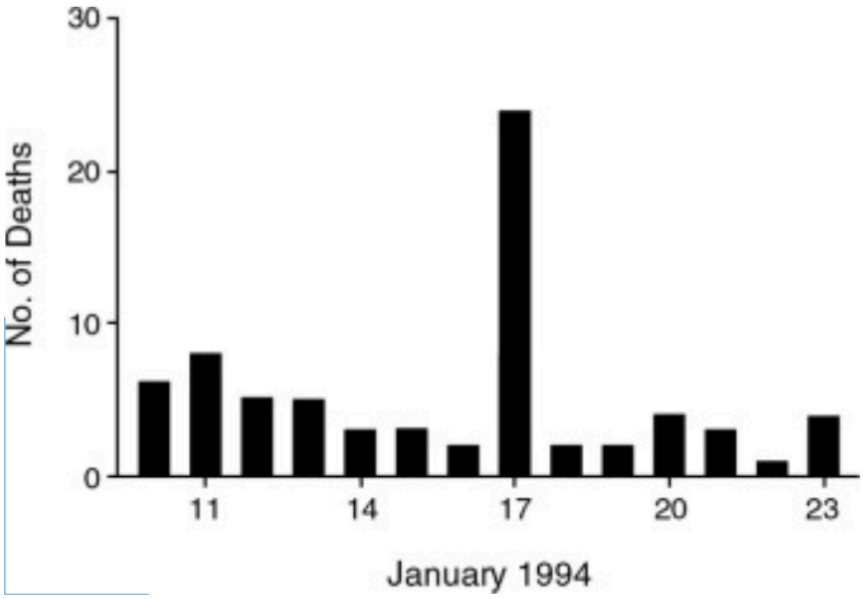

Figure 2: Sudden Cardiovascular Deaths During the 1994 Northridge Earthquake
This bar graph illustrates the number of sudden deaths due to atherosclerotic cardiovascular disease in January 1994, coinciding with the Northridge earthquake in California. The data shows a significant spike on January 17, the day of the earthquake, with 24 deaths recorded, compared to a daily average of 4.6 ± 2.1 in the preceding week. This sharp increase underscores the immediate cardiovascular impact of acute psychological stress induced by natural disasters. Figure received from (source).

While stress negatively affects cardiovascular health, mental health disorders like depression and anxiety also significantly contribute to coronary artery disease.

Roles of Psychosocial Factors in Coronary Artery Disease

Psychosocial factors such as depression and anxiety are crucial risk factors for Coronary Artery Disease (CAD), affecting disease development and patient outcomes. Research proves that individuals suffering from mental health disorders are at a higher risk of cardiovascular events.

Depression is related to the vulnerability to CAD in various ways. It can lead to poor lifestyle habits such as smoking, poor dieting, and eventually the progression of heart disease. Harry Hemingway, a senior lecturer in epidemiology, highlights in his research paper that a strong correlation with CAD increases the possibility of risks (1999).

For instance, LaCroix reports that high control jobs with high demands led to a 2.9 increase risk in coronary heart disease (CHD) among women (1984). Another report from Haan found that people with low job control and high physical strain had a likelihood of 4.95 for CAD (1988). Proving that stress at work contributes to negative CAD results. Furthermore, Alfredsson demonstrated that high working demands along with limited learning can lead to a 1.5 increase risk of MI (1985). Ultimately, these reports show the crucial relation between psychosocial factors and the development of CAD.

While the risks posed by negative psychological states, positive well-being can provide protective benefits for cardiovascular health.

Positive Psychological Well-being and Cardiovascular Health

Positive psychological well-being is associated with reduced cardiovascular risks and improved health outcomes. Individuals who are optimistic, sociable, and develop stress management skills are prone to a sustainable and healthy blood pressure and better cardiovascular health (Bohem, 2012). It is essential to value patients not only physical health but mental health because it is a huge contributor to patients mortality and disease risks. These findings highlight the importance of integrating psychological care into cardiology practice through behavioral cardiology. Behavioral cardiology integrates psychological care into cardiac treatment, addressing the psychosocial factors impacting heart health (Figure 2).

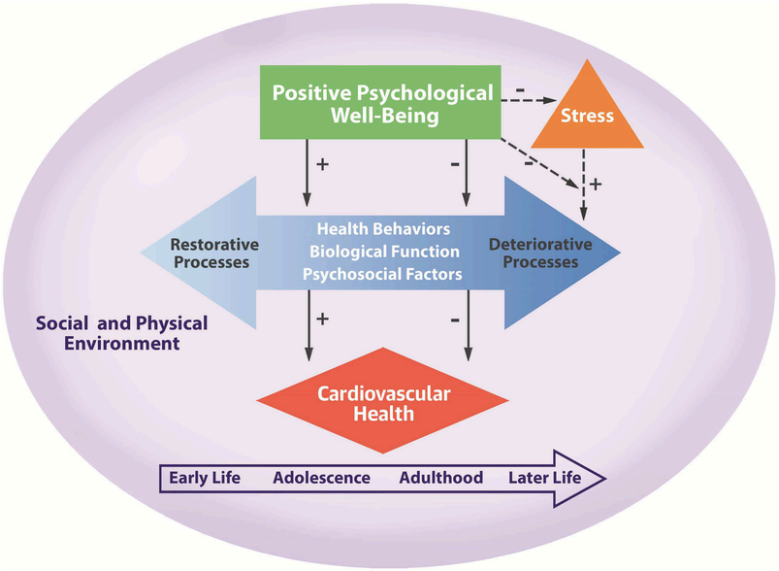

Figure 3: The Effects of Positive Well-Being on Cardiovascular Health *This diagram illustrates the relationship between psychological well-being and cardiovascular health throughout life stages. Positive psychological well-being supports restorative processes and promotes healthy behaviors, biological function, and psychosocial factors that improve cardiovascular health. Conversely, stress triggers deteriorative processes, negatively impacting these factors and worsening cardiovascular health. The social and physical environment influences these interactions, highlighting the importance of considering psychological, behavioral, and environmental factors in cardiovascular health management. Figure received from (Kubzansky, 2018).*

Conclusion

The relationship between Psychology and Cardiovascular health is a prominent focus. Psychological stress, whether its acute or chronic stress, can elevate blood pressure levels and raise the risk of heart disease. Mental illnesses such as depression and anxiety can play a role in also elevating blood pressure levels and leading to Coronary Artery Disease. However, positive mental well being can decrease a patient's risk of heart disease. Staying optimistic and having a support system can regulate blood pressure and reduce the risk of cardiovascular disease. Acknowledging mental health issues and promoting psychological interventions can help support these struggling patients. Healthcare professionals must prioritize mental health, as it is increasing disease and death rates, and create advancements to assist patients suffering from mental health challenges.

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What Impact Does Running Have on One's Vital Organs?

Elizabeth Gerber

Running is a fundamental form of physical exercise which includes various styles with unique demands and benefits. Recreational running, often for fitness and enjoyment, helps maintain general health and well-being. Marathon running involves long distances and requires intense training and significant physical strain. Both forms of running necessitate considerable effort and dedication, each having significant effects on the body (lund0982, n.d.). Thousands of studies have found that running is a highly impactful form of aerobic exercise that profoundly impacts the body's vital organs. In addition to this, it is widely perceived that marathon runners are very healthy; however, running expansive distances requires the body to be under prolonged stress for a long duration of time, potentially leading to severe adverse long-term effects on the body. This is not to say that running not only boosts cardiovascular health but also enhances lung function, strengthens muscles and bones, and increases gut health; however, it is vital to recognize that long-distance running can take a toll on the body and negatively impact one's physical health.

Impact on One's Heart

The cardiovascular system is forced to work faster during high-intensity workouts like running. Running strengthens the heart muscle, which makes it easier for the heart to pump blood, lowers one's heart rate, and lowers the risk of cardiovascular diseases (CVD). There are many benefits to running, but there are also drawbacks. In a particular study, to track the impact of running on the heart, researchers examined the lower ventricular diastolic function and blood markers, finding that after marathon running, one's body mass decreases as well as one's lower ventricle internal diameter during diastole (LVIDd)- the heart's ability to fill up with blood - and thus leads to a reduction in preload. Specifically, a reduction in preload leads to the left ventricle having less blood to pump out to the body, which can signify possible detrimental effects of running on the cardiovascular system. In conclusion, the study found a reduction in diastolic function and evidence of minimal cardiac damage in marathoners, meaning that though the impacts of marathons were not life-threatening to runners, conformational changes due to running were seen. (Figure 1) Moreover, more research would need to be conducted to determine these changes' impact (WHYTE et al., 2004).

Conversely, another study focusing on the impact of running on one's lifespan found that overall, runners have a lower risk of all-cause and CVD mortality compared to non-runners. Running at a competitive pace is unnecessary to see significant mortality benefits, and consistency, when running is also correlated with mortality reduction (Lee et al., 2014). Thus,

running was beneficial to one's cardiovascular health in the long term, even if modifications to one's heart occurred.

	Pre-marathon	Post-marathon	*P* value
E (cm/s)	0.79 ± 0.11	0.64 ± 0.16	< 0.001
A (cm/s)	0.48 ± 0.11	0.60 ± 0.12	< 0.001
E/*A*	1.74 ± 0.48	1.10 ± 0.31	< 0.001
E′ (cm/s)	24.4 ± 5.1	19.8 ± 4.3	< 0.001
A′ (cm/s)	16.3 ± 1.9	17.9 ± 3.6	0.04
E′/*A*′	1.45 ± 0.32	1.13 ± 0.37	< 0.001
SV (ml)	112.3 ± 28.7	100.5 ± 28.1	< 0.001
EF (%)	75.0 ± 6.1	74.4 ± 6.4	0.36

Figure 1: *Pre-marathon and Post-marathon lower ventricle function. All measures of diastolic functions decreased after marathon running, but these changes proved the null hypothesis. Pre-marathon and Post-marathon lower ventricle functional levels were not significantly different, so researchers cannot assert that marathon running affects the lower ventricle (WHYTE et al., 2004).*

Impact on one's gut:

Although not immediately recognized as impacted by running, the gastrointestinal system and its associated biological pathways are profoundly influenced by the chemical signals generated during exercise. A study investigated the effects of long-distance running on the gut microbiome, finding significant metabolic changes in the gut biome, changes in fecal metabolites, and a change in the level of organic acids (Zhao et al., 2018). These modifications led the researchers to suggest that the microbiota-derived metabolism is promoted by running, meaning that running increases serotonin production, which affects both the nervous and immune systems (Swer et al., 2022). Another study focused on how different running intensities affect one's gastrointestinal tract differently. It was found that running at a mild to moderate intensity plays a protective role against gastrointestinal transit-related disorders. At the same time, high-intensity exercises often lead to gastrointestinal distress when associated with dehydration and abdominal stress. Thus, experts recommend hydrating throughout training to induce

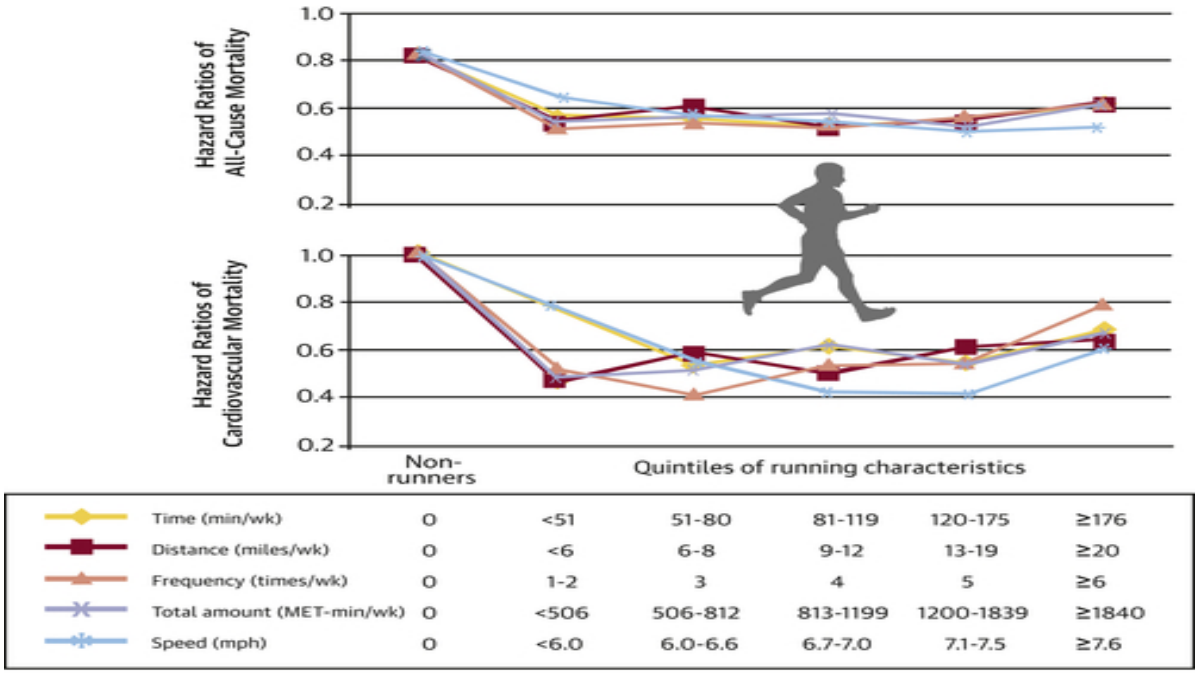

Figure 2: *The difference between non-runners and different running intensities on cardiovascular and all-cause mortality. Emphasizes that running periodically and consistently, often not prioritizing pace, decreases the threat of death and cardiovascular diseases.*

gastrointestinal protection during high-intensity exercises (de Oliveira & Burini, 2009). Furthermore, a study published by Griffith University found that while microbial changes were induced by ultra-marathon running, these changes returned to pre-race values within a period of recovery (Craven et al., 2021).

Impact on one's musculoskeletal health:

Running is perceived to be very detrimental to one's musculoskeletal health, specifically joints. However, numerous studies have found that reductions in cartilage morphology and composition, which refers to the tissue lining one's joints, are minimal immediately after running in healthy individuals. If any cartilage changes occur, they are not permanent in healthy knees, as the volume and composition appear to return to pre-run levels within a day. In essence, the studies concluded that running does not threaten cartilage damage in individuals with healthy knees (Coburn et al., 2022). Researchers also found that running allows nutrients to penetrate one's cartilage and aids in squeezing out metabolic substances, such as water, which helps the body remove toxins (Dong et al., 2021).

Additionally, supporting the notion that running does not severely impact one's joints, research led by Lane and her team questioned the potential of running to cause osteoarthritis. Osteoarthritis is a degenerative joint disease where the cartilage that protects one's bones from grinding against each other wears down. (Mayo Clinic, 2021) After conducting a study on the

impact of running on osteoarthritis, Lane found no impact of running on osteoarthritis (Lane, 1986). Therefore, the perception that running poses a short-term threat to one's joints and deteriorates various studies has debunked them.

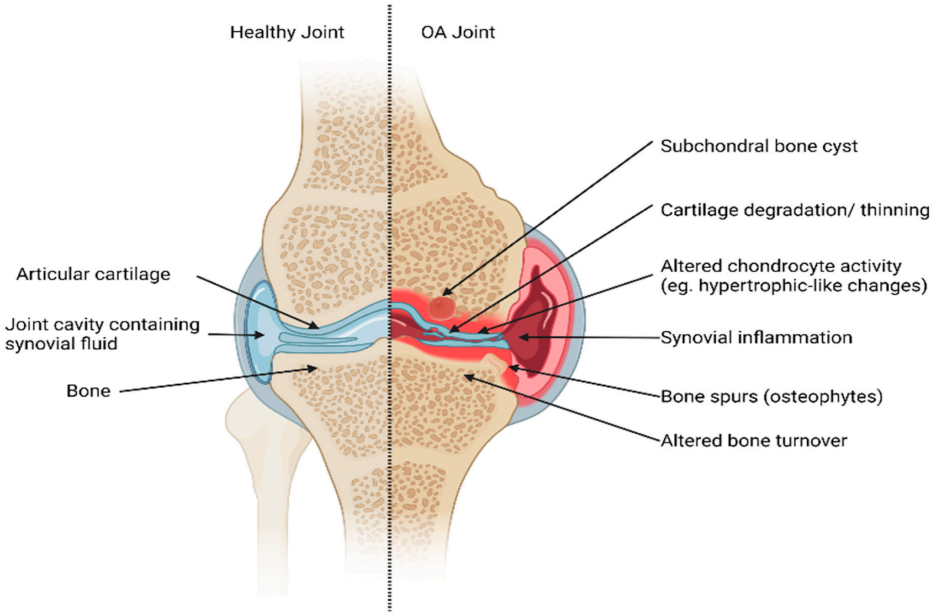

Figure 3: *In osteoarthritis, the protective cartilage deteriorates and thinness, causing inflammation, bone spurs, and swelling. (Mayo Clinic, 2021)*

Does Running Increase Life Expectancy?

Societal changes such as prioritizing one's health contribute to death rates decreasing and life expectancy continuing to increase. One way in which individuals remain healthy is through running. An article published by Chakravarty found that running correlates with significant reductions in disability and mortality. The study monitored around 400 individuals, separating them into two groups, runners and non-runners, and collected data using the Health Assessment Questionnaire Disability Index (HAQ-DI) to assess one's functional ability in multiple facets of their life, like rising and eating (Chakravarty, 2008).

Conclusion

After reviewing numerous studies and articles about the impact of running on one's health and specific organs, one can conclude that running has many benefits to one's health. While many studies found that conformational changes did occur after running, these changes were not found to have negative health implications. This does not preclude that running can have severe

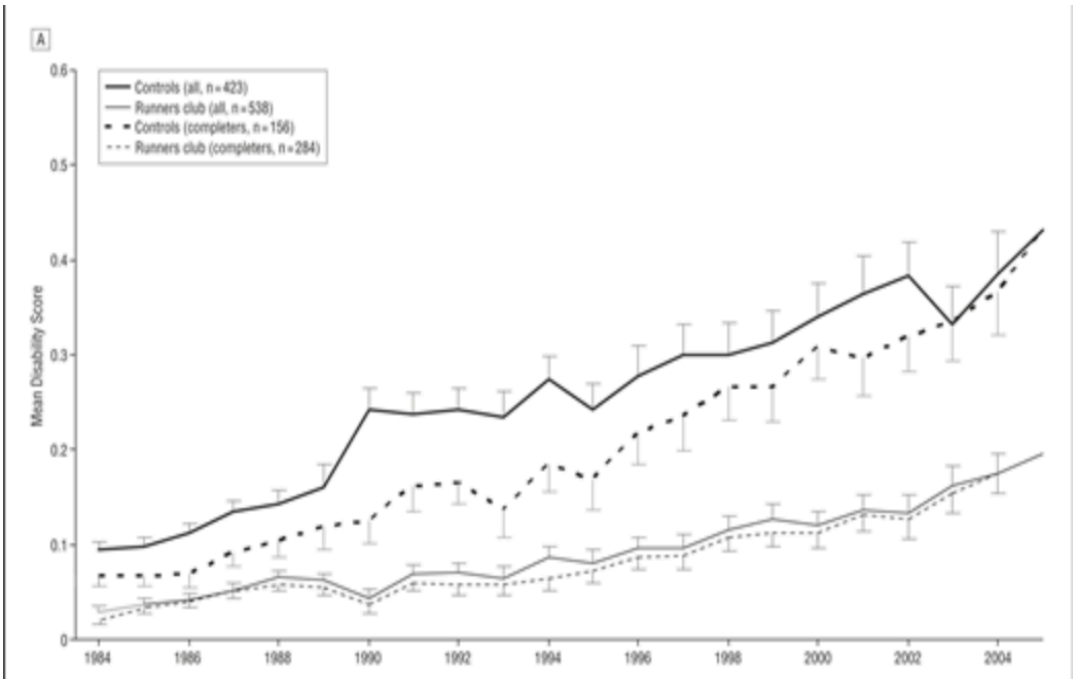

Figure 4: *Individuals who participated in a running club or had running experience, on average, experienced a much lower disability score than non-runners, meaning that the risk of disability was much lower for runners.*

effects on one's health, as these studies are conducted on humans, and in order to understand the long-term effects of running, we need longer-term studies if symptoms occur over longer periods of time (Scheer et al., 2021). Additionally, it is vital to consider the differing ages and health of individuals as these factors can have significantly different results on whether or not running would be beneficial. To conclude, running will only benefit one's health if one gets the nutrition required, stretches, trains smartly, and listens to one's body.

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Ethical and Practical Implications of AI Integration in Healthcare: A Comprehensive Review of Data Security, Biases, and Human-Robot Interactions

Kirat Kaur

The integration of artificial intelligence (AI) in healthcare promises numerous advancements, including enhanced diagnostic accuracy and optimized treatment protocols. However, this integration also raises significant ethical and legal concerns, such as data privacy, loss of human interaction, and potential biases in decision-making. This review draws from multiple sources to address these issues: "Ethical Conundrums in the Application of Artificial Intelligence in Healthcare" highlights the ethical and legal challenges, while "Ethical Implications and Future Prospects" critically assesses privacy and bias issues. "AI-Driven Innovations in Healthcare" highlights AI's benefits in diagnostics, contrasted by "Artificial Intelligence in Healthcare: A Critical Analysis" which discusses legal and ethical disadvantages. Additionally, "The Impact of Machine Learning on Patient Care" focuses on practical limitations, and "Advancing Patient Care" explores AI's potential to transform healthcare.This review will bring together various perspectives to offer a thorough analysis of AI’s benefits and challenges in healthcare, while also providing suggestions for how future policies and practices can tackle these issues effectively.

Data security and privacy is essential when incorporating AI into healthcare. It demands strong frameworks and regulations to safeguard patient information and uphold trust. While AI holds great promise for transforming diagnostics and patient care, it also brings significant concerns regarding the protection of patient data and privacy (Kasula, 2021). The International Meridian Journal highlights the significant ethical implications related to privacy and bias in AI integration within healthcare systems (Kasula, 2021). ScienceDirect discusses the need for strong privacy protections to effectively implement machine learning (ML) in clinical settings (Ben-Israel et al., 2019). A review of the ethical implications of AI and robotics in healthcare emphasizes the importance of robust privacy protections, transparency, and clear responsibility frameworks. Breaches in data security can lead to the loss of patient trust and potential legal consequences, illustrating the need for rigid data protection measures. The International Journal of Law and Information Technology discusses current regulations and laws, emphasizing the need for their evolution to address emerging AI technologies, ensuring no discrimination and maintaining trust. Additionally, the review on ethical implications demonstrates the importance of ethical guidelines and global collaboration in creating a secure environment for AI applications in healthcare. These sources highlight the interdependence of data security, ethical considerations, and the need for comprehensive regulatory frameworks, transitioning from findings on data security and privacy to broader implications for patient trust and regulatory needs.

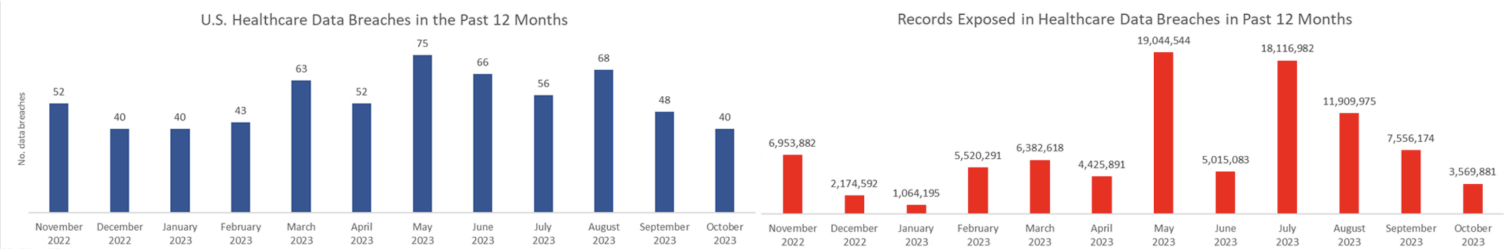


Figure 1*[1]*: *As seen on the left, the rise in AI adoption in 2023 has increased the attack surface for cybercriminals. AI systems, particularly those handling sensitive patient data, can be targeted due to their integration into healthcare IT infrastructure. On the right in figure 1 we see the records exposed vary with no general trend. This variability highlights the ongoing challenges in securing healthcare data.*

Biases and errors in AI algorithms pose significant ethical challenges in healthcare, necessitating careful scrutiny and strategies to ensure fair and accurate outcomes. The International Meridian Journal discusses biases in AI decision-making and their impact on patient care, while the International Journal of Machine Learning and Artificial Intelligence highlights how these biases can affect diagnostic accuracy and treatment protocols, potentially leading to unequal healthcare outcomes (Kasula, 2024). Ethical Conundrums in the Application of AI in Healthcare addresses knowledge gaps related to biases and provides recommendations for an ethical framework. ScienceDirect examines the challenges in gaining physician acceptance due to potential biases and errors in machine learning tools (Ben-Israel et al., 2019). Examples of biases in AI algorithms leading to misdiagnosis or unequal treatment underscore the detrimental effects on patient trust and outcomes. Strategies to reduce biases, such as developing diverse datasets, enhancing algorithm transparency, and ongoing monitoring and evaluation, are emphasized in Ethical Implications of AI and Robotics in Healthcare: A Review (Elendu et al., 2023). The International Journal of Law and Information Technology illustrates the need for government measures to address biases and ensure non-discrimination in AI. These sources highlight the importance of addressing biases and errors in AI to safeguard patient care.

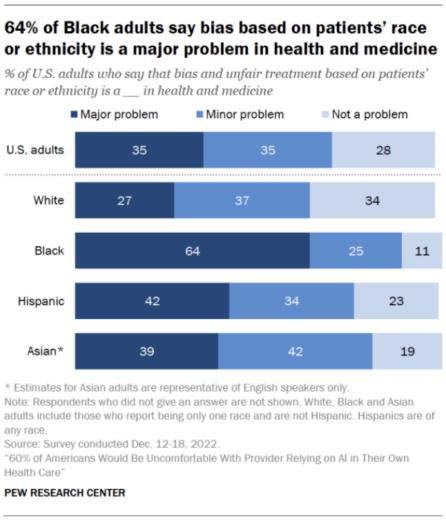
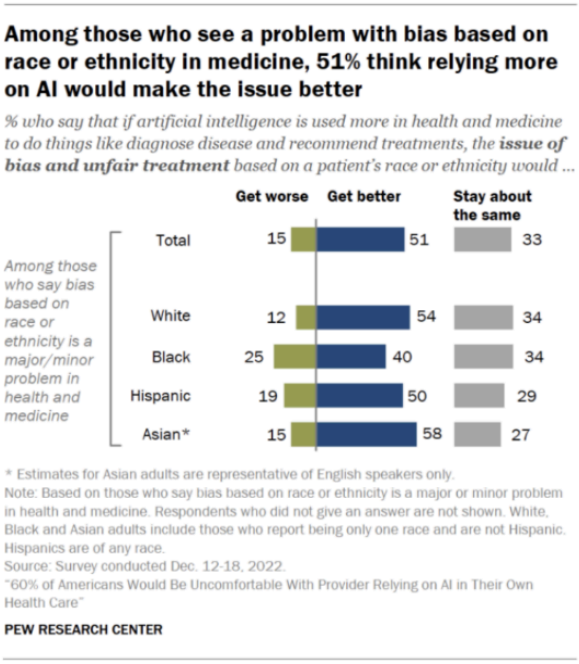


Figure 2*[2]*: *shows the percentage of U.S. adults who perceive bias and unfair treatment based on patients' race or ethnicity as a major, minor, or non-existent problem in health and medicine. The survey indicates that 64% of Black adults consider it a major problem, compared to 42% of Hispanic adults, 39% of Asian adults, and 27% of White adults.*

[1] (Alder, *October 2023 Healthcare Data Breach Report* 2023)
[2] (Tyson, *60% of Americans would be uncomfortable with provider relying on AI in their own health care* 2023)

Figure 3[3]: *Among those who perceive bias based on race or ethnicity as a problem in healthcare, 51% believe increased AI use would improve the issue, 15% think it would worsen, and 33% feel it would stay the same. White respondents are the most optimistic (54% better), while Black respondents are more skeptical (40% better, 25% worse). Hispanic respondents are evenly split (50% better). Asian respondents, represented by English speakers only, show the highest optimism (58% better).*



The dynamic between human-human interactions in healthcare is being reshaped by AI to robot-human interactions, necessitating clear communication protocols and ethical guidelines to maintain trust and ensure effective collaboration. The 2018 AAAI/ACM Conference on AI, Ethics, and Society discusses how AI impacts trust between patients and healthcare providers, emphasizing the need for regulatory approaches to enhance this trust (LaRosa & Danks, 2018). The International Meridian Journal highlights the ethical challenges and potential of AI in transforming human interactions in healthcare. "Advancing Patient Care: How Artificial Intelligence Is Transforming Healthcare" examines AI's role in improving patient outcomes through enhanced diagnostics and personalized treatment while addressing the impact on human-human relationships (Poalelungi et al., 2023). A review of the ethical implications of AI and robotics in healthcare emphasizes the

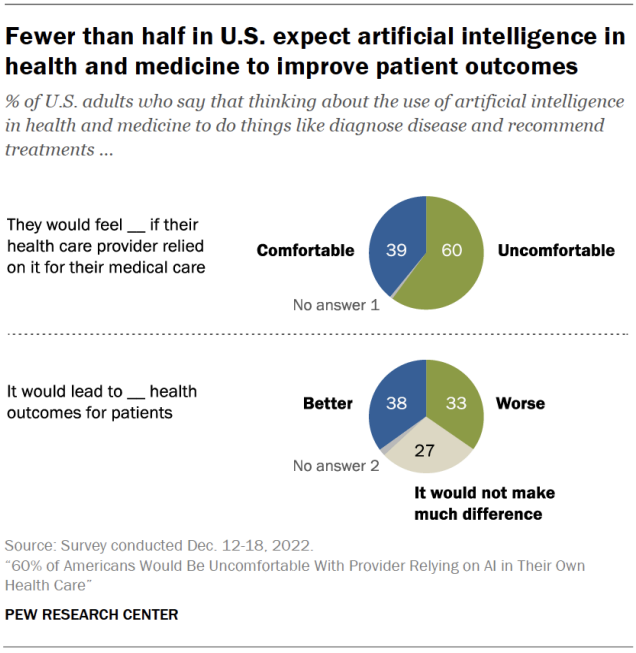


Figure 4[4]: *The results of a survey conducted by the Pew Research Center in December 2022, revealing that 60% of U.S. adults feel uncomfortable with their healthcare provider relying on artificial intelligence for their medical care. Additionally, 38% believe that AI would lead to better health outcomes for patients, while 33% think it would lead to worse outcomes, and 27% feel it would not make much difference.*

[3] (Tyson, *60% of Americans would be uncomfortable with provider relying on AI in their own health care* 2023)

[4] (Tyson, *60% of Americans would be uncomfortable with provider relying on AI in their own health care* 2023)

necessity of strong ethical frameworks to ensure that AI supports rather than undermines human interactions. Examples of how AI can boost or damage trust in healthcare show the importance of using it ethically. The International Journal of Law and Information Technology discusses the need for universal guidelines to govern AI, focusing on maintaining trust and collaboration. Additionally, the review of ethical implications underscores the importance of ethical guidelines and collaboration to ensure AI supports effective human-human and robot-human interactions. This highlights the ethical considerations in biases, errors, and human interactions with AI, reinforcing the need for ethical AI integration in healthcare.

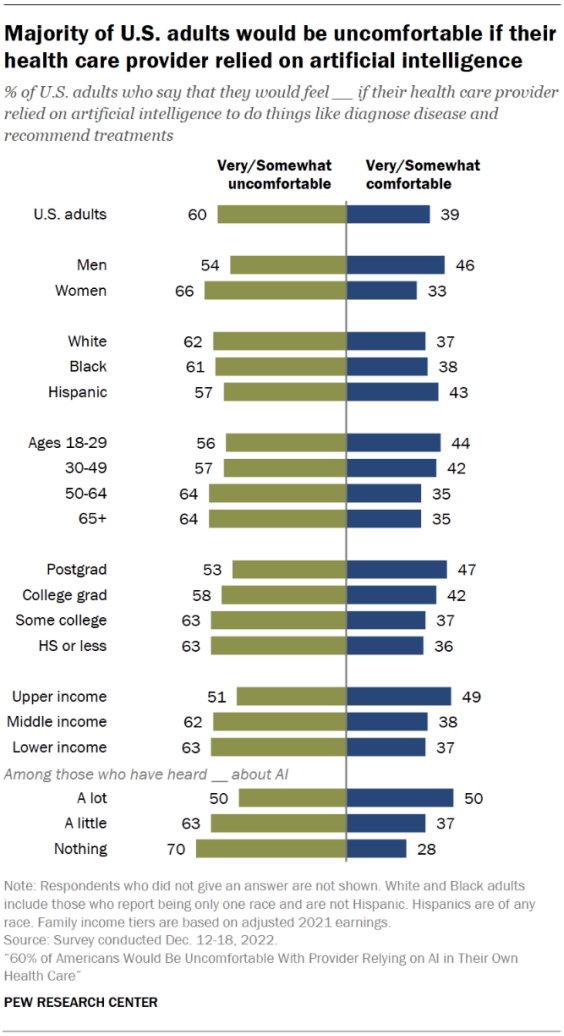


Figure 5[5]: *This figure shows that 60% of U.S. adults feel uncomfortable with AI in healthcare, while 39% feel comfortable. Discomfort is higher among women (66%) than men (54%). The figure also highlights how familiarity with AI can affect comfort. 70% of those who know nothing about AI feel uncomfortable, while those who know a lot are evenly split (50% comfortable, 50% uncomfortable). While incorporating AI into healthcare has many benefits, ultimately, the patient should be comfortable with their healthcare provider and have a say in their care.*

In conclusion, the integration of AI in healthcare brings concerns about data security, biases, and the dynamics of human-robot interactions. Current frameworks need updates to address these challenges effectively, such as enhancing real-time data access, developing effective ethical guidelines, and encouraging collaboration. Despite significant advancements, limitations in research highlight the need for continuous improvement. As AI will continue to transform the medical field, it is crucial to address these issues to ensure responsible, equitable, and effective use of technology. This will ultimately improve patient care and maintain trust in the evolving healthcare landscape.

[5] (Tyson, *60% of Americans would be uncomfortable with provider relying on AI in their own health care* 2023)

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The Effects of Reperfusion Injuries on Mitochondrial Function and Cellular Respiration

Leon Lin

Introduction

Oxygen, the element that supports life on Earth, is surprisingly hazardous when reintroduced to the bloodstream of a person who is ischemic, someone who lacks oxygenated blood flow in the body. During reperfusion, microvascular dysfunction occurs as a result of endothelial cells becoming significantly more activated, which leads to a production of excess oxygen radicals (ROS) and less nitric oxide (Carden, 2000). The imbalance between ROS and nitric oxide greatly damages the injured area. Similarly, the white blood cells in capillaries create blockages, restricting oxygenated blood flow to vital organs. Most significantly, the mitochondria, the organelle essential for energy production and cellular signaling, is gravely harmed by reperfusion injuries. When a person is ischemic, the vital process of cellular respiration is disrupted, causing ATP levels in the blood to deplete. However, once oxygenated blood flow returns to the mitochondria, complex I of the mitochondria rapidly releases reactive oxygen species (ROS), triggering massive inflammation. Treating and preventing reperfusion injuries is even more important in ischemic heart disease, a leading cause of cardiovascular-related deaths. When reperfusion occurs, the mitochondria within the cardiomyocytes (a type of heart cell) suffer from oxidative stress, mitophagy, and apoptosis, all of which lead to a larger, life-threatening heart attack (see Figure 1).

Most sources agree that therapeutics targeting mitochondrial dynamics is the best method to inhibit oxidative stress, stabilize energy metabolism, and enhance mitochondrial integrity (Su, 2022). These may be perfected and become widely available in the next few decades. Research suggests that mitochondria, the powerhouses of the cell, face great danger during ischemia-reperfusion, causing worldwide deaths from cerebral, cardiac, or liver-related reperfusion injuries. The sudden shutdown of cellular respiration due to imbalanced molecular concentrations and abnormal rates of mitochondrial processes drains ATP levels in the body, which causes the death of cells. Therefore, emerging therapeutic treatment techniques targeting mitochondrial stress are anticipated to positively influence the medical field and change the global perspective on medicine.

This literature review will discuss a basic introduction to the mechanisms of ischemia-reperfusion injuries and their effects on the body as a whole before elaborating further on the effects of reperfusion on the mitochondria specifically, including ROS imbalances, oxidative stress, and imbalanced mitochondrial dynamics (fission, fusion, mitophagy, biogenesis). A brief synopsis of potential treatment methods will also be highlighted. This study will inform people about the harms of reperfusion and why quick and effective treatment is

critical to prevent permanent damage to the injury site. In a world where healthcare is not widely accessible, it is necessary to conduct studies to spread awareness of the underlying mechanisms of reperfusion injuries and to develop more effective treatment strategies to improve clinical outcomes in the medical field.

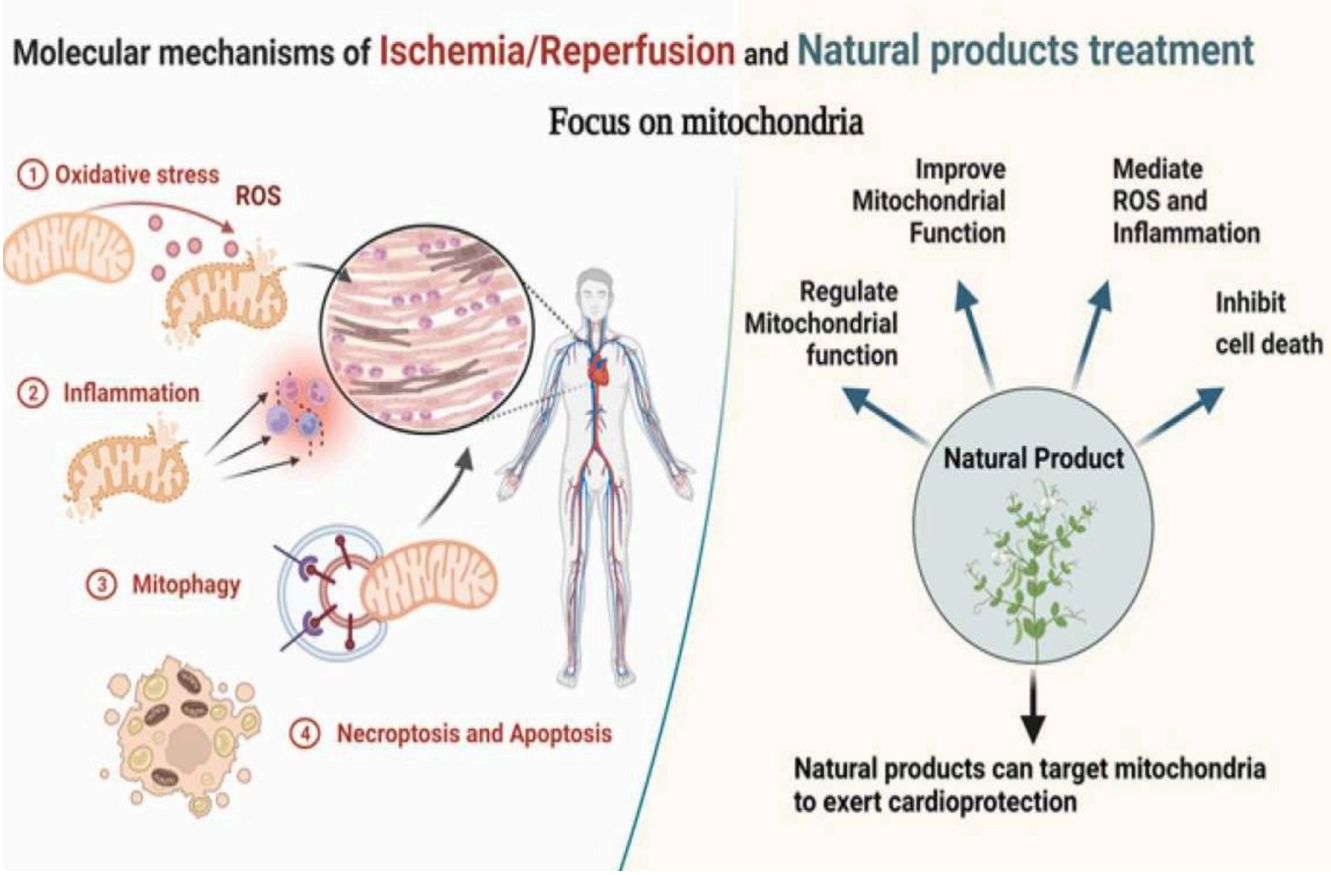

Figure 1: The molecular mechanisms of reperfusion and natural plant products (NPPS)
Ischemia-reperfusion causes the rapid influx of ROS, which triggers a chain reaction that results in cell death. Severe oxidative stress caused by abnormal ROS concentrations leads to substantial inflammation and mitophagy, causing complexes of the organelle to shutdown. This results in apoptosis and the halt of cellular respiration. NPPs can be integrated into medicine to target mitochondrial health/dynamics and regulate ROS.

The Effects of Ischemia-Reperfusion Injuries On the Body

Ischemia-reperfusion injuries are very complex, but its effects are simple to understand – severe interference to biochemical processes within cells and tissues at the site of injury. During ischemia, a continuous blood supply flow to a tissue is stopped, preventing the tissue from performing its usual functions. However, reperfusion is what actually causes the death of deoxygenated tissue. The death of tissue, specifically microvascular tissue, is mainly caused by

the hyperactivation of endothelial cells (cells that line microvascular walls) due to imbalances between ROS, superoxide and nitric oxide concentrations (Khalil, 2006). These imbalances lead to inflammation, impaired capillary function, leukocyte trafficking, and ineffective blood distribution (Carden, 2000). Although reperfusion is necessary to reestablish the flow of blood to the body, it also destroys a vital part of cells, the mitochondria. As the powerhouses of cells, the mitochondria are responsible for the synthesis of ATP; if reperfusion inhibits mitochondrial function, it can kill the host as cells cannot function without this indispensable nucleic acid.

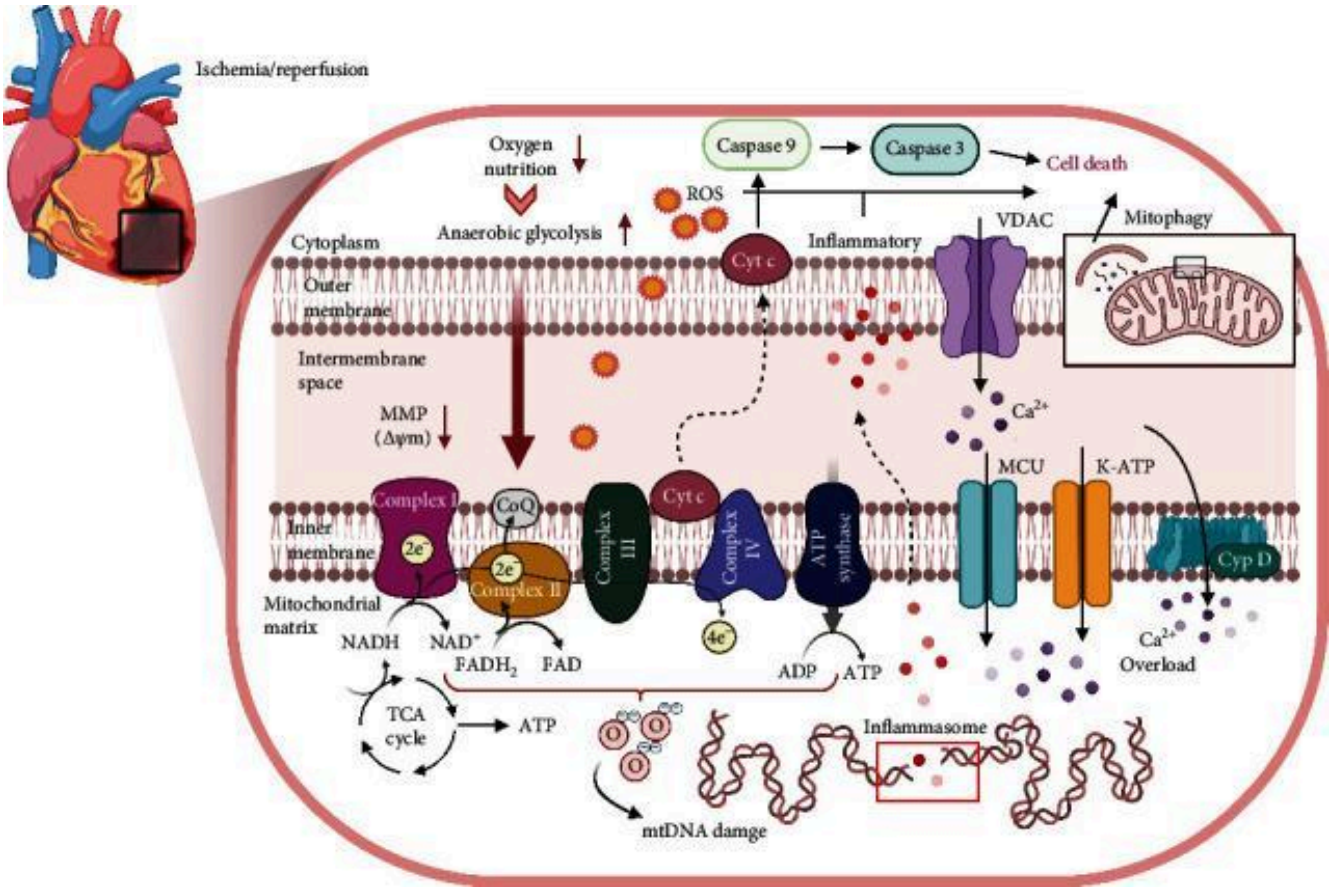

Figure 2: The vital mitochondrial mechanisms affected by ischemia-reperfusion injuries on a molecular level
As reperfusion occurs and oxygen rushes into the mitochondria, ROS levels increase substantially, causing oxidative leak and the activation of inflammasomes that trigger inflammation at the site of injury. Also, the calcium ion overload causes the rapid depolarization of the mitochondrial membrane potential (MMP), leading to disrupted dynamics and signaling. Additionally, the hyperactivation of mitophagy causes the mitochondria to "eat itself" and become severely defragmented. All of these processes disrupt cellular respiration and drain ATP levels in cells, leading to apoptosis.

ROS Imbalance and Oxidative Stress

The most harmful effect of reperfusion on the mitochondria is the uncontrolled production of ROS. ROS (reactive oxygen species) are highly reactive molecules containing oxygen which generate through many biological processes. These include superoxide anions, hydrogen peroxide, and hydroxyl radicals (Andreadou, 2020). Healthy mitochondrial function ensures that the ROS concentrations are normal. During reperfusion, excessive amounts of succinate accumulate, which produce hazardous amounts of ROS (Panconesi, 2022). A sudden spike in ROS concentrations causes inflammation and increases oxidative stress at the injury site, preventing the efficient synthesis of ATP and destroying mitochondrial metabolism (Huang, 2023). Severe oxidative stress, the imbalance of ROS concentrations and the inability to neutralize unstable ROS, leads to dysfunctional mitochondria by inducing oxidative leak (see Figure 2). Once the ROS leaks out of the mitochondrial membrane, it can react with O_2 and produce even more ROS. The abnormally high concentration of ROS shuts down the complexes, resulting in apoptosis or ferroptosis (Jassem, 2002).

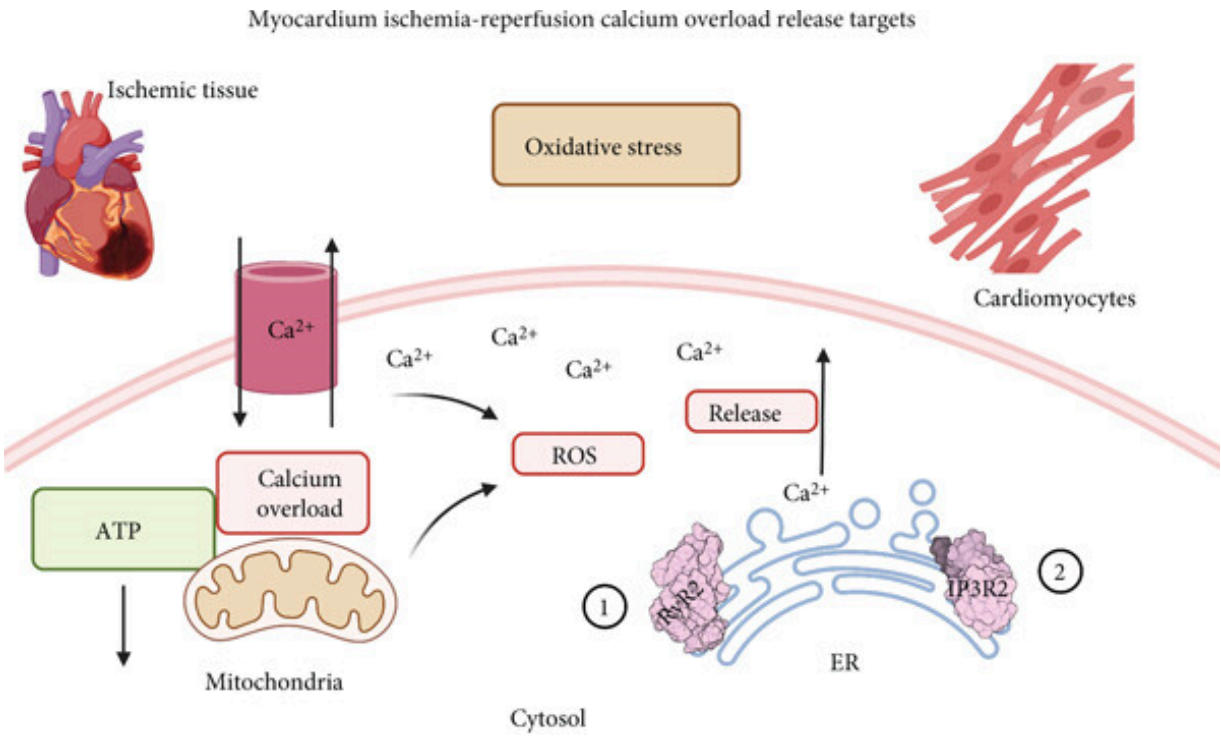

Figure 3: The effects of calcium overload in the mitochondria of cardiomyocytes
The rapid influx of ROS and calcium ions into the mitochondria leads to severe oxidative stress. The calcium ion overload also rapidly depolarizes the organelle, resulting in a very high mitochondrial membrane potential (MMP). As the MMP is critical to mitochondrial function, the organelle can no longer synthesize ATP through oxidative phosphorylation. During reperfusion, the ER also releases a major amount of calcium ions, which enter the mitochondria and contribute to further oxidative stress. When the stress is severe enough, the cardiomyocytes undergo apoptosis.

Mitochondrial Membrane Potential

Similarly, the electron transport chain of cellular respiration is greatly impaired during reperfusion. Calcium ion concentrations are crucial for various metabolic pathways, including cell division, maintenance, signaling, and oxidative phosphorylation (Kuznetsov, 2019). An abnormally low or high concentration of calcium ions interferes with ATP synthesis, causing the collapse of these endergonic pathways (Bagur, 2016). For example, as shown in Figure 3, massive spikes in ROS and calcium ion concentrations cause the collapse of a stable mitochondrial membrane potential (Su, 2022). The membrane potential of the mitochondria (MMP) is critical for the stable transfer of biomolecules (e.g. Na+, K+, Ca2+, NADH, and ATP) during respiration. While the normal MMP is 150-160mV, it can depolarize at rapid speeds (MMP skyrockets) during reperfusion, which activates apoptosis (Su, 2022). The result of immense cell death is incredibly detrimental to vital organs such as the brain and heart. The brain consumes 20% of the body's total oxygen input, and unless ROS and Ca2+ homeostasis are maintained, the blood-brain barrier will be at high risk of irreversible damage (Huang, 2023).

Mitochondrial Dynamics

Furthermore, stable mitochondrial dynamics are disrupted. During reperfusion, mitochondrial fission increases while fusion decreases (Zhou, 2021). The balance between mitochondrial fission and fusion is necessary for vital functions, including signaling, respiration, and relative size maintenance (see Figure 4). The disruption of the balance between fission and fusion alters the size of mitochondria, preventing the proper execution of cellular respiration (Zhou, 2021). Mitochondrial fission is incredibly significant as it regulates autophagy, the self-degradation of dysfunctional cellular components, which maintains a stable balance for respiration (Rangel, 2022). Reperfusion increases fission, which causes the hyperactivation of mitophagy (mitochondrial autophagy), contributing to severe mitochondrial fragmentation and function impairment (Su, 2022). The rate of mitochondrial biogenesis cannot keep up with the rapid mitochondrial fission (Zhou, 2021). A stable balance between mitochondrial fission, fusion, autophagy, and biogenesis are necessary for stable cellular conditions (Zhou, 2021). Taken together, sources suggest that the harmful effects of reperfusion injuries on mitochondrial function is the reason why numerous people pass away due to heart attacks and strokes every year. When the vital functions of the mitochondria (signaling, respiration, etc.) are impaired, the rest of the cell cannot survive. However, reperfusion does not affect only one cell, but rather, tissues and organs. The rapid death of heart tissue is why heart attacks can happen so suddenly and dangerously. It is important for people to be aware of certain risk factors for these injuries and seek therapeutic treatment as soon as possible for the greatest odds of survival.

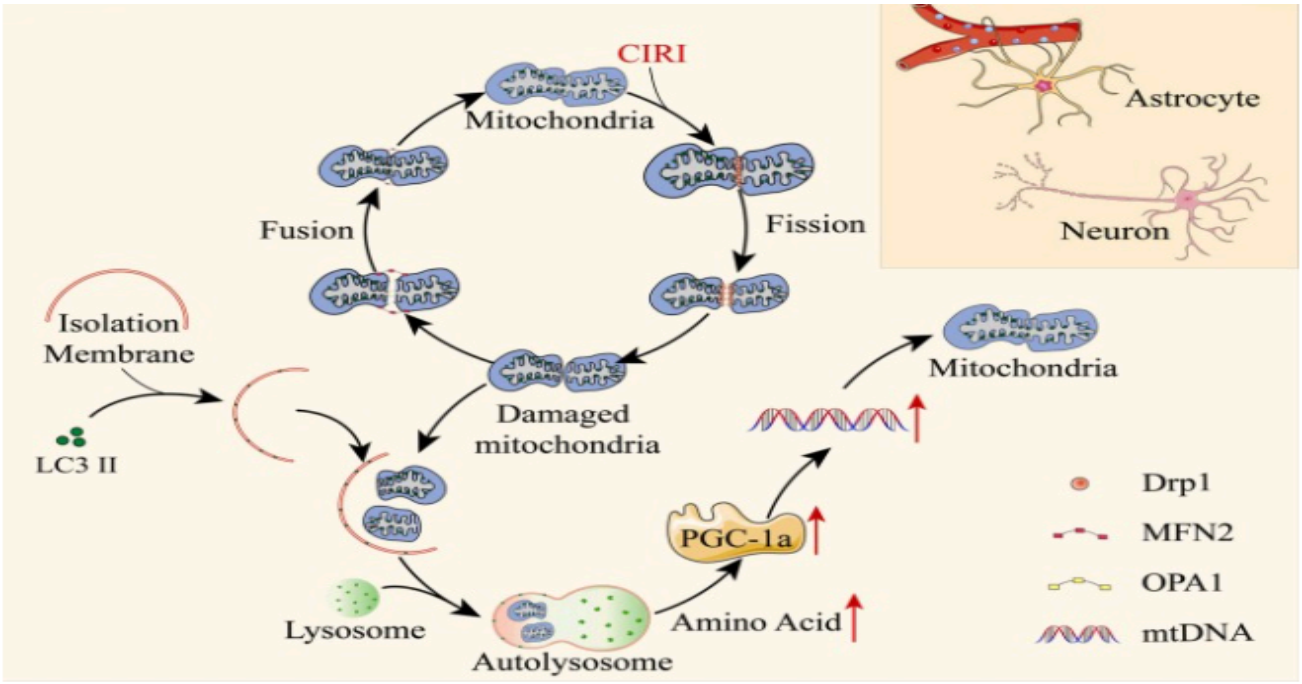

Figure 4: The disruption of the control system of mitochondrial dynamics due to a cerebral ischemia-reperfusion injury

Mitochondrial fission and fusion are the division and merging of mitochondrial parts respectively. The balance between fission and fusion is crucial for mitochondrial health and function. If parts of the mitochondria are damaged, it undergoes mitophagy, the degradation of damaged mitochondria through lysosomal enzymes. The new mitochondria is synthesized using mtDNA. Various proteins catalyze these vital processes. During cerebral ischemia-reperfusion injuries, this control system is disrupted, causing mitochondrial defragmentation and the halting of metabolism, signaling, and respiration.

Conclusion

Ultimately, reperfusion injuries are a leading cause of death worldwide due to their negative impacts on numerous metabolic pathways. Organs that suffer from ischemia are in dire need of oxygen, yet the input of oxygen into the bloodstream causes inflammation and white blood cell blockages. The reason for these harmful effects is due to an imbalance in ROS levels, which spike massively during reperfusion. More importantly, reperfusion injuries disable mitochondrial function, which again is due to chemical imbalances. As sudden reperfusion disrupts the balance of ROS, calcium ions, and succinate concentrations, the mitochondria suffer from intense oxidative stress. Consequently, they fail to efficiently carry out cellular respiration, the source of ATP for the body. Similarly, the rate of mitochondrial fission increases, causing severe defragmentation of these organelles. As the mitochondrial rate of biogenesis falls behind, the fragmented mitochondria are not restored in time, further contributing to disrupted cellular respiration and a severe lack of ATP. No cell can function properly without a constant supply of ATP, which is the reason why ischemia-reperfusion injuries take away the lives of countless

individuals every year. The development of therapeutic treatments is a great way to prevent reperfusion injuries by boosting mitochondrial health, inhibiting ROS imbalances, and establishing more efficient blood flow. Natural plant products (NPPs) are being actively researched to improve blood circulation, cardiovascular health, and mitochondrial dynamics. The mechanisms of mitochondrial processes are incredibly complex and a substantial amount of further research (a couple of decades worth) must be done before these therapeutic techniques can be integrated in the medical field. It can take years or decades of research and analysis just to produce and test one specific type of therapy/medicine, but health practitioners and medical researchers can all agree that it is worth it in the end as the lives of numerous patients will be saved.

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Peer Relationships in Childhood: Their Influence on Social, Emotional, and Cognitive Development

Diya Makkapati

Introduction

Peer relationships play a pivotal role in the social, emotional, and cognitive development of children, with effects carrying on into adulthood. These early peer interactions influence the developmental trajectories of children in both positive and negative ways. Positive peer experiences can act as buffers against various risk factors, fostering resilience and healthy development. Conversely, negative peer interactions, such as bullying and rejection, can contribute to developmental psychopathology, leading to a range of psychological issues. This review explores the multifaceted influence of peer interactions, emphasizing how both positive and negative peer experiences shape an individual's psychological and neurological trajectory. By synthesizing findings from diverse studies, this review seeks to explore the nuanced roles that peer relationships play across different developmental stages, with a focus on understanding their implications, strategies for fostering healthy relationships, and long-term effects on individual development.

Background of Peer Relations

During adolescence, children's lives are filled with a plethora of different peer relationships. A peer relationship refers to a relationship of mutual cooperation and influence between children of similar age during their day to day lives ("The Importance of Peer Relationships For Social-Emotional Development", 2018). Peer relationships play a crucial role during these formative years of 0-8 years when childrens' brains are highly plastic and responsive ("Healthy Relationships in Adolescence"). During this time, children learn how to form meaningful relationships with friends, parents, teachers, etc. Through these relationships, children are able to develop their social and emotional skills through acts of making and keeping friends. Their personal skills, such as regulating feelings and controlling impulses. are developed. Their interpersonal skills, such as understanding, communicating, and problem-solving, are also developed (Chen). They also form their own identity during this time, and peers play a particularly important role in identity creation ("Healthy Relationships in Adolescence"). Along with peer relationships, social stressors and peer conflicts are inevitable ("The Importance of Peer Relationships For Social-Emotional Development", 2018). 10-15 percent of children experience serious peer difficulties relating to rejection, exclusion, victimization, and harassment ("The Importance of Peer Relationships For Social-Emotional Development", 2018). In the last 20 years, research shows that a growing number of children are being exposed to peer difficulties through daycare (Boivin, 2023). As children enter teenage

years, these peer relationships become even more crucial. This is because children develop more autonomy from their parents and gravitate more towards their peers for both social and emotional support ("Teens and Peer Relationships", 2020). During the change into teenage years, strong peer relationships enhance well-being while problems in relationships, such as bullying, can lead to psychological, physical, academic, and social-emotional consequences for both victims and perpetrators ("Teens and Peer Relationships", 2020).

Social and Emotional Implications

To start off, positive peer relationships help develop many skills at a young age, ultimately contributing to positive personality qualities, including communication skills, and overall positive mental attitude. William A. Corsaro states that early peer relationships allow children to express qualities of friendship, sharing, and social participation as well. The emotional development aspect comes from experiencing feelings of "affirmation, pleasure, and support" ("The Importance of Peer Relationships For Social-Emotional Development", 2018). These emotions ultimately contribute to a child's actions and language. Furthermore, a child's educational situations have a major influence on the social development aspect. Through school, children are able to understand and adapt to society, develop social skills, and engage in imitation learning. Prosocial behaviors during school should be encouraged to promote these skills' development ("The Importance of Peer Relationships For Social-Emotional Development", 2018). On the other hand, children who do not have healthy peer relationships are more prone to issues both socially and emotionally. These issues can manifest as aggressiveness (Shin et al., 2016). Children who are skilled in interacting with their peers and display prosocial behavior are more likely to be accepted by them. On the other hand, aggressive children are often rejected, although aggression doesn't necessarily prevent them from being accepted. Peer relationships can be particularly challenging for children with disorders or those who lack the necessary emotional, cognitive, and behavioral skills for positive interactions. Children with early behavioral and emotional issues face increased risk due to the peer rejection they often encounter. However, early friendships and positive peer relationships can help protect children from future psychological and cognitive issues. Ultimately, all of this contributes to cognitive development (Hay).

Cognitive Implications

Not only do adverse peer experiences impact social and emotional development, but they can also distort developmental pathways, ultimately contributing to psychopathology (Prinstein et al.). Starting as early as birth, children are born ready to form connections with the people surrounding them. As a result of these early interactions, a baby's brain matures. As the emotional and physical needs of children are met, more learning pathways are formed in the brain, which leads to learning in all developmental domains ("Social-Emotional Development").

The early childhood years are especially a critical time for brain development (Konrad et al., 2013).

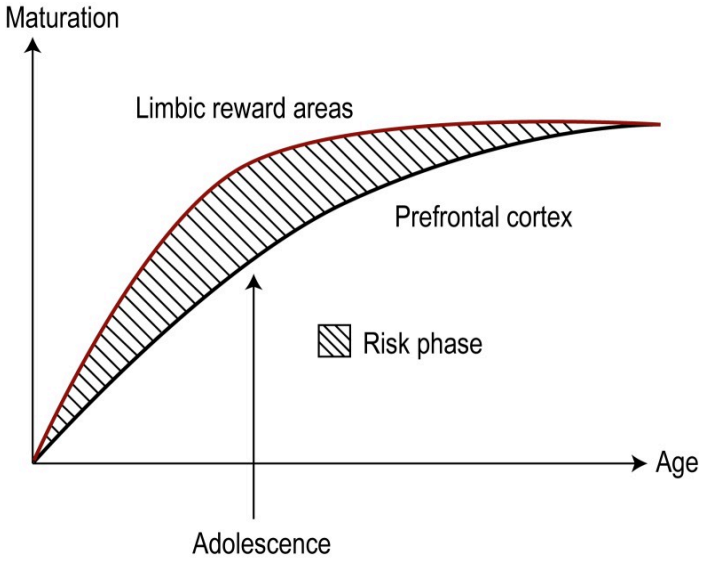

Figure 1: Changes in adolescent brain causing it to become extra sensitive

Children who are able to form positive feelings towards themselves and the people around them are more likely to not struggle as much with their mental health. On the contrary, children who experience neglect, rejection, or abuse have a greater risk for mental health challenges ("Social-Emotional Development"). During teenage years, brains undergo more changes that make children "highly attuned to social situations" ("The Power of Peers", 2021). Moreover, the reward system in the teenage brain is highly sensitive. Both of these components go hand in hand to make teens especially responsive to peer influence. The reward system is activated by social rewards, and teenage years is when the social world comes more into play. Teenagers can be more easily influenced by their peers in aspects of clothing choice, music taste, smoking, and drinking ("The Power of Peers", 2021). They may also be more sensitive to the ways they are treated by their peers, such as body language and tone. Although peer relationships can be a slippery slope during teenage years, they can also help teens thrive if healthy ("The Power of Peers", 2021).

Long-term Implications

Peer relationships can have long-term implications in social, emotional, and cognitive aspects. The realm of childhood popularity during adolescence and its long term effects are especially prevalent. High popularity during adolescence was linked to positive, prosocial, and assertive behaviors and status, while lower popularity was associated with fewer of these traits in emerging adulthood. Acceptance or lack of rejection typically signifies positive peer experiences, but the dynamics of popularity are more nuanced. Being admired can be a positive experience,

but popular youth might also face envy or dislike. Popularity can bring expectations and pressure, as those who are popular have a status to maintain. Like accepted peers, popular youth have opportunities to develop social skills and relationships. However, concerns about their reputation might lead them to engage in antisocial behaviors to keep their status. This combination of prosocial and coercive behaviors is known as bi-strategic resource control (Chmielowice‐Szymanski et al., 2024).

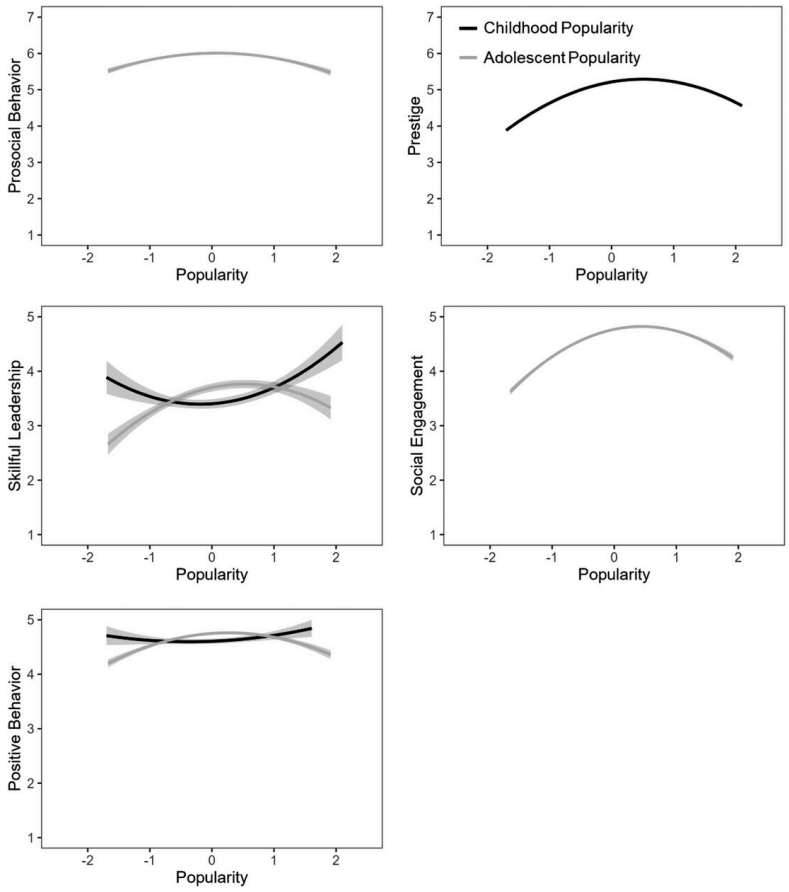

Figure 2: Associations of childhood popularity

This figure illustrates the significant links between childhood popularity and outcomes related to positive, prosocial behavior and status in early adulthood, taking into account the influence of adolescent popularity. It also highlights the significant connections between adolescent popularity and similar outcomes in early adulthood, adjusted for the impact of childhood popularity (Chmielowice‐Szymanski et al., 2024). Adolescent popularity was linked to three out of five outcomes: self-reported proactive relational aggression, dominance, and peer-reported influence. For proactive relational aggression, the relationship with adolescent popularity formed a U-shaped curve, suggesting that this type of aggression was less common among adolescents of average status compared to those at the high or low ends of the status spectrum. Adolescent popularity also correlated positively with self-reported dominance, meaning that higher

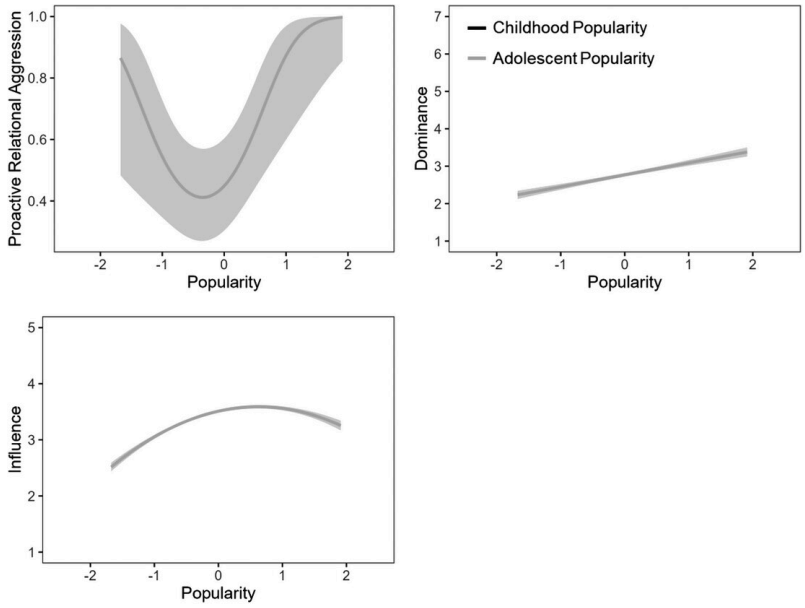

Figure 3: Traits associated with childhood popularity

popularity during adolescence was associated with greater dominance in early adulthood. The relationship between adolescent popularity and peer-reported influence showed a curvilinear pattern, resembling an inverted J-shape, indicating that particularly low popularity was associated with reduced influence in early adulthood (Chmielowice‐Szymanski et al., 2024).

Strategies for Healthy Peer Relations

As can be seen, healthy peer relationships are crucial for children in many ways and there are many approaches to promoting healthy relationships.

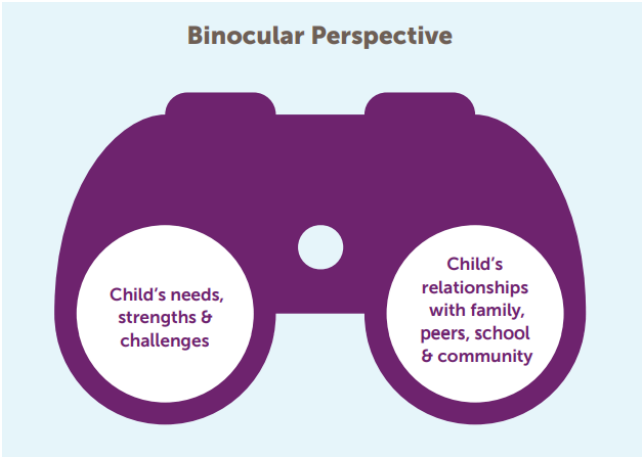

Figure 4: Binocular perspective to promote healthy social and emotional development, while disrupting negative peer dynamics

One effective intervention is taken by looking at peer relationships from a binocular perspective. One lens looks at ways that social and emotional skills can be strengthened, while the other lens is more focused on disrupting negative peer dynamics by organizing children's peer experiences ("The Importance of Peer Relationships For Social-Emotional Development", 2018). As children grow up, the strategies used to promote positive peer relationships evolve. For toddlers and preschoolers, it is important that they learn to take turns and engage in play dates. For young children, it is important to learn to act with kindness and take different perspectives. At the middle school level, discussing popularity, encouraging the development of friendship skills, and nurturing self confidence comes into play. Finally, during teenage years, it is crucial to normalize their insecurities and help them honor themselves (DeAngelis, 2023).

Conclusion

All in all, childhood peer relations impact children in social, emotional, and cognitive ways. While positive experiences support well-being, negative ones can be detrimental and lead to social and emotional challenges. The influence of childhood peer relationships are not only prevalent during childhood, but their impact carries on into adulthood. This is why it is crucial to foster healthy peer relations which will allow children to effectively navigate the complexities of social life and build a foundation for long-term well being.

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Hydrological Dynamics of Greenland Lakes: Understanding The Process In Which Rapid Drainage Can Occur

Vrishank Malik

Introduction

The Greenland ice sheet (GrIS) is rapidly melting due to an increase in surface temperature and ocean warming. Since 1985, Greenland has lost about 1,140 billion tons of ice, correlating to 30-35% of the global sea level rise. Greenland's contribution is expected to increase to 50% over the next few decades, primarily due to the effect of global warming (Fiondella, 2024). As global temperatures continue to rise, the amount of Greenland's meltwater contributing to rising sea levels is exponentially increasing.

Paleoclimatic reconstructions—methods used to understand past climate conditions before instrumental records were available—have demonstrated that meltwater contributions can cause sea levels to rise several meters. Specifically, they claim that the maximum levels of meltwater released can exceed 1 meter/century (Overpeck et al., 2006). However, other studies suggest that Greenland's contribution to sea level rise will be approximately 22 cm by the end of the century (Bindschedler et al., 2013), with a potential increase rate of 0.7–0.8 mm/year (Fettweis et al., 2008). These claims contradict each other's predictions due to one pivotal unknown: what portion of the meltwater produced on the surface of the GrIS becomes runoff into the ocean (Rennermalm et al., 2013).

This proportion of runoff relies closely upon the drainage of Greenland's supraglacial lakes. However, the exact mechanisms and pathways of the lake's drainage are poorly understood. Supraglacial lakes are bodies of meltwater in the ablation zone of glaciers and ice sheets—the lower part of the glacier where snow loss exceeds accumulation. These lakes are typically found during the warmer months when surface melting occurs more extensively. While lakes may be present on the surface for months, they can mysteriously drain in seconds (Otto, 2022). In this paper, we will explore Greenland's major drainage systems to discuss how meltwater from the GrIS contributes to rising ocean levels.

Greenland Ice Sheet Hydrologic System

The GrIS has three main components: water across the surface (supraglacial), internally through (englacial), and beneath the bed of the ice sheet (subglacial) (Nienow, 2017). Efficient meltwater routing through ice sheets can significantly increase the ice flow velocity and thus ice discharge into the ocean, leading to greater contributions to sea level rise (Smith et al., 2017).

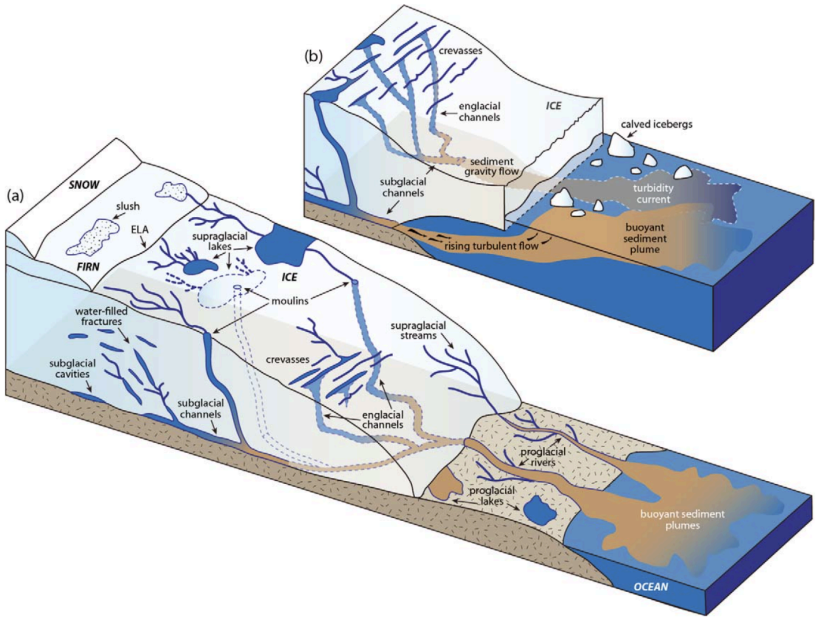

Figure 1. *Elements of the Greenland ice sheet hydrologic system. (a) Above the equilibrium line altitude (ELA) in the accumulation zone, water moves through snow and firn, forming slush regions and supraglacial streams. Below the ELA in the ablation zone, meltwater gathers in supraglacial lakes and flows into crevasses and moulins, eventually reaching proglacial rivers and lakes. (b) For marine-terminating glaciers, the meltwater exits differently. Sediment-rich subglacial discharge, released underwater, can rise to form a plume or create a turbidity current beneath the surface.*
Note. Modified from Cuffey and Paterson (2010).

Supraglacial Lakes

Before the twenty-first century, there had been little research on the hydrology of supraglacial lakes. However, in the past few years, there has been increased attention on the subject due to supraglacial lakes' importance in meltwater storage and drainage. Meltwater can accumulate in depressions over impermeable ice or dense firn, forming supraglacial lakes that often reappear in the same locations over multiple years (Chu, 2014). While some supraglacial lakes appear in the same area, numerous studies have shown that the lake's location is dependent on the time of season, elevation, and topography. Supraglacial lakes can release large amounts of meltwater into the ice sheet through rapid drainage events—a sudden and swift release of large volumes of meltwater from surface lakes or subsurface reservoirs within an ice sheet.

The creation and drainage of supraglacial lakes depend greatly on summer melt intensity—the GrIS has experienced the greatest summer melt intensity since 1990 (Otto, 2022). Some lakes store their water throughout the winter, however, they do not drain in the winter because the drainage network beneath a glacier becomes more efficient during melt seasons. As the glacier warms and more meltwater is introduced, subglacial channels (the conduits for water flow

beneath the glacier) develop (Schoof, 2010). It is due to the development of subglacial channels that rapid drainage events happen in greater frequency during the summer season.

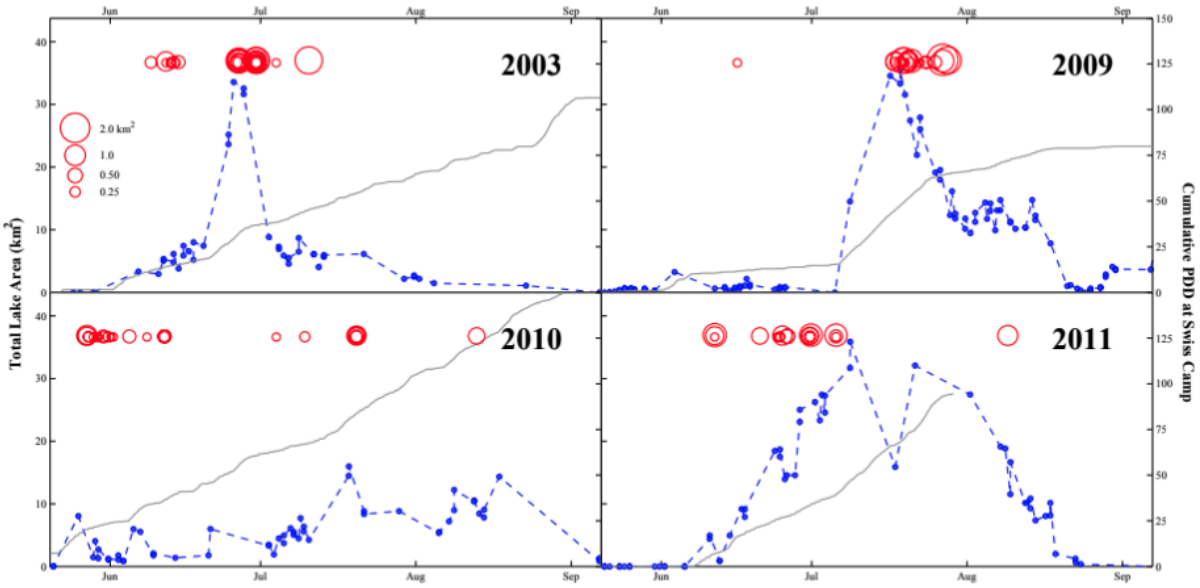

Figure 2. *Total lake coverage (blue) and rapid drainage events (red circles, see inset scale) versus cumulative positive degree days (PDD, gray) from the GC-Net station at Swiss Camp for selected years. Rapid drainage events are plotted at an arbitrary vertical axis value to show temporal relationships. PDD, or Positive Degree Day, is a measure used in glaciology and meteorology to quantify the melting potential of snow and ice. It represents the cumulative sum of daily average temperatures that are above the freezing point (0°C or 32°F) over a specific period. Data from 29 July 2011 to 30 September 2011 is unavailable.*
Note. Adapted from "A ten-year record of supraglacial lake evolution and rapid drainage in West Greenland using an automated processing algorithm for multispectral imagery" by Morriss et al.

Figure 2 visualizes how the total lake area directly correlates to the number and intensity of rapid drainage events. However, such a correlation was not seen with PDD, suggesting that there can be a minimum lake area for rapid drainage to occur. Nevertheless, no such correlation has been established yet.

Hydrofracture of Supraglacial Lakes

Hydrofracturing is the process of water fracturing unconsolidated sediments and bedrock when high fluid pressure surpasses the material's cohesive strength (Ravier, 2024). This process occurs primarily during the melt season when increased surface melting generates substantial volumes of water inside sediments which creates high pressures. This causes the sediments to crack, lowering the pressure by letting the water escape to subglacial channels.

In Nienow's 2017 study they analyzed 2000 Greenland lakes over 5-years and estimated that 13% of the lakes in Greenland were 'fast-draining' (Nienow, 2017). Fast (rapid) lake drainage can result in large volumes of water entering the subglacial drainage system over a few hours

with rates of up to 8700 and 3300 m^3/s (Das, 2008). Before meltwater reaches the ocean, it is first transported across the ice sheet surface in supraglacial stream networks. The meltwater then navigates through the ice along any permeable pathways. In temperate glaciers, these pathways allow rapid routing through localized macroporosity, such as moulins and crevasses, or slower drainage through microporosity within the ice's permeable vein structure (Nienow, 2017).

Figure 3. *Crevasses found on the GrIS.*
Note. Adapted from Jason Box.

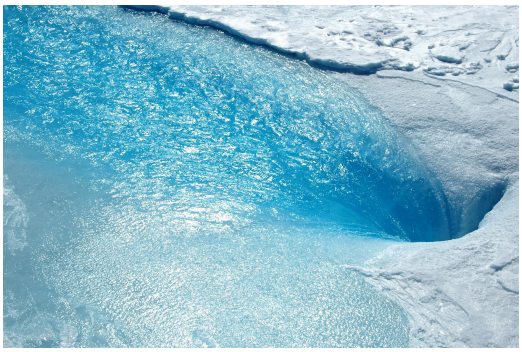

Figure 4. *Meltwater flowing through a moulin.*
Note. Adapted from Jason Box.

Crevasses (Fig. 3) and moulins (Fig. 4) are responsible for connecting supraglacial and englacial environments. Crevasses are formed primarily due to surface tension and their pattern is determined by the direction of their principal stressors (Chu, 2014). Crevasse fields are common in the lower ablation zone—where ice melts more than it accumulates—and let meltwater drain into channels within the ice (Lampkin et al., 2013). The amount of drainage is closely linked to the size of the area covered by these crevasses. While crevasses are responsible for around 48% of the total meltwater output (Mc Grath et al., 2011), they discharge steadily over a short period.

Unlike crevasses, moulins provide rapid and near-vertical drainage. Moulins form when summer meltwater corrodes ice. Modeled drainage through crevasses shows reduced diurnal variations, slower transfer times (indicating sustained meltwater input), and lower meltwater drainage per crevasse (Chu, 2014). In contrast, moulins enable rapid pulses of meltwater to drain from large, well-developed catchments (Colgan et al., 2011). This makes moulins crucial for quickly transferring water into the ice sheet, potentially overwhelming the subglacial hydrologic system. This can lead to uplift and increased basal sliding—resulting in increased ice detachment from the ice bed.

Conclusion

The drainage of Greenland lakes plays a pivotal role in understanding the dynamics of the Greenland ice sheet and affecting global sea levels. As per current scientific knowledge, little is known about the reasons or requirements for rapid drainage systems. However, due to this topic being fairly new, Greenland’s rapid lake drainage will continue to be explored and uncovered.

Rising surface air temperatures and increased availability of meltwater have caused the GrIS's supraglacial lakes to expand further inland to higher elevations in recent decades—a trend expected to persist. As supraglacial lakes migrate, there will be an exponential increase in the risk of rapid drainage via hydrofracture. This risk will have greater implications beyond the drainage of supraglacial lakes; rapid drainage of lakes can accelerate the movement of ice, possibly destroying more of the Greenland ice cap. This will not only serve as problematic to the species living in the continent itself but will also affect those residing in the world's coastal regions. For example, changes in ice melt can lead to rising sea levels and alterations in ocean salinity and temperature, disrupting marine ecosystems and impacting species dependent on stable conditions. Additionally, increased freshwater runoff will affect nutrient cycles and the health of coastal habitats. This makes it pivotal that action must be taken to prevent the melting of the GrIS by understanding the reasons for rapid drainage of meltwater in supraglacial lakes.

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Pig Kidney Xenotransplantation: The Solution to Dialysis and Long Donor Lists

Towa Mikami

Introduction

In 2023, the CDC estimated that around 35.5 million people were affected by chronic kidney disease (CKD) in the United States alone (*Chronic Kidney Disease, 2023*, 2023). Of that 35.5 million, it was estimated that over 500,000 Americans suffered from end-stage renal disease (Hashmi et al, 2023). These numbers have been observed to be rising, making kidneys an even more necessary resource. Having said that, researchers are taking steps towards a conceivable solution. The science of xenotransplantation has greatly progressed in recent years, particularly in the field of kidney xenotransplantation. As of recently, researchers have advanced the science of pig kidney xenotransplantations so much so that its practical use in the future is conceivable. This work reviews and synthesizes sources written by researchers and institutions focused on pig xenotransplantations, such as Dr. David K.C. Cooper and Massachusetts General Hospital. The work will discuss the following: the dangers of Chronic Kidney Disease, the current status of Pig Kidney Xenotransplantations, the significance of the procedure if it were to become publicly available, and theoretical issues that may arise from its advancement. Pig kidney xenotransplantations show an incredible potential; if they become a viable resource for the public, it would be an optimal solution to lengthy waiting lists and dialysis.

Pig Kidney Xenotransplantation

Researchers have been exploring the possibility of pig kidney xenotransplantations for some time now. Pigs are relatively cost-effective animals, and to an extent, they share anatomical and physiological similarities with man, making them suitable for xenotransplantation. (Golriz et at, 2012). It was not until recently, however, that development in pre-clinical research has enabled the beginning of clinical trials. The use of pig donors gives researchers the ability to modify the donor, opening up a new myriad of possibilities; this ability has been most importantly used to edit a donor's genes. An obstacle that has long been troubling is the human autoimmune response, which responds rapidly and strongly to certain porcine antigens. Particularly, the humoral immune system has developed antibodies that target 3 glycans: the Neu5GC antigen, the aGal antigen, and SdA. The genome editing technology CRISPR-Cas9 allows for the gene knockout of enzymes responsible for the production of those three glycans (Vadori & Cozzi, 2024). Furthermore, the addition of certain human genes has shown to improve a kidney's compatibility with humans, including complement inhibitors, such as CD46, CD 55, or CD59. Certain risk factors in the pigs such as endogenous retroviruses are targeted as well, and

immunosuppressive therapy is done to combat adaptive immune responses to other antigens which the human body has no natural antibodies for (Cooper & Hara, 2023).

Genetically-edited kidneys have shown incredible results: in 2021, UAB and NYU conducted breakthrough trials on brain-dead patients, the results of which showed promising results on the basis of urine production and kidney appearance (Pierson, 2023); consecutive trials involving edited kidneys in non-human-primates showed consistent survival (Eisenson et al, 2024), Most recently, Massachusetts General Hospital transplanted a genetically-altered porcine kidney into a living human in March 2024, the first pig kidney xenotransplantion done on a living man (Chase, 2024). 62-year-old Richard Slayman received a porcine kidney with the following CRISPR alterations.

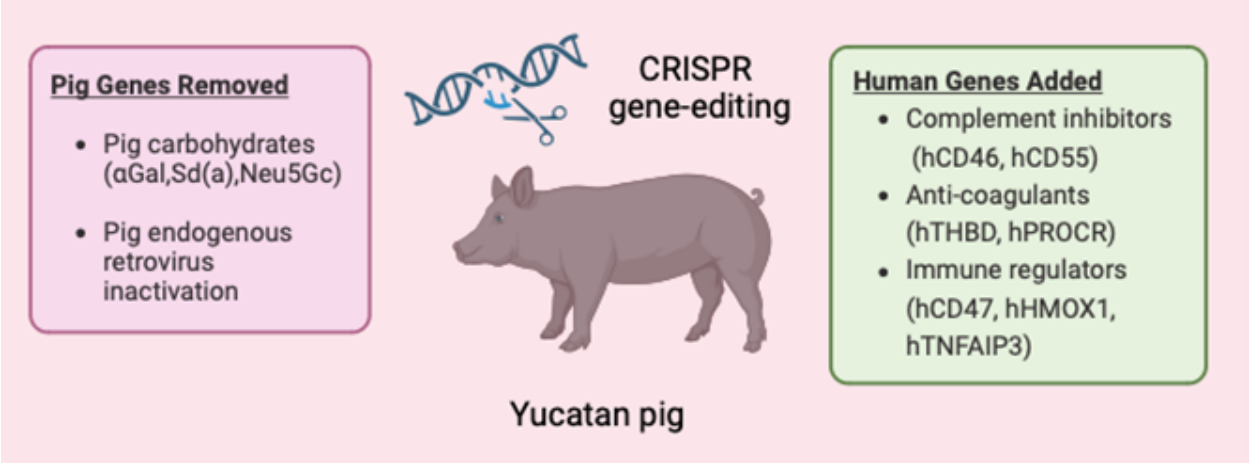


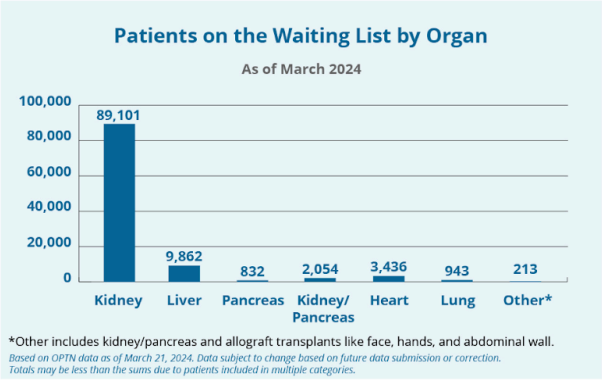
Figure 1: The gene editing done on the porcine donor used in Massachusetts General Hospital's operation on 62-year-old Richard Slayman. The genes that were added make the porcine subject more compatible with a human. The genes removed from the pig contribute to hyper-acute rejection and necessitate removal. Image retrieved from https://hms.harvard.edu/news/first-genetically-edited-pig-kidney-transplanted-human

We are closer to pig kidney xenotransplantation than ever; clinical trials, the first of their kind, have shown us promise of pig kidney xenotransplantation. However, much advancement remains to be accomplished in order to achieve routine use. Certain immunologic, physiologic, and biosafety obstacles are yet to fully be conquered (Vadori & Cozzi, 2024). For example, a specific immunosuppressive standard for gene editing has yet to be set. Sadly, Richard Slayman passed away in May 2024, although, according to Mass General, there was no indication that it was due to the kidney. Currently, researchers are focusing on accomplishing the long-term survival and function of porcine kidneys. At least for now, pig kidney xenotransplantation remains in its trial stage.

Chronic Kidney Disease

Chronic kidney disease is the constant and prolonged deterioration of the kidney's function. Solely in the U.S, approximately 14% of adults, or 35.5 million Americans, have CKD. This

number is predicted to continually rise consequently to the rise in diabetes and high blood pressure, two risk factors of CKD (Katella, 2024). In addition to the aforementioned diabetes and high blood pressure, heart disease, drug use, and certain genetic factors also can be contributing risk factors. Chronic kidney disease is separated by five stages; end-stage renal disease (ESRD), is the fifth and final stage of CKD where the kidney can no longer function on its own. The stages are measured by the kidney's glomerular filtration rate, the rate in which the kidney filters waste out of blood. By clinical guidelines, ESRD is when the kidney's glomerular filtration rate is less than 15 mL/min. A patient in this stage must undergo kidney transplantation or dialysis. However, even with dialysis, the mortality rate of ESRD patients within 24 months can be as high as 50%, and the survival rate for 5-year patients is 35%; that number being even lower for those with diabetes (Hashmi et al, 2023). This makes kidney transplantation a far more effective solution. As of March 2024, 89,101 patients are waiting to receive a kidney transplant. However, because of an extreme lack of donors, over eleven people die a day waiting for an organ. And with rising CKD numbers, the shortage becomes an ever more imminent issue every day.



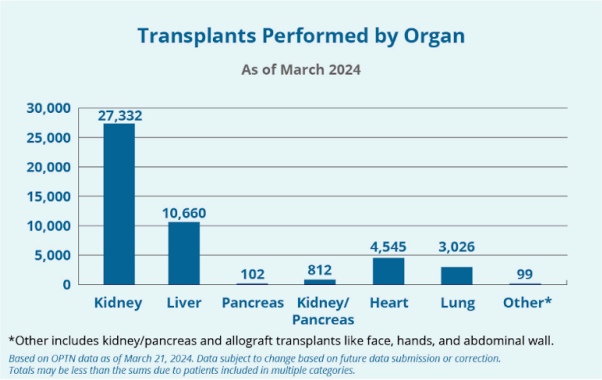


Figure 2a: HRSA statistics regarding organ waiting lists in the United States as of March 2024. A large majority of patients are in need of a kidney compared to other organs.
Figure 2b: Number of transplants performed by organ as of March 2024. Compared to the 89,101 patients on the waiting list for kidneys (see image 1), only 27,332 kidney transplants have been performed. Images retrieved from https://www.organdonor.gov/learn/organ-donation-statistics

Advantages and Impact of Pig Kidney Xenotransplantation

Pig kidney xenotransplantation brings about an effective solution to the global shortage of kidney donors (Yang et al, 2024). Pigs are widely available and easily breedable, and researchers are accustomed to genetically-engineering them (Cooper et al, 2015). They show potential for a nearly limitless supply of safe, suitable kidneys for patients. Pig kidney xenotransplantation would enable the prompt performance of transplantation, rendering waiting lists and dialysis unnecessary (Gorth, 2007). No longer will patients have to wait 3-5 years for a kidney, all while undergoing expensive and constant dialysis; nor will they need to concern themselves about dying while waiting for a kidney. Age limits that were placed due to donor shortages may be

removed as kidneys become far more accessible. Not only are human kidneys difficult to come by, the procedure itself is incredibly expensive; the cost of kidney harvesting from porcine donors will likely be cheaper than from a human donor, lowering the overall cost for patients. The use of pig kidneys would also likely reduce the activity of illegal kidney trade as well as unethical human-organ harvesting (Gorth, 2007).

	Pig	**Baboon**
Availability	Unlimited	Limited
Breeding potential	Good	Poor
Period to reproductive maturity	4–8 months	3–5 years
Length of pregnancy	114 ± 2 days	173–193 days
Number of offspring	5–12	1–2
Growth	Rapid (adult human size within 6 months)*	Slow (9 years to reach maximum size)
Size of adult organs	Adequate	Inadequate†
Cost of maintenance	Significantly lower	High
Anatomical similarity to humans	Moderately close	Close
Physiological similarity to humans	Moderately close	Close
Relationship of immune system to humans	Distant	Close
Knowledge of tissue typing	Considerable (in selected herds)	Limited
Necessity for blood type compatibility with humans	Probably unimportant	Important
Experience with genetic engineering	Considerable	None
Risk of transfer of infection (xenozoonosis)	Low	High
Availability of specific pathogen- free animals	Yes	No
Public opinion	More in favor	Mixed

Figure 3: Comparative table showing suitability and advantages of pigs compared to baboons. As can be seen, pigs are easily breedable and are experienced with genetic engineering, making them ideal for use in kidney transplantations (2015). Image retrieved from A Brief History of Clinical Xenotransplantation by David K.C. Cooper, Burcin Esker, and A. Joseph Tector. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684730/

Theoretical Issues regarding Pig Kidney Xenotransplantation

When it comes to theoretical concerns regarding pig kidney xenotransplantation, the majority of concerns regard ethical and moral dilemmas. In their 2022 work, *Ethics and Theoretical Issues in Kidney Xenotransplantations*, Wayne John Hawthorne, Adwin Thomas, and Richard N. Pierson discuss certain issues that may arise from the procedure. Firstly, there is a concern regarding pig wellbeing; the ways they are bred, raised, and all the many conditions they experience up until

their eventual euthanasia. Furthermore, although there is a huge potential in pig kidneys with its reproducible, safe, and more accessible nature, it is a question whether it is right to treat and use animals as biological resources. When innovations such as artificial pancreases exist, one may question if there is a necessity to use living animals.

Secondly, religious perspectives. Notably, Islam and Judaism have a similarity in being halal and kosher respectively. Swine has a symbolic nature to Muslims; pig is forbidden to eat, and if one cannot consume pork, would they be allowed to have a whole porcine organ within their body? This reasoning may deter some Muslims from receiving pig xenotransplantations. However, on the subject of medical treatment, seeking care is viewed as mandatory in lifesaving situations, so using that principle, kidney xenotransplantations would not go against Islamic law (Hawthorne et al, 2022). Similarly to Islam, Jewish tradition put importance on being kosher; swine is viewed as impure and dirty. However, Jewish belief also puts importance on healing and saving lives, to an extent where it can even be considered obligatory. So Jewish people would not be barred from the procedure, given that it would save lives, however individual Jews may be deterred by the idea.

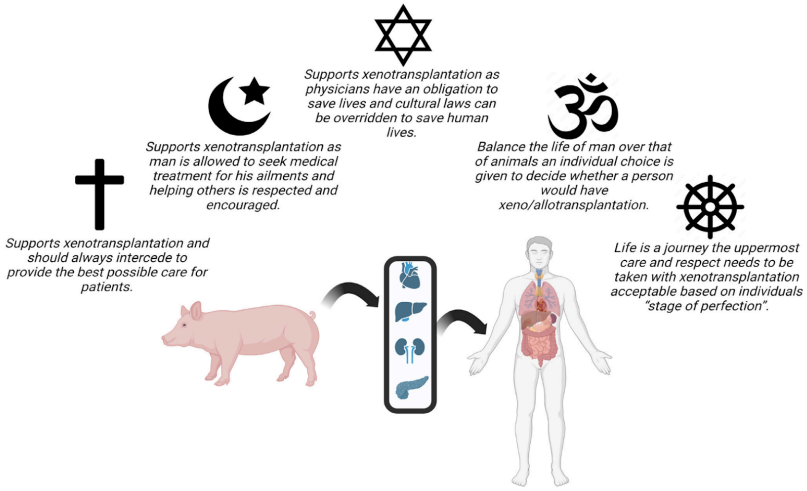


Figure 4: Various religious interpretations of the use of xenotransplantation. From left to right: Christianity, Islam, Judaism, Hinduism, Buddhism. Image retrived from https://www.sciencedirect.com/science/article/abs/pii/S0270929522000705

Apart from religious reasons, individuals may also simply not trust porcine kidneys, or dislike the idea of it. Animal rights activists may protest the endeavor, and choose to abstain from the procedure even if necessary. This is to say, even if pig kidney xenotransplantations become publicly available, it will likely take quite a while for it to be widely accepted as a norm.

Conclusion

In the past couple years, researchers have made great progress towards pig kidney xenotransplantation. The advent of its public accessibility will close the large gap between those who need transplants and those who receive them. Research has shown hope and promise for a

future where kidneys are readily available and quickly transplantable. Immunological issues still are the largest obstacles. Certain milestones need to be completed, such as long-term survival and function. As clinical trials have begun just recently, no one can say for sure how long it will take. To an extent, human donors will likely still be necessary; firstly because many patients will likely prefer a human donor, and secondly to properly make transplantation accessible to those who have moral or religious deterrents/restrictions against porcine donors. Regardless of possible issues, the vast majority of researchers seem to be hopeful and excited for the future of pig kidney xenotransplantations, a bright future where long-waiting lists and long-term dialysis are no longer necessary.

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Enhancing Robotics with Deep Reinforcement Learning and Sensors to Perform in Unknown Environments

Anisha Mulinti

Deep Reinforcement Learning (DRL) is a field under a much broader category of Artificial Intelligence (AI). DRL has unique capabilities to help combat current challenges and create new inventions in many fields such as healthcare, robotics, and finance. We have the ability to help enhance robot navigation's efficiency and adaptability, particularly in unknown environments, by optimizing DRL algorithms. This review will focus on the use of DRL on robotics and DRL's impact on a robot's decision making capabilities with the use of vision and ranging sensors.

DRL stands out within machine learning because of its unique way of learning optimal behaviors through interactions. As shown in Figure 1, reinforcement learning can simply be described as an agent making decisions and performing actions in effort to receive rewards in an environment. DRL is especially unique because it relies on trial-and-error to learn. Supervised learning relies on labeled data to make decisions and unsupervised learning is typically used to identify patterns in data without instructions.

The "deep" aspect of DRL involves using deep neural networks to approximate complex functions. This enables the agent to handle sensory inputs and learn policies. A supervised learning model, on the other hand, is trained with certain inputs and outputs within data. Unsupervised learning models attempt to identify hidden structures in unlabeled data. DRL algorithms are completely different. In DRL algorithms, the agent interacts with its environment by doing certain tasks based on its policy. The policy is a strategy that has the best actions to take in a given state. The environment responds to these actions by transitioning to new states and giving rewards or penalties. The agent uses this to update its policy. The agent should aim to develop a policy that receives the most rewards over time.

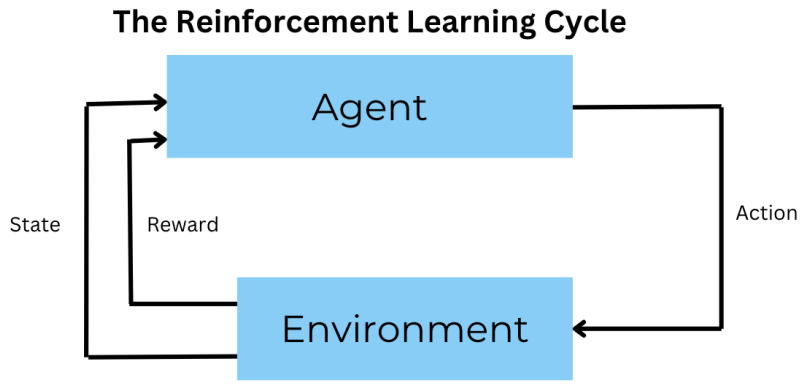

Figure 1: The agent performs action in the environment. This results in a new state and a reward, which are fed back to the agent to help determine future actions.

DRL has revolutionized several fields with its complex decision-making tasks that were previously difficult for traditional algorithms. In healthcare, DRL is used to enhance medical diagnostics and create personalized treatment plans. If DRL algorithms can learn from patient data, they can predict illnesses, recommend treatments, and help assist in procedures. For example, DRL can possibly help detect cancer early by analyzing medical images. There may be some patterns that aren't visible to the human eye that DRL algorithms can point out. DRL plays a crucial role in risk management and trading algorithms when it comes to finance. Financial markets are always changing and with the help of DRL algorithms, risks can be more effectively managed, leading to improved financial outcomes. In robotics, DRL has significantly advanced autonomous navigation and task performance. Robots with DRL can learn to navigate complex environments, perform intricate tasks, and adapt to new situations. DRL has many possible applications and industries are beginning to use it more and more to innovate.

One of the most promising applications of DRL is in enhancing robot navigation. Specifically, enabling robots to efficiently and safely move in unknown environments. Robot navigation involves several challenges, such as obstacles, unknown environments, and real-time decisions. Traditional navigation algorithms struggle with these tasks, especially in unpredictable settings. DRL addresses these challenges by allowing robots to learn from their interactions with their environment. By continuously exploring and receiving feedback, robots develop strategies to navigate complex terrains, avoid obstacles, and ultimately, accomplish their goal. There have been several successful implementations of DRL in robot navigation. For example, DRL has been used to develop self-driving cars that can navigate urban environments. DRL's implementations demonstrate its potential to enhance the capabilities of robots in various domains.

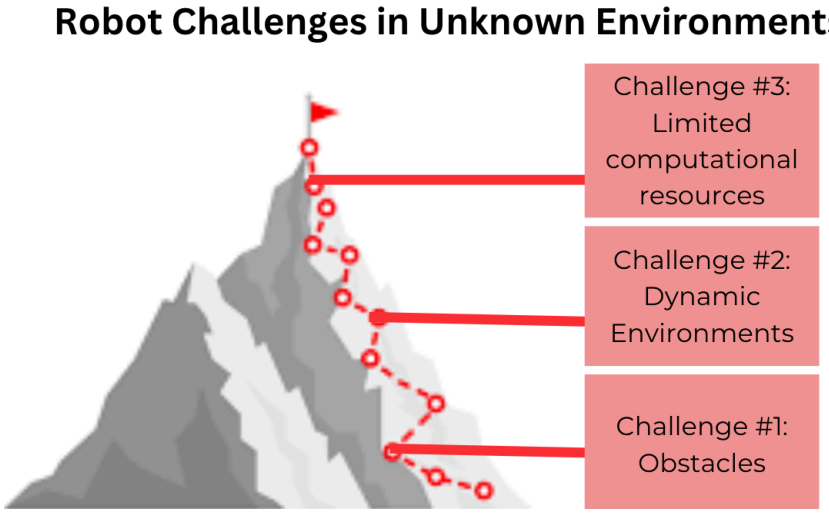

Figure 2: A robot can face several challenges in an unknown environment before being able to successfully complete a task.

DRL algorithms with vision and ranging sensors can significantly improve the decision-making capabilities of robots. Sensors such as LiDAR and cameras, help provide

environmental data that enhance the robot's actions. Cameras are responsible for capturing visual information and LiDAR sensors help measure distances to objects. Both help create detailed 3D maps of the surroundings. Robots can see their environment with high accuracy with these sensors. Data from vision and ranging sensors can allow robots to gain a comprehensive understanding of their environment. This information is used by DRL algorithms to make informed decisions. Many studies have shown the immense benefits of integrating vision and ranging sensors with DRL. For example, one study encompassed autonomous drones with both cameras and LiDAR to navigate forests and urban areas. The results were very informative as the droner was able to more effectively navigate the challenge environments with these sensors. Many autonomous vehicles are also integrated with sensor systems as they help achieve higher levels of safety and efficiency.

These studies highlight the importance of sensor integration in enhancing the performance of DRL-powered robots.

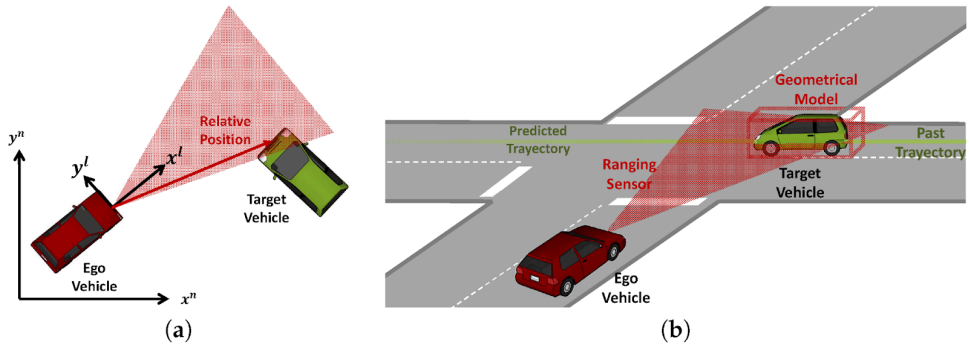

Figure 3: Ranging sensors detecting nearby vehicles. Image from article: "Survey on Ranging Sensors and Cooperative Techniques for Relative Positioning of Vehicles" A tracking algorithm can help predict a future position.

DRL's unique learning mechanisms and applications have revolutionized various fields, particularly in enhancing robot navigation. The integration of vision and ranging sensors has further boosted the decision-making capabilities of robots, enabling them to operate more effectively in complex environments. Despite its advancements, DRL faces several limitations, such as high computational costs and significant data requirements. Additionally, integrating sensors and deploying DRL algorithms in real-world scenarios present challenges, including sensor reliability and the need for extensive training data.

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Photonic Quantum Computing

Raj Pahilwani

1. INTRODUCTION

Quantum computing is a field that relies on the manipulation of quantum information. Researchers still strive to find the perfect medium for quantum computing, however, as it is a relatively new field current solutions are not perfect. One popular medium used to manipulate quantum information is photons. These photons play a crucial role in managing and improving the performance of qubits, the fundamental units of information in quantum computers. In superconducting qubits, microwave photons can be used to control the qubit states and how they interact. By adjusting the energy levels of photons, researchers can precisely tune the behavior of qubits, which directly affects how accurately they can perform quantum computations. Understanding how photon energy levels and movement influence the control and efficiency of qubits is essential for the development of the field and the future applications of quantum computing as a whole. As the field and technology that supports it develop, quantum computing will revolutionize our computers and reshape industries. As this technology develops, it promises to revolutionize computing by enabling faster processing of complex problems and enhancing our ability to solve tasks that are currently beyond the reach of classical computers. The ongoing advancements in photon-based qubit control will play a key role in shaping the future of quantum computing and its applications.

2. BACKGROUND

In traditional computers, information is encoded using bits, represented by either a 0 or a 1, off or on. The computer understands a 1-bit as an electrical current flowing through a wire and understands a 0-bit as no electricity flowing through a wire. These bits are then decoded into videos, text, and more (Nielsen & Chuang, 2010). However, a qubit, unlike a traditional bit, can exist in a state of 0, 1, or partly both 0 and 1 simultaneously, which is called superposition. A common misconception is that qubits can be read directly as their superposition. In reality, when being measured, a qubit is flattened to either a 0 or 1, depending on the probabilities defined by its superposition state. Think of a qubit as a coin that is constantly spinning. When the coin is flattened, it is either heads or tails, depending on which side it is closer to. This property of superposition is what allows a qubit to be much more efficient and powerful compared to a bit. Quantum computation is important, as problems that would have taken years on a traditional computer would take just minutes on a quantum computer (O'Brien 2007). In a process called quantum entanglement, shown in Figure 1, multiple qubits can be correlated, where the state of one qubit becomes directly related to the state of the other qubit. For example, if two entangled qubits were to calculate a coin flip, they would

either land on heads or both land on tails, the chance of each occurring being 50%. Superposition is typically shown through the equation $\alpha^2 + \beta^2 = 1$, called the normalization rule(Hughes et al., 2021). Figure 2 visualizes this relationship of possible superpositions of a qubit, contrasting qubits from classical bits. In the normalization rule, amplitudes are very important because they yield the probability of finding the particle in that specific state when measuring a qubit. The probability of measuring the particle in state 0 is α^2, and the probability of measuring the particle in state 1 is β^2(Hughes et al., 2021). It is squared as it gives the correct experimental percentages and predictions. Squaring α and β is similar to squaring a wave's amplitude to find the energy of the wave. Since the total probability of observing all the states of the quantum system must add up to 1 the amplitudes must obey this rule: $\alpha^2 + \beta^2 = 1$. Knowing this background information makes it much easier to address the following question: how do photon energy levels and movement influence the control and efficiency of qubits in quantum computing?

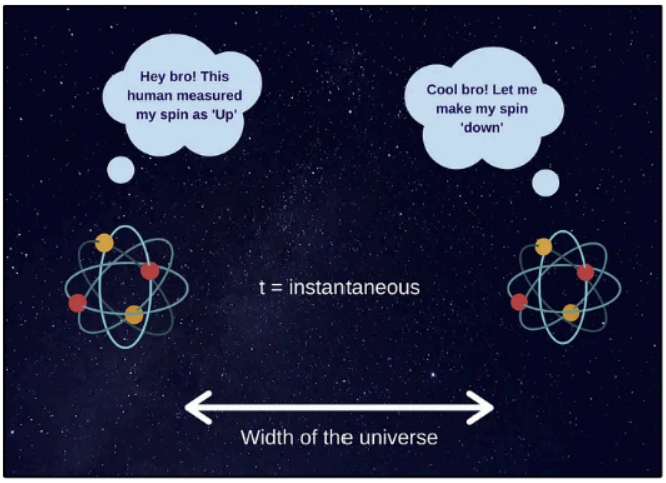

Figure 1. Shown are two entangled qubits. When two particles are entangled, a change in one instantaneously affects the other, no matter the distance—even across the width of the universe.

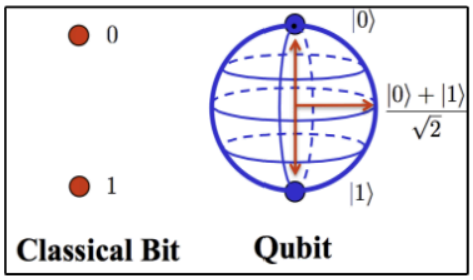

Figure 2. On the left, there is a representation of classical bit, 0 and 1. On the right, there is a Bloch sphere, which demonstrates the capability of superposition, a combination of both 0 and 1. Arrows on the Bloch sphere represent different superpositions of a qubit.

3. Why photons?

Due to the extremely complex nature of qubits, it is important to find a suitable way to represent them in the physical world. Although research have found and support many different realizations of qubits, the properties of photons make them an extremely attractive choice (Nielsen & Chuang, 2010). First of all, photons are massless particles, which means it does not interact with other particles through mass-based forces. This property that allows photons to travel at the speed of light is the same property that allows photons to convey information without too much interference, compared to other mediums (Rezai et al., 2018). Due to these minimal environmental interactions, photons are less affected by noise compared to other qubits. They can travel long distances through fiber optic cables, connecting quantum computers at the speed of light for future quantum networks. Moreover, photons can keep their state long enough to be useful for global applications. All of these factors make photons a suitable way to implement quantum networks. However, it is important to address the drawbacks that photons present, as some researchers believe they are not an optimal choice.

3.1 Drawbacks of Photons

While photons can travel through mediums such as fiber optic cables, photons are susceptible to loss in any medium they travel in. When traveling through imperfect materials and less transparent materials, photons can get absorbed into the medium, reducing the accuracy of the qubits. Along with absorption, photons are likely to deviate from their intended path due to imperfection (Nielsen & Chuang, 2010). Some photons can be reflected instead of transmitted through mirrors, beam splitters, or other optical components within the quantum computer. Although proper alignment and anti-reflective coatings can help minimize these losses, they cannot be eliminated. In addition, photons often travel through optical fibers or integrated waveguides in photonic quantum computers (Hughes et al., 2021). These transmission lines have inherent losses due to imperfections in the material and the manufacturing process(Nielsen & Chuang, 2010). Bends, splices, and connectors in the fibers or waveguides can introduce additional losses, further reducing the number of photons that reach their destination (Rezai et al., 2018). These challenges highlight the areas where further research and development are needed to make photonic quantum computing more practical and efficient.

3.2 Photon Energy Levels

Photon energy levels play a crucial role in the control and efficiency of qubits. By adjusting the energy levels of photons, researchers can control superconducting qubits by tuning their transition frequencies. This tuning is essential for implementing quantum gates, which are the building blocks of quantum circuits, and for conducting accurate quantum operations. When the energy levels of photons are adjusted, they can induce the desired transitions between qubit states, allowing for precise and accurate computations. Variations in photon energy can also alter qubit state populations. This means that the probability of a qubit being in a specific state (0 or 1) can be influenced by the energy of the interacting photons. As shown in Figure 3, the ground state of the photon represents a qubit at state 0, while the excited state represents the qubit at state 1. It is imperative to understand that the photons are not directly the qubits, however a representation of them. Properly controlling these energy levels is important for maintaining high accuracy, and ensuring that quantum computations are performed correctly. Inaccurate energy adjustments can lead to errors in qubit operations, impacting the overall performance of quantum calculations. To fix any errors in qubit operations, many types of quantum error correction codes have been developed, further increasing the accuracy of quantum operations. Overall, this precise control of photons energy levels as a qubit allows for further accurate computations.

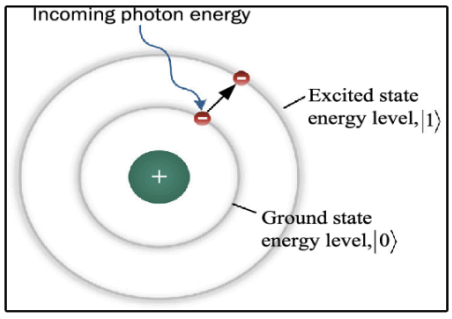

Figure 3. Depiction of a qubit by two energy levels of a photon. For example, the higher energy level depicts a 1 state while the ground state depicts 0.

3.3 Photon Movement

The movement of photons through optical systems significantly affects qubit performance. Photons often travel through fibers or waveguides, and their path must be carefully managed to preserve the integrity of the

quantum information they carry. Any deviation from their intended path can lead to loss of information and reduced coherence time, which is the duration over which a quantum system can maintain its quantum state.

Proper management of photon movement involves ensuring precise alignment of components to maintain the correct path for the photons (Rezai et al., 2018). Figure 3 illustrates a sample schematic for a setup that demonstrates photon movement and how they can be directed in a controlled system. This includes minimizing transmission losses by reducing scattering and absorption, which can occur due to imperfections in the materials used in fibers and waveguides. Additionally, controlling environmental factors such as temperature fluctuations and mechanical vibrations can help prevent misalignment and maintain the photons' intended trajectory (Rezai et al., 2018). Efficient movement of photons through optical systems is crucial for maintaining high qubit performance and ensuring reliable quantum operations. By carefully managing the movement of photons, researchers can minimize information loss and maximize coherence time, leading to more accurate and efficient quantum computations. The ability to guide photons precisely through optical systems is a key factor in unlocking further advancements in quantum computing technologies.

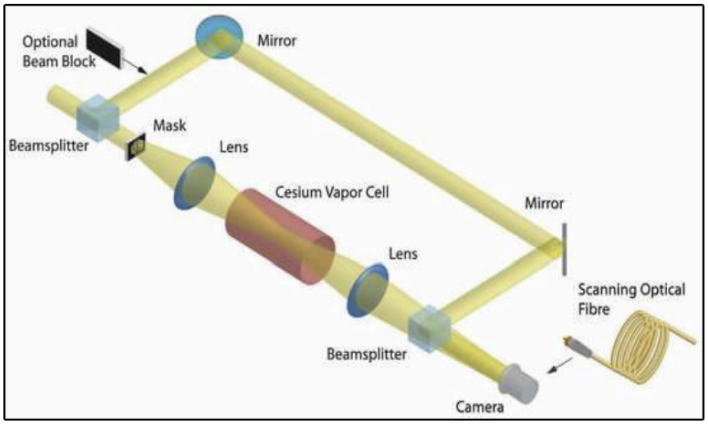

Figure 4. Schematic diagram of a photonic quantum computing setup, showing the use of mirrors, beam splitters, and a cesium vapor cell for precise control of photons.

4. Conclusion

The development of quantum computing will hinge on the integration of photons. Photons are ideal for qubit control and enhancement due to their massless nature and minimal interaction with their environment. Their ability to transmit information with minimal disturbance makes them suitable for maintaining both the integrity and coherence of quantum states over long distances, which is crucial for the development of quantum networks and global quantum communications. However, implementing photons in quantum computers presents several challenges. To improve the efficiency and accuracy of quantum operations, barriers such as photon absorption, path deviations, and reflection losses must be addressed. Despite these challenges, precise control of photon energy levels and their movement through optical systems remains essential. Fine-tuning these factors can lead to more accurate quantum computations and overall better-performing quantum computers. Advancements in photon-based qubit control will play a significant role in unlocking the full potential of this technology. Although seeing quantum technology in an everyday iPhone is a long time away, as quantum computing continues to evolve, it promises to revolutionize computing by solving complex problems with unprecedented efficiency using photon-based technologies.

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The Growing Use of Plant-Derived Pesticides In Pest Management

Juwon Park

Pesticides are compounds designed to prevent, destroy, or eliminate pests, fungi, and other organisms that can harm crops, humans, or animals. Despite the tremendous progress made by agriculture, the losses caused by pests alone are 18-20% annually of the overall production, valued at more than USD 470 billion. (Souto et. al., 2021). Since the introduction of DDT in 1939, chemical pesticides have been introduced in agricultural practice for crops like rice, maize, sugarcane, groundnut, cotton, and banana. These crops are susceptible to certain pests, which can cause as high as 10-15% loss in the yield of global production. (Chengala et. al., 2017) While traditional pesticides have been effective in pest control, the consensus among researchers is growing around the need for lower-toxicity alternatives that are less harmful to humans and the environment. An example of the effects of pesticides in the environment and the process is shown in Figure 1 to the right. Among the upcoming options for pest control are biopesticides: microbial, botanical, biochemical, and PIPs. In most cases, plant-derived natural pesticides have become known as a more commendatory option as they are cheap and eco-friendly, but also able to protect themselves from insects and diseases. Unlike synthetic pesticides, plant-derived pesticides are biodegradable and cause fewer harmful risks to human health and the environment. The use of natural compounds in natural plant products helps decrease the dependence on chemical pesticides, which are known to contribute to pest resistance, food production, solid degradation, and pollution. This literature review will review the advantages, limitations, and specific mechanisms of action of plant-derived pesticides, arguing that plant-derived pesticides offer a sustainable and effective alternative to synthetic pesticides, as they are biodegradable, environmentally friendly, and reduce reliance on harmful chemicals.

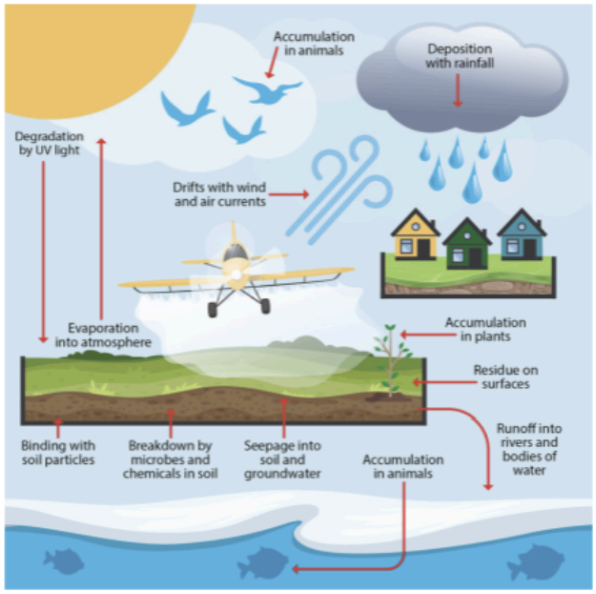

Figure 1: Pesticide in the Environment
The various entry pathways of pesticides into the environment: directly upon application, through volatilization in the air, runoff and leaching in water, and uptake into plants and animals. Pesticides degrade or persist in various compartments of the environment and contaminate soil, water and ecosystems.

History of Used Pesticides and the Recurring Problem

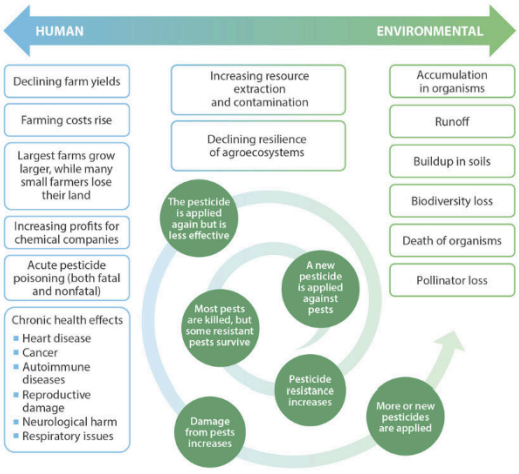

Figure 2: The Pesticide Treadmill and Its Environmental and Ecological Consequences
The pesticide treadmill where repeated applications of pesticides result in resistant pest populations. In a crescendo effect, as resistance increases, higher dosages or more deadly pesticides are applied to try to control pest populations, resulting in increased environmental contaminations and harm to non-target species, and reduced effectiveness of pest control measures.

Long-term use of synthetic pesticides has been linked to increased problems associated with pesticide resistance and environmental impact. Traditional methods of pesticide application-including most of the current chemical synthesis and broad-spectrum pesticides - have been useful in controlling pests and diseases. However, history indicates that these means have generated a myriad of severe problems. The major concerns are with pesticide application.

The pesticide resistance developed by pests makes them increasingly hard to control effectively. (Souto et. al., 2021). Secondly, the massive application of chemical pesticides has already caused environmental contamination by-products, directly influencing the quality of the soil and water and posing a health risk to both human beings and wildlife. It exposes people to chemicals that have a likelihood of causing serious health problems such as neural defects, congenital disorders, cancer, and immune system dysfunctions (Williams, 2023). The Pesticide Treadmill and further ecological consequences are shown in Figure 2 above. Among many available choices, integrated pest management (IPM) focuses on the combination of biological, cultural, physical, and chemical tools with reduced harmful impacts. For example, the infamous pesticide DDT, which was heavily utilized at the time because of its effectiveness, is now found to cause persistent negative environmental effects and non-target impact, therefore more sustainable methods are urgently needed. (Sustainable Agriculture, n.d.) Another encouraging product line is that of biopesticides, including microbial pesticides, plant-incorporated protectants, botanical pesticides, and biochemicals. In comparison with chemical pesticides, these biopesticides, based on natural products, are less harmful to human health and the environment, reducing dependence on chemical pesticides under the principles of IPM. (IMP, n.d.).

Introduction of Plant-Derived Pesticides

There are various forms of natural pesticides that provide effective and very biologically friendly ways of controlling pests. Biopesticides, derived from natural sources such as plants, animals, bacteria, fungi, and other microorganisms, differ greatly from synthetic pesticides. Contrary to synthetic chemicals, which in most cases have broad-spectrum effects, biopesticides

are typically more specific in targeting pests, reducing the chances of any collateral damage to useful organisms or the environment. The major types of biopesticides include microbial pesticides, botanical pesticides, biochemical pesticides, and plant-incorporated protectants (PIPs). (Tripathi et. al., 2023) Major types are shown in Figure 3 below.

Microbial pesticides, such as Bacillus thuringiensis (Bt), utilize bacteria, fungi, or viruses to target and kill certain pests. They provided an efficient, focused, biochemical way of managing some particular pests. Botanical pesticides are derived from extractants of plants like neem or pyrethrum, which contain bioactive compounds that act against a wide array of pests. (Souto et. al., 2021)

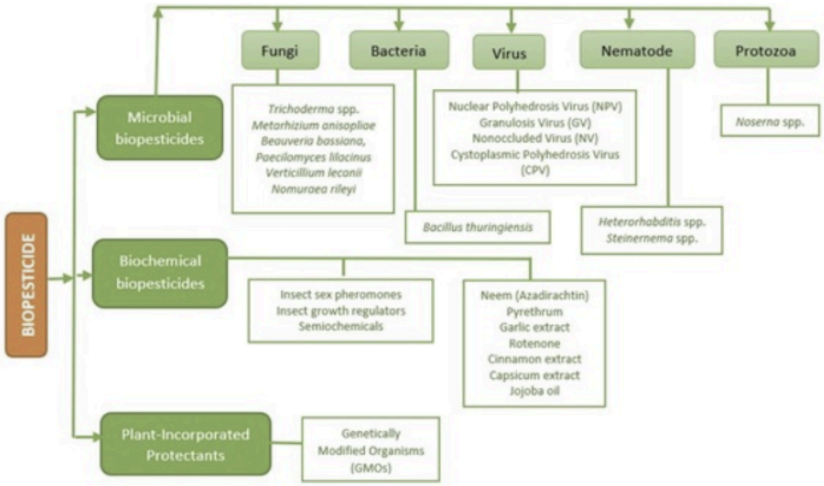

Figure 3: Classifications of Biopesticides
Diagrammatic representation of the 3 broad categories of biopesticides (excluding botanical) and the common types: microbial (bacteria fungi, viruses, nematode, protozoa), biochemical (natural substances) and plant-incorporated protectants (GMOs).

Biochemical pesticides, like pheromones, work by disrupting the mating patterns and habits of pests or by repelling them without directly killing them. PIPs are plants that are genetically engineered to acquire pest resistance by producing certain substances that include pest management in the plant's biology. (Williams, 2023) For instance, neem-based pesticides and the use of Bt crops have demonstrated efficacy in managing agricultural pests while minimizing adverse environmental impacts. (Daraban et. al., 2023) Such biopesticides not only provide a highly needed sustainable alternative to chemical pesticides but also support the principles of Integrated Pest Management through reduced chemical inputs and facilitated ecological balance.

Benefits and Advantages of Plant-Derived Pesticides

Many advantages exist about plant-derived pesticide use over synthetic ones in terms of safety and sustainability. Natural pesticides, in their chemical structure, become biodegradable

and easily broken down in the environment, hence reducing their chances of long-term contamination. Moreover, they have less potential to accumulate pesticide-resistant pest populations, which have been a major problem with synthetic pesticides. The selectivity of plant-derived pesticides also holds less risk to non-target organisms such as human beings and helpful insects. They, as a result, become very useful in sustainable agriculture, which is based on the premise of high crop yields cooped with low environmental damage

Plant-Derived Pesticide Effects on Insects and Pests

The efficacy of plant-derived pesticides in controlling pests arises from various bioactive compounds that affect specific physiological functions in pests. Botanical pesticides contain active compounds such as terpenes, flavonoids, alkaloids, polyphenols, and many others, which present varied mechanisms of action against pests. (Headrick, 2021) One of the primary ways such compounds act is through the disruption of the insect's nervous system. For instance, pyrethrins, found in chrysanthemum flowers, affect voltage-gated sodium channels, inducing neuroexcitation, and resulting in subsequent paralysis. Example of a specific compound effect, Bacillus thuringiensis (Bt) on Lepidoptera Larvae is shown in Figure 4 to the right. Similarly, compounds like nicotine act on their respective target sites–the nicotinic acetylcholine receptors–leading to continuous activation and eventual insect death. (Souto et. al., 2021) Other mechanisms include the inhibition of acetylcholinesterase (AChE) by compounds such as coumarin from Lantana camara, which inhibits the hydrolysis of acetylcholine at the synapse and therefore causes neuroexcitation and subsequent paralysis. Apart from neurologic effects, some plant-derived compounds/phytochemicals disrupt the developmental stages and reproductive biology of pests. Triterpenes and other phytochemicals, mimic or inhibit juvenile hormones, disrupting normal growth and development, while compounds like 2-BCA inhibit chitin formation, weakening the insect exoskeleton. (Souto et. al., 2021) Other compounds, such as rotenone, interfere with cellular respiration and eventually lead to the death of cells by affecting ATP production. The wide range of bioactive compounds in plant-derived pesticides allow them to act as antifeedants, repellents, insect growth regulators, and

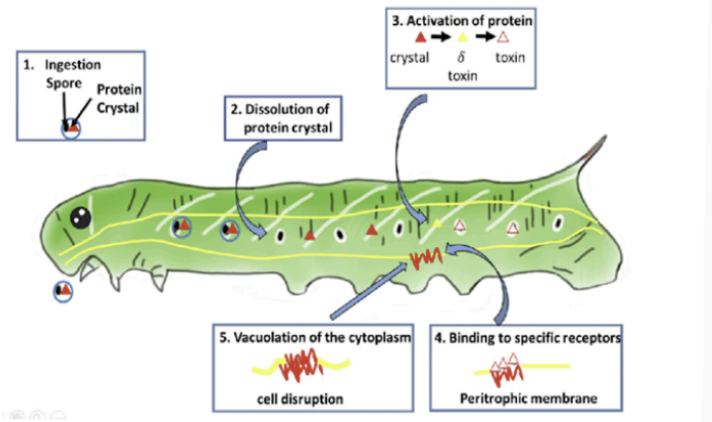

Figure 4: Effect of Bacillus thuringiensis (Bt) on the Lepidoptera Larvae Diagram showing the process through which spores from Bacillus thuringiensis (Bt) release endotoxins into the Lepidoptera Larvae midguts cells and will then bind with specific receptors. The binding of these toxins to its receptors disrupts the membrane of gut cells, leading to cell lysis, subsequent paralysis, and finally death. This process can be highlighted with the following steps: 1) ingestion of Bt spores, 2) dissolution of protein crystals, 3) toxin activation in the gut, 4) toxin-receptor binding, and 5) gut cell disruption.

disruptors of water balance through oils and saponins, by damaging protective wax layers on the body of the insect, causing dehydration. These multi-targeted actions make botanical pesticides a valuable tool in integrated pest management (IPM) systems, offering environmentally friendly and effective alternatives to synthetic pesticides. (Headrick 2021)

Conclusion

In conclusion, while synthetic pesticides have historically been important in pest management, their environmental and health drawbacks have prompted the search for safer alternatives. Plant-derived pesticides offer significant benefits, including lower toxicity and a variety of mechanisms that target pests effectively. However, biopesticides face limitations, such as high costs for farmers, lack of widespread knowledge, and inconsistent effectiveness due to environmental factors like UV sensitivity and temperature variability. Addressing these limitations requires further research into cost-effective production methods and more broad support for the adoption of biopesticides. As the need for sustainable pest management solutions grows, improving this limitation is essential to ensure the long-term viability of agriculture.

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How Does a Missile Work?

Kendrick Park

Weapons and modernization has always the greatest risk of danger to peace. Nowadays it's missiles that put humanity on the brink of destruction. Most don't understand how they work and what really makes them so dangerous to humanity and why some missiles are stronger than others weighing power into different directions. That is why I have chosen to research how these missiles perform and what improvements have been made to them to enhance it. What I conclude is that missiles include all parts of technology, engineering, and science and that every bit of STEM is necessary to understand missiles and their functions.

The functions of a missile are simple but it is best to understand them first to continue to make everything make some more sense. The main functions of a missile are how they soar through the air and how they explode on contact. These features are called thrust and payload delivery, they work in their own special ways and parts.

Missiles use a power called thrust to move through the air. Thrust is a mechanical power that is made by a rocket propellant and is a product of accelerating gas. That is made by a rocket propellant. Thrust is made as a product of accelerating gas. When gas accels or shoots back because of combustion to the rear, it forces the engines to accelerate in the opposite direction which forces the missile to be pushed or lifted up. Rockets have another part called the nozzle which accelerates the rocket as more exhaust passes by it. Finally rockets gain these gasses from their propellants; the type of propellant really doesn't matter, so long as it can produce a gas long enough to achieve thrust such as nitrogen and when that propellent runs out so will the gas and thrust.

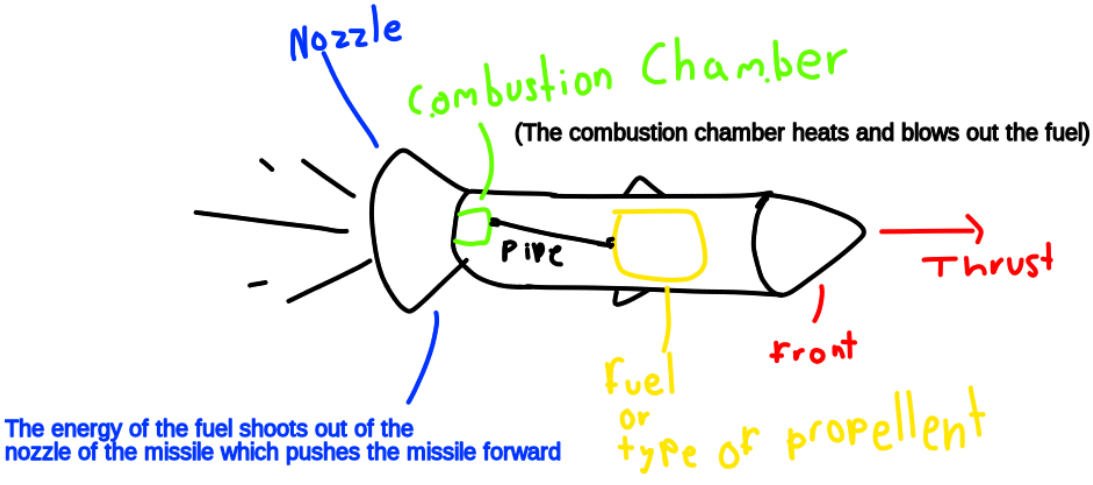

Figure 1: Diagram of a basic missile structure as it propels towards its target.

The next function is how missiles deliver an explosion. Missiles have something called a payload which usually stands in the front of the missile. There are many ways a missile may deliver its payload upon landing. One way is via contact. After the thrust of a missile has run out, the warhead can now rely on gravity and be pulled to the Earth's center to reach its target. All things need to be precisely calculated, including the gravitational force and the right amount of velocity to send the missile on its path. Finally upon contact with the surface, the payload will detonate. Another way to send off a payload is by thermonuclear explosion. Within this upon contact of ground, a process known as nuclear fusion happens. A chain reaction of different hydrogen isotopes combining under immense heat which causes a massive detonation.

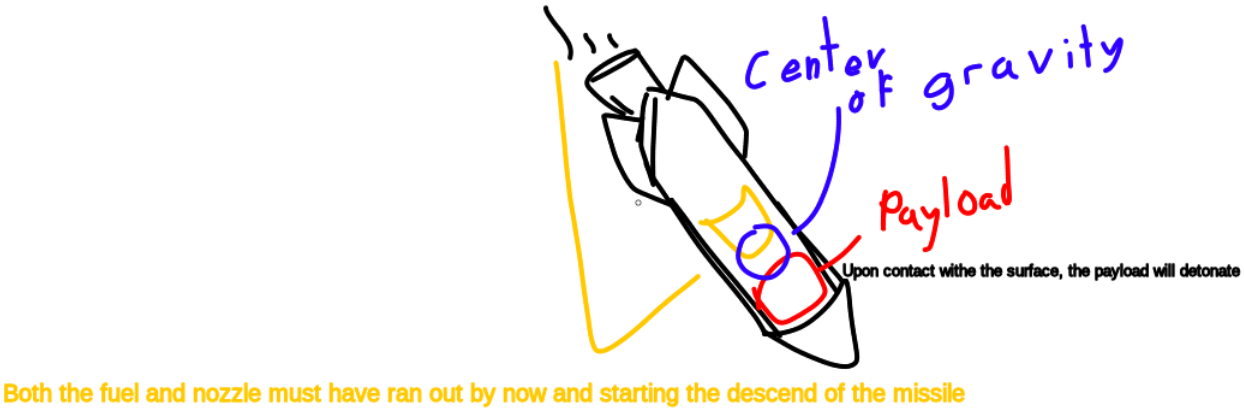

Figure 2: Diagram depicting the factors affecting missile descent.

To sum it all up, the functions of a missile are known as thrust and payload, and they help to create how a rocket works acting as the main parts. Thrust is how the missile is shot through the air via combustion by shooting a propellant in an opposite direction to push the rocket upwards. Finally the payload is a bomb around the front of the rocket so when it hits the ground it will detonate.

The next concept to review over is the parts and systems of a missile. The main parts of a missile to review are the guidance system, which is how the missile knows where to go, and the parts of the missile that control its aerodynamics.

Firstly, missiles have target guidance systems which stand in the front of the missile to target its landing. Not all missiles have the same targeting system and all have different ways to identify and lock on to the target. For example, tactical missiles rely on electric sensors which will identify a target via any energy emitted from it, whereas anti radiation missiles have sensors that allow them detect radar emissions or another way they can target is by locking onto an image of the target or an idea usually caught by cameras. Finally ballistic missiles can compare the speed it is going at and the speed of its target and try to predict the rate it can go at to achieve a hit.

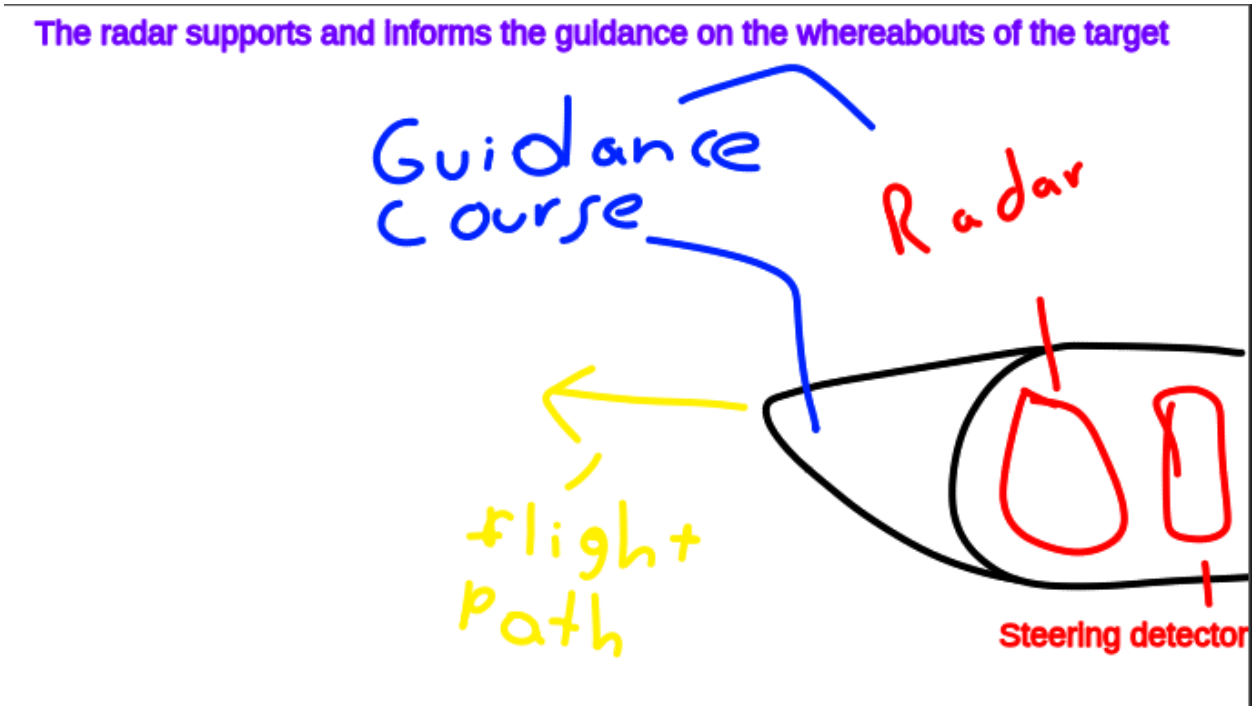

Figure 3: Radar role in missile guidance.

The next function is how aerodynamics apply to missiles. Aerodynamics is how objects or solid bodies interact with the air whilst moving through it. Next there are some forces such as weight and lift. The more mass or weight an object has, the more gravitational force there will be, meaning something with less mass could achieve better lift. Lift can only be achieved if there is more of it than weight. For airplanes, wings are essential to achieve lift due to aerodynamics. Curved shapes reduce drag by pushing air and wind away from the main body by pushing it off to the sides along its curves, whereas a boxy object would have lots of drag since air would constantly be pushing on it. Missiles have a few parts that allow it to be greatly aerodynamic to sustain air pressure, including the body, wings, and tail. All of these parts of the missile were specifically designed to decrease the amount of drag acting upon the missile. In addition, the nose cone in front of the missile can too affect the aerodynamics of the missile as it sustains most of the air pressure for the missile.

To sum it all up, the parts of a missile give it the abilities it needs to truly make it effective and reliable. Each part was carefully made to better assist the missile to reach its target and have better direction. The guidance system of the missile helps to ensure a more direct hit on the target and the fins help the missile soar through the air easily, controlling the air pressure.

Finally, while all missiles can produce a deadly explosion that all have the potential to be fatal, some missiles are clearly better than others and for different reasons. All the parts of a missile can somehow be improved to be better than other less modified missiles giving it an advantage.

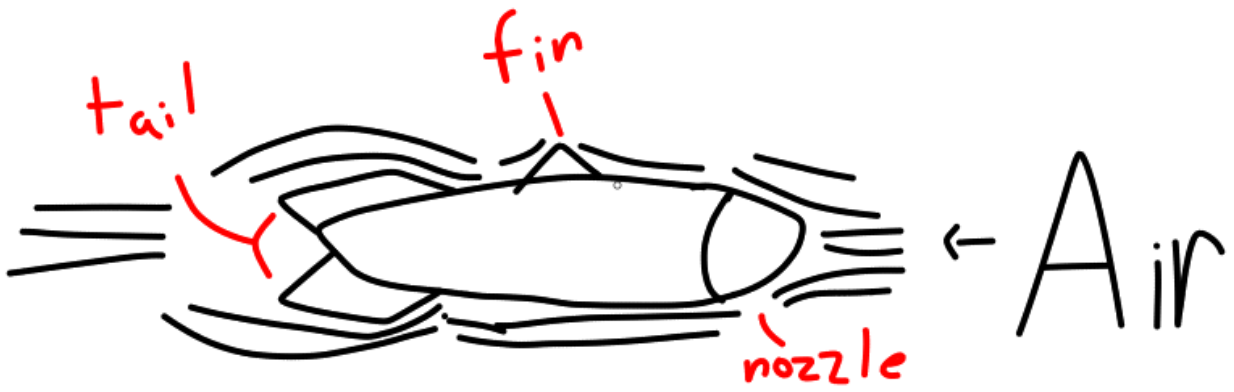

Figure 4: Diagram detailing how missiles are designed to be aerodynamic to combat air resistance.

Firstly, the type of propellant and its mass definitely affect how long a missile can fly for. For starters, increasing the fuel tank size can allow for more fuel to be stored, allowing more thrust to be achieved, therefore resulting in a longer flight duration. However, a larger fuel tank can increase the weight of the rocket therefore making thrust less useful. Some countries have attempted to work around this by inserting multiple smaller rockets at the base of the missile to achieve a greater liftoff. Alternatively, countries have created more effective propellants, however those can be expensive and are quite dangerous since you are greatly increasing temperature and velocity. This is because to make a propellant more effective it needs to have a greater rate of combustion to let off more exhaust to thrust the missile. Also the material used for the propellant is very important since, for example, liquid propellants are much more effective since they let off more exhaust of gas but are also more environmentally friendly.

The next improvement that can be made to a missile is its weight. Trying to cut down on a missile's weight is vital since it helps the rocket ascend into the air and achieve thrust better. One way this has been done is with the payload. Countries have attempted to lower the weight of the explosive payload in the front by making it smaller and ensuring greater missile distance. However this may not be ideal since the less payload there is, the less deadly or lethal of an explosion there will be. This will be making the rocket less useful for damage upon contact with the surface. Another way countries have decided to reduce the weight of the missiles is by cutting off dead weight from the fuel tanks. If any fuel is deemed unusable or ineffective, it will be taken out of the missile to ensure the fullest potential out the missile without disruption.

In a nutshell, there are multiple ways to improve a missile, the main way being lowering the weight or removing excess weight from the missile to achieve better lift off. Making smaller payloads or any other part allows the missile to have less drag since there is less gravitational force pushing it down. Also allowing more fuel to be stored or having a better fuel source can help, since some fuel sources are better than others achieving a greater amount of thrust.

In conclusion there has always been modernization and technological advancement in the field of war and missiles are one of its many products. Missiles have shown to utilize science technology and engineering to work and function. Missiles have multiple parts that allow them to perform the actions they can such as their payload delivery and lift off to thrust . Many innovative ideas and functions have been made to enhance the effectiveness of missiles. However even though it all sounds nice, it is to help others better understand how and why missiles can be destructive and what there is to know about them in these modern times.

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The Negative Impacts of Modern Agricultural Techniques

Leonard Park

In the 1960s and 70s, Norman Borlaug helped spur on the Green Revolution with the introduction of wheat and rice variants that had massively increased productivity. Borlaug also popularized the use of nitrogen fertilizers and new agricultural techniques that went on to help stave off famine and to a certain extent poverty in nations like India and Mexico (The Green Revolution: Norman Borlaug and the Race to Fight Global Hunger, 2020).

Figure 1: Image of Norman Borlaug, taken from https://agrilifetoday.tamu.edu/2020/10/16/the-borlaug-legacy-helping-feed-the-world/

However, many of these technologies have created a multitude of problems that affect not just the environment, but also the nutritional content, yield sizes, and overall human health. This paper will go into detail about how modern agricultural techniques decrease nutritional content in foods consumed, harm the environment, and have harmed their own ability to produce food, as well as negatively impacting human health in America. This paper will talk about how air, soil, and water quality have been affected by modern farming practices, and in turn have affected agricultural yields, how the packaging and processing of produce negatively impacts their nutritional content, as well as potential solutions to these problems.

3 of the most important environmental factors in the growth of crops is the quality of the soil, air, and water used, which in turn extends to produce being edible and nutritious for human consumption, so the quality of these factors can have serious effects on human health. Water is critical as it's needed for cooling, circulation of nutrients within the plant, and is a necessary component for photosynthesis. Water alone has many factors that can affect crops, from its pH, concentration of soluble salts, and concentration of suspended solids like sand, weed, algae, and weeds. Poor quality water with high pH, salt concentration, and/or suspended solids can not only clog up irrigation systems, but can harm plant's growth in many ways, including, but not limited to injuring roots, interfering with nutrient intake, increased susceptibility to disease, etc(University of Massachusetts Amherst). Soil is important to plant growth as not only does it contain many nutrients like nitrogen, phosphorus, and potassium(University of Hawaii at Manoa), but also contains many bacteria and fungi who do multiple roles from nitrogen fixing to outcompeting other harmful pathogens(Jacoby et al, 2017). Last, but certainly not least is air, which provides the oxygen and carbon dioxide needed for plants to create glucose to sustain themselves.

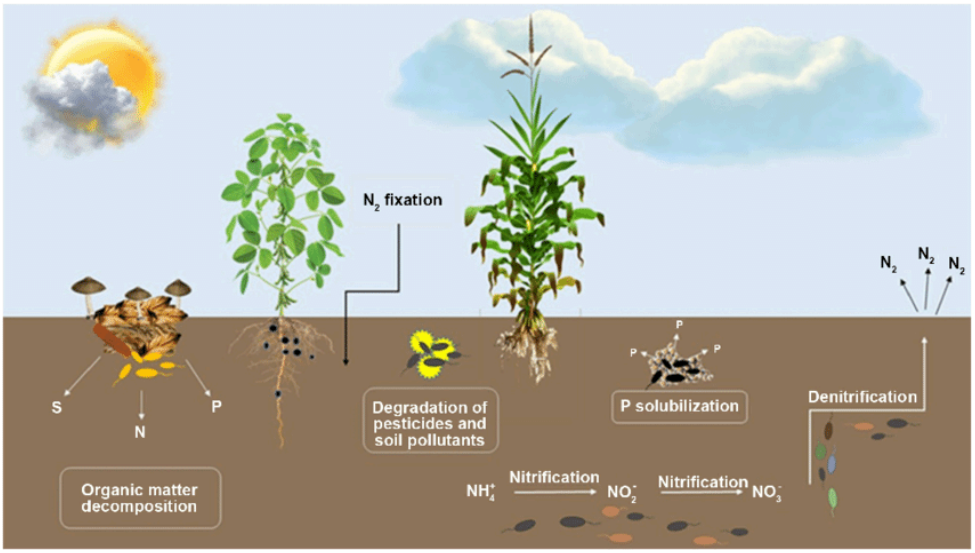

Figure 2: This image from ResearchGate shows a few examples of important roles microorganisms play in helping plants grow

However, despite the importance of these factors to a farm's success, many farms often hurt themselves with unsustainable practices that end up affecting crop production. Common soil practices like tilling and heavy use have led to nearly a third of the world's soil being moderately to severely degraded(Gray 2019), making it practically useless to farm on. If the topsoil is heavily degraded, it can also lead to soil erosion, where not only is the soil unusable for growing any vegetation, but it can also have other adverse effects. leading to a process called desertification where an otherwise biodiverse ecosystem is turned into a desert(Nunez 2019). Topsoil is also crucial for other reasons like water retention and preventing floods, hosting many

of the microorganisms who help plants develop, and supporting plant roots as many plants have their roots in topsoil(World Wildlife Fund).Farms create tons of agricultural runoff containing a multitude of chemicals like pesticides, herbicides, fertilizer, and other materials, if not treated properly, can not only make the water harmful for use on plants, but can create algal blooms in lakes or rivers hit with runoff, potentially killing off entire ecosystems and much biodiversity(EPA 2023).

Figure 3: An image of agricultural runoff being disposed of in a body of water. Photo taken by John R. Albano on Getty Images

As for air, the agriculture industry is responsible for 10% of greenhouse gasses produced in the U.S., producing gasses like nitrous oxide and methane(Joiner 2023). Even without considering how much these gasses contribute to climate change and its negative effects, gasses like nitrous oxide can harm plant cells and can stunt their growth, with estimates reporting that if the amount of nitrous oxide emissions alone were cut in half, crop yields could increase up to 25%(Lobell 2022). One of the places where these changes have been most drastic is in the Amazon Rainforest. While it is common knowledge that the Amazon as one of the most biodiverse places in the world and as the “lungs” of the Earth, as the forest got cleared, of which agricultural industries like cattle farming and soybean farming make up 80% of the deforested land(DGB Group, 2023), many of the aforementioned problems with air, water, and soil quality sprang up. Not only has deforestation eliminated many carbon-dioxide absorbing trees, but it has worsened rain cycles. Because there are less trees and plants overall, less moisture can be captured and returned into the air as rainwater, leading to more plants dying off and the cycle intensifying.

Another huge part of the equation that is modern agriculture is GMOs, short for genetically modified organisms and pesticides. While traditionally the creation of these came down to breeding the crops with the highest yields, nowadays scientists are able to isolate individual traits from any plant that they desire and insert it into the plant of their choosing(Powell, 2015). On paper, this is an absolutely great advancement for humanity as not only can GMO crops be engineered to grow bigger, but other desirable traits like lower nutrition requirements, faster growth cycles, disease resistance, longer shelf-life, etc (MedlinePlus 2022). Pesticides and their weed killing counterpart herbicides are also, on paper, massively successful as they help kill out undesirable weeds. When used in tandem, however, is where problems arise. As more and more plants began having weed resistant properties, farmers kept on using more and more herbicide. This overdosage of weed killer, much like with antibiotics and super bacteria, has led to the development of superweeds, who when left uncontrolled, can ravage farms. A recent case that ended up getting covered in the New York Times happened in 2023 back when the Ninth Circuit Court of Appeals had overturned E.P.A. approval of three products containing dicamba, a controversial weed killer.

Figure 4: An example of a weed in a crop field.

Despite it being one of the few counters farmers can use against Palmer amaranth, a common class of superweeds, it was still banned over concerns of spreading to other wildlife. Monsanto took a decade to develop a new product to counter these weeds, who then proceeded to develop resistance within 5 years(Brown, 2023). If the problem of superweeds isn't properly addressed, then it could potentially destroy many giant farms that source many consumers' food, potentially causing societal issues from there.

While food production is super important, the food is useless unless it is transported to people such that it hasn't lost much of its nutritional value. While previous methods at food preservation like drying, curing, pickling, etc often significantly changed the nutritional content of the preserved food, modern technologies like refrigeration, pasteurization, and canning, along with chemical preservatives like sorbic acid,benzoic acid,sulfur dioxide and sodium propionate,etc(Anderson, 2019) are significant improvements and are able to maintain produce's freshness for extended durations of time. Transportation methods of foods have seen significant improvements as well as the development of railroads, highways, shipping containers, among others, allowing foods to be given to consumers in a higher quality state. With all that being said, food preservation along with the access to these foods, whether it's due to socioeconomic or technological problems, still have a hard effect on people's consumption of produce. 3 of the most common ways produce is sold to consumers (canned, frozen, and fresh) have varying levels

of nutrition levels, with some vitamins and nutrients like vitamin B showing 7-70% loss in concentration when canned and 20-60% when frozen(Barret). Many canned foods are prepared by setting the contents to high heat and rapidly cooling in order to kill off pathogens, aiding in their longevity.

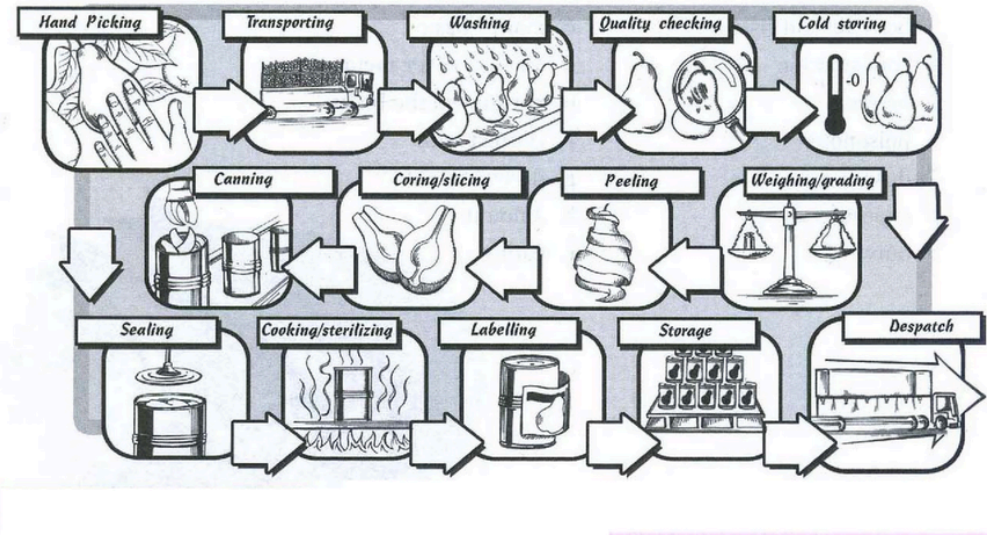

Figure 5: The timeline of events involved in the production and distribution of canned foods

However, this ends up destroying water-soluble vitamins like the aforementioned vitamins B and C(Ellis, 2023). Canned foods also exhibit significantly increased amounts of salt and added sugars, and in some rare cases trace amounts of BPA could be found along with deadly bacteria called Clostridium botulinum which can cause botulism(McDonnel, 2019). However, an even bigger problem than just the nutritional content of these foods is whether people can even have access to these options. In over 6000 areas in the U.S. alone are “food deserts” where access to any and all affordable, nutritious foods are limited. These areas tend to be ones distraught with poverty and limited transportation access, regardless if it was an urban or rural area, making them unattractive to groceries or supermarkets to set up business(Dutko, 2012). People with sufficient nutrition learn better and are able to live longer, healthier lives (World Health Organization), so giving people greater access to it is a critical pillar to having a greater society.

While the problems presented in the paper are no doubt significant issues to face, there are some solutions to them. For soil erosion, there are already known methods like crop rotation using cover crops, but there are other methods introduced like vegetative barriers, which are narrow parts of land covered with vegetation, usually at the edges. Another method is contour farming, where crops are farmed near the edge of a hill (NRCS, 2009). However, as for water, air, and to a certain degree soil quality, these are going to require regulations that need to be strictly enforced if the quality of these resources are going to be preserved as otherwise farmers will just continue on with their practices, continuing to degrade the quality of the environment

around them(Kjellstrom, 2006). Superweeds are an interesting case in that there is a combination of methods to curb them. Many farmers like Darren Nicolet have to resort to older methods of weed control like scouting them out and pulling them out early along with planting cover crops in the winter in order to minimize the space weeds take up. However, there is a new technology, albeit risky and dangerous one called flame weeding, where farmers apply a high heat source, usually a propane torch, to kill weeds early. However, it has limitations with which conditions it can be used in. Windy days and particularly dry vegetation do not go with it(Steil, 2024). Lastly, to address food deserts, this is going to require a multitude of socioeconomic factors to change. Fresh food is going to be more readily available, but it isn't as simple as just dropping a grocery store or farmers market into a low income area. Various economic incentives like vouchers for farmers, increased permits for community gardens and healthy food carts and trucks, even opening greater transportation access are all necessary components to make healthy food more available(Harvard T.H. Chan School of Public Health).

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Effects of Metformin and Sulfonylureas on Cardiovascular Health in Patients with Diabetes

Aastha Patel

Introduction

Diabetes mellitus (DM) is one of the most prevalent diseases in the world. Centers for Disease Control and Prevention reports that more than 38 million Americans have diabetes and about 90% to 95% of them have type 2 diabetes mellitus (T2DM) (CDC, 2024). Worldwide there are about 462 million people that have T2DM which is about 6.28% of the world's population (Khan et al., 2020). Usually, patients with diabetes mellitus are at greater risk of developing heart failure [HF] (Leung et al., 2016). Insulin is a type of hormone produced by the pancreas. It functions as a key to allow blood sugar to enter a person's body cells to be used as fuel. The people with type 2 diabetes can't respond to insulin normally. This is known as insulin resistance. The person pancrase tries to make more insulin to get the cells to respond. Overtime, pancreas can't keep up and the blood sugar level rises which sets the stage for T2DM (CDC, 2024). Metformin and Sulfonylureas are two different types of oral antidiabetic medications taken by the patients with T2DM. These two medications help to lower the blood sugar levels in the people with T2DM. The main objective of this literature review is to examine the effects of these two antidiabetic treatments on patient's cardiovascular health. By studying the effects of these medications, researchers and doctors may be able to improve the long-term outcomes in patients with diabetes mellitus and limit the risk of developing heart failure.

1. Background

A. Metformin

Metformin is a widely used first-line antihyperglycemic treatment [increasing the action of insulin in targeted organs] in T2DM because of its safety profile. Metformin helps to increase insulin sensitivity. It is also used as monotherapy and in combination with other antidiabetic treatments (Kenny & Abel, 2019). Compared to glibenclamide, second-generation sulfonylureas, metformin has been shown to reduce diabetes mortality and other types of complications by 30%. (Nasri & Rafieian-Kopaei, 2014).

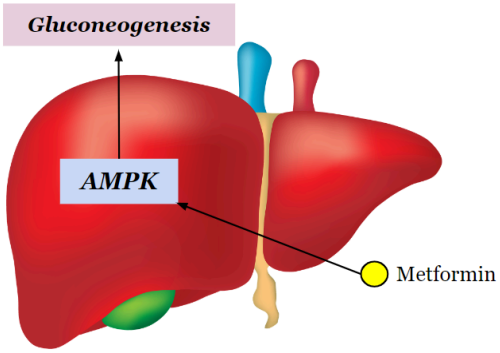

Figure 1: The primary effect of metformin is to activate the enzyme called AMPK (Adenosine Monophosphate-Activated Protein Kinase). Metformin activates the AMPK enzyme in the liver which inhibits gluconeogenesis. This increase in gluconeogenesis leads to decreased glucose levels. One of the other mechanisms include that it delays gastric emptying and reduces appetite.

B. Sulfonylureas

Sulfonylureas is another prescribed medication for lowering glucose levels. Sulfonylureas help stimulate insulin secretion. They are generally used as a second-line treatment choice for lowering glucose levels after metformin. Sulfonylureas can be used as monotherapy or in combination with metformin or other medications. (Hirst et al., 2013). There are also first-generation sulfonylureas, which include chlorpropamide and tolbutamide. However, first-generation medications are rarely prescribed by doctors nowadays. (Costello & Shivkumar, 2020).

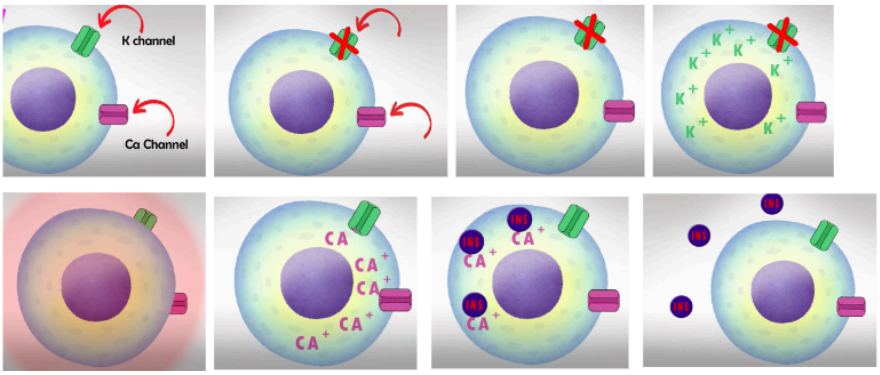

Figure 2: They work by blocking potassium channels in beta cells. Which causes the accumulation of intracellular potassium. Then this accumulation depolarizes the cell and opens the calcium channels. Next, calcium flows in and binds to the insulin vocals which results in insulin release. These medications require functioning beta cells to be effective.

2. Comparative Studies on the Cardiovascular Effects of Sulfonylureas and Metformin

Heart failure (HF) is commonly caused in patients with T2DM. It is unclear how the use of oral drug class compares to others and if one drug class increases or decreases the risk of HF than another. One retrospective cohort study conducted by McAlister and his colleagues examined the effects of oral antidiabetic therapies and the risk of HF in diabetic patients. Their results show that the incidence of HF does not differ across various oral antidiabetic drug classes. However, from their observation, it was found that patients who have higher doses of sulfonylurea were more likely to develop HF. This adverse dose relationship was observed in the sulfonylurea monotherapy patients**,** whereas this was not observed with metformin. (McAlister et al., 2008). This outcome showcases high doses of sulfonylurea medications that can be harmful to a patient's cardiovascular health. On the other hand, no significant results were found with the use of metformin. Even though the results show that sulfonylurea has a higher risk of HF, the study has several limitations. One of the limitations is that this was an observational and retrospective study based on administrative databases and not on clinical information. This type of study may not have considered other factors like the severity of diabetes or glycaemic control over time. Furthermore, it is hard to classify the diastolic from systolic HF based on the administrative databases, which could have affected the results.

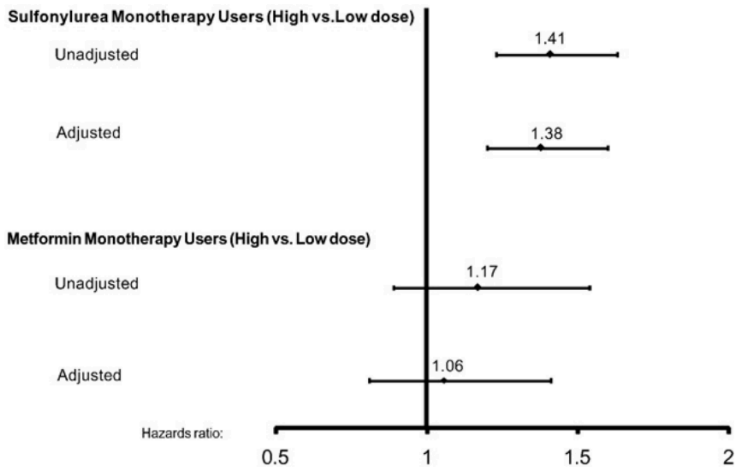

Figure 3: This data shows risk of incident HF in 5631 individuals with T2DM who are treated with higher versus lower doses of monotherapy of metformin and sulfonylureas. The upper half of the plot shows patients receiving high-dose sulfonylurea versus low-dose. While the lower half of this plot presents data comparing the risk of incident heart failure in patients receiving high-dose metformin versus low-dose.

Furthermore, another study done by Khan et al. on the effects of metformin and sulfonylurea therapies among patients with heart failure and diabetes shows that people taking metformin have fewer hospitalizations due to HF compared to people who don’t take it. This study did a subgroup analysis of an individual's ejection fraction (EF). It was found that for people with EF

< 40%, taking metformin was linked to a lower risk of HF. For those with EF < 40%, metformin did not show any significant benefit. Meanwhile, it was found that there were no significant differences in hospitalizations due to HF between the people who took sulfonylurea and those who didn't take it. However, it was found that there was a higher risk of death from any cause for the individuals who started sulfonylurea than those who didn't. The subgroup analysis by the ejection fraction showed increased risks linked to sulfonylurea for people with both lower and higher EF. (Khan et al., 2021). This study further supports the idea that sulfonylureas medications might be less beneficial to patients' cardiovascular health in people with T2DM than metformin. However, there were also limitations presented in this study. One of the main limitations was that it included Medicare beneficiaries aged 65 or older, so the results might not apply to younger patients with HF and DM.

Another cohort study done by Roumie and colleagues on the comparative safety of sulfonylurea and metformin showed that patients with DM taking sulfonylurea had a higher risk of developing HF or cardiovascular health problems compared to similar patients initiating metformin. Metformin was hypothesized to have lowered the HF rate because this medication improves insulin sensitivity and limits weight gain. Conversely, sulfonylureas increase endogenous hyperinsulinemia and facilitate weight gain. Patients with T2DM are usually linked to obesity and develop an independent risk factor for cardiomyopathy. Therefore, metformin can be a more beneficial medication that will help with limiting weight gain than sulfonylurea. Leading to a lower risk of heart failure or cardiovascular health problems. (Roumie et al., 2017). There were also limitations presented in this study. One of the limitations was that the study didn't take into account the patients taking other medications like diuretics, which could affect their cardiovascular health. Furthermore, the study mainly includes male veterans, so the results may not apply to other groups.

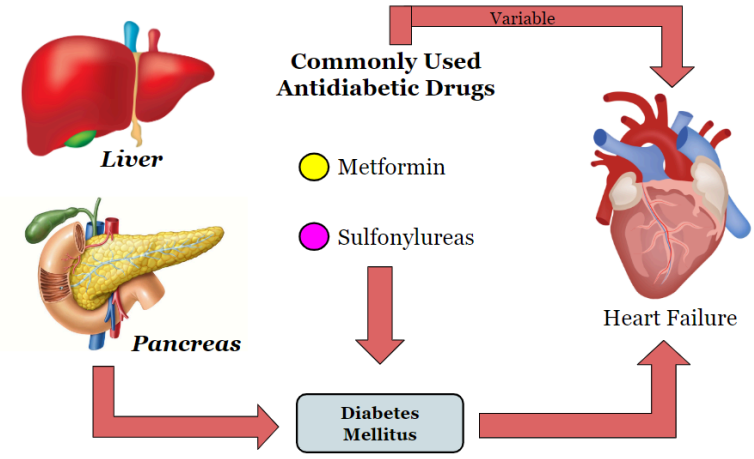

Figure 4: Metformin and Sulfonylureas targets controlling blood sugar levels through different processes that could module diabetes mellitus associated with heart failure.

3. Conclusion

The direct cause of cardiovascular risk in DM is complex to understand. The realization is that some medications can have divergent effects on cardiovascular health and that some medications might reduce HF risks. This review has provided an overview of the current state of knowledge about the cardiovascular risks of metformin and sulfonylureas based on different studies. While the studies have showcased a rationale that metformin leads to lower HF risk, at the same time, sulfonylureas increase the risk. There are many other variables to consider, such as other medications, the mechanisms of DM, and HF itself. Many medications are available to achieve glycemic control, but the next challenge will be to identify medications that not only maintain glycemic control but also help to reduce other risks due to high blood glucose. The development of these medications has been a starting point in the healthcare industry; however, to overcome more varied ranges of outcomes and fully understand the connection between T2DM treatments and cardiovascular health, further continuous research is required to evaluate significant changes in the future.

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Role of Autophagy in the Molecular Investigation of Protein Aggregation in Amyotrophic Lateral Sclerosis

Vedanti Patil

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive motor neurodegenerative disorder. In ALS, the nerve cells in the brain and spinal cord that control voluntary muscle movement and breathing are affected; motor neurons degenerate and die, and in turn, stop sending messages to muscles. This can result in weakness, twitching, and muscle atrophy. The inability to control voluntary movement can lead to an impairment of numerous functions, including breathing. Some early symptoms involve tight or stiff muscles (spasticity), slurred or nasal speech, and difficulty chewing or swallowing. Later on, progressive symptoms include drooling, inability to speak or form words, constipation, and near the end of a patient's lifespan, an inability to use their limbs and take care of themselves. However, it's important to note that ALS does not impact reasoning, memory, or cognitive functions. ALS treatment involves drugs that can prolong survival, but there is currently no treatment that can stop the progression. With the onset of symptoms, ALS can be fatal within 3-5 years, and there are no clearly associated risk factors for sporadic ALS[12]. There are two types of ALS: sporadic and familial. Sporadic ALS (sALS) is when the disease occurs at random, seemingly with no familial basis. Sporadic ALS is more common, with 90-95% of ALS cases being sporadic[4].

Neurodegenerative disorders typically affect cellular proteostasis – a process that maintains the proteome in the proper concentration – and correct protein folding[7]. The main pathological hallmark of ALS is the presence of cytoplasmic inclusions or ubiquitinated aggregates in the degenerating motor neurons and surrounding oligodendrocytes, which are glial cells in the brain and spinal cord that coat axons with myelin sheath. One common aggregated protein in ALS is TAR DNA-binding protein 43 (TDP-43), which is a major component of ubiquitinated inclusions[3]. A mutated TDP-43 is observed in almost all sALS patients[1]. Some more aggregates observed in sALS cases are FUS, SOD1, and C9orf72[3]. Two main systems prevent the formation of impaired proteins: the Ubiquitin-proteasome system (UPS), which degrades functional and dysfunction proteins, and the Autophagy-lysosomal system (ALP), which is responsible for the degradation of whole organelles and large protein aggregates. Dysfunction in these two pathways is implicated in ALS; altered degradation pathways and environmental influences are among the many factors that can lead to protein aggregation and misfolding[7]. In non-diseased patients, the autophagy-lysosomal system would remove the aggregated proteins.

Autophagy is a catabolic cellular degradation and recycling process that is responsible for the removal of protein aggregates and damaged organelles. It is a homeostatic process[9] and

possesses a role in development, cell differentiation, apoptosis, and more[8]. Macroautophagy, the most researched type of autophagy, is involved in the degradation of protein aggregates, strongly linking it to neurodegeneration[14].

Autophagy has three key stages: initiation, maturation, and degradation[9]. Defects during any stage of autophagy are associated with mutations of ALS-linked genes such as SOD1 and TDP-43[8], which can lead to abnormal protein aggregation[14].

This paper is a systematic review analyzing the role of autophagy dysfunction in sporadic amyotrophic lateral sclerosis in connection to protein aggregation. It will focus on the role genetics play in autophagy dysfunction in sALS, autophagy pathways, and mechanisms. In addition, it will cover dysfunction in autophagy stages during ALS, the role it plays in protein aggregation, bodily stress, and ALS therapeutics targeting autophagy dysfunction.

Genetics' Basis in Autophagy Dysfunction in ALS

There are currently over 40 mutant genes associated with ALS. Any of these genes could potentially overwhelm the autophagy pathway and cause dysfunction, since mutations decrease the stability of protein production within the cell and increase misfolding and aggregation propensity[2]. This section reviews and analyzes the mutant genes SOD1 and TDP-43, both of which have been implicated in sALS[15]; it also covers the role mutations play in affecting autophagy dysfunction in sALS. These genes have regulatory functions when healthy (Figure 1); however, mutations in them can have adverse effects. Disease-causing mutations such as SOD1 and TDP-43 have enabled pathophysiologists to identify and characterize corresponding proteins[15].

SOD1

Superoxide dismutase 1, or SOD1, is a highly conserved cytoplasmic and mitochondrial antioxidizing enzyme, involved in scavenging and converting toxic superoxide radicals into reactive oxygen species (ROS) and hydrogen peroxide. Currently, about 1% of sALS cases are associated with SOD1. However, despite SOD1 being the first discovered genetic link to ALS, it's still widely researched. SOD1 in sALS affects tissues in the spinal cord, and lewy body-like, fibrillized ubiquitination are the characteristic pathologies associated with SOD1-sALS[15]. A study conducted to see if SOD1 was a pathological feature in sporadic ALS came to the conclusion that misfolded SOD1 was present in the spinal cords of patients with not just familial ALS (fALS), but sALS as well[13].

SOD1 is involved in numerous pathways that are affected when it is mutated. The mutant SOD1 associates with the Beclin1-B cell lymphoma 2 (Bcl2) complex to disrupt the activity of Beclin1, resulting in the impairment of autophagosome formation and expansion. In addition, the mutant and misfolded wild-type SOD1 sequesters can impair retrograde transport and

autolysosome formation. When the mutant binds to voltage-dependent anion-selective channel protein 1 and Bcl2, this also impairs mitophagy. Another result of mutant SOD1 is its binding to optineurin, also impairing mitophagy[2].

There is a prominent link between autophagy and SOD1. Early sympathetic stages of an SOD1-ALS mouse model showed impaired degradation of damaged mitochondria through mitophagy, and the first evidence of increased autophagy in SOD1-mutant animals was the high occurrence of autophagosomes, indicating a cellular attempt to decrease misfolded proteins. This is corroborated by the loss of BECN1 in mice expressing SOD1, who showed an impaired autophagic flux, early onset, faster progression of the disease, and a significantly shorter lifespan. Contrastingly, an increase in BECN1 showed the opposite effect: a delay in disease onset, increased animal lifespan, and lowered ER stress[15].

TDP-43

Mutations in the TARDBP gene account for the transactive DNA-binding protein 43, or TDP-43. TDP-43 is a heterogeneous nuclear protein and is a prominent feature of ubiquitinated cytoplasmic inclusions found in numerous tissues in ALS. TDP-43 is an RNA-binding protein involved in RNA metabolism, such as mRNA and miRNA processing, alternative splicing, cellular transport, and stability. TDP-43-ALS – mutations in the TARDBP gene, not counting other gene-associated ALS cases that still involve TDP-3 in ubiquitinated inclusions – makes up nearly 1% of sALS cases, and most mutations take place in the C-terminus of the protein[15].

Mutant TDP-43 impairs autophagosome formation through the ER-Golgi transport and ER-mitochondrial interactions as well as impaired mitophagy by decreasing Parkin[2]. In addition, the TDP-43 deficiency destabilizes Atg7 mRNA and proteins, impairing autophagosome expansion[15]. Mutant TDP-43 also inhibits dynactin and HDAC6, impairing retrograde transport for autolysosome formation. These all contribute to the dysfunction of autophagy[2].

Characteristic pathologies associated with TDP-43-sALS are ubiquitinated, hyperphosphorylated C-terminal fragments. TDP-43 is a major component of ubiquitinated inclusions in the spinal cord, hippocampus, frontal cortex, and glial cells in sALS. TDP-43 inclusions in the motor cortices and spinal cords are found in 97% of fALS and sALS patients, and are associated with many other neurodegenerative disorders[15].

ALS-causing mutations in TDP-43 result in both the accumulation of wild-type TDP-43 and cytoplasmic accumulation of the insoluble TDP-43. Additionally, TDP-43 is not limited to just TDP43-ALS cases – cases that only have a mutation only in the TARDBP gene – as shown by TDP-43 inclusions being present in non-TDP43-ALS cases. Sequestration of TDP-43 in aggregates prevents it from carrying out its function, leading to cellular toxicity. TDP-43 is also involved in autophagy. One of TDP-43's target mRNA codes for the autophagy related protein ATG7, so TDP-43 could potentially regulate autophagy. ALS-causing mutations in TDP-43

impair its ability to bind and stabilize the ATG7 mRNA, leading to autophagy dysfunction. Further evidence linking TDP-43 to autophagy points to the involvement of TFEB[15].

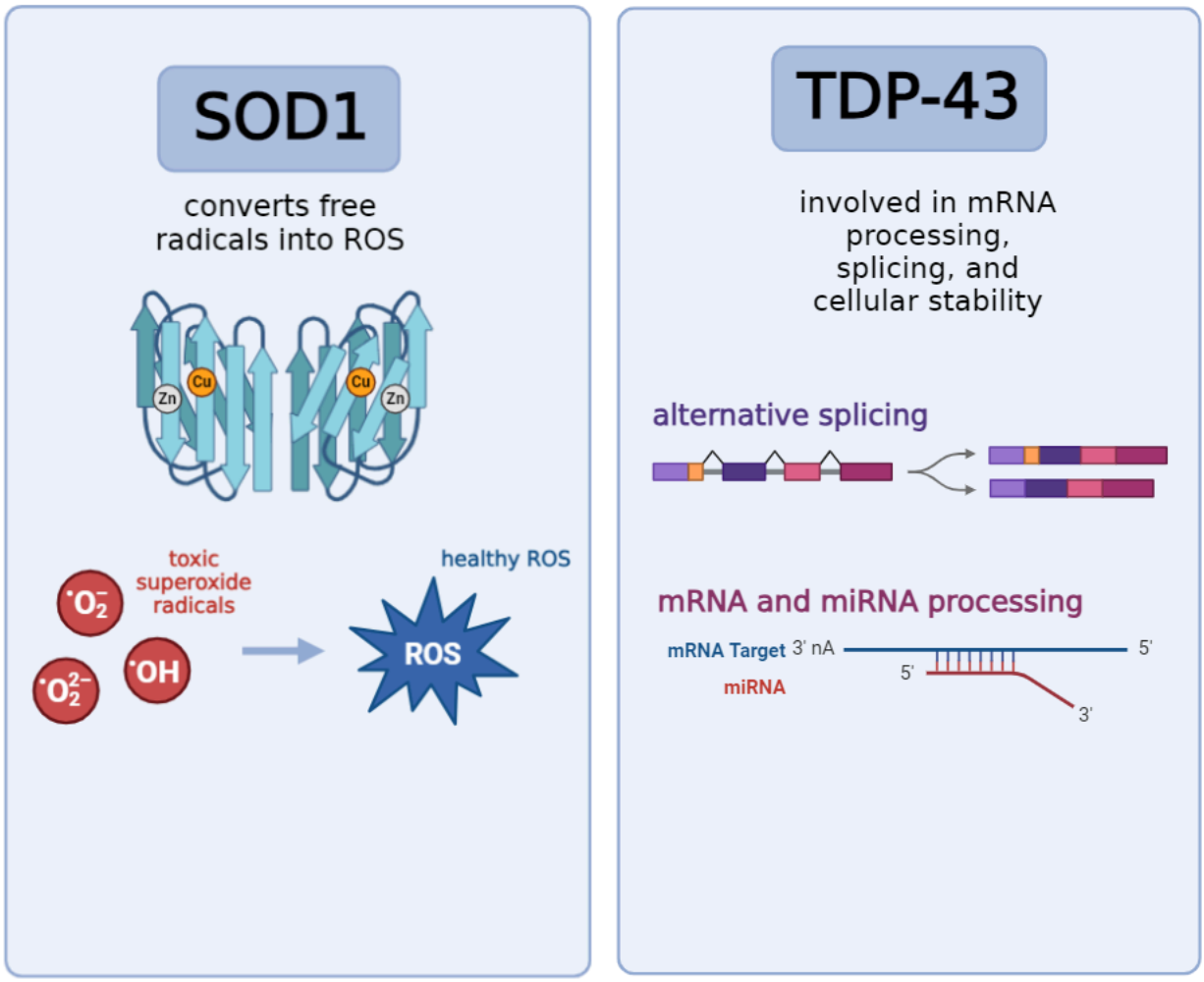

Fig. 1: Shows the role of SOD1 and TDP-43 non-mutated genes and the proteins they code for. Created with Biorender.

Autophagy Mechanisms

Autophagy can be divided into key stages: induction, initiation, phagophore elongation, maturation, and degradation (Figure 2). To initiate autophagy, AMP-activated protein kinase (AMPK) recognizes autophagy-inducing signals[2]. In addition, mutant sALS genes have been shown to affect autophagosomes[9]. This section will be covering macroautophagy, as its involvement with autophagosomes is implicated in ALS.

Induction and Initiation

Metabolic or therapeutic stress leads to induction, which involves inducing a nascent autophagosome regulated by a structure called the phagophore assembly site (PAS). Initiation involves rearranged subcellular membranes to allow sequestration of cargo in autophagosomes[9] and the dissociation of mTOR from the PAS. Typically, mTOR drives cell growth; however, under nutrient starvation or rapamycin treatment, mTOR is activated, allowing the PAS to form. The PAS works with a complex to nucleate the autophagic membrane[6], regulating the formation of a double-membrane cistern called a phagophore[15].

Phagophore Elongation

Phagophore elongation and autophagosome formation is facilitated by 2 ubiquitin-like conjugation systems which are recruited to the phagophore[15]. The system guides phagophore elongation, resulting in maturation of its membrane[5]. After elongation, the phagophore seals around the cytoplasmic substrates to form a double-membrane autophagosome[15].

Maturation and Degradation

The newly-formed autophagosome surrounds a part of cytoplasm[5]. Autophagosomes with cargo for degradation are transported along microtubules to endosomes and lysosomes. Then, the autophagosomes fuse with endosomes or lysosomes to form autolysosomes. This fusion process results in a mature autophagosome. The final step of autophagy is degradation. Lysosomal enzymes degrade the autolysosomes' cargo to maintain homeostasis[15].

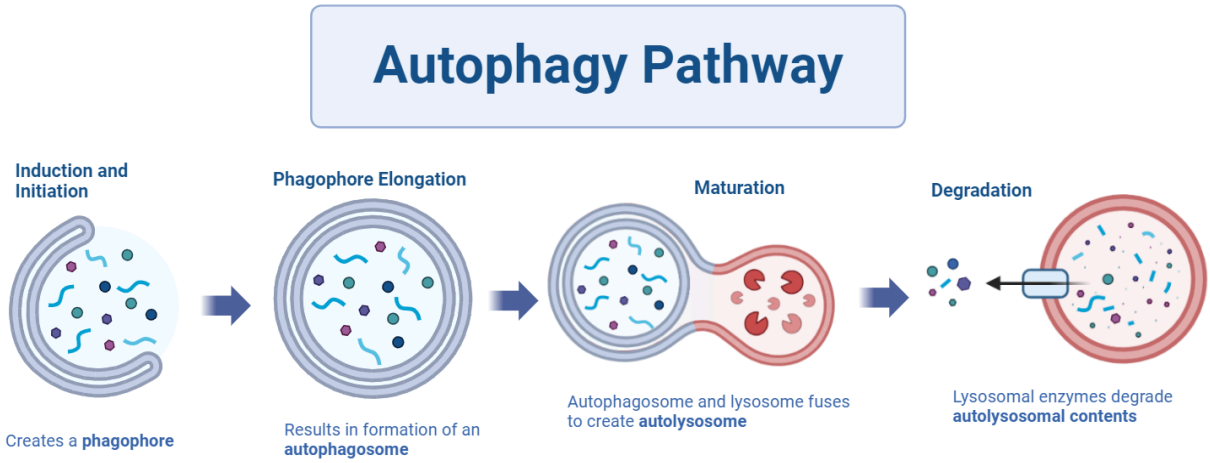

Fig. 2: Depicts the autophagy pathway - induction and initiation (1), phagophore elongation (2), maturation (3), and degradation (4). Created with Biorender.

Autophagy Dysfunction in ALS

In the autophagy process, numerous components have been implicated in neurodegenerative diseases such as ALS. Defects in the autophagy process discussed previously are often the result of mutant genes affecting protein complexes and the regulatory processes involved.

During the initiation stage, the genetic ablation of Atg5 and Atg7, required for autophagosome formation, has been shown to give rise to motor deficits associated with protein aggregation in motor neurons in the CNS of mice. This suggests that defective autophagosome formation contributes to the pathogenesis of ALS[9].

During the maturation stage, defective dynein can disrupt the transport of autophagosomes to lysosomes, leading to protein aggregation. In addition, accumulation of p62 or ubiquitin-positive aggregates results in reduced activity of the DCTN1. It can also be affected by ALS-linked mutations, disturbing the processes that occur during maturation such as axonal transport and fusion[9]. During degradation, mTORC1 can interact with and phosphorylate TFEB, preventing its translocation to the nucleus[9]. ER and mitochondrial dysfunction can also impair the degradation pathway. Additionally, excessive autophagosome accumulation puts stress on the cell and leads to type II autophagic cell death and potentially apoptosis[2]. Autophagy dysfunction leads to waste in cells that does not get cleared efficiently, not only placing more stress on the cell but leading to aggregation. One type of aggregation that is present in ALS is protein aggregation. When autophagy fails to clear out the accumulation of excess protein, the protein begins to aggregate and can have harmful effects, causing ALS and other neurodegenerative disorders.

Bodily Stress

Aside from protein misfolding, cellular biology is affected during ALS (Figure 3), in part due to stress that protein misfolding and mutant genes place on the cells' typical processes.

ER Stress

The endoplasmic reticulum (ER) is an organelle where proteins are synthesized for protein folding. Typically, the cellular response to misfolded proteins is the unfolded protein response (UPR), which decreases the load of unfolded proteins and restores protein homeostasis. However, factors such as nutrient deprivation or missense mutations can enhance protein misfolding, resulting in ER stress; this leads to the accumulation of misfolded proteins, potentially leading to apoptosis. ER stress is shown to be an early pathological hallmark of ALS[15].

Research supports the presence of ER stress in motor neurons of sALS, and shows a link between ER stress and the common gene mutations in ALS: TDP-43, FUS, and SOD1. Mutant

forms of these genes can induce one or all three of the different UPR activators – Protein kinase RNA-like endoplasmic reticulum kinase (PERK), endoplasmic reticulum to nucleus signaling 1 (ERN1), and activating transcription factor 6 (ATF6). Each of these three UPR pathways have been shown to stimulate autophagy to relieve cell stress and in extreme cases, cell death. Despite these regulatory functions, ER stress persists due to the dysfunction of autophagy, persistent and unrelenting protein misfolding, and the UPR pathways inducing apoptosis[15].

Mitochondrial Dysfunction

Mitochondrial dysfunction is prominent in ALS, seen in numerous pathological mechanisms such as impaired oxidative phosphorylation complexes, reduced respiration and ATP synthesis, disrupted calcium homeostasis, and increased ROS production. In addition, dysfunctional mitochondria is ubiquitinated by autophagy receptors. The ALS-associated mutations in the autophagy receptor proteins lead to the disrupted clearance of damaged mitochondria. To summarize, mitochondrial dysfunction is the primary source of ROS production, resulting in the elevation of oxidative stress and in turn, oxidative stress-induced autophagy[15].

Oxidative Stress

Oxidative stress in ALS is caused by the imbalance between the production of ROS and other oxidants, and the elimination of these species by cellular antioxidant defense systems. Since neurons use 10 times more oxygen than other tissues, they are particularly vulnerable to oxidative stress. Additionally, oxidative stress can change the native conformation of proteins, allowing them to misfold and giving them an increasing propensity to aggregate. The source of ROS in autophagy signaling occurs via mitochondrial dysfunction, as discussed in the previous section. Oxidative stress holds an important role in the stress granule formation witnessed in ALS associated with the mutant genes FUS and TDP-43[15].

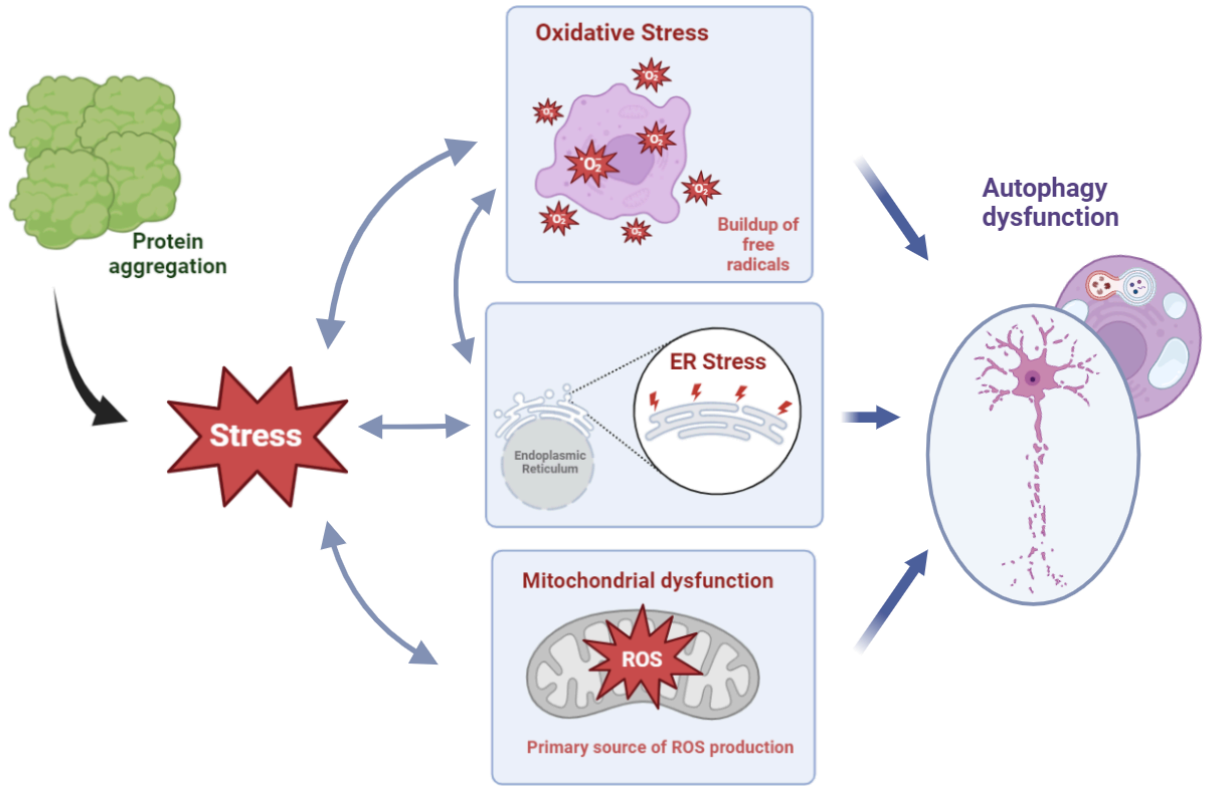

Fig. 3: Demonstrates the interconnectedness of bodily stress. Protein aggregation causes cellular stress. Oxidative stress, ER stress, and mitochondrial dysfunction all contribute to cellular stress and vice-versa as well as leading to autophagy dysfunction. In addition, oxidative stress and ER stress impact each other. These stressors (oxidative and ER stress, mitochondrial dysfunction) result in autophagy dysfunction, thus leading to the inability to clear out harmful proteins which, in turn, degenerate motor neurons. Created with Biorender.

Key Findings

This paper covered the basis of genetics in autophagy, gene mutations, the typical autophagy pathway, autophagy dysfunction in ALS, and the impact of bodily and cellular stress on ALS. The genes analyzed were SOD1 and TDP-43. Both genes code for vital proteins that have all been implicated in the processes relating to autophagy and stress regulation. However, in ALS, these genes are mutated and they form proteins that differ from the native conformation, impacting autophagy pathways and building up in the cell as toxic aggregates, contributing to cellular stress. Bodily stress was also a key factor discussed; the toxic protein buildup resulted in stress on the endoplasmic reticulum and mitochondria as well as oxidative stress.

This paper also covered the standard autophagy mechanisms and introduced some pathways that are negatively affected in ALS. Autophagy usually regulates protein buildup by removing it. However, the excessive protein buildup and dysfunctional autophagy mechanisms lead to an inability for the autophagy pathway to maintain homeostasis.

Therapeutics

There are currently two FDA-approved drugs for ALS: Riluzole (Rilutek) and Edaravone (Radicava). Riluzole decreases excitotoxicity by blocking glutamatergic neurotransmission, non-competitively inhibiting NMDA receptors. Edaravone eliminates free radicals and reduces oxidative stress. However, both drugs are extremely costly, with 50 mg of Riluzole costing $5360 for a 3-month lifespan extension and 30 mg of Edaravone costing $190,880 for the first year of dosage[10]; as a result, research has shifted to searching for more cellular targets[16].

Limitations

Therapeutics for ALS possess many limitations that impact how potential medications are investigated and administered. One major limitation is the blood-brain barrier, or the BBB. The BBB is a selectively semipermeable network of blood vessels that acts as a barrier to the brain. It lets in water, carbon, and some small molecules among other substances; however, it keeps many medications from entering the brain. Many medications are unable to pass over the BBB due to factors such as size. One way scientists are overcoming the BBB is through the use of nanoparticles, which encapsulate drugs. Nanoparticles are able to cross the BBB due to their small size, and they contain drugs conjugated to their surface or encapsulated inside that are released when successfully in the brain[11]. This introduces another limitation: repurposed drugs, such as metformin, are not originally targeted toward the brain, so when they are used for a neurodegenerative disease such as ALS, they struggle to cross the BBB and access the nervous system to affect neuronal autophagy[2].

Another limitation is that treatment with autophagy-modulated drugs runs the risk of side effects, especially if the target does not have a high specificity; room for interference in the therapeutic target's pathway can result in adverse effects[5]. There is a pressing need for more specific and targeted agents when it comes to ALS treatments, as seen when investigating rapamycin[15].

The stage of disease and when the treatment commences and its duration can affect the efficacy of the drug, as some drugs tend to be potent only during a certain stage, or over a certain time period. The stage of autophagy that the drug is acting on is also important – some drugs only show efficacy when targeting a component of a specific stage of autophagy. In addition, results can differ based on the experimental models employed. Some mice models show different effects compared to other models, demonstrating a variability when it comes to administering treatments, further adding difficulty to the treatment of ALS[2].

Therapeutic Implications

There are numerous potential medications currently being investigated (Figure 4). The previously discussed limitations act as barriers to further development in these medications.

Rapamycin can reduce aberrant protein aggregation in TDP-43 and SOD1, as evidence suggests. However, contradictory evidence shows that rapamycin could worsen motor neuron degeneration and lower ALS-SOD1 lifespan. A potential compromise is that rapamycin may have off-target effects when acting upon its pathway that manifests in certain models. This demonstrates a need for targets with higher specificity[15]. Rapamycin does have some drawbacks: nephrotoxicity, cytopenias, and metabolic syndrome[5].

One study investigated the Bax inhibitor 1 (BI1) in neurodegenerative diseases. The study showed that BI1 overexpression could mitigate SOD1-induced apoptosis, nuclear damage, mitochondrial dysfunction, and axonal degeneration. BI1 also prolonged the onset time and lifespan of ALS mice, improved motor function, and alleviated bodily damage. The results also suggested that BI1 could inhibit TDP-43 morphology and stimulate autophagy through TDP-43 interactions. This provided researchers with the knowledge that BI1 overexpression could be an effective therapeutic method to target[17].

Some non-traditional treatment approaches are being explored for ALS as well. Healthy caloric restriction can induce autophagy by reducing glucose and insulin levels, thus inactivating mTORC1. However, caloric restriction can have harmful effects if not tightly regulated and it is time-inefficient. Mimetics have shown to be more promising, as they mimic caloric restriction without the side effects. Mimetics include rapamycin, trehalose, spermidine, resveratrol, and metformin[5].

Future therapeutics that specifically target upstream cellular events could prove beneficial through alleviation of cellular stress. Combination therapy with drugs that upregulate autophagy could be a potential avenue of exploration[15].

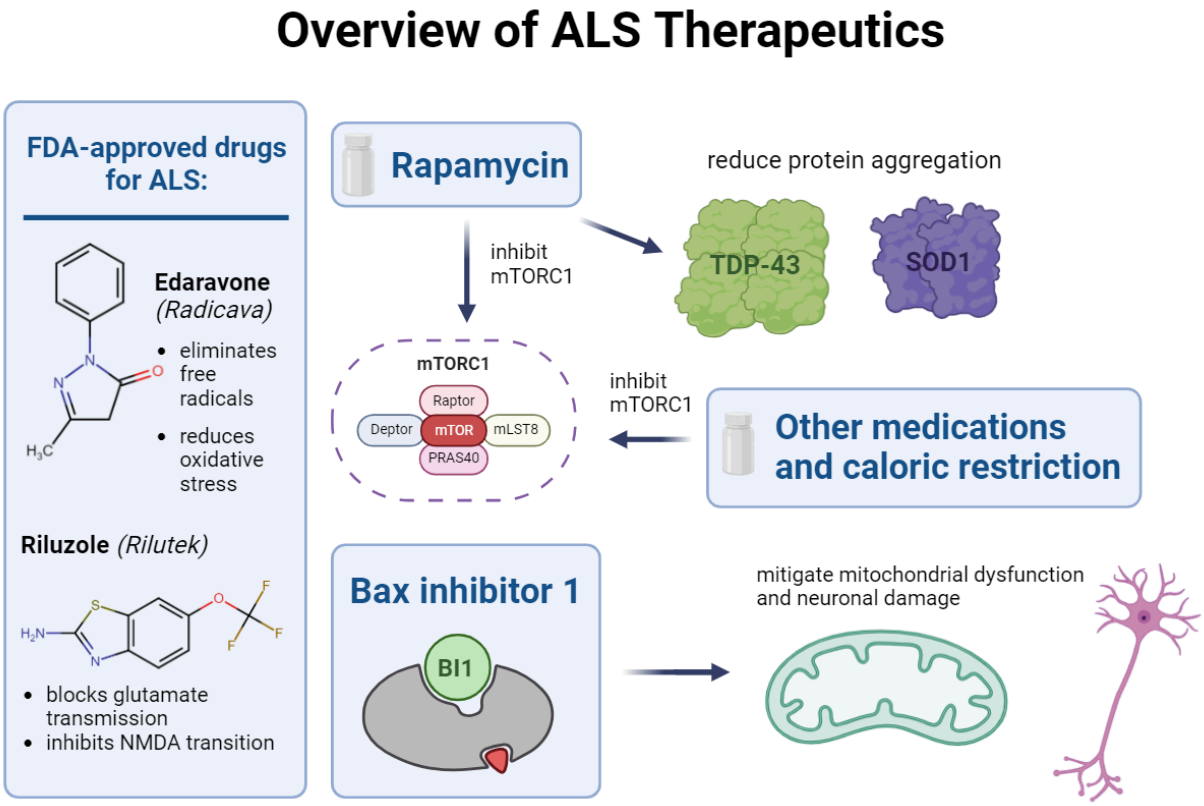

Fig. 4: A summary of discussed ALS therapeutics. There are two FDA-approved drugs for ALS: Edaravone (Radicava) and Riluzole (Rilutek). Edaravone eliminates free radicals, which reduces oxidative stress while Riluzole blocks glutamate transmission, thus inhibiting NMDA transition. There are numerous therapeutics being explored currently, although none are FDA-approved. Rapamycin reduces protein aggregation and inhibits mTORC1. Caloric restriction and other medications also inhibit mTORC1. Bax inhibitor 1 (BI1) could be a potential therapeutic as well, as it mitigates mitochondrial dysfunction and neuronal damage, specifically in the axon.

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Epilepsy in Immature and Mature Brains: The difference in Neurocognitive Impact

Maya Piel

Background

Epilepsy is a disease that affects 1 in 26 people. Over time it can also impact neurocognition, affecting memory, attention, concept comprehension, learning, information processing, and more. While there are a wide range of epilepsies, epilepsy in general tends to have a greater degree of impairment on the neurocognition of immature brains.

In order to understand how epilepsy affects different brain stages, one must understand how these seizures occur and how they impact the brain through its different stages. One cause of many seizures is when brain waves have crossed a threshold based on a stimulus to induce a seizure. In many epilepsy cases, interneuron abnormalities are found, which alter neuron firing, therefore causing seizures with overexcited brains. (Zhu et al., 2018) People with epilepsy typically have a lower threshold, meaning that it takes less brain activity to start having a seizure for a person with epilepsy. (Staff, 2021) In some cases, seizures can occur without any overactivity in the brain that crosses this seizure-threshold. These cases are called non-epileptic seizures (NES). (Staff, S., 2022) The immature brain is more likely to have seizures due to an imbalance between excitation and inhibition, as the immature brains have lower seizure threshold than mature brains. (Holmes, 1997)

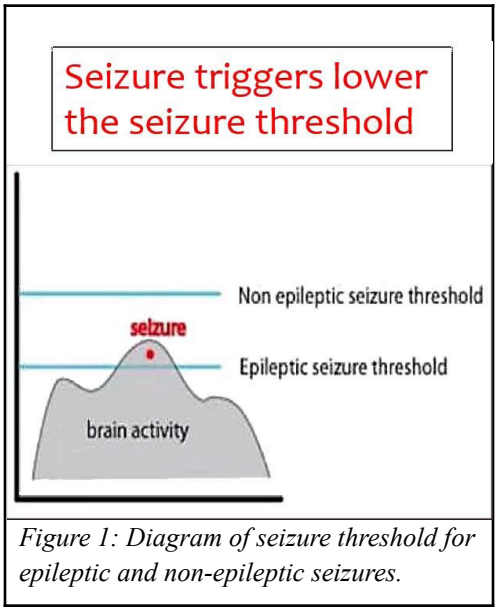

Figure 1: Diagram of seizure threshold for epileptic and non-epileptic seizures.

Immature versus Mature Brains

Immature

One aspect of some seizures is how they have deleterious impacts on synapse connections. These effects are age dependent, meaning it will affect mature brains differently than it will affect immature ones. Synapse connections contain information, and the deletions result in decreased cognition. (Caire et al., 2023) As immature brains have fewer synapse connections and less developed neurons, these deletions have a more damaging impact than those seizures on a mature brain, which already has a larger network. The larger networks in mature brains are less damaged by the deletions as a less developed network. As such, in this case seizures are more damaging to immature brains. (Ben-Ari & Holmes, 2006) Not all epilepsies have seizures that act this way, many have various effects and many don't impact all children or all adults.

Another effect of seizures can be changes to neurogenesis, the process of neurons being formed, and synaptogenesis, the process of synapses being formed. As well, some seizures have an effect of changing excitability/inhibitory balance, network connectivity and temporal coding, which is high frequency firing-rate fluctuations that are found to carry information in a neural code. (Holmes, 2016) This can have a much larger impact on immature brains because of how seizures may impair the formation of these neurocognitive skills. A mature brain that has already developed these skills would not face the same impairment as an immature brain. These are just some of the specific processes that occur due to seizures that impair neurocognitive functions.

As shown in the graph, epilepsy has social, economic, and physical impacts beyond cognition. These lead into daily life and are linked with many typical functions of the working adult. These include personal factors, such as self esteem, which are critical as well. As this web is so interconnected, the effect on both immature brains and mature brains could be life-altering. However, the effects of epileptic seizures in childhood could potentially have impacts that continue on into a patient's adulthood during brain formation. Especially combined with hormones during puberty these impacts could be more damaging to a brain that is not fully formed. (Kerr et al., 2011)

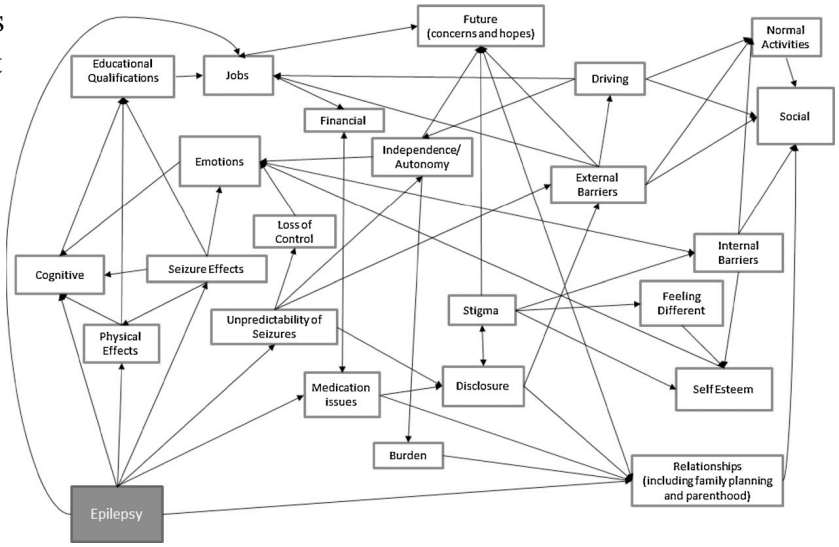

Figure 2: A diagram showing the interconnected impacts that connect to epilepsy.

In an investigation comparing healthy children and children with recent onset

of both idiopathic localization-related and primary generalized epilepsy, the results reveal a pattern of cognitive difficulties for epileptic children.

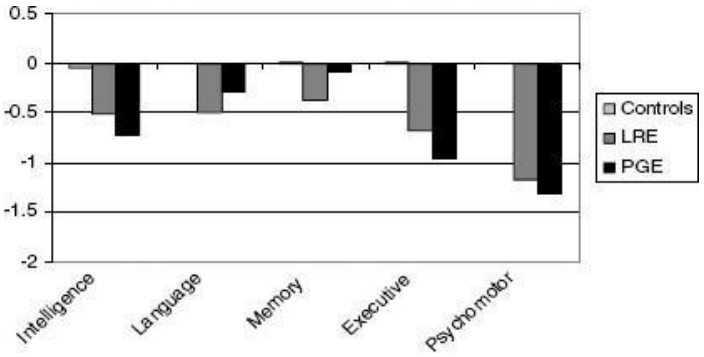

Figure 3: Y- axis is Z score. This graph compares different cognitive skills between healthy children and children with localization-related and primary generalized epilepsy respectively. This shows the damage to cognition due to the epilepsies for immature brains.

This figure compares these two groups and their z-scores, Y axis, to different cognitive functions, X-axis. This explains that both the localization-related epilepsy (LRE) and primary generalized epilepsy (PGE) groups perform significantly worse than controls in intelligence, executive function, and psychomotor speed. LRE differs from controls in language and memory, but not PGE. There are no significant differences between LRE and PGE groups. This expresses the damage done to cognitive functions in children with epilepsy compared with healthy children. (Hermann & Seidenberg, 2007)

In a study about the effect of epilepsy on children's neurocognitive abilities, it was found that children with epilepsy demonstrated more difficulties in understanding false belief ($p < .001$) and intentional lying ($p < .05$) and exhibited more behavioral problems ($p < .05$) than their typically developing peers. Additionally, there was significant data showing that children with epilepsy were worse in attention, executive, verbal, and fine motor tasks ($p < .05$). In this study as well, children with epilepsy showed a positive correlations between understanding of false belief and in executive ($r = .6$, $p < .05$), verbal ($r = .45–.49$, $p < .05$), and visuospatial, visual perception of spatial relationships between people/objects, skills ($r = .34–.48$, $p < 0.01$). (Raud et al., 2015)

In other clinical studies using rats, it also shows that seizures have a more damaging impact on the neurocognition of more immature brains. The method they used to determine the effect of age on seizure-induced cognitive impairment with rats was by Morris water maze, radial-arm water maze, open field, and active avoidance. These tested synaptic strength, network excitatory, and inhibitory function using long-term potentiation (LTP), an increase in synaptic strength after

high-frequency stimulation of a chemical synapse, and paired-pulse facilitation/inhibition. The conclusions of the tests showed that recurrent seizures during development were associated with long-term behavioral deficits in learning, memory and activity level, as well as impaired synaptic efficiency. As such it is shown the damaging effect that epilepsy has had on immature brains that has led them to lack neurocognitive skills that are developed in childhood. (Karnam et al., 2009)

Mature

In some cases however, there is evidence that suggests that immature brains are actually less affected by seizures. Brain damage received from seizures of the same duration and intensity on differing age stages are said to have had more impairment in mature brains. (Holmes, 1997) Additionally, in a research study examining older adults with epilepsy, all above 60, and their cognitive function, the research found that older adults performed worse in all cognitive areas. As well as putting them more at risk for different types of dementia. (Martin et al., 2005) It is also significant to recognise that these cited studies are from the late 1990s and early 2000s, epilepsy as a field is hugely fast moving and the data and takeaways from these studies may no longer represent the best understanding we have about epilepsy. As well, these cases had small and similar sample sizes, which is a notable limitation. (Novak et al., 2022)

Future Ideas and Treatments

As mentioned, epilepsy as a field is fast growing, with new discoveries in research being uncovered all the time. Due to how the different types of epilepsies affect the world population, and with how many people are affected, work is being done to learn more about how to control and cure these epilepsies at every brain stage. It’s important to realize that these different types of epilepsies mean that they do not all have the same effects on each brain.
One of these treatments is transplantation of GABAergic interneurons/progenitors from embryos. The seizure suppression works as follows: designer receptors exclusively activated by designer drugs (DREADDs) are used to dissect neural circuits responsible for behavior that eventually results in seizures.

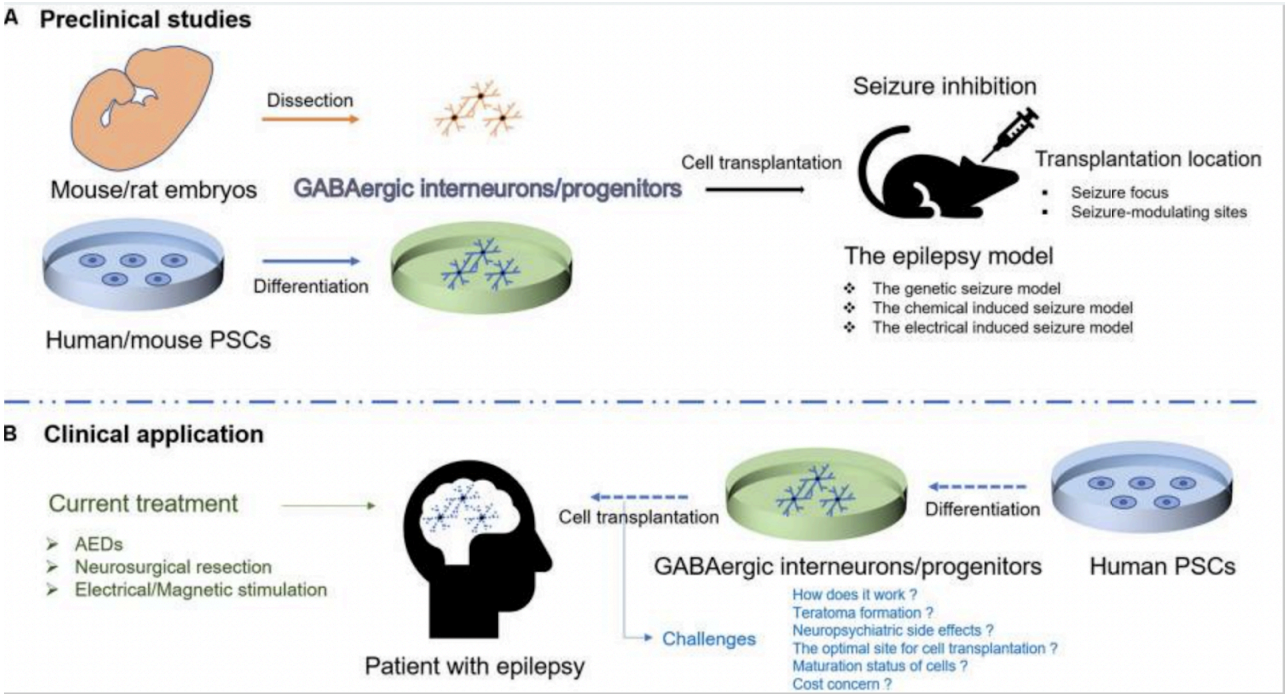

Figure 4:
(A) Transplantation of GABAergic interneurons/progenitors from mouse/rat embryos or human/mouse PSCs into the location of the seizure focus to create a epilepsy model.
(B) Human PSC-derived GABAergic interneurons/progenitors would be a promising cell source for transplantation to target epileptic foci in humans though the challenges exist.
(Zhu et al., 2018)

Illustration B explains the clinical application of how treatments such as antiepileptic drugs (AEDs), Neurosurgical resection, and Electrical/Magnetic stimulation differ from the GABAergic interneurons/progenitors as they present challenges and unknown risks for the patient. Additionally, it is unknown if it has different effects on different brain stages. (Zhu et al., 2018)

This is only one of the upcoming treatments for epilepsy, many more are emerging. People all around the world suffer from epilepsy, with differing degrees of severity. There is a need for treatments for both immature and mature brains. The different impacts that medication can have on brain developmental stages means that not all medication works for everyone, and there is a need for research about understanding the effects and long term ramifications.

Conclusion

As shown, epilepsies in general tend to have a greater degree of impairment on the neurocognition of immature brains. The threshold for epilepsies are lower for immature brains and therefore easier for immature brains to have a seizure. In addition, neurocognitive impairment on immature brains has lifelong effects due to how immature brains are developing critical parts of the brain whilst mature brains are fully developed.

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AI In Early Disease Detection: Is it Successful or is AI a False Hope?

Anish Rangarajan

Fundamentals of Early Disease Detection and Artificial Intelligence and how they collaborate

"With the increase of pandemics there it is mandatory we need a form of automation" (Allam, Dey, and Jones 13). With so many health problems in today's world, such as chronic diseases and sudden pandemics, there is an urgent need for better predictive technology. One vital advancement in modern medicine is early disease detection, which has the potential to save lives and improve healthcare significantly. Early disease detection refers to the practice of identifying diseases at their initial stages, often before a patient faces symptoms. By using advanced technology and screening methods, doctors can catch illnesses sooner, leading to more successful treatments and better patient outcomes.

Early disease detection is crucial because it allows patients to receive treatment as soon as possible, often leading to better outcomes and higher survival rates. It can also help reduce healthcare costs by decreasing the need for more unnecessary and expensive treatments required at advanced illness stages. Additionally, early disease detection helps prevent the spread of contagious diseases, protecting public health and saving innocent lives. Due to the importance of early disease detection, advanced technologies are crucial to speeding up the process. A technology that has this capability is Artificial Intelligence. Artificial Intelligence or AI is a technology that allows computers to emulate a human's intelligence while containing an immense amount of knowledge.

In this review I will examine how AI can help with early disease detection, how AI is currently used in the medical environment, the previous downfalls of the system, how valid relying on AI is, and the use of AI during a recent global pandemic, COVID-19.

AI's Assistance with early disease detection and how is it currently used.

AI has become vital to numerous fields, offering transformative capabilities that elevate the speed and accuracy of processes. AI is used in finance to predict stocks and in math to aid with equation solving. These advancements display AI's potential to automate and innovate in many STEM fields.

Moreover, AI has transformed the world of medicine as well. Analyzing medical images with precision and speed displays that training a machine is far more successful than a human's

capabilities. Whether it's seeing small cells in lung tissue that humans can't or discovering new virus cells that humans aren't even aware of, AI can also simplify a doctor's workload by developing personalized treatment plans tailored to a patient's specific needs. AI can look at certain symptoms and understand what the potential cause is while it will take doctors longer to do them in bulk.

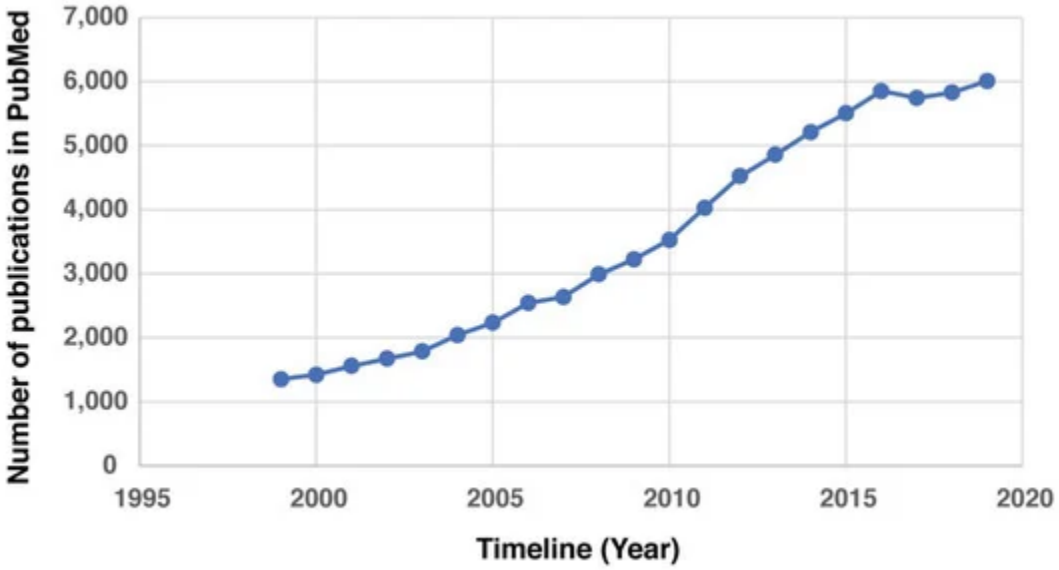

Figure 1: *Increase of AI in publications of PubMed (Allam, Dey, & Jones, 2021*)

It is evident that AI in medicine is a recipe for success but what about preparing patients for their future? AI is helpful by managing and analyzing large volumes of a patient's medical data and then identifying patterns and anomalies that could line up and be a potential disease. As previously introduced, AI can also examine medical images like X-rays, CT scans, and MRIs to spot even minor conditions of a disease that the human eye can miss. A system some hospitals use is *electronic health records* (EHR) to manage clinical and operational needs. Using AI, EHRs can be deeply analyzed to recognize a pattern of causes for a disease. Using genetic, environmental, and lifestyle factors, analyzing EHRs with AI will be a swift and successful process for studying and predicting possible risks. While humans can accomplish the same thing of predicting disease occurrence to an extent, AI is far superior due to the speed, accuracy, and on average how long it takes to teach a human vast amounts of medical knowledge.

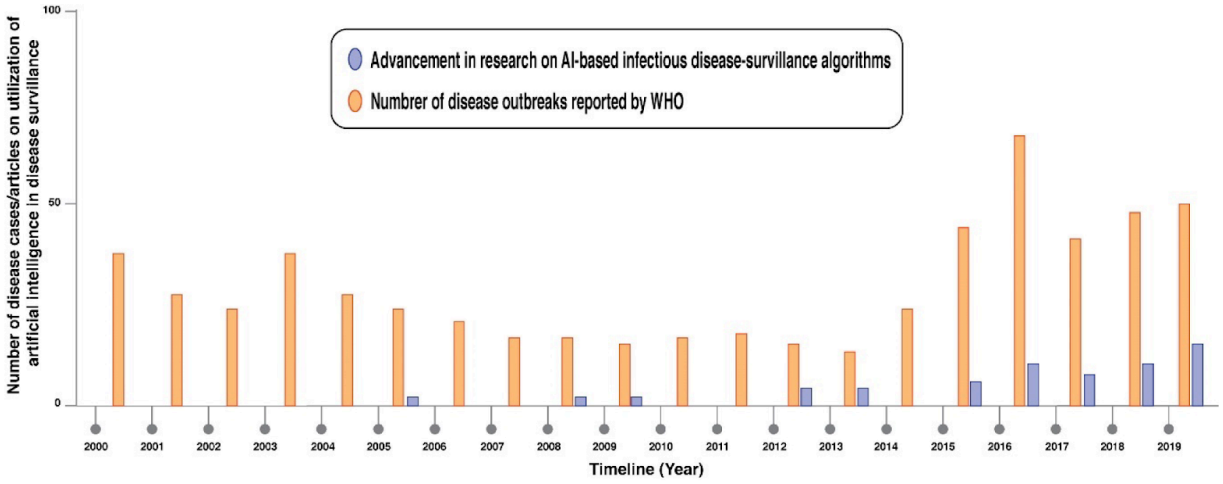

Figure 2: *Usage of AI in predicting all diseases (Allam, Dey, & Jones, 2021)*

Potential downfalls of the current health industry

Although current healthcare departments are effective, relying on humans can become problematic and detrimental at times. Harvard Business Review states, “No matter how much you enjoy your job, there is a higher chance of making mistakes if you work long hours” (Carmichael 2015). Regardless of someone's interest and perseverance, it is inevitable that at some point in time, mistakes can be made. When it comes to someone’s health making mistakes can become disastrous. In turn, relying on AI, a system without feelings or wear down of the brain, is far more reasonable, given that someone’s life is on the line.

Another issue with modern healthcare in today’s world is understaffing and the cost of hospital treatment. Patients with harmful conditions often have to wait for an available doctor which is unfair for the money they will eventually pay. Costs can also be unruly and not justified for the treatment. For example, hospitals may charge hidden fees like a service fee or a facility fee. AI can help mitigate this by preventing additional service or facility fees since it is only going through on the device. Over time, these charges add up simply making healthcare unaffordable. Lastly, patients may face biases from certain medical professionals which can lead to an uncomfortable experience.

Both, the imperfection of humans and the unjust truth of hospitals can be resolved by automating the healthcare system. AI acts as a concise and unbiased doctor less likely to make mistakes. Although attaining perfection is impossible a trained machine is far more successful compared to a seasonal professional. The solution to the flawed medical system and its reliance on top-of-the-line professionals can be simply fixed by AI.

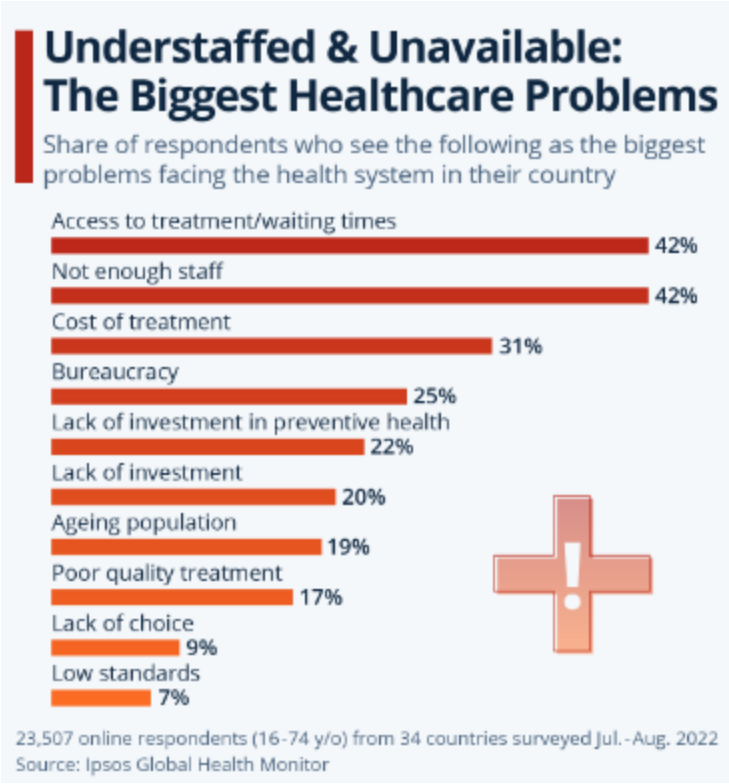

Figure 3: *Healthcare's biggest issues (Richter, 2023)*

How effective is it to rely on AI?

Integration of AI comes with various techniques for early disease detection and healthcare, but along with the assistance comes a few drawbacks. For instance, AI in healthcare stores bulk amounts of sensitive patient data. Once this data is on the cloud extra security is required to protect a patient's personal information. Another issue is the time and experimentation necessary to implement a foolproof AI system. This requires vast amounts of money, as well as an abundance of healthcare professionals to look over and break down a patient's needs, and even new technologies. While the idea of a fully automated system seems wonderful it's impractical due to the time and money needed to pull AI integration off in hospitals. Finally, there are some circumstances where a human's input is more valuable compared to stone-cold facts. When addressing a person's feelings other humans are better suited as computers don't feel a sense of sympathy. Overall, the lack of security, resources, and sympathy are preventing the transformation of healthcare systems.

Putting AI to the Test

A recent example of AI's use in early detection of disease was during the COVID-19 pandemic. AI was used during the COVID pandemic not only in medical fields but also in real-world situations by processing and analyzing data from airlines, social media, and public health. While AI in health is important many health research companies focused on trends outside of healthcare to monitor the rapid spread of COVID.

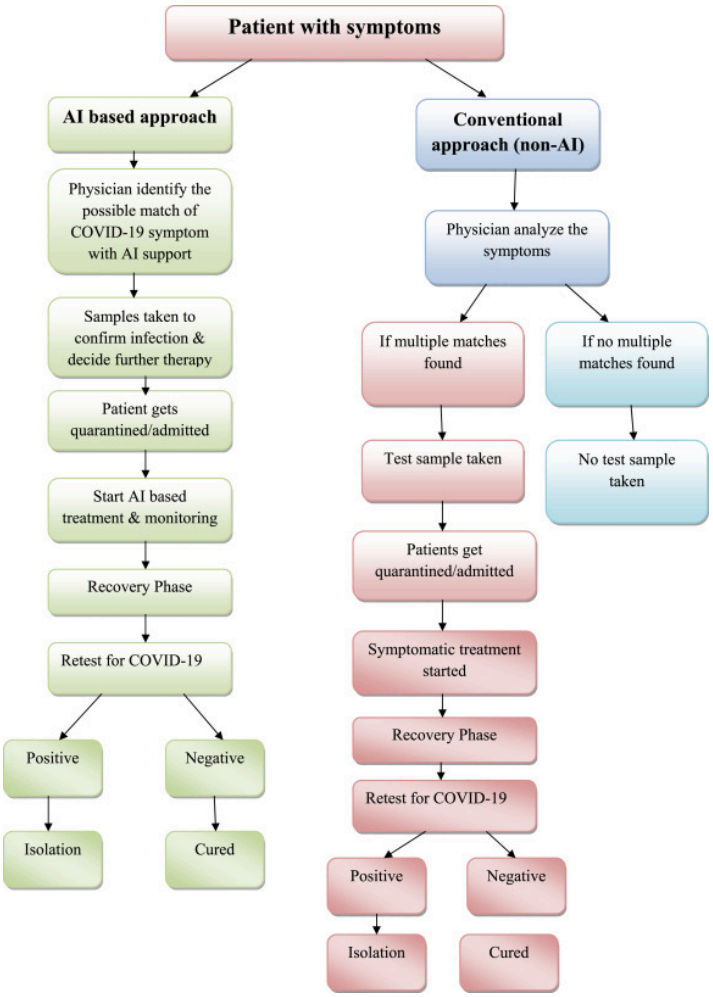

Figure 4: *A COVID patient's treatment with and without AI (Vaishya, Javaid, Khan, & Haleem, 2020)*

For example, a Canadian AI model called *BlueDot* was one of the first to detect the COVID outbreak in Wuhan, China. "*BlueDot* recognized a small group of suspicious pneumonia cases in Wuhan, China" (Stieg 2020). *BlueDot* then detected COVID-19 nine days before the World Health Organization (WHO) and their public statement. How could they beat the official WHO to a global pandemic? They analyzed social media trends and unusual pneumonia cases in the news. Connecting the patterns led them to a new disease, COVID-19.

A more familiar concept that has been previously introduced is deep analysis of CT scans and detection of COVID-19. Conventional Neural Networks or CNN are used to complete this task with absolute precision. A CNN called *VGG16* is a deep transfer learning architecture that uses knowledge from an already trained deep neural network and uses it in aiding with a specific task, in this case, anomaly detection in medical images. Studies show that the " VGG16 model had a high accuracy and speed rate in analyzing X-ray images." (Bhatt, Carretero, Martinez, Khandhar, Visuña, and Yang). *VGG16* was nearly perfect in detecting potential diseases in the lung region. Other models also detected various virus cells in the nose and mouth, areas notorious for carrying potential disease cells.

AI played a crucial role in disease detection during the COVID-19 pandemic by improving the speed and accuracy of diagnosing the virus. AI-assisted in identifying patterns and predicting outbreaks, which allowed for better use of resources and improved patient health. As introduced above, seeing a rise of pneumonia cases in Wuhan led to the discovery of COVID-19. AI is not only vital to be implemented into healthcare but the prediction of disease as well due to the edge it can provide on keeping the world safe. Automation is often better than other strategies because it substitutes relying on humans with important analysis, while still allowing medical professionals to carry on with diagnosis. I think AI will benefit medical agencies and the world, as it decreases the hard work required of medical professionals and is almost always accurate. AI's future in disease detection requires hospitals and facilities to implement this

technology and experiment with a variety of tests to make it safe for patient use. Artificial intelligence has come a long way in a short period, so this technology's potential applications are exciting.

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Brain-Computer Interface: Future Clinical Treatment for Motor Impairment?

Steven Ren

Edited by: Mehreen Zakaria

Introduction

Brain-computer interface (BCI), first developed in the 1970s, is a class of neurotechnologies developed for medical assistive applications in the clinical field (Lance et al., 2012), intended to provide direct communication between the human brain and an external device without muscular stimulation. Using a computer-based system to receive, analyze, and translate brain signals into motor commands (Figure 1) (Shih et al., 2012), BCI has been commonly used for motor impairment, classified as "partial or total loss of function of a body part," otherwise known as a paralyzed or locked-in state (International NeuroModulation Society, 2021). In the U.S., approximately 39 million Americans have motor impairments (Inclusive City Maker, 2022). Some neurological conditions affected by motor impairment that BCI has assisted with are amyotrophic lateral sclerosis, quadriplegic cerebral palsy, and chronic stroke. While BCI has aided several motor-impaired patients to successfully restore motor movement in parts of their body, there are consequently drawbacks to the usage of such technology including medical risks regarding invasive BCI and problems around data processing and privacy. This literature review provides a history and overview of the benefits and drawbacks of BCI in the clinical field with emphasis on BCI as a promising clinical treatment for motor-impaired patients.

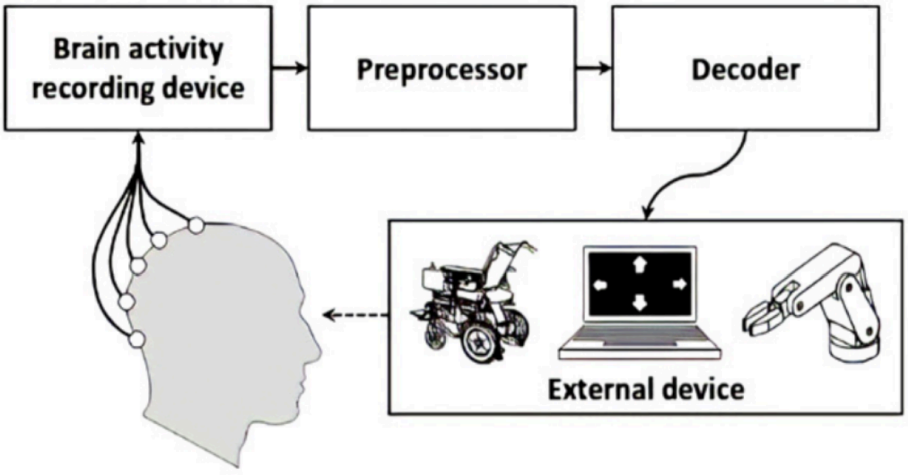

Figure 1: General BCI process (Anitha et al., 2019).

History

When it was first developed, BCI was envisioned as a potential technology for replacing neural rehabilitation and assistive devices (Lance et al., 2012; Saha et al., 2021). BCI is further classified as invasive

and noninvasive BCIs (Figure 2). Invasive BCIs involve surgically implanting electrodes directly into the brain tissue (Birbaumer, 2006) and using electrocorticography (ECoG) to measure neural activity from the brain's cortical surface (Todaro et al., 2018). Noninvasive BCIs involve implanting electrodes on the scalp (Birbaumer, 2006) and using electroencephalography (EEG) to measure electrical signals of neural activity (Blinowskwa et al., n.d.), or magnetoencephalography (MEG) to measure the magnetic field of neural activity (Singh, 2014). These applications were primarily used for improving the quality of life for specific clinical populations including patients with prosthetics, wheelchair, or those classified as in a locked-in or paralyzed state (Lance et al., 2012). Currently, the focus of BCI still remains on providing voluntary movements for motor-impaired patients as it overall improves the quality of life for these individuals.

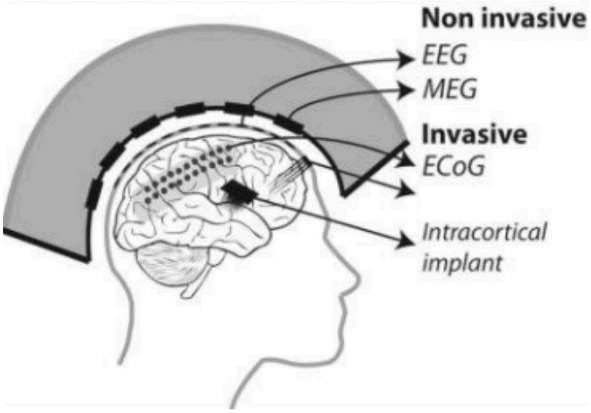

Figure 2: A visual indicating where invasive and noninvasive BCI applications reach (Gani, et al., 2021).

BCI Benefits

a. Patients with amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disease of unknown causes (Lewis, 2017). In ALS, the nerve cells controlling muscle movement (motor neurons) degenerate (Birbaumer et al., 2006), ultimately leading to complete paralysis (Lama, 2022). ALS has no cure, and one problem ALS patients face is the insufficiency of existing treatments unabling to address long-term ALS conditions.

However, BCI has shown to be an effective treatment for ALS patients. One example includes a complete locked-in patient identified as K1 in a study conducted by Dr. Niels Birbaumer and Dr. Ujwal Chaudhury (Lama, 2022). This patient had lost the ability to walk, talk, and control his eyes. Yet, soon after implanting a microelectrode device into his brain, he successfully used neurofeedback, a BCI method that uses EEG to control brain waves and activity (Mahrooz et al., 2024). He was not only able to select letters to spell out words and phrases, but also gave clear instructions on how he should be cared for, emphasizing the broad applicability of BCI (Lama, 2022). Another example comes from a late-stage ALS patient, who was only able to communicate using eye movements (Vansteensel et al., 2016). Shown in Figure 3, electrodes were placed onto the patient's brain that interacted with other BCI components,

allowing the selection of specific letters on a tablet through brain signaling (Vansteensel et al., 2016). The patient performed several spelling tasks with significantly high accuracy, as seen in Figure 4 (Vansteensel et al., 2016). Both patients with locked-in ALS conditions were shown to effectively utilize BCI application to carry out desired tasks even when they were unable to move. Such results demonstrate high potential for BCI as a treatment for ALS patients as well as many other patients at various ALS stages.

b. Patients with quadriplegic cerebral palsy

Cerebral palsy (CP) is a neurological disorder that is common in childhood and associated with lifelong motor disability (Cans et al., 2008; Morgan et al., 2018; Zauderer, 2023). CP affects various parts of the body including the arms, legs, and face; some CP patients also have difficulty with speech, vision, or hearing (Zauderer, 2023). CP has no cure, and both current

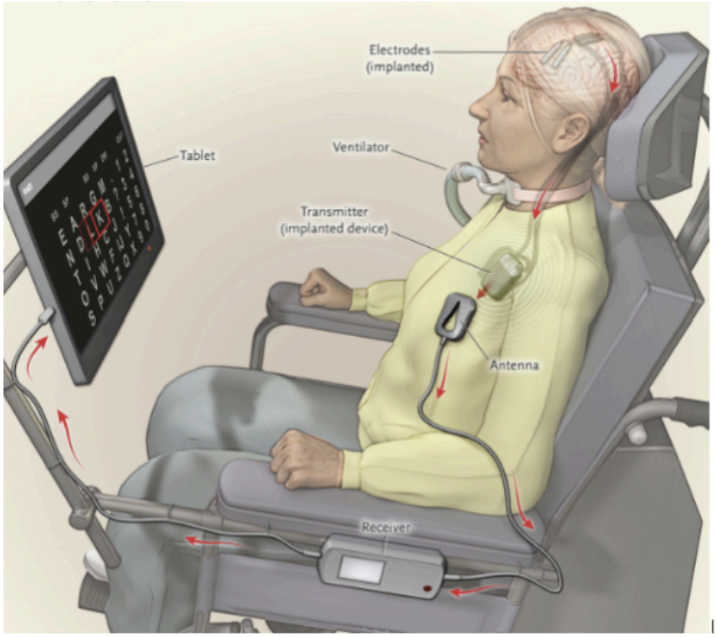

Figure 3: Components of BCI system used for the late-stage ALS patient.

Patient shown to be set up with a BCI system that allows her to select specific letters on a tablet. This BCI system includes two electrode sheets with electrodes placed on the surface of the brain; a transmitter device that senses and records electrical signals; and an antenna and receiver that carry the brain signals to the tablet, which allow the patient to manipulate the screen (Vansteensel et al., 2016).

medicinal and therapeutic treatments are temporary and do not effectively address severely paralyzed CP patients.

However, recent studies have shown BCI to be an effective treatment for CP. In a noninvasive BCI program for children with severe neurological disabilities, including quadriplegic CP (QCP), results have shown successful performance of utilizing BCI to perform specific tasks (Jadavji et al., 2022). The study's method involved the use of an EMOTIV EPOC+ headset, a form of EEG recording (Figure 5A), and recording of specific regions of the brain with electrodes (Figure 5B). Participants wore the EPOC+ headset and were asked to perform several tasks, including floating a cube, racing cars, and Sphero painting (Figure 6A-E). All participants that completed the program demonstrated successful BCI performances. For example, patient 7 had no functional use of his limbs and no verbal communication, but after attending months of weekly BCI sessions, he demonstrated voluntary control during all EPOC+ tasks and had his first opportunity to create independent work (Jadavji et al., 2022); patients with

similar conditions also displayed significantly improved motor control, something which they could have never done before. These findings echo the potential benefits that could come from the usage of BCI as a more effective therapeutic treatment for CP patients.

Figure 4: Spelling performance results for the late-stage ALS patient.

Spelling performance from 44 spell runs. Mean percentage of correct and incorrect responses are indicated: 87±7% correctness and approximately 10±5% incorrectness (Vansteensel et al., 2016).

c. Patients with chronic stroke

Stroke is classified as a neurological deficit caused by vascular injuries to the central nervous system (Fajri et al., 2024) that may result in plegia (paralysis). Current treatments for stroke-induced paralysis lead to complete motor recovery for only less than 15% of patients (Hendricks et al., 2002), but BCI has been shown to vastly improve such motor impairments, as shown in a recent study of eight adult patients with chronic hand plegia (Buch et al., 2008). MEG measurements, representing brain activity evoked by the patients' intent to move a mechanical orthosis (a device used to correct limbs or the spine) attached to the paralyzed hand (Figure 7), were used to train patients to control the orthosis via BCI. Six out of eight patients displayed significant motor improvement over the period of BCI training and were able to achieve control of the orthosis (Figure 8A-B), demonstrating how BCI can effectively minimize motor impairments in severe conditions such as stroke.

Figure 5A: EMOTIV EPOC+ headset.

An image of an EMOTIV EPOC+ headset used for noninvasive BCI testing in the pediatric BCI program for children with severe neurological disabilities (Jadavji et al., 2022).

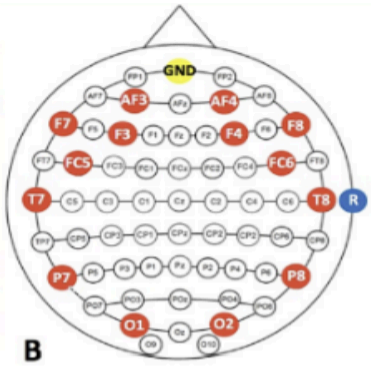

Figure 5B: Diagram representing the general location of electrodes placement.

The red circles indicate electrodes that detect brain activity; the yellow circle indicates ground electrode that is placed on the forehead of the patient to cancel out foreign electrical disturbances; the blue circle indicates the reference electrode that can placed on either side of the patient's earlobes to provide a battery source (Jadavji et al., 2022).

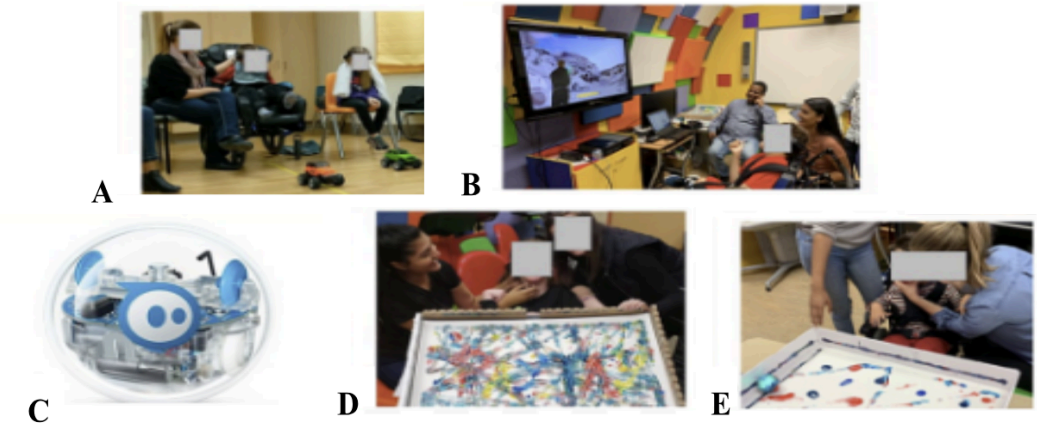

Figure 6A-E: Images showing tasks performed by the children in the pediatric BCI program.

Figure 6A shows participants racing with remote control cars. Figure 6B shows participant performing BCI gaming. Figure 6C displays a Sphero SPRK+ robot which was used to create BCI paintings as shown in Figure 6D and 6E (Jadavji et al., 2022).

BCI Drawbacks

a. Medical risks

Invasive BCI has been a major concern for BCI treatments. Currently, the database of invasive BCIs for communication purposes in paralyzed patients are insignificant to address their effectiveness, and many patients are unwilling to agree to implantation treatments as long as noninvasive BCIs are available (Birbaumer, 2006). Furthermore, the practice of surgically implanting electrodes into the brain tissue raises many problems including causing damages to nerve cells and blood vessels, leading to potential infections (Maiseli et al., 2023). Biocompatibility is also factored in as the body may reject the implant (Maiseli et al., 2023). Additionally, possible formation of scar tissues can form after surgery, potentially degrading the quality of acquired brain signals (Maiseli et al., 2023).

While invasive BCI treatment poses risk factors, many companies and neuroscientists have been developing new BCIs to mitigate these problems. Wyss Center has developed a fully implantable invasive BCI called ABILITY, which contains biocompatible materials, allowing long-term implantation and home usage (Wyss Center, n.d.). Moreover, ABILITY implant is also

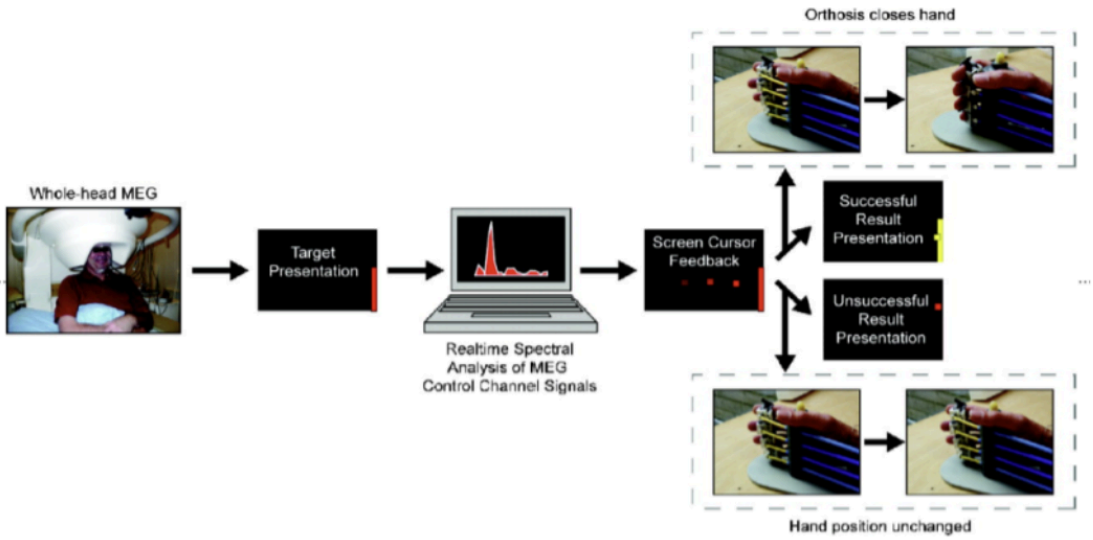

Figure 7: A diagram of BCI application on patients with chronic hand plegia.

Patients were seated with their head centrally positioned within the sensor array and a mechanical orthosis attached to the plegic hand (all fingers excluding the thumb). Orthosis had 2 possible positions: hand-opening (top left image) or hand-grasping (top right image). Patient's goal was to manipulate the screen cursor to touch the target by controlling the Mu rhythm (a type of emitted brain wave that is measured through MEG) amplitude after cursor reaches the right edge of the screen in order to control the orthosis. If successful, the target will turn from red to yellow indicating hand transitioned from opening to grasping, and unsuccessful when the color remains the same, indicating no change in hand positioning (Buch et al., 2008).

connectable to various electrodes, providing broad applicability of neural data acquisition (Wyss

Center, n.d.). Even though current invasive BCIs do not address all aspects of implantation risks, companies and neuroscientists are continuing to develop newer BCIs to solve these issues.

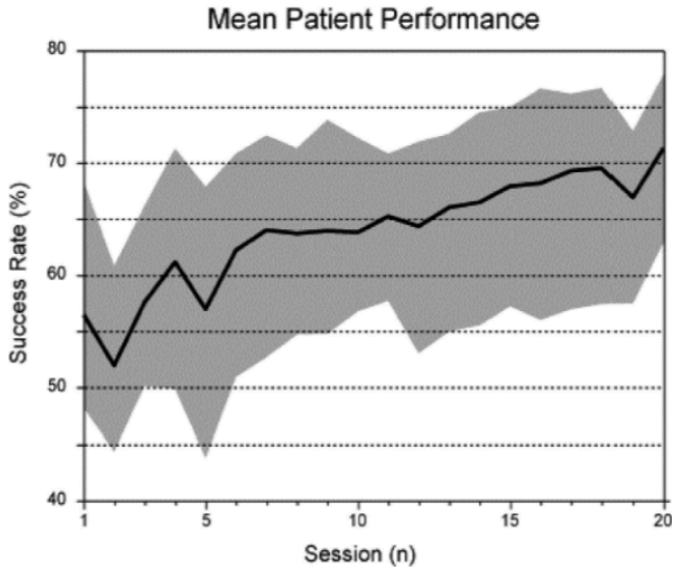

Figure 8A: Data on average success rate as a function of training session.

Average success rate means patients were successful at contacting the target with the cursor or producing the requested Mu rhythm amplitude. The total number of training sessions for each individual was unique and was resampled to 20 sessions. Shaded gray area represents the 95% confidence interval of the median (dark gray) estimate (Buch et al., 2008).

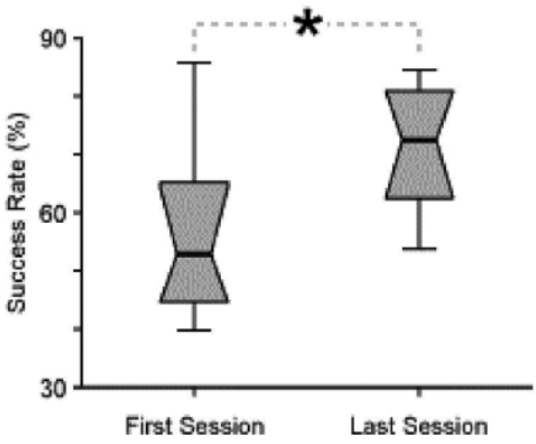

Figure 8B: Boxplot data on pre- and post-training sessions

First session median and interquartile range were 52.84±20.59%; last session median and interquartile range were 72.48±18.36% (Buch et al., 2008).

b. Data processing and privacy

Accurate data processing has been a major problem for BCI. However, recent advances in neurotechnology have been able to address this issue. One solution is the integration of deep learning (DL), a type of artificial intelligence, into BCI (Forenzo et al., 2024). This allows the BCI system to accurately decode larger and more complex datasets (USC Viterbi, 2023), making it suitable for decoding mass quantities of neural activities. DL has also shown successful results in many other fields that require complex data modeling (USC Viterbi, 2023), overall making it a promising addition to the improvement of BCI data processing.

BCI application also lacks specific standards, resulting in unrestricted access to the brain data (Maiseli et al, 2023). However, various policies have been proposed to address this concern. One proposal to protect data privacy is enforcing more granular consents (Jwa & Poldrack, 2022), allowing BCI users to be fully informed about the collection and processing of their data. Additionally, regulations also exist to prohibit illegal use of neural data. The Federal Trade Commision (FTC) has the authority to inspect users' data stored by neuroscience companies,

punishing those that fail to comply (Jwa & Poldrack, 2022). These countermeasures effectively provide privacy measures for BCI application, further pushing BCI as a safe treatment method for motor impairment.

Conclusion

To conclude, BCI serves as an effective treatment for motor-impaired patients suffering from various kinds of neurological conditions like ALS, QCP, and chronic stroke. Even though many issues are encountered with BCI treatment, several neuroscience companies and neuroscientists have been working on solutions to address these concerns including developing tailored BCIs to mitigate these problems. As neurotechnology continues to advance, more applications of BCIs can potentially enter the clinical field, reaching a larger population of clinical patients and serving as a treatment for other neurological conditions.

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Nurture, Nature, and Nuance:

How Epigenetics is Reconceiving the "Nature vs. Nurture" Debate

Nana Ama Sam

"In the real world, there is no nature vs. nurture argument, only an infinitely complex and moment-by-moment interaction between genetic and environmental effects." The discussion of nature vs. nurture has been around since the 1800's, first used by Francis Galton, an English Victorian polymath from the mid-1800s. It stems from his publication of *English Men of Science: Their Nature and Nurture,* where Galton claims that traits like intelligence and various mannerisms came from hereditary factors. As the 20th century approached, the debate would continue to be a pressing subject but would soon reach a breaking point around the start of the 21st century. The breaking point? The realization that it should be nature and nurture. With that, the implication of epigenetics would come in. Epigenetics is the process that modifies gene activity without affecting the DNA sequence, resulting in alterations that are transferable to offspring cells. It is key to research and put into motion the question of how much epigenetics affects the conversation of Nature vs. Nurture because the concept of epigenetics provides the link between nature and nurture by showing how inheritable traits can be disfigured and reshaped through environmental influences. The reveal of a complex dynamic between nature vs. nurture because of epigenetics upends the conversation that the way a person develops is solely based on their "nature" or "nurture" and puts into heavy consideration how the two interact.

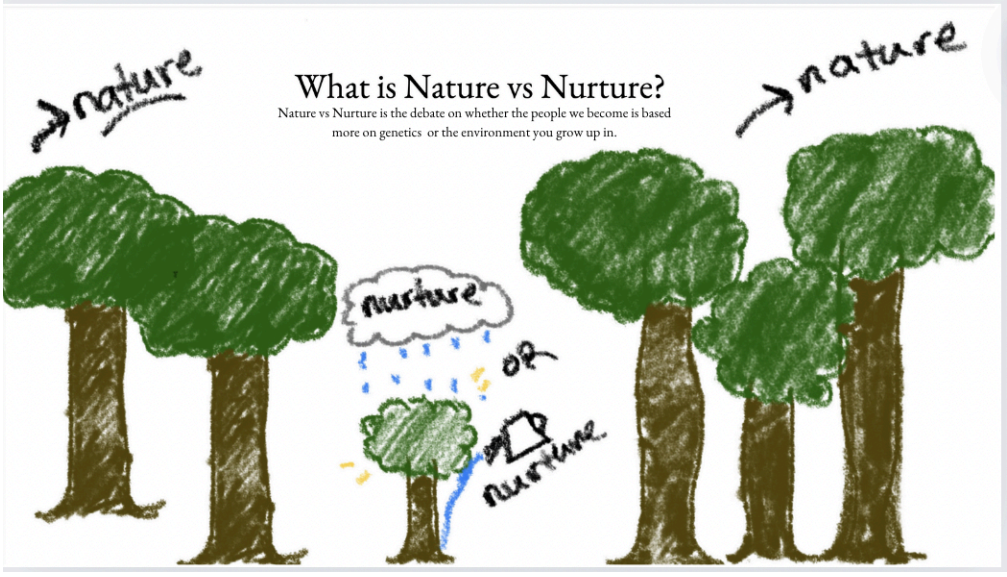

Figure 1. An image created by me depicting a manner in which the "Nature vs. Nurture" debate can be perceived.

As mentioned, the debate of nature vs nurture has subsided over the years since epigenetics research has advanced. An infographic by the Center on the Developing Child at Harvard University gives an impeccable overview of just what epigenetics is followed by an in-depth text about what the infographic touches on. This text outlines the new research that environmental changes and factors can change gene impression and how even early expressions can turn off and on certain genes, making it so certain genes can't even be expressed at all. Here I discuss how epigenetics disprove the thought that the genes gained from parents are set in stone for the offspring. Positive experiences like learning opportunities and helpful connections can impact the epigenome, whereas bad experiences like stressful living situations or environmental toxins can leave a distinct epigenetic "signature" on the genes. These markers influence the ease with which genes can be turned on or off, and they can be either transient or permanent. It takes a lot more work, may not be able to change every component of the signatures, and is expensive to reverse some detrimental modifications and restore healthy functioning, according to recent studies. Therefore, the ideal course of action is to encourage responsive connections and lessen stress in order to help children develop strong brains from an early age and become healthy, contributing members of society.

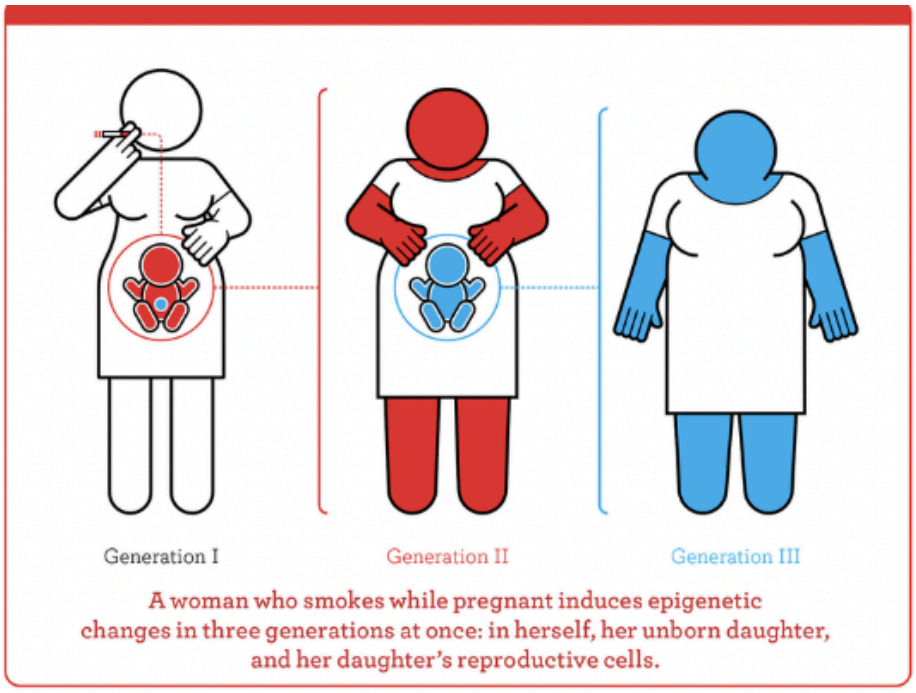

Figure 2: An illustration by Jude Buffum taken from the "Harvard Magazine", depicting the epigenetic long-term effects of behaviors such as smoking.

Based on the article before, this working paper from the Development Child Center in Harvard, titled "Early Experiences Can Alter Gene Expression and Affect Long-Term Development: Working Paper No. 10" extensively goes into what was touched upon in the infographic. A problem arises in the paper and breakthroughs are apparent because of the

addressed issue. The ordeal is essentially about the term “structural genome” which is about 23,000 genes that children inherit from their parents. Researchers compare the structural genome to a computer's hardware because, while both define the bounds of what is possible, none function without an operating system to provide commands. That operating system is known as the epigenome in the genome. The epigenome controls what the genetic "hardware" can and cannot do, much like the software in an operating system. With that, both negative and positive experiences leave a chemical signature, affecting how genes can be switched on and off. The understanding of the epigenome offers an argument for the persistence of lifelong effects of early positive and negative events. This information can help policymakers make decisions about how best to allocate funds for interventions that improve the lives of young children. Among that information, the paper goes on to discuss that popular misrepresentations of science are corrected with the main points being that 1. “Contrary to popular belief, the genes inherited from one’s parents do not set a child’s future development in stone.” 2. “Although frequently misunderstood, adverse fetal and early childhood experiences can—and do—lead to physical and chemical changes in the brain that can last a lifetime.” 3. “Despite some marketing claims to the contrary, the ability of so-called enrichment programs to enhance otherwise healthy brain development is not known”. This working paper gives a more clear concise explanation and excuse to what epigenetics is as a whole and how it affects the debate of nature vs. nature because it combines them whole. Nurture is possible without a preconceived nature given.

Putting the concept of epigenetics into practice is important because although this can be researched until there is no more to even look for, there needs to be a way to experiment to further push the agenda in some sort of way. That is exactly what Penn researchers were trying to do and succeed with two experiments to note one. The Florida carpenter ant (Camponotus floridanus) and the Jerdon's jumping ant (Harpegnathos saltator), two common ant species, had their genomes reported on in 2010 by Shelley Berger's laboratory, working with a wide collaborative team. They discovered that while female workers and queens behave very differently, there aren't many genetic distinctions between them. Instead, it seems that their fate is determined by epigenetic changes to the chromatin. Subsequently, the team discovered that in Florida carpenter ant colonies, two distinct types of worker ants are distinguished from one another by epigenetic variations. "Majors" are large-headed, powerful-jawed soldier ants. They are principally in charge of keeping the colony safe. On the other hand, "minors" are smaller and function as caregivers, gathering food and tending to the young. A study on epigenetics wasn’t just done on insects, it was also done on an animal, especially mice. In more recent years, associate professor of Neuroscience in Psychiatry at Penn along with colleagues from Massachusetts General Hospital in Boston. and their finding proved Berger’s prior outcome. They reported that “cocaine-induced changes in physiology are passed down from father to son in rats.” The investigators allowed male rats to self-administer cocaine for 60 days and then mated those animals with females that had no cocaine exposure. When the researchers offered the offspring the opportunity to self-administer cocaine, the males were slower to administer the

drug than either the females or male offspring from control rats that had no drug exposure. After further examination, the researchers theorize that because the offspring has a parent that expressed cocaine-fueled changes to their sperm and the chromatin in it, the addiction in turn protected the offspring from addiction.

Investigating and addressing the extent to which the concept of epigenetics influences the nature vs. nurture debate is crucial because it establishes a connection between the two by demonstrating how inherited traits can be distorted and reshaped by environmental factors. When accepting this complexity increases scientific understanding and contributes to the development of better methods for promoting well-being and resolving issues that people encounter throughout their lifetimes.

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Links Between the Gut Microbiome and Alzheimer's: What are the Future Implications?

Iftekhar Samir

Introduction

Centered in the digestive tract, the gut microbiome (GM) refers to the community of bacteria, fungi, viruses, and other microbes. The GM serves crucial functions in digestion, immunity, metabolism, and brain health. Bidirectional communication occurs between the enteric nervous system in the gut and the central nervous system in the brain, and the microbiota plays a major role in this process. This communication is possible due to the complex network of nerve cells, microbes, proteins, and chemicals known as the gut-brain axis (GBA). Recently, researchers have started to dive deeper into the connections within the microbiota-gut-brain axis and its effects on the brain. In patients with neurodegenerative diseases (NDs) such as Alzheimer's, Parkinson's, multiple sclerosis, and epilepsy, there are connections and early hallmarks found in the GM (1, 2).

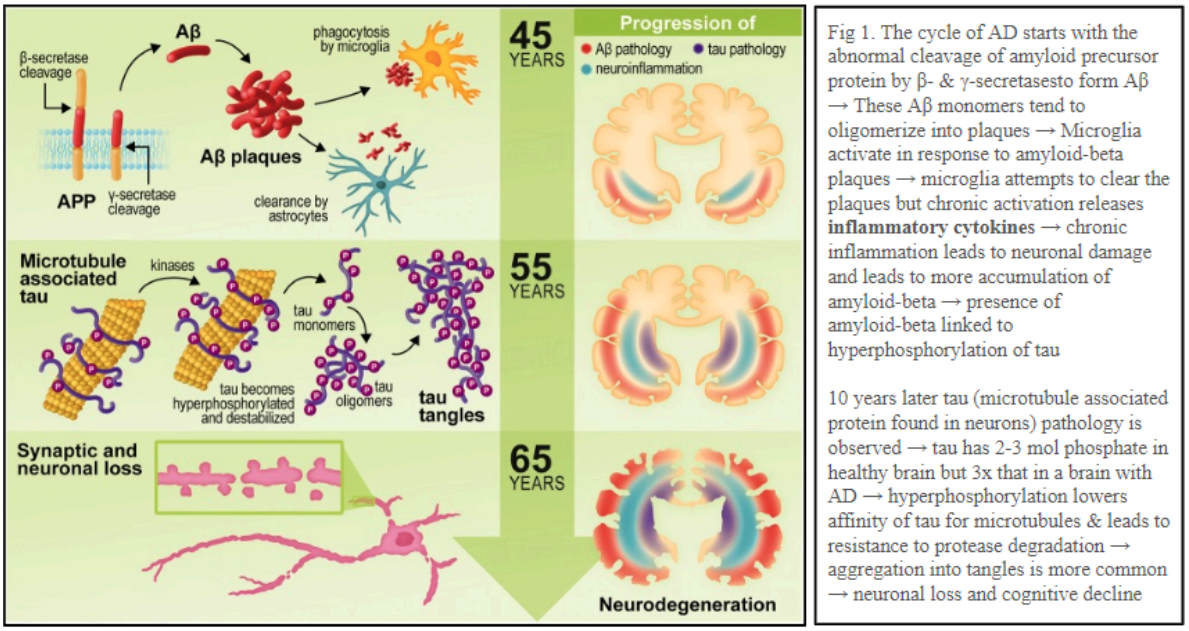

Figure 1: Inflammatory Connections Between Alzheimer's and GM
Source: *Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. J Neuroinflammation. 2018 Sep 24;15(1):276. doi: 10.1186/s12974-018-1313-3. PMID: 30249283; PMCID: PMC6154824.* (3)

Alzheimer's disease (AD) is the most common type of dementia that affects the parts of the brain controlling thought and memory. AD can further be defined and characterized by the progressive

accumulation of Aβ plaques and oligomers in the neurons alongside high amounts of hyperphosphorylated Tau proteins inside neurons and synapses (3, 4). Chronic inflammation exacerbates the presence of amyloid-beta, facilitating the hyperphosphorylation of Tau proteins (Fig 1). Chronic inflammation is a main perpetrator in the progression of AD, and studies are showing links between chronic inflammation and the GM.

In a study by Cattaneo et al, it has been found that there seems to be an increased amount of proinflammatory bacteria such as *Escherichia* and *Shigella*, whereas, in contrast, there is a decreased quantity of anti-inflammatory bacteria like *Eubacterium rectale* in patients with AD (5). Cytokines are signaling proteins that help maintain and control inflammation within your body; however, a high number of cytokines can lead to inflammation. Cattaneo's research showed that in the group of patients with amyloid plaques, there were higher levels of pro-inflammatory cytokines and decreased proinflammatory bacteria. This suggests there is a possible link between the gut microbiome and neuroinflammation as cytokines signal immune cells for help, but the extended duration of this signal leads to chronic inflammation which leads to the neuronal damage associated with AD and other neurodegenerative diseases (4, 5).

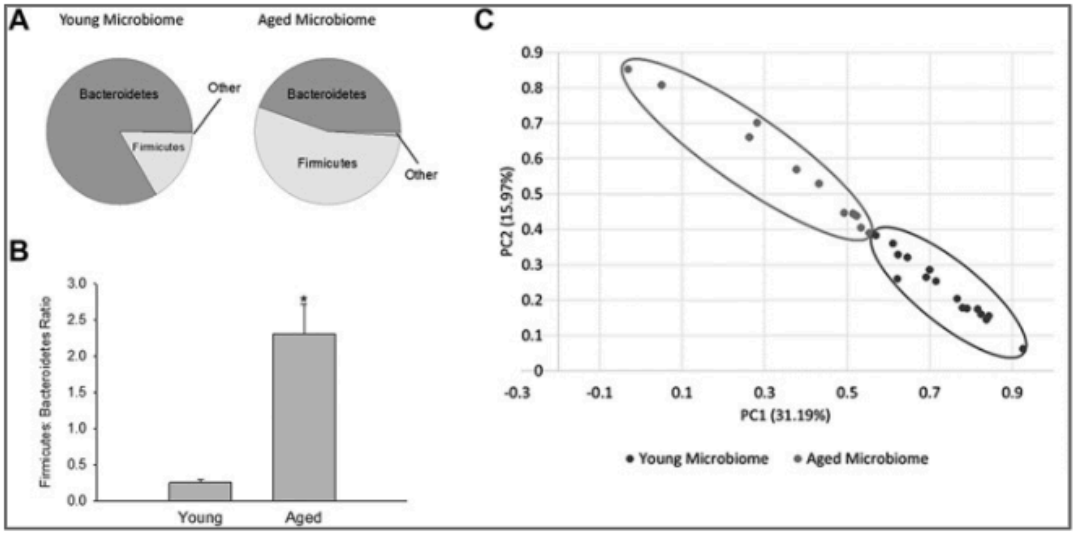

Fig 2A. Young vs Aged Microbiome phyla obtained from 16S rRNA gene analysis in fecal matter

Fig 2B. Firmicutes to Bacteroidetes ratio in young vs aged microbiota; probability of this increase in F:B ratio is 0.001

Fig 2C. Principal coordinates analysis test showing differences in microbiota composition between two age groups has a p-value of 0.009; Analysis done on similarity of UniFrac distance

Figure 2: Connections between Strokes and the GM
Source: Spychala MS, Venna VR, Jandzinski M, Doran SJ, Durgan DJ, Ganesh BP, Ajami NJ, Putluri N, Graf J, Bryan RM, McCullough LD. Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome. Ann Neurol. 2018 Jul;84(1):23-36. doi: 10.1002/ana.25250. Epub 2018 Jul 18. PMID: 29733457; PMCID: PMC6119509. (6)

Through the use of fecal transplant gavage (FTG) to switch the microbiomes between old and young mice, professor and neurologist Louise D. McCullough worked to see if a young gut microbiome in old mice and an aged microbiome in young mice could lead to different survival rates post-stroke. In the old mice with the young microbiome, the post-stroke survival rate increased to 50% and above, while the younger mice with the aged GM presented cognitive problems and died after a stroke. This led to further analysis, and it was discovered that short-chain fatty acid (SCFA) levels were higher in the young microbiome compared to the older microbiome. A study conducted by Ling Zhang et al. showed similar results of reduced levels of SCFAs in mice with AD. (7). These findings of lowered SCFAs denote that AD affects both brain functions and can worsen cognitive defects by possibly lowering SCFA levels by affecting the gut microbiome (7). It's important to note that this is a noticed correlation. However, it is key to note that there is varying information associated with the F: B ratio (*Firmicutes*: *Bacteroides, Bacteroidetes* is a phylum of bacteria that includes the genus *Bacteroides*) in the GM, as research done to identify changes in the gut microbiome in pigs with ischemic stroke, showed a decrease in *Firmicutes* rather than an increase (8). The purpose of this figure is to highlight the effects of dysbiosis (an altered GM) on neural functions. In addition, it's important to highlight the lowered production of SCFAs.

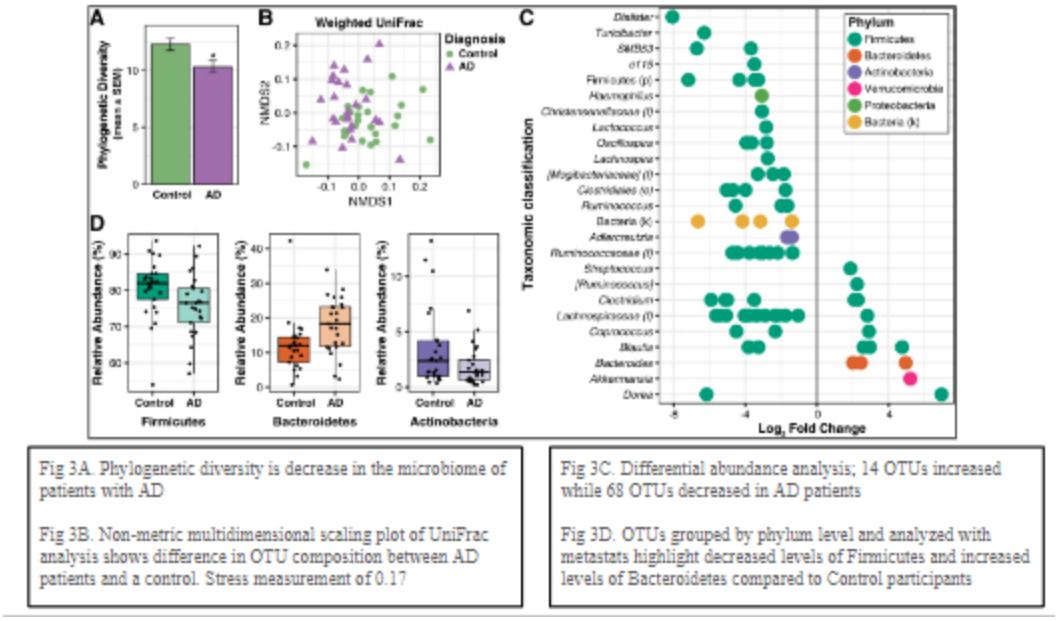

Fig 3A. Phylogenetic diversity is decrease in the microbiome of patients with AD

Fig 3B. Non-metric multidimensional scaling plot of UniFrac analysis shows difference in OTU composition between AD patients and a control. Stress measurement of 0.17

Fig 3C. Differential abundance analysis; 14 OTUs increased while 68 OTUs decreased in AD patients

Fig 3D. OTUs grouped by phylum level and analyzed with metastats highlight decreased levels of Firmicutes and increased levels of Bacteroidetes compared to Control participants

Figure 3: Analysis of the Gut Microbiome in Patients With AD.
Source: Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, Carlsson CM, Asthana S, Zetterberg H, Blennow K, Bendlin BB, Rey FE. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017 Oct 19;7(1):13537. doi: 10.1038/s41598-017-13601-y. PMID: 29051531; PMCID: PMC5648830. (11)

Types of bacteria found in the colon, known as *Firmicutes* such as *Eubacterium nodatum* produce SCFAs like butyrate, an important metabolite that mediates inflammation with its anti-inflammatory properties (9). As previously discussed, the associations between the decrease

in or increase in the number of *Firmicutes* in strokes are not clear. However, research associated with Alzheimer's shows AD patients had lower levels of *Firmicutes* and higher levels of *Bacteoidetes* than their healthy counterparts (10, 11). Figure 3 highlights lowered levels of *Firmicutes* and *Actinobacteria* in patients with AD, whereas the level of *Bacteroides* increased. This association is supported by previous research showing that *Bacteroides* species can secrete Lipopolysaccharide (LPS), which has been linked to the gut's endothelial dysfunction and neuroinflammation induction in microglia cells (12). However, researchers led by Chinese studies showed there was no association between *Bacteroides* and AD (12). Researchers believe this is due to differences between diets which can be linked to differences in which microbes tend to be abundant in the GM (12).

The decreased diversity found by the study is parallel to results in conditions starting to be linked to GM dysbiosis such as Parkinson's disease, obesity, and diabetes (11). The decreased diversity of the gut microbiome has been linked to diet, and studies show that immigrants to the US show a lower diversity in the gut microbiome than they started with before immigrating (12). This is due to the unhealthy consumption of the American diet, where processed foods run rampant alongside the lack of organic products in the market (12). When diet is such a large part of what can contribute to the development of neurodegenerative diseases, it brings the question of whether stronger food regulations need to be put into place to decrease the risks of obtaining neurodegenerative diseases in the future.

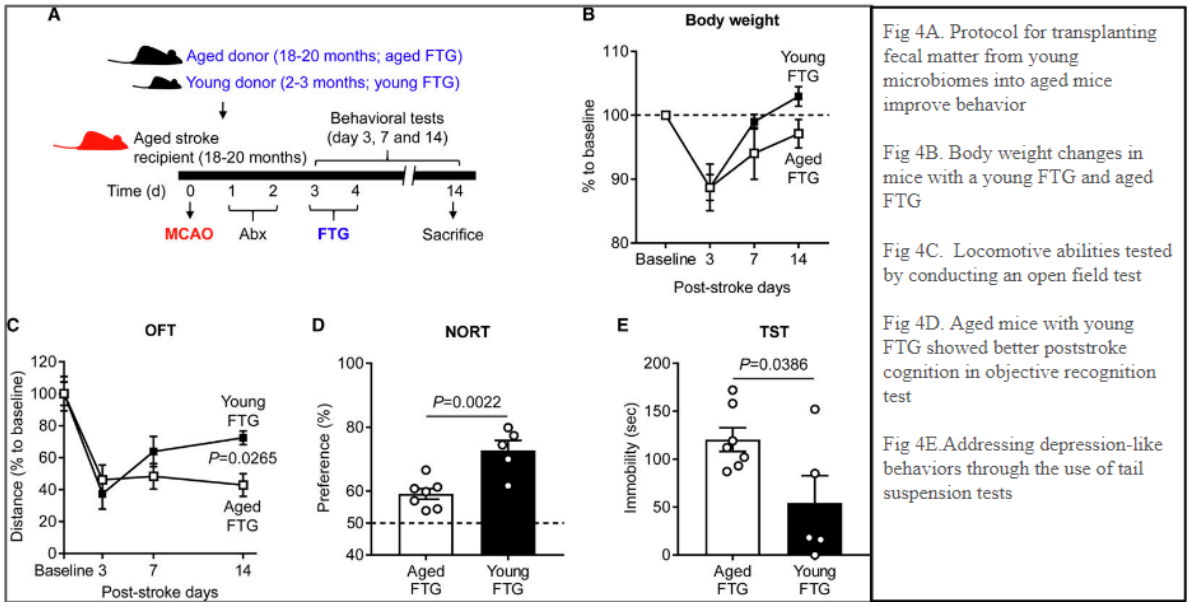

Fig 4A. Protocol for transplanting fecal matter from young microbiomes into aged mice improve behavior

Fig 4B. Body weight changes in mice with a young FTG and aged FTG

Fig 4C. Locomotive abilities tested by conducting an open field test

Fig 4D. Aged mice with young FTG showed better poststroke cognition in objective recognition test

Fig 4E.Addressing depression-like behaviors through the use of tail suspension tests

Source: Yifeng Zhang,Hang Yang,Shuai Hou,Yulei Xia,Yan-Qiang Wang,Influence of the brain-gut axis on neuroinflammation in cerebral ischemia-reperfusion injury (Review), International Journal of Molecular Medicine, 53, 3, (2024). https://doi.org/10.3892/ijmm.2024.5354 (13)

Yifeng et al. also used FTG to study differences in aged mice with older microbiomes and aged mice with younger microbiomes post-stroke. Their results showed better cognitive recognition and locomotor activities in aged mice with a young FTG, a younger GM, compared to aged mice with an older FTG. In addition, young microbiota showed reduced immobility in the tail suspension test (Fig 4E) which suggested there's an antidepressant-like effect. Another important finding was the lack of a significant difference in infarct damage (infarct: tissue death due to a lack of blood supply) suggesting that these noticeable changes in locomotive activity, memory, and depression-like behavior were independent of infarct size (13). This research shows the possibilities of what a young microbiome can have on the cognition, behavior, and activity of older mice which signifies the importance of the GM in both physical and mental capability.

Conclusion and Discussion

While this field of research is still new, some new discoveries can be linked to already previous discoveries. While this research isn't all set in stone and a lot of the results are correlations, this research is a big step toward identifying possible treatments for neurodegenerative diseases like strokes and Alzheimer's in the future. Results from mice show the importance of young gut microbiota in physical and mental capability and this further highlights how important taking care of our GM is to the health. When research shows that our GM experiences changes in its composition due to diet, it brings to the spotlight the importance of a healthy diet and nutrition in preventing future damage to our bodies. It's important to look at what we can do to improve the health of our gut microbiome, and it is very possible that research in the future can help use the gut microbiome to identify and even slow down the progression of neurodegenerative diseases. As more discoveries are made, the importance of government regulations on food become more important as nutrition and maintaining the gut microbiome can be the difference between higher risks of Alzheimer's and surviving strokes.

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What is the Difference Between Arctic and Antarctic Ozone Depletion, and How Have We Studied Them Over Time?

Yun (Kerry) Shen

Introduction

Over the past four decades, from 1985 to 2024, research has been conducted to study the character of ozone depletion. Analysis is made to compare between the Antarctic and Arctic region in several categories. Different analysis techniques were used, from studying historical data from ground-based sites to measuring data using ozone radiosondes and satellites. The chemical mechanism, chlorine activation, temperature changes, and meteorology of the winters were found to play their respective roles in the ozone loss process. From the eight pieces of literature being studied, a common conclusion is drawn that the same mechanism is responsible for ozone decay in both poles.

Analytical methods

Over the years, various analytical techniques have been employed to study and analyse the severity of ozone depletion in polar regions. From January 1993 to June 1994, a series of measurements were made to compare the amount of tropospheric ozone depletion in the Antarctic (Neumayer-Station, 70°S, 8°W) and Arctic (Ny-˚Alesund, Spitsbergen, 79°N, 12°E) using ozone sondes and ECC (electrochemical concentration cell)-sondes with modified RS80 radiosonde on 1200 balloons. Meteorological parameters, trajectories, ice charts are also used in analysis together with the support from German Weather Service and Japanese Meteorological Agency. In a research follow up in 1998, a similar method was used to study Stratospheric cooling of Antarctic and Arctic due to ozone depletion. Together with radiosonde, data from satellite and National Centers for Environmental Prediction was also studied. After the 20th century, scientists started using GOME instrument aboard ERS-2 (D.W, 2002) and Long balloon-borne (Soloman, 2007) (Solomon, 2014) as their way to obtain direct measurements. Satellites are still being used to take observations from the Microwave Limb Sounder on Aura, in conjunction with the passive-tracer method. Moreover, historical records play an important role in data analysis as well; database have been taken from IPCC (Intergovernmental Panel on Climate Change), AR4 global climate models, Climate Model Diagnosis, Intercomparison (PCMDI), Coupled Model Intercomparison Project, Phase 3 (CMIP3), and SRES scenarios (Walsh, 2009).

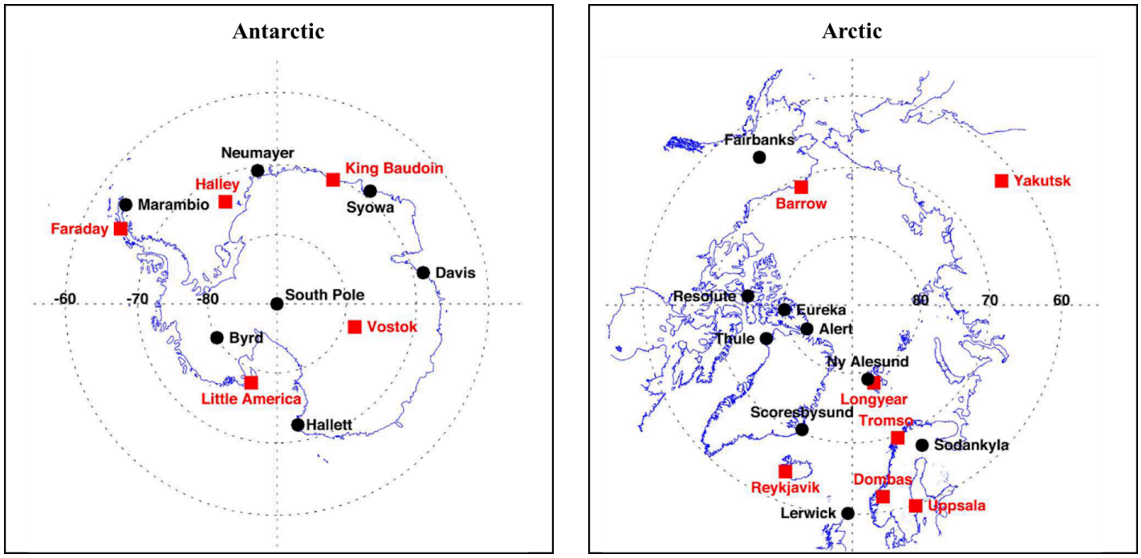

Fig. 1. *Selected Antarctic (Left) and Arctic (Right) stations. Stations in red provide only total ozone data, whereas ozonesondes or both ozonesondes and total ozone are available for stations shown in black. The stations include those with the longest and earliest observations for each polar region (Soloman, 2007).*

Chronological order of ozone depletion

The ozone hole refers to the thinning of ozone gas (O_3) in the stratosphere above Antarctica and the Arctic. While ozone is toxic at ground level, it plays a crucial role in the upper atmosphere by blocking harmful ultraviolet rays from reaching the Earth's surface. Scientists discovered the ozone hole in 1985 and identified that it was caused by man-made chlorine and bromine compounds, commonly found in chlorofluorocarbons (CFCs) used as refrigerants. In response, the Montreal Protocol was established in 1987 to phase out these chemicals (Pappas, 2017).

<u>The chemical reactions</u>

Since 1993, it has been believed that the same chemical mechanics are responsible for frequent tropospheric ozone decay in the Antarctic and Arctic (Wessel, 2017). It was further proved in 1998 that there are similar space-time patterns in both poles, hinting at the same mechanisms (J, 1999). In both poles, ozone destruction is due to catalytic reaction by reactive bromine. Natural-occurring bromine substances such as brominated organic compounds and sea-salt aerosols (Wessel, 2017), together with high concentrations of tropospheric BrO, are found to be a fundamental factor causing large areas of depletion events in both poles (D.W, 2002). In 2015, the chlorine activation was the weakest (1.9 ppbv) and the wave fluxes were the lowest. According to an estimation, ozone loss is at its minimum (2.5 ppmv or $10^7 \pm 10$ DU at 400–600 K), proving chlorine activation also influences the variability of ozone (Roy, 2024).

<u>The significance of temperature and winter influences</u>

Temperature variations at the surface of the Stratosphere play a significant role in ozone depletion activities. Extreme cold conditions at polar regions are ideal for the formation of polar

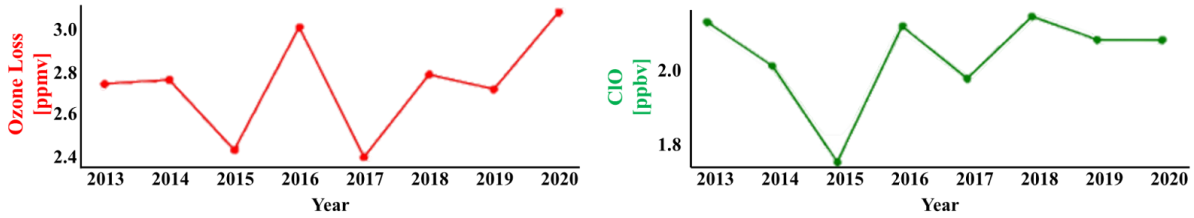

Fig. 2. *The vortex-averaged ozone loss estimated from the MLS measurements using the passive method, compared with peak CIO measurements for the period 2012-2020. The mean ozone loss is estimated over the altitude range 450-550K and between day 270 and 300 (maximum ozone loss days). The CIO measurements are averaged over the altitude range 450-550K and between day 210 and 270, representing the strong chlorine activation period and altitudes (Roy, 2024).*

stratospheric clouds (PSCs), which acts as the activating surface for ozone-depletion substances (ODSs). This means lower surface temperature is usually correlated to greater ozone decay. Winter corresponds to a long period of minimal temperature, so the PSC area grows from the beginning of winter, reaching its maximum in August (up to 28×10^6 km^2).
In 1998, substantial cooling occurred during spring, which is believed to have caused Stratospheric ozone depletion in both hemispheres (J, 1999). Coinciding with a research in 2002, the differences in the frequency of depletion events appear to be related to differences in average springtime surface temperatures (D.W, 2002).

In 2017, there was a sudden increase in temperature during late August with a higher minimum temperature at about 205K and a sharp decrease in the polar stratospheric clouds (PSC) area towards the end of September. This caused a higher heat flux magnitude in winter 2017 (up to -60 km s^{-1}), suggesting a warmer winter. As a result, minimal ozone loss was found in 2017, and it stayed less than 2.8 ppmv (110 ± 11 DU at 400–600 K) for most of October and September (Fig. 3). Chlorine activation was also below 1.8 ppbv during August and September in the year. On the other hand, spring of 2019 showed a high ozone loss, although the year had a rare minor warming in mid-September. The highest ozone loss (about 3.5 ppmv) occurred in 2020, owing to the high chlorine activation (about 2.2 ppbv), steady polar vortex, and huge expanses of polar stratospheric clouds (PSCs) (12.6×10^6 km^2) in the winter (Roy, 2024).

Ozone minima
Ozone minima is also an important variable in studies, which is a measure of times when the least amount of ozone is present in the surface of the stratosphere. The advection of marine, which is derived from weather charts using temperature, humidity and wind direction, is a main contributor to ozone minima variations. Moreover, ozone minima are also correlated with the polar air masses giving off above ice covered, and sunlit regions. Every ozone depleted air mass originated from sunlit sea-ice covered regions. During the advection towards the measuring sites, they can be lifted up by central katabatic winds. It is observed that ozone minima in the Antarctic seem to occur one or two months earlier in the year than that of in the Arctic (Fig. 4). This is

because the sea-ice covered regions in the Antarctic are at much lower latitudes, receiving solar radiation earlier compared to the Arctic (Wessel, 2017).

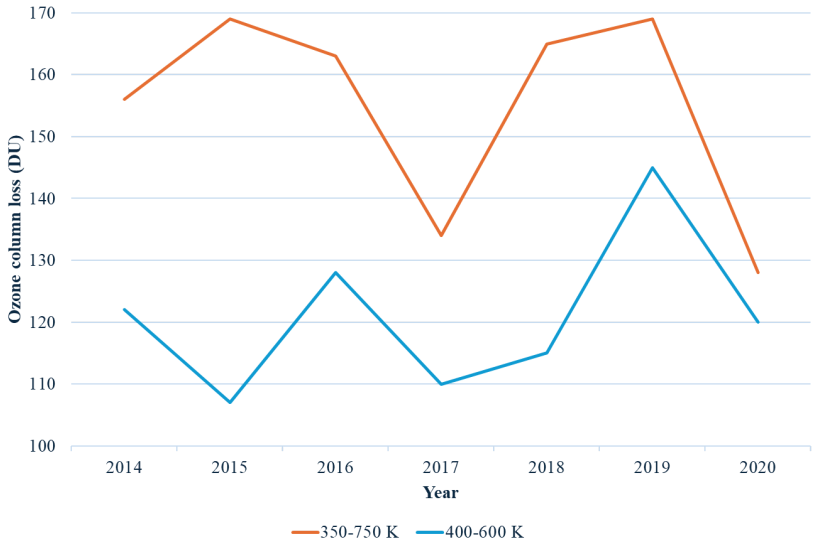

Fig. 3. *The partial column ozone loss computed using the MLS ozone measurements and modeled tracer by applying the passive method. The column loss is estimated for the peak ozone altitude ranges of 350–750K (orange) and 400–600 K (blue). The ozone column loss estimates have an uncertainty of about 10 %.*

Recovery

Antarctic ozone depletion has historically been more severe than that of the Arctic, although recent signs suggest a potential recovery of the Antarctic ozone layer. In 2006, the total ozone

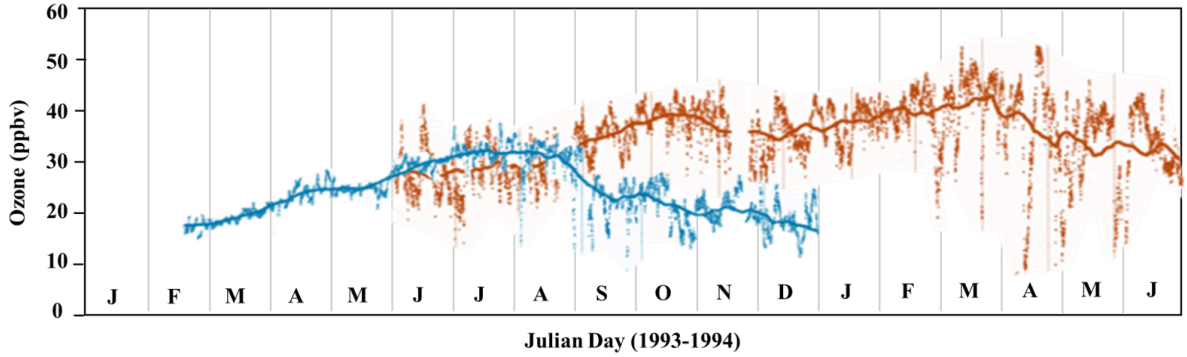

Fig. 4. *Annual cycle of surface ozone mixing ratio for Ny-Ålesund, Spitsbergen, Arctic, 1993-1994 (orange) and for Neumayer-Station, Antarctic, 1993 (blue). The solid line corresponds to the running mean over 30 days and the dots to mean hourly surface ozone mixing ratio (Wessel, 2017).*

depletion column in the Antarctic autumn fell much farther outside the historical range than that of in the Arctic spring, even in the most depleted years. This also shows massive depletion events associated with Antarctic ozone holes have not been mirrored in the Arctic (Soloman, 2007). In 2021, there are indications of the recovery of the Antarctic ozone layer from the effects

of ODSs. However, it is not certain that ODSs is the main factor since all of the metrics are directly related to stratospheric halogen loading, thus the ozone levels over Antarctica (Bodeker, 2021).

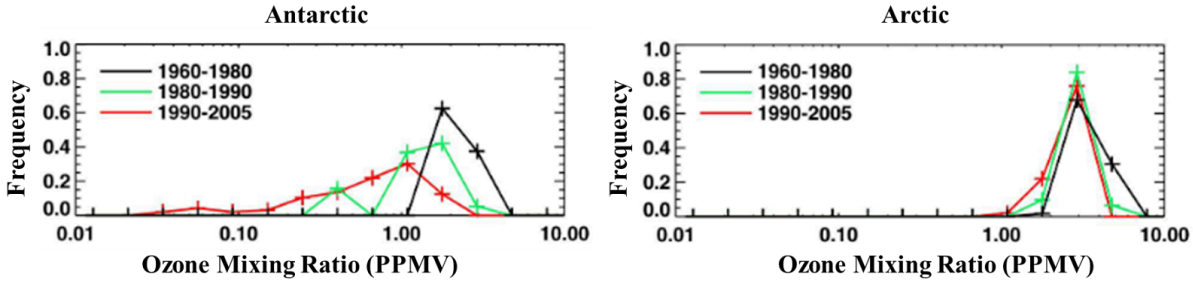

Fig. 5. *Changes in the distribution of ozone at available sites with the longest Antarctic (Syowa; Left) and Arctic (Resolute; Right) records at (±2) mbar (~18 km) for September and March since 1960. Symbols show the midpoints of bins for each grouping of data in these probability distributions. (Soloman, 2007).*

Conclusion

In conclusion, the comparative study of ozone depletion in the Antarctic and Arctic regions from 1985 to 2024 reveals both shared mechanisms and notable differences. The chemical processes driving ozone loss in both poles, primarily involving reactive bromine and chlorine compounds, have been consistently identified since 1993. However, while similar mechanisms are responsible for ozone decay in both regions, the Antarctic experiences more severe and earlier depletion events compared to the Arctic. The role of temperature, with its influence on polar stratospheric clouds, is crucial in both regions but varies in impact. Recent observations suggest a potential recovery of the Antarctic ozone layer, likely influenced by the Montreal Protocol's success in reducing ozone-depleting substances.

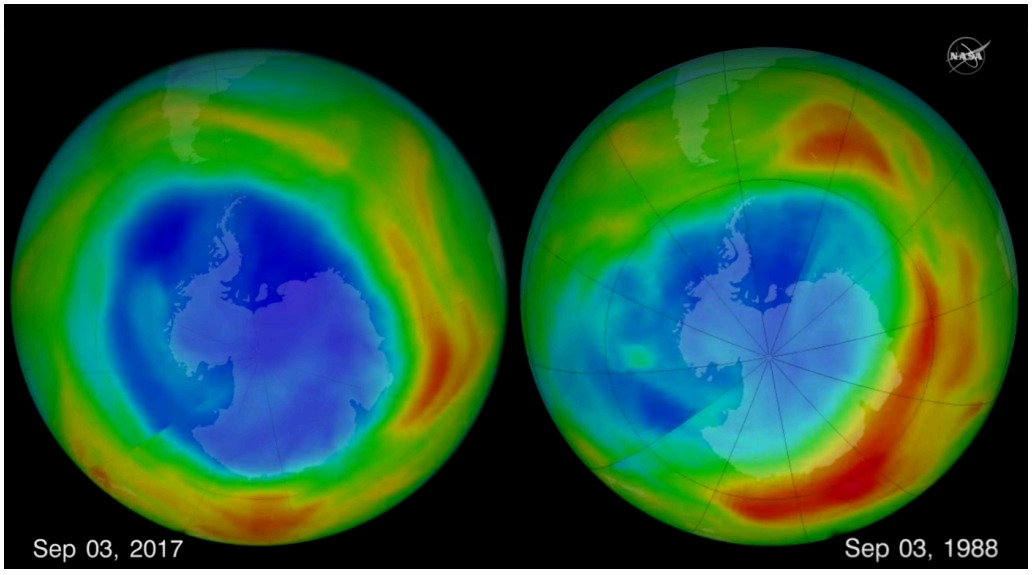

Fig. 6. *The hole in Earth's protective ozone layer that forms over Antarctica each September was the smallest seen since 1988, according to NASA and NOAA.*

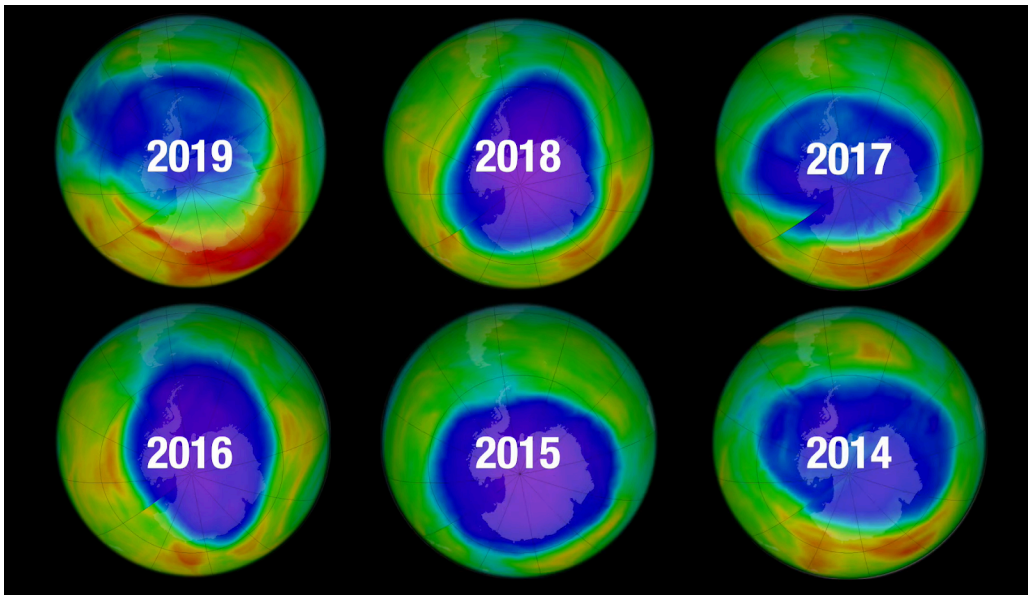

Fig. 7. *Scientists from NASA and NOAA work together to track the ozone layer throughout the year and determine when the hole reaches its annual maximum extent. The ozone layer has shown overall signs of improvement as a result of the Montreal Protocol (2019 Ozone Hole Is the Smallest on Record Since Its Discovery, 2019).*

Looking to the future, the stratospheric ozone in polar regions will be influenced by various environmental and human factors. As sea ice retreats, realistic simulations of sea ice, ozone, and water vapor are crucial to accurately predict future changes(Walsh, 2009). Arctic ozone recovery, anticipated by the mid-2030s, could be delayed due to significant variability and potential large depletion events (Pommereau, 2018). In contrast, the Antarctic ozone hole is expected to contract around 2020 and disappear by 2050 due to reduced emissions of ozone-depleting substances (Staff, 2006) (Pappas, 2017). Overall, the recovery of the ozone layer is progressing, yet it remains imperative to maintain robust observation systems and realistic modeling to address the uncertainties and ensure effective monitoring and mitigation strategies.

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Integration of Metal Nanoparticles in Colorimetric Assays and Point-of-Care Systems

Jayson Suan

Introduction

Sodium imbalances, such as hypernatremia and hyponatremia, occur when blood sodium levels deviate from the physiological norm of 138-142 mEq/L (Tsipotis et al., 2018), typically resulting from an increase of sodium, a decrease of free water, or both simultaneously (Linder & Funk 2013). These disturbances can be indicative of underlying medical issues, including acute kidney injury (Muhsin & Mount, 2016), cancer (Salahudeen et al., 2013), and cerebral demyelination (Lindner & Funk, 2013). Therefore, accurate measurement of sodium levels, in either blood or urine, is paramount for effective medical diagnosis and prognosis.

The standard methods for accurate and error-free medical diagnoses involve sophisticated laboratory analysis instruments. Determining sodium concentration in urine involves methods such as ion chromatography (Chapp et al., 2018), which are expensive and inefficient. However, alternative solutions such as Point of Care (POC) systems have already been developed. POC systems are portable, quick, and cost-efficient platforms for partial analysis and diagnosis. These can be operated without the interference of qualified medical personnel, adding the advantage of being noninvasive (Chandran et al., 2022). A common instrument of POC systems is test strips. Test strips have a reaction zone impregnated with specific test reagents. However, the color intensity of the strips can vary due to axillary factors such as agglomeration, contact time with the solution, and oxidation (Schwenke et al., 2019). A solution to this is the integration of copper nanoparticles (Cu NPs) into colorimetric sensor strips. Their strong SPR spectra in the visible range and fluorescence properties make them highly effective for this application as shown in thr study of Chandran et al., 2022. This presents just one of many studies exploring nanoparticle-integrated assays for enhanced sodium detection.

In this review article, we aim to address the question, “How can the integration of metal nanoparticles in colorimetric assays improve the accuracy and efficiency of sodium concentration detection in point-of-care systems?” by analyzing and synthesizing existing research. We will first explore the fundamental principles of metal nanoparticles and their optical properties that contribute to enhanced colorimetric sensing. Next, we will evaluate the advantages of using nanoparticle-based sensors over traditional methods, focusing on their application in point-of-care systems. Finally, we will examine specific case studies and recent advancements in the field, to provide a comprehensive understanding of how these technologies can address current limitations and improve diagnostic outcomes.

Applications of Metal Nanoparticles

Metal nanoparticles (MNPs), such as copper (Cu NPs), gold (Au NPs), and silver (Ag NPs), have risen in prominence due to exhibiting promising functionality. This is because of the appearance of a strong frequency band that does not exist on most of the metal spectrum, commonly known as the Surface Plasmon Resonance (SPR) peak (Priyadarshini & Pradhan, 2017). It appears when the metal particles are decreased to nanometer size. In recent times, nanoparticles with appropriate sizes have been suitable for colorimetric analyses (Hatamie et al., 2014).

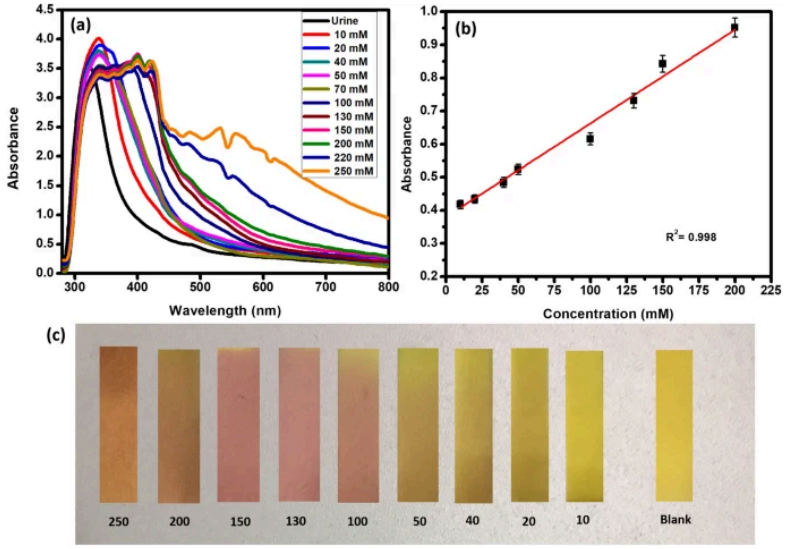

Figure 1: (a) Photograph of CuC-paper test strips exposed to blood serum samples with varying concentrations of Na+. (b) Absorbance spectra of blood serum samples upon the addition of CuC sensing solution. (c) Curve fitting showing the linear responses of absorbance Vs Concentration at 557 nm. (Chandran et al., 2022).

Advantages of using nanoparticle-integrated colorimetric assays

Existing methods to perform analysis tasks with vital contributions to humanity's quality of life, such as ICP-MS, AAs, and ICP-AES, have their associated shortcomings. They are lengthy, have long pre-concentration procedures, and require expensive infrastructure. Nanoparticle-based colorimetric assays have provided a path for developing cost-effective, feasible, and rapid methods for various analyses. For instance, their application in waste management (Priyadarshini & Pradhan, 2017), usage as an antibacterial agent (Gong et al., 2007), and measurement of specific ions in bodily fluids (Chandran et al., 2022).

Current limitations in nanoparticle-integrated colorimetric technology

A major difficulty when using MNPs is the tendency for their surface to oxidize some time after synthesis (Hatamie et al., 2014). As such, the use of MNPs requires a modification in their surface through conjugating the MNPs with target-specific ligand molecules. This process is referred to as functionalization (Priyadarshini & Pradhan, 2017).

Nanoparticle-based Assays for Quantification of Sodium Concentration

Research on useful sensing technologies such as lateral flow strips has progressive contributions regarding the early diagnosis of diseases (Toubanaki et al., 2020). Some biomarkers that are specific only to some life-threatening diseases have been able to be detected with the help of microfluidic devices (Kim et al., 2021). As such, colorimetric sensing has risen in importance as it is a cost-effective, easily replicable, and highly reliable technique to detect the presence of urinary sodium excretion, amino acids, metal ions, proteins, etc. Furthermore, they are easy-to-use devices as POC diagnostic tools (Zhou et al., 2012). The study of Chandran et al. (2022) was particularly dedicated to the development of paper strips infused with curcumin-functionalized Cu NPs for Na+ ions sensing. The assay exhibited a linear response of absorbance at 557 nm for Na+ concentrations ranging from 20 to 200 mM (R2 = 0.932) and from 1 to 80 mM (R2 = 0.996), making it suitable for detecting Na+ in the biologically relevant range of 20–250 mM. The colorimetric Na+ assay has been tested with simulated urine samples to mimic hyponatremic and hypernatremic conditions. The assay showed a linear response to Na+ concentrations ranging from 10 to 280 mM, with minimal interference from other components like urea and creatine. This demonstrates the assay's robustness in complex biological matrices.

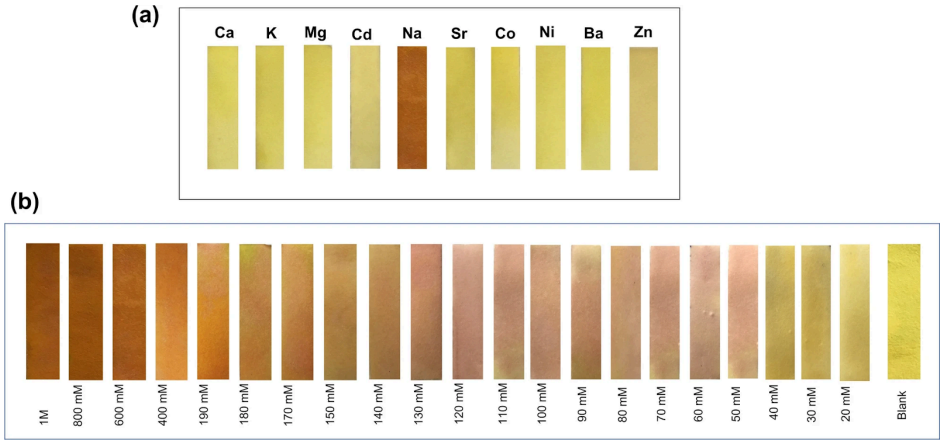

Figure 2: (a) Selective visual colorimetric response of Na+. Photograph of CuC paper test strips exposed to different metal ions. (b) Photographs of CuC based test strip with increasing concentration of Na+ from 20 mM to 1 M exhibiting color changes. (Chandran et al., 2022)

Other existing colorimetric assays integrated with metal nanoparticles

There is a need to monitor the toxic metal content in bodies of water used as inputs for clean drinking water. This is because heavy metals are toxic to humans with a very low lethal dosage, making them responsible for a multitude of life-threatening diseases. A study by Priyadarshini and Pradhan (2017) was able to use Au NPs as colorimetric sensors for the detection of arsenic in water. Using the properties of arsenic, like the strong binding affinity of As3+ to compounds that contain sulfur, they were able to apply respective Au NPs with different functionalizations. These Au NPs were functionalized with reagents such as cysteine,

dithiothreitol, and glutathione. They also furthered the previous minimum detection limit of 5 ppb using dynamic light scattering analysis (Priyadarshini & Pradhan, 2017).

Researchers continue to search for new antibacterial agents due to the outbreak of infectious diseases and the growing amount of antibiotic resistance. Ag NPs have been shown to have good antimicrobial efficacy against eukaryotic microorganisms (Gong et al., 2007). The Ag NPs attach to the cell membrane and penetrate inside the bacteria. This is due to the Ag NPs interacting with sulfur-containing proteins in the bacterial membrane, while also interacting with phosphorus-containing compounds like DNA. However, the Ag NPs form a low molecular weight region in which the bacteria conglomerates thus, protecting the DNA from the silver ions. The Ag NPs preferably attack cell division eventually leading to cell death (Rai et al., 2009). Ag NPs are commonly synthesized through chemical reduction using organic and inorganic reducing agents. Sodium citrate, ascorbate, sodium borohydride (NaBH), elemental hydrogen, polyol process, Tollens reagent, and N-dimethylformamide (DMF) are some of the reducing agents used to reduce silver ions (Ag^{+}) in aqueous or non-aqueous solutions. The reduction of Ag^{+} leads to the formation of metallic silver (Ag^{0}), which then agglomerates into oligomeric clusters. These clusters eventually form metallic colloidal silver particles. To stabilize dispersive NPs during metal nanoparticle preparation, protective agents are used to prevent the NPs from being absorbed on or binding onto nanoparticle surfaces, which can cause agglomeration. Surfactants containing functionalities such as thiols, amines, acids, and alcohols can be used to stabilize particle growth and protect particles from sedimentation, agglomeration, or losing their surface properties (Iravani, 2014).

Conclusion

The integration of metal nanoparticles has emerged as highly effective in the development of colorimetric sensors. Numerous recent studies, including Chandran's research, have highlighted the significant advantages of metal nanoparticle-based assays, including high sensitivity, selectivity, and stability, making them a robust tool for monitoring sodium levels in biological samples. This approach not only offers a cost-effective and user-friendly diagnostic method but also provides a reliable means for tracking sodium homeostasis, which is critical for diagnosing and managing various health conditions. The successful application of such sensors underscores the potential of metal nanoparticles in enhancing the performance of diagnostic assays, paving the way for advanced point-of-care testing solutions.

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Ethics in Expressive AI

Shreya Swaminathan

Abstract

This paper delves deep into emotional AI ethics. It provides an overview of the staged process to construct the technology. Then, it studies the ethicality of the outcomes. Each step of the building process is complex because of the deep emotional understanding required. Emotion has molded many concepts in society, even in unexpected places like the courtroom. It is embedded in daily lives; of course, when some promote emotional reasoning, others will oppose it. Either way, emotion's prominence is very difficult to ignore because many of our decisions are based on emotion, whether we admit it or not. The emotional AI constructing procedure is extremely complicated and is nothing to skimp over - although it is very easy to do so. For this reason, any artificial intelligence mimicry can make great strides - or cause great harm. To prevent harm and misuse, this paper builds an understanding of the technology before focusing on the ethical aspects that must be considered when advancing it.

Introduction

As the realm of AI develops, ethical concerns also grow. Expression is now being incorporated into AI and is beginning to carry potency. Expressive AI has incredible potential for emotion recognition, decision making, etc., but also has grave ethical concerns relating to influence, data, etc. that must be addressed before exposure. Growth rates of emotional AI have been steadily increasing over the past decade, and they are predicted to grow further. This technology is profound today and is an area of intense research. This paper will cover the research by reviewing literature of analysts in this field.

A key source this paper will refer to is "Consciousness vs Sentience" written by Douglas C Youvan. It encompasses many important aspects like emotional influence, emotion in law, ethical ramifications, and a comparison to human consciousness. To deepen understanding in emotion in law, this paper reviews Susan Bandes's journal article for the DePaul University College of Law. To discuss expressive AI development, Saif M Mohammad's Ethics Sheet will be particularly useful. His sheet will also be referenced in applications and ethical concerns. There will be more references throughout the paper, but these are the main few that are very relevant to review. These topics are all intertwined in that they build on each other. Some will focus on the broad picture, while others will narrow into specific aspects of the topic.

This research space is now rooted in our society. It is imperative to consider every ethical roadmap before extending visibility and usage rights, which explains the relevance of this field.

Definition and Differentiation of Emotions

Emotion is a very complex topic and requires extensive knowledge to truly grasp. We will preface with consciousness versus sentience.

Consciousness is the phenomenon of awareness between oneself and one's environment. It encompasses sensations, thoughts, and opinions, which create debate and study in society. French philosopher and scientist Rene Descartes's fundamental principle was, in Latin, "Cogito, ergo sum." This translates to, "I think, therefore I am." He justifies his existence with his ability to think logically. This was the first legitimate link between consciousness and the physical environment (Youvan, 2023).

Sentience, contrastingly, is when we feel different emotional responses to different experiences, called "qualia". Qualia is how we distinguish between feelings (Markie, 2004).

One in ten people has a disorder called alexithymia, in which . individuals struggle to recognize their emotions. It amplifies anxious feelings and causes unregulated emotion and is often seen in those with autism. On a broader scale, this disorder puts great strain on relationships, increases likelihood of substance use, and impairs the development of children who possess it. Other emotional disorders include depression, post-traumatic stress disorder (PTSD), and anxiety (Joseph, 2024). Many expressive AI applications fail to account for this demographic, which we will explore in a later section.

Emotional Sway

Emotions hold profound impacts on us. Many of our morals are shaped by our emotions. These emotions help us create societal concepts like justice and unfairness (Youvan, 2023).

However, some disagree with using emotion to support judgment. Philosophers like John Locke and Baruch Spinoza believed that reason was the foundation of knowledge (Markie 2004). This was the rationalist philosophy, and it would certainly prevail if not for emotional sentience. Nevertheless, this has flaws in itself. Promoting a rigid ethical system with no room for emotion may result in decisions being ethically righteous but lacking in compassion. As such, it is important to draw the line between rationalism and emotional morals. But establishing this balance is easier said than done. Complicating this matter further, it is important to consider individual subjectiveness. Each person possesses different morals, and we can only vaguely outline society's morals before examining each person's. These corresponding factors create a vast ethical calamity.

Recognizing the difficulty with which emotional ethics resides, let us review what laws government officials have placed to draw the boundary between emotion and reason. It has been stated that emotion is not required to form an unbiased judgment after hearing both sides of a conflict. . Ultimate judgment should be formed harnessing only the law. In reality, this is far from feasible. Emotion is laced within the legal system. Explicit emotional bias causes this emotion to be invoked, and inappropriate punishments to be allotted. The insidious component of this is that

superficially, these decisions seem logical, but are actually ineffective in the long-term. Implicit emotional bias applies more to cases where usage of specific words in court is allowed in some scenarios but not others, depending on the victim and crime. Using words like sympathy is only permitted when it is being directed towards the victim - and in this case, it is seen as rational (Bandes, 2016). Due to these hazy principles, emotion in law holds much more command than many claim it should.

Emotion, indisputably, is an integral part of society. This plays out in relationships, cooperation, cultural shifts, art, education, the professional sectors, etc. Sentience is central to foster empathy and compassion, which is what many relationships are built on. This is a staple requirement to maintain a relationship. In personal relationships, a lack of sentience can lead to transactional rather than meaningful interactions. Relationships would become seen as a beneficial factor. Emotion also evokes social awareness, which is a necessity in relationships.

Without sentience, cultures that value emotion and relationships might be reduced to pragmatism. Art and literature, which currently reflect societal and personal emotion, might become centered on abstract ideas. Education would hypothetically focus more on cognitive development and less on emotional and social skills, though social skills are vital to navigating professional and personal sectors. These effects are not unlikely with the introduction of expressive AI, considering misuse and manipulation (Youvan, 2023).

Expressive AI Development and Applications

There is a lengthy process involved in building expressive AI. In order to extensively cover ethical concerns, there are certain questions developers must answer, which we will evaluate in a later section.

First in the process comes task design. Developers must decide the focus of the task and pick their designated emotions. They also must consider the repercussions of their work.

Next is data aggregation. There are multiple types of data to be utilized. One type is Large Language Models (LLMs) which train models on text from the Internet. Another type is emotion lexicons, which associate words with emotions. Within these data types, there are different dimensions of data. These include size, custom versus naturally occurring data, more private versus less private data, etc. These all can cause skews of data, which must be avoided.

The third step in this process is to train the machine learning models. There are multiple methods to accomplish this. Developers can compare less accurate models to more accurate models. They can use a White Box vs Black Box method, where White Box understands why the system makes a prediction and Black Box does not understand this. They can measure energy efficiency. They can calculate the amount of data required for the model, and also the amount of privacy permitted through the model. Finally, they must estimate inappropriate biases and must test which algorithms deepen these biases and which ones don’t.

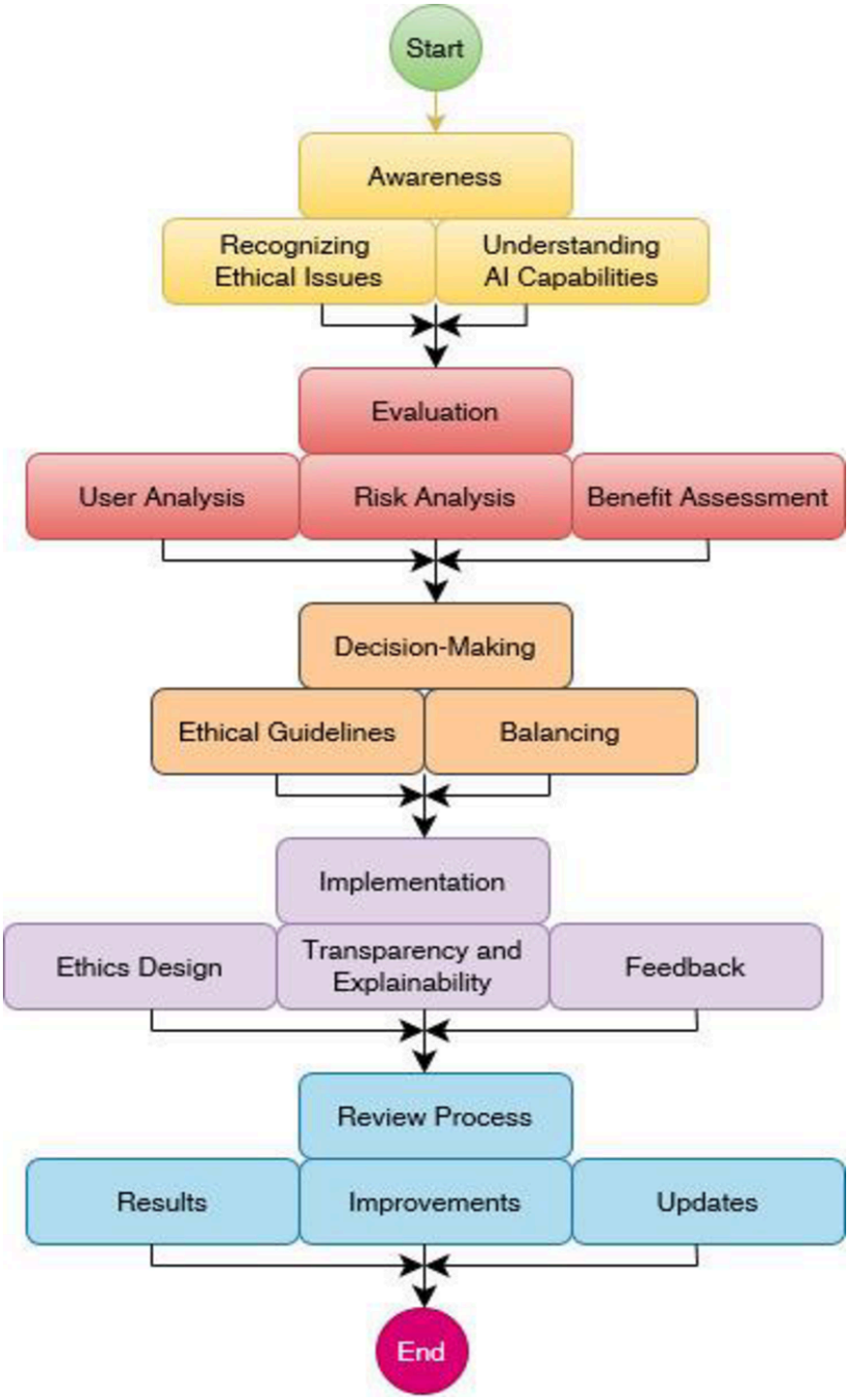

Figure 1: Expressive AI development process, including ethical factors of each step to be considered. (Zlatena, Steshina, Petukhov, and Velev, 2024)

The fourth and final step of development is evaluation of the model. Accuracy is unquestionably relevant. If the machine is not accurate, there will be serious repercussions. Along with this comes reliability, especially in a field derived from emotion. Emotional

recognition must be reliable, and information outputs must account for all demographics. Furthermore, as the sensitivity of the application increases, the quality of emotional recognition should advance as well. This is not to say that for less sensitive applications quality will be poor, rather that higher stake applications should not be taken lightly. For example, in the health sector, patients and health experts should not have to doubt their machines before taking weighted decisions. Also, the methods with which the machine is evaluated should be accurate and thorough. They should identify potential limitations. Next, the machine should provide a means for users to report feedback and should constantly be adapting services based on its societal benefits and harms. Finally, transparency from developer to user is crucial. The user must understand the interface with which they are interacting and should feel comfortable under all circumstances.

Expressive AI can be extremely versatile. It can influence public health through depression, anxiety, and mental health disorders. It can promote commerce by tracking emotional reactions towards posts and videos. It can contribute to business by providing virtual assistance, writing assistance, and advertisements. It can gauge public opinions for government policy on issues that are impactful, especially with crises like climate change. It can facilitate a better understanding of elements like interactions in art and literature pieces. In neuroscience and psychology, it can answer commonly asked questions about humans, use language to identify emotions and well-being, and understand how different people thrive. It is even applicable to the military intelligence field, where it can track social misinformation. While its versatility seems extremely beneficial, it is also this versatility that places enormous responsibility on developers (Mohammad, 2022).

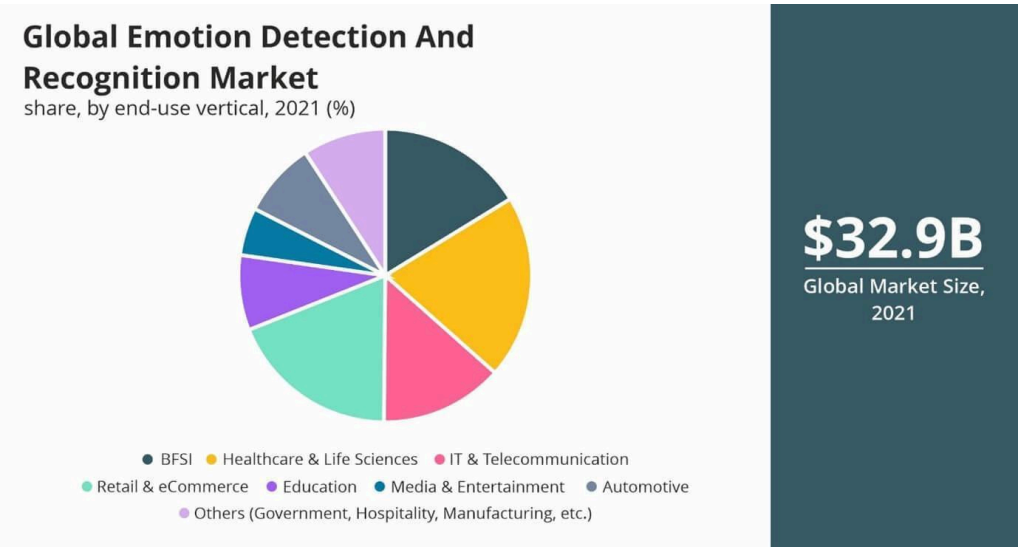

Figure 2: Sectors of expressive AI applications. Each field in proportion to the next. Global Market Size as of 2021 as well shows the increasing commonality of the device. (Kaushik and Dhankar, 2021)

Ethics

This is the section in which we will combine everything we have reviewed. Every aspect of expressive AI contains ethical voids.

First is to design the task of the machine. When framing the emotional task, it must be planned such that the purpose of the task is ethical and serves an intentional purpose. To accomplish this, developers should consider all implications. They should identify who benefits from the machine, and where there is a power shift. If there is an imbalance, then the focus should be redesigned so that it balances out to people in need. Also, this particular machine can help so many people. When picking a purpose, it would be most beneficial to society to consider where imbalances already exist, and then design this machine to directly fix these imbalances. Finally, the purpose should address neurodiverse people. Most expressive AI work has not accounted for neurodiversity, alexithymia, and autism. Or, at the very least, these systems should address their limitations.

Next, there's numerous concerns in data compilation. Data can be collected through LLMs. These can lead to documentation debt, curation difficulty, inappropriate biases, and perpetuation of stereotypes. Alternatively, it can be collected through emotion lexicons. These can misinterpret words in context, confuse historically changing perspectives, and differing consensuses across groups of people. Next, the dimensions of data can vary. Size of data, custom or naturally occurring data, privacy, language representation, and degree of documentation - these are all factors that can affect the ethicality of data. Data must be diverse and include all voices. However, within this there are controversies. For example, how can certain voices such as sexist, racist, malicious, and disingenuous voices be distinguished from uncommon but valid opinions? Beyond this, the data must be extracted with regards to privacy. Privacy cannot be violated, and compliance should be ensured when using robot exclusion protocol. Finally, the amount of data that collectors are exposed to at a time should be minimized, as sensitive topics can bear heavily on emotional health.

Third, when training the models, the methods used should be inclusive. They should contain the correct amount of context, and should never cause any pain or unpleasantness. They should understand the user's emotions and appropriately convey information. The technology should not be misused by companies and governments, to influence political decisions like voting. Lastly, the training methods and machine's needs must be environmentally friendly. Efficiency and restrained energy consumption are considered benefactors to science.

The final step of the process is evaluation. The machine must provide accuracy and reliability, recognizing all demographics. It must mold itself to support its application. Testing methods must produce accurate results. Developers must offer users a way to report feedback on the service, and the machine itself should adapt itself based on visible benefits or harms in society. The final necessity is transparency. The user should understand and feel comfortable

with their interface (Mohammad, 2022).

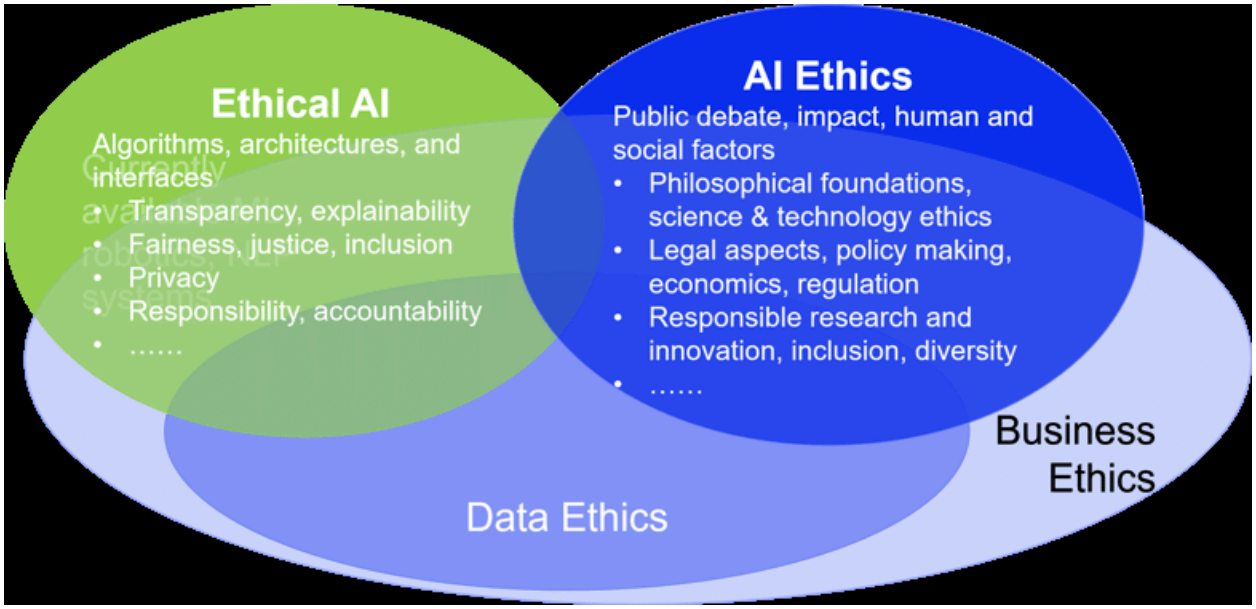

Figure 3: This chart shows ethics in different fields and how they impact different aspects of society. (Zhou, Chen, and Berry, 2020)

Conclusion

In summary, emotional AI can benefit society greatly in many fields as long as we don't lose sight of our ethics. Crafting the machine is a complex process, and it holds great power since emotion is integrated in our lives. While this paper has provided the essential information, expressive AI is exceedingly nuanced. To balance these nuances, the field of ethics can never fade. AI ethicists are constantly working to ensure that society doesn't face repercussions of new developments. Ethical expressive AI has made great strides, and will only continue to grow in the future.

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Figure 2. AI Ethics disciplinary landscape (adapted from [20]). (n.d.). ResearchGate. https://www.researchgate.net/figure/AI-Ethics-disciplinary-landscape-adapted-from-20_fig2_348263066

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Artificial Intelligence Computation of Partial Differential Equations

Ruthvik Venkatesan

Artificial Intelligence Computation of Partial Differential Equations

One of the long-standing problems of computing technologies has been their inability to solve analytically complex problems. Because computers, by their nature, are forced to discretize solutions to equations, they are forced to make exponentially high amounts of calculations in order to calculate solutions to advanced problems. One such problem is the numerical solution of partial differential equations, a field of applied mathematics that has various real-world uses in finance, science, and engineering. Due to their nature, partial differential equations are very difficult to compute, and compute complexity rises exponentially with the number of dimensions that the equation requires. The computation of partial differential equations can be made more efficient through the usage of machine learning algorithms to better discretize numerical solutions; one such example of this can be seen in methods used to solve the Black-Scholes equation.

Partial differential equations are mathematical equations that describe a multivariable function in terms of its partial derivatives. Because of this nature, rather than describing the value of a function at a particular point, they describe the motion of a function through multiple independent variables. The numerical solution of these equations can be computed through a variety of computationally expensive methods: one of which being the finite difference method (FDM). The FDM is similar to Euler's Method for approximating single-variable functions through their derivative definitions. Simply put, the FDM approximates the solution to a partial differential equation (a multivariable function) by means of discretizing the solution. The FDM to approximate a partial differential equation of "n" variables involves a N-dimensional nested array and a N-dimensional nested for

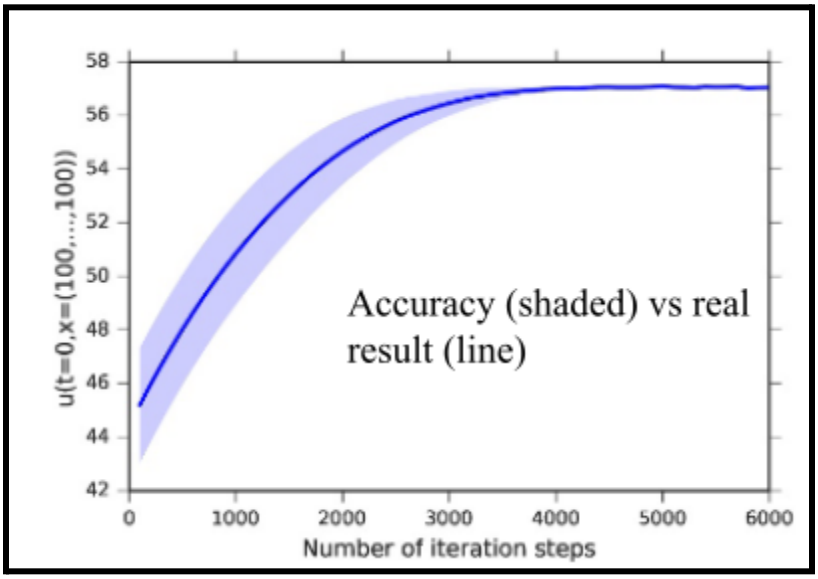
```
vector<vector<float>> V(float vol, float intRate, bool putCall, float strike, int expiration, int nas){


    // initialized number values.
    vector<float> S(nas + 1, 0);

    float dS = 3 * strike / nas;
    float dT = 0.9 / (vol * vol) / (nas * nas);
    int nts = (expiration / dT) + 1;
    dT = expiration / nts;
    vector<vector<float>> V(nts + 1, S);

    int q = (putCall) ? 1 : -1;

    float delta;
    float gamma;
    float theta;

    for (int i = 1; i < nas + 1; i++) {
        S[i] = i * dS;
        V[0][i] = max((double) q * (S[i] * strike), 0.0 );
    }

    // finite difference method:

    for (int timeStep = 1; timeStep <= nts; timeStep++){
        for (int assetStep = 1; assetStep < nas; assetStep++) {
            delta = (V[timeStep - 1][assetStep + 1] - V[timeStep - 1][assetStep - 1]) / 2 / dS;
            gamma = ( V[timeStep - 1][assetStep + 1] - (2 * V[timeStep-1][assetStep]) + V[timeStep-1]
            [assetStep-1]) / dS / dS;
            theta = -0.5 * vol * vol * S[assetStep] * S[assetStep] * gamma - intRate * S[assetStep] * delta +
            intRate * V[timeStep-1][assetStep];
            V[timeStep][assetStep] = V[timeStep - 1][assetStep] - dT * theta;
        }
    }


    return V;
}
```

Example of a C++ function using the FDM to compute a set of solutions to the Black-Scholes-Merton Partial Differential Equation.

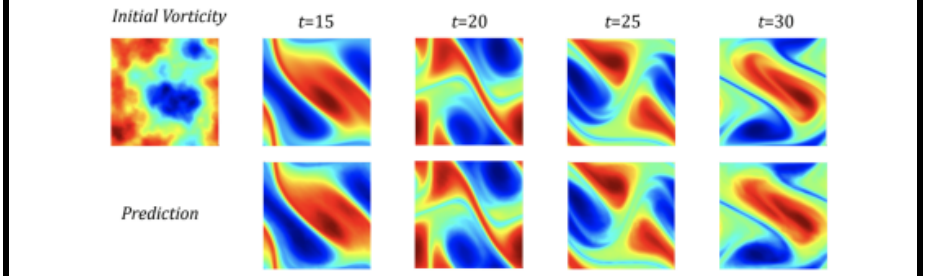
loop. (Bayen, 2021) This means that the complexity of the algorithm is O(x^n), where "x" is the maximum number of discrete steps that the algorithm will take and n being the number of variables, leading to exponentially slow algorithms as the number of variables increases. Equations with smaller numbers of variables, such as Black-Scholes (two variables) are already impractical to calculate with only two variables, making more complex equations such as Schrodinger's Time Equation or higher dimensional examples of the heat equation almost impossible to calculate.

Similarly difficult to calculate problems are very frequent in the world of computer science. One such famous problem was the issue of natural language processing. Due to the complexity of human linguistics, computer scientists found it nearly impossible to create a reliable way to process and produce human language algorithmically. However, with the advent of powerful artificial intelligence large language models, it became very possible to approximate natural language processing through the means of machine learning algorithms. Machine learning algorithms essentially use very precise approximation networks to approximate solutions to very difficult problems. In the case of natural language processing, these algorithms convert words into "tokens" and then tokens into multi-dimensional vectors in a vector database, so that they can refer to one another through operations in linear algebra. (For example, car + crash = crashed car, train + crashed = crashed train). (Lee, 2023) However, due to the fact that machine learning algorithms effectively are just making precise guesses, they represent a tradeoff between accuracy and computation time.

The usage of machine learning models is very useful in regards to the numerical solution of partial differential equations. Just like how they are used as heuristic approximations to nearly unsolvable problems such as natural language processing, machine learning can be used as a means of approximation in the field of Partial differential equations as well. (Hao, 2021) This is done by a neural network, a machine learning system that effectively replicates the human brain's ability and methodology of learning things: by repetitively studying training examples and making valid estimations on data based on observations from the examples. In this method it is possible for a machine learning algorithm to make predictions about things that traditional computing paradigms would have struggled to properly calculate. (Han) However, these algorithms need to be tuned so that they can properly fit their intended use cases; in this case, that would mean tuning the algorithm so that it knows what to "look for" when training itself. In this case, the Fourier Operator comes into play,



a revolutionary new method that allows for machine learning algorithms to pick up on and understand partial differential equations. The Fourier Neural Operator or FNO takes its name from the Fourier transform, a mathematical method that transforms any function into a (potentially infinite) sum of trigonometric functions. (Wang, 2023) This usage of trigonometric functions stems from the fact that since these functions have very simple derivatives and integrals, they are very easy to solve as idealized solutions to partial differential equations. (Sanderson, 2019) In fact, their origin comes from the solution of the heat diffusion partial differential equation in the case where the heat of a one dimensional rod can be graphed as a two dimensional sine wave. (Sanderson)



Zero-shot super-resolution: Navier-Stokes Equation with viscosity $\nu = 1e{-}4$; Ground truth on top and prediction on bottom; trained on $64 \times 64 \times 20$ dataset; evaluated on $256 \times 256 \times 80$ (see Section 5.4).

When Fourier Neural operators are used, their accuracy only nears 80%. (Li, 2020) Although an 80% success rate appears to be somewhat “decent”, the truth is, staying within 80% of an estimate is not near close enough when the necessary preciseness for some of these equations are considered. Partial Differential equations are frequently used for calculations that require a high level of precision. (Han) Because of this, the success rates presented by the Fourier Neural Operator system are much too low to be considered a worthwhile replacement at this time for the traditional methods of computation.

By making the worthwhile tradeoff of accuracy for speed, machine learning based methods make the process of computing partial differential equations much quicker. AS these equations have applications in many fields, this means that modern machine learning technologies can be used to progress the study of many fields of science and technology. Although the examined example was for the financial field, it is possible to use these methods to compute equations used for computational fluid dynamics, heat diffusion, and many more. (Kochkov, 2021) However, the complexity of machine learning brings up many necessary problems needing research and study in order to properly take advantage of this technology for computational purposes.

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Engineering Bacteria for Targeted Cancer Therapies

Estella Yee

Introduction

Cancer affects nearly every family in the world. According to the World Health Organization, there were almost 10 million deaths worldwide in 2020–one in six deaths caused by cancer [1]. Despite the significant advancements in the past century, current treatments for cancer including chemotherapy, radiotherapy, and surgery are accompanied by serious side effects from damage to healthy tissue. Therefore, the development of innovative and effective targeted cancer therapies is necessary.

Recently, the popularity of synthetic biology—the research and creation of bioengineered devices and systems with customized functionalities [2]—has increased, especially in disease therapy due to its potential for precise cancer detection and treatment, targeted drug delivery, and manipulation. This paper will explore the recent advancements in bacterial engineering through genetic modifications, including promising studies with drug deliveries and CAR-T cells to target tumor tissues. These approaches aim to enhance the specificity and efficacy of cancer therapies, minimizing off-target effects and reducing the toxicity of healthy tissue associated with traditional treatments. This review highlights the methods used in the genetic modification of bacterial systems for drug deliveries, advancements in bacterial immunotherapies, and regulation techniques for gene expression and immunogenicity, while addressing concerns for efficacy and safety, reflecting on relevant studies, and looking into the future.

1. Background

Engineered bacterial therapies have held significant promise since the 19th century, when William B. Coley first injected bacteria into his patient with inoperable cancer and he found that the patient's tumor had shrunk. Coley concluded that a bacterial infection promoted an elevated immune response, therefore causing the shrinkage of the tumor. His work eventually fell out of favor as chemotherapy and radiation methods came into play, but as scientists now observe the toxic side effects traditional methods have on healthy tissue, William Coley's bacterial therapy is being recognized for its potential [3].

Studies have shown that bacteria have unique anti-tumor and targeting mechanisms that overcome the current limitations of therapies. Many bacterial strains have been genetically engineered as biocarriers that can release pharmaceutical molecules, cytotoxins, signaling molecules, enzymes, nanobodies, or transfect genetic material into host microbes [4].

2. Bacteria in Immunotherapies

The immune system classifies foreign substances based on presenting antigens and activates the body's innate immunity which consists of macrophages, killer (CD8+) T-cells, NK cells, etc. Usually, the immune system has anti-tumor mechanisms, but genetic mutations in cancers allow for the evasion of the immune response. For example, tumor cells can mutate to no longer express the classifying molecules sensed by nearby immune cells, leading to undetected tumor growth. They can also suppress T-cells by releasing inhibitory molecules that deactivate the T-cell's immune checkpoints [5]. Immunotherapy is less effective in solid tumors than in the blood, but bacterial-based immunotherapies are promising because they can selectively colonize in tumors and be modified to release molecules that coordinate a domestic immune response [6].

CAR-T Cells

Chimeric antigen receptor T-cell therapy (CAR-T cells) is coming along as a new therapeutic. CAR-T cells are a patient's T-cells reprogrammed to recognize and eradicate the tumor [7]. Since CAR-T cells for leukemia were FDA-approved, further research has been performed to make it more successful. One idea is to program bacteria to produce chemokines and antigens to tag tumors for CAR-T cell targeting. Engineering CAR-T cells for targeting solid tumors is quite complicated, but bacteria already possess the ability to preferentially grow in a tumor's hostile and necrotic microenvironment. Vincent et al. produced a two-step approach involving a nonpathogenic, probiotic strain of *E. Coli* that delivers antigens to the tumor microenvironment. Probiotic-led CAR-T cells (ProCARs) recognized these antigens and killed them. Clinical trials in mice with ProCARs have been reported to have inconsistencies with efficacy, but overall minimal toxicities in patients with solid tumors [8].

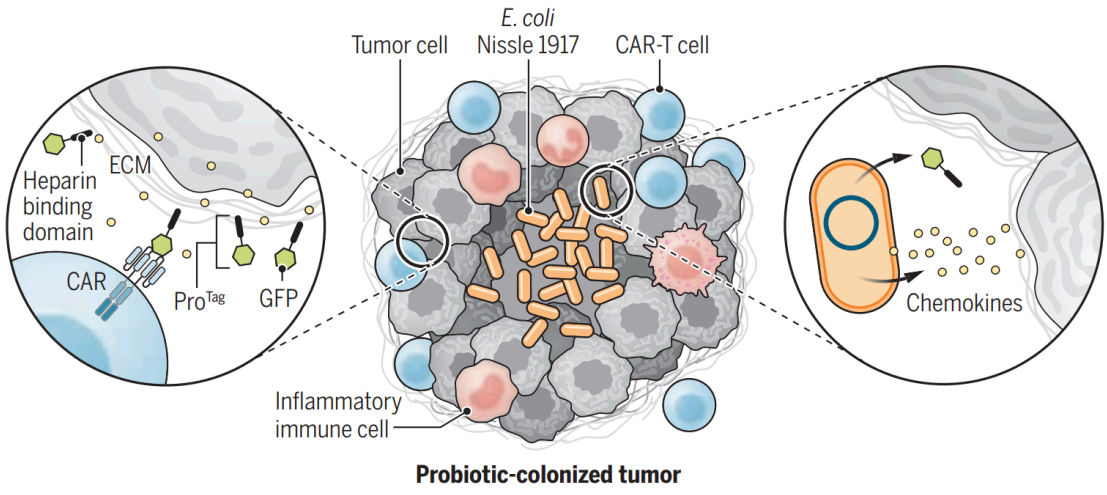

Figure 1. The combination of modified E.Coli that release antigens and chemokines and CAR-T cells to create a probiotic-colonized tumor [9].

3. Designing Bacterial Engineering for Drug Delivery

Dysfunction in the gut microbiome is associated with many chronic metabolic and immune diseases including obesity, type 2 diabetes, atherosclerosis, cancer, non-alcoholic fatty liver disease, and inflammatory bowel disease. Therefore, harnessing host-microbial interactions in the human body through live bacterial therapeutics has generated substantial interest. One bacterial therapeutic idea is chassis—the engineering of a host bacteria to release therapeutics for the restoration of a healthy microbiome [10]. Advancements in genetic engineering techniques including Clustered regularly interspaced short palindromic repeats-cas9 (CRISPR-cas9), DNA transfection, and large DNA fragment cloning allow for the design of smart bacterial strains that produce desired responses to specific environmental signals in the body [11]. In addition, certain bacteria may prefer to grow in areas already infested with diseases, therefore they are a perfect platform for engineered disease-targeting therapies.

To engineer bacteria to selectively grow in tumors without affecting nearby healthy tissues, Zhao et al. modified auxotrophic Salmonella typhimurium to survive only in tumor tissues depending on purines, amino acids, and nutrients specific to the tumor, producing the desired effect of curing breast cancer in clinical mouse trials [13]. Tumor targeting abilities can also be improved through modification of surface proteins and tumor antibodies, as demonstrated by Massa et al. via a surface-expressed antibody targeting a tumor antigen (CD20) [14].

Bacteria Cargo

As mentioned before, bacteria are increasingly useful in immunotherapy due to their ability to selectively colonize tumors and produce bioactive compounds such as proteins in the tumor. IL-2 is a class of cytokines that is crucial for the growth, activation, and differentiation of cytotoxic T-cells and natural killer (NK) cells. One study locally delivered IL-2 in tumors using engineered *Escherichia coli Nissle 1917*, and the results showed a moderate decrease in the rate of tumor growth and the ability of the optimized strain to modulate the tumor microenvironment (Figure 2). Therefore, bacterial delivery systems that produce bioactive signaling or growth molecules in tumors hold significant promise [15].

4. Methods of Modulation

Synthetic biology allows for the modification and regulation of genetically engineered microbes, increasing control of bacterial activity and the safety and efficacy of this new form of therapy. The possibility of toxic bacterial translocation, immunogenicity, and uncontrolled gene expression must be considered.

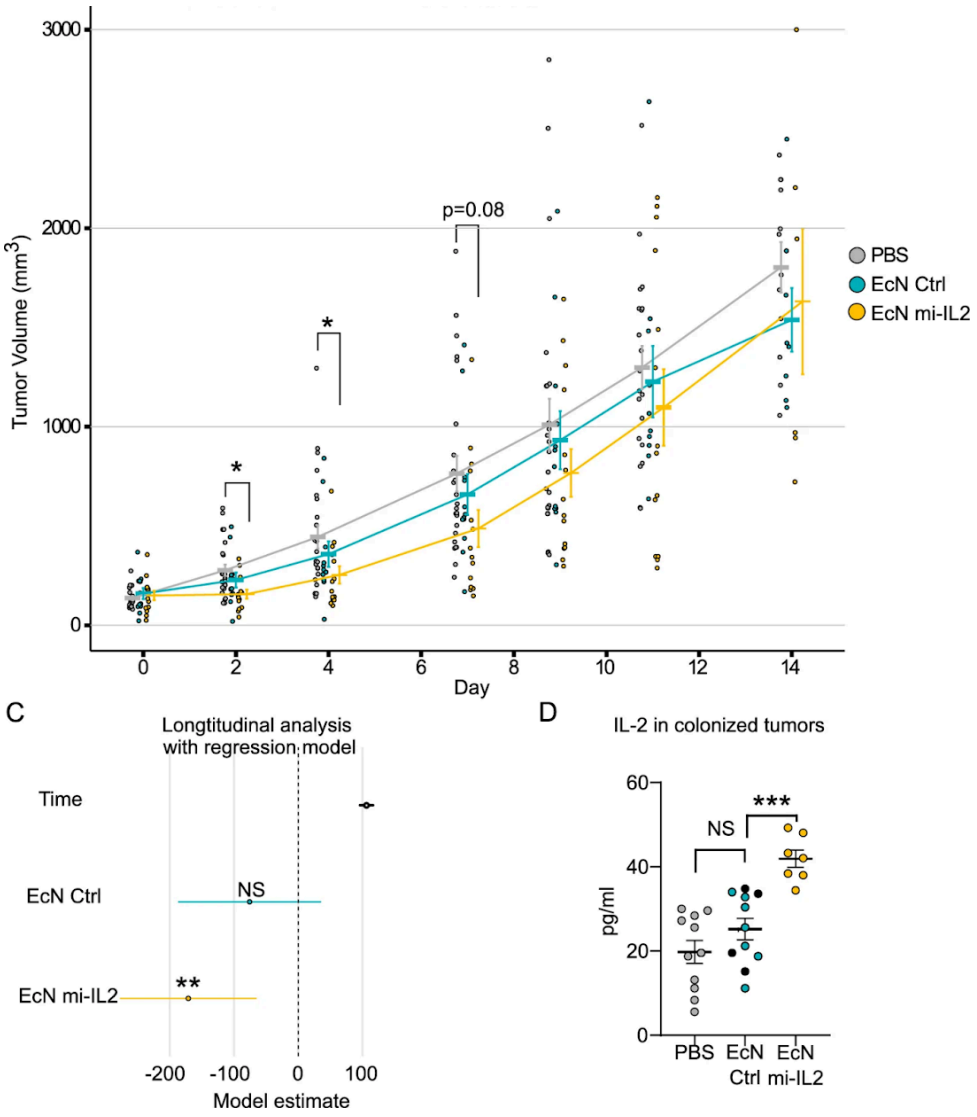

Figure 2. ***(b)*** *Tumor volumes in all mice treated with PBS (gray), EcN Ctrl (blue), and EcN mi-IL-2 (yellow). Mean tumor volume and SEM are shown.* ***(c)*** *Longitudinal analysis of tumor growth rate using a linear regression model. The 95% confidence interval of the estimates is shown. The model estimate is the change in tumor growth rate compared to the PBS group.* ***(d)*** *IL-2 levels in colonized tumors with mean and SEM shown [15].*

Quorum Sensing

There have been many possible approaches to circumvent the toxicity of living bacteria which are highly likely to proliferate and translocate. Many include reigning bacteria's unique ability of quorum sensing. Quorum sensing (QS) is a method for communication in bacterial colonies: bacteria utilize acyl-homoserine lactones (AHLs), autoinducing peptides (AIPs), and autoinducer-2 (AI-2) signals—which differ in concentration in gram-negative and gram-positive bacteria—that accumulate in an extracellular environment. When these signals cross a certain threshold, they bind to QS transcriptional regulators in the microbes and promote a response [16]. This can include the inhibition of gene expression or the release of therapeutic cargo. This

method ensures that the therapeutic will only be released in bacteria-dense areas, such as the site of therapeutic injection, preventing infection on nearby healthy tissues.

One study synthesized a pulsating delivery cycle by coupling the expression of a lysis gene (negative feedback loop) and the activator of the *luxl* promotor (positive feedback loop) which controls both the lysis gene and regulates the production of AHL autoinducer. This allows for a synchronized death loop, where AHL binds to LuxR receptors that activate the *luxl* promotor, which further produces autoinducer and triggers cell death. This method controls population and drug levels [17].

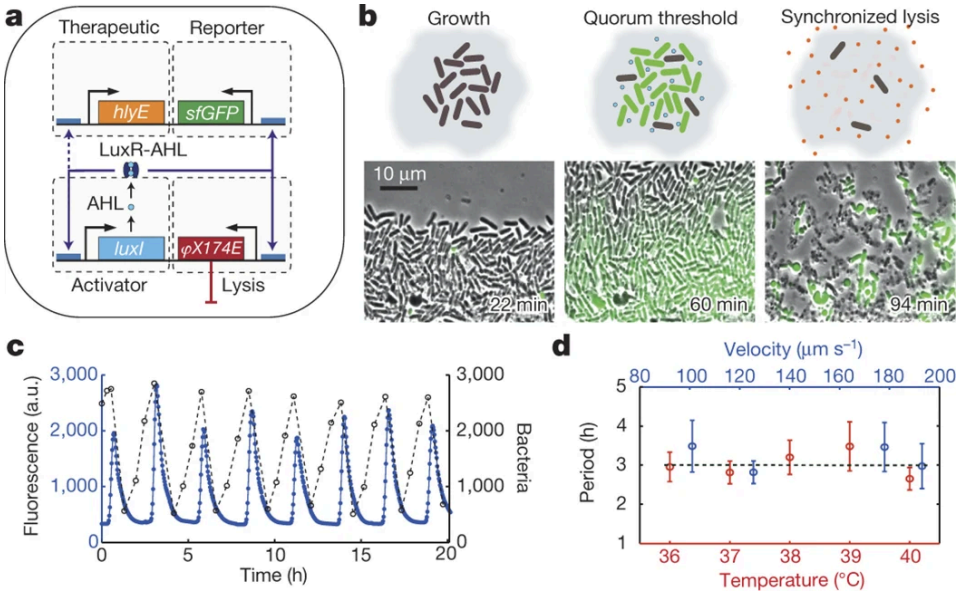

Figure 3. ***(a)*** *Synchronized lysis circuit. A common promoter (luxl) drives the expression of AHL and the lysis gene (φX174).* ***(b)*** *The main stages of each lysis cycle from seeding to quorum 'firing'. Fluorescent sfGFP is used to observe growth.* ***(c)*** *The fluorescence profile of an experiment reveals that lysis events correspond to peaks of sfGFP.* ***(d)*** *Tests with variable growth conditions with different temperatures ((36 °C to 40 °C) and perfusion rates [17].*

Circumventing Immunogenicity

In addition to protecting the body from bacteria, engineered bacteria must also be protected against the body. The body's immune system can detect and exterminate any foreign substances, whether beneficial or not. One solution to immunogenicity proposed by Harimoto et al. is surface modulation to cloak delivery vehicles, specifically utilizing capsular polysaccharides (CAP). CAP is a natural biopolymer located on the extracellular membrane and protects microbes from environmental factors. The construction of a tunable CAP expression system that regulates bacterial interaction with external substances allows full control over the immunogenicity and translocation of the microbe. Harimoto et al. explored various genes and levels of CAP that differentially sensitized bacteria to immune factors when expressed under regulation [18].

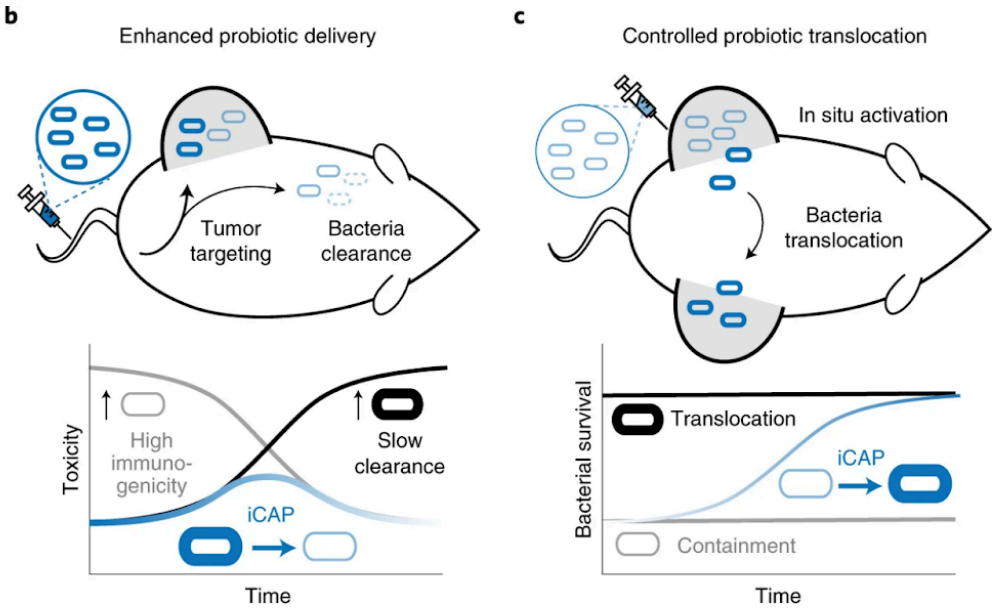

Figure 4. ***(b)*** *The programmable CAP system transiently expresses CAP. Non-CAP bacteria (thin gray) expose the immunogenic bacterial surface while permanently CAP-expressing bacteria (thick black) lead to overgrowth. The iCAP (blue) system enables momentary encapsulation of bacteria, reducing initial toxicity while still effectively clearing bacteria over time.* ***(c)*** *The CAP system controls bacterial translocation by allowing the activation of CAP in one tumor, which results in bacteria translocation to distal, uncolonized tumors [18].*

Conclusion

William Coley's immunotherapy techniques have recently experienced a resurgence. Many promising studies and clinical trials show a bright future in bacterial engineering's role in more targeted cancer therapies, holding the potential to diminish off-target toxic effects on healthy tissue that current traditional therapies are accompanied with. Advancements in drug delivery systems have paved the way for exciting research on combination therapy with CAR-T cells and bacterial therapeutics. Much effort has also been dedicated to making these therapies safer, including regulatory means to control gene expression, product release, immunogenicity, and translocation. Other research delves into differences between gram-positive and gram-negative bacteria, as well as engineering probiotic strains for other diseases such as type II diabetes. For future exploration, improvements in current technologies—especially bacteria-led immune responses—are necessary, and differences between mice and human clinical trials should also be considered for safer and more successful therapies.

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Gene Therapy: Potential Unintended Effects of Gene Editing to Treat Cystic Fibrosis, and Ways to Minimize Them

Ivan Zhu

Introduction

A new dimension in the outlook of the medical field has been introduced, all thanks to the discovery of gene therapy. This treatment procedure will open the doors for treatment of genetic disorders previously thought to be untreatable due to the root causes of such disorders at the molecular level. Gene therapy is further divided into two major categories, ex vivo and in vivo. Ex vivo means "outside of the living body" in Latin, in which gene therapy removes cells from patients, introducing new genetic material, packaged in a “delivery vehicle” called a vector, then returned to the cells to the patients (Filesler, 2020). On the other hand, in vivo means' “within the living”, in which gene therapy is done through direct IV infusion of the vector into the bloodstream or by injection into the target organ (Filesler, 2020). The possibilities for gene therapy, so far, have skyrocketed with the constant studies about its utilization, which expands its potential to combat an increasing number of disorders.

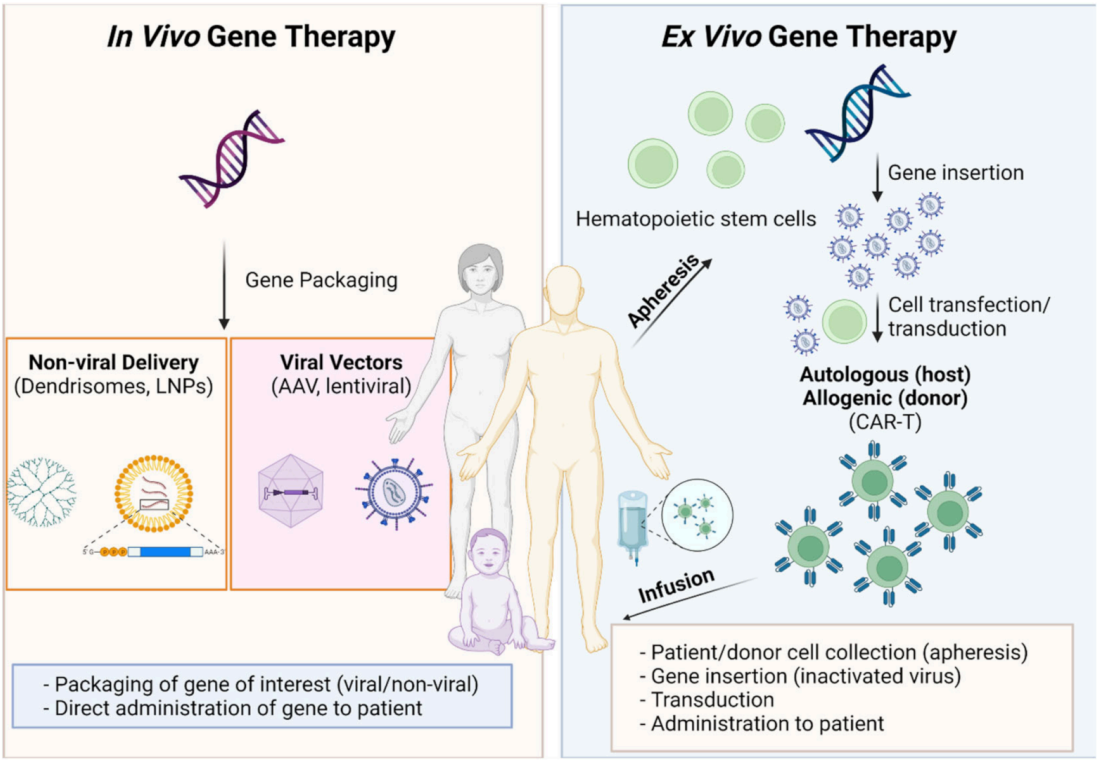

Figure 1 - Differentiating the differences between in vivo and ex vivo.

Cystic fibrosis (CF), is a genetic disorder, individuals who have cystic fibrosis have a faulty protein that affects the body's cells, tissues, and glands that is responsible for producing mucus and sweat. Normally, mucus is characterized as slippery and protects various areas of our body: the airways, digestive tract, and other organs and tissues; however, cystic fibrosis causes mucus to become thick and sticky, once it builds up, it may cause complications. In other words, instead of acting as a lubricant, the mucus blocks up tubes, ducts and passageways, especially in the lungs and pancreas inflicting detrimental damage to one's body (Chalmers, 2021).

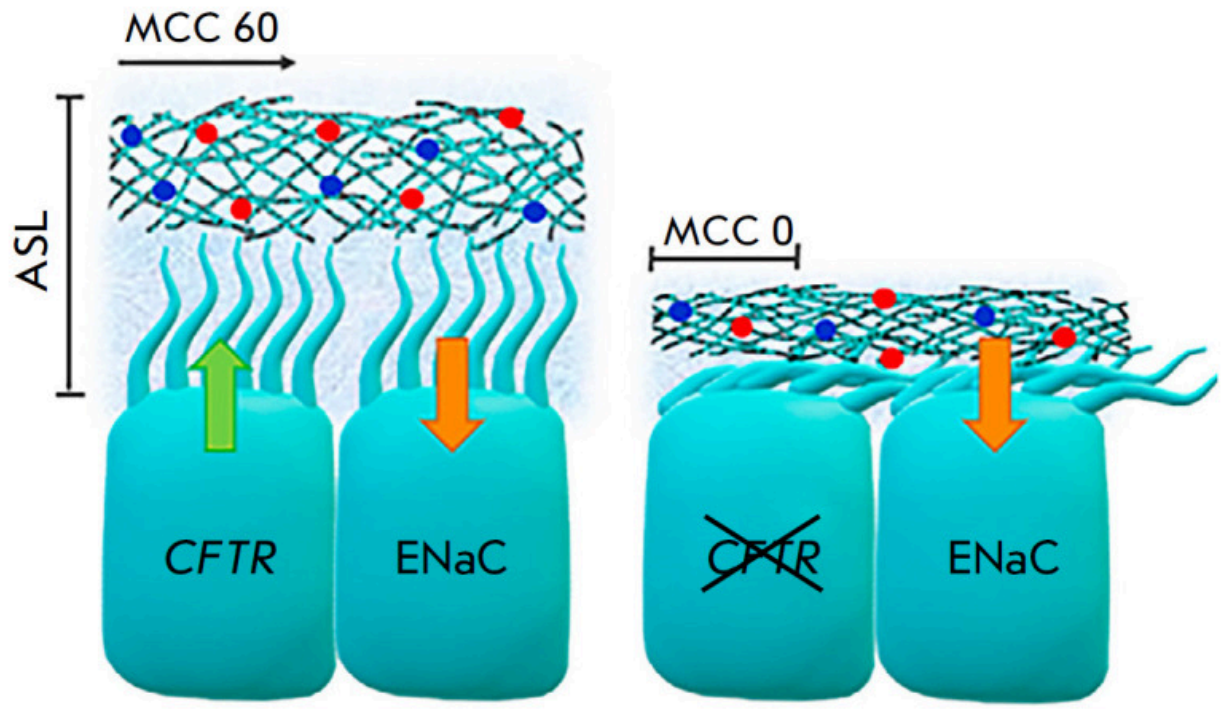

Figure 2 - In healthy individuals (left), the thickness of the airways mucosal layer (ASL, airway surface liquid) is a result of the normal functioning of the CFTR and ENaC channels. In cystic fibrosis (right), due to a defective CFTR, a decrease in the number of chloride ions leads to excessive transport of sodium ions resulting in dehydration of the airway epithelium surface, increased secretion viscosity, and compression of the cilia. Weak secretion mobility triggers an inflammatory reaction, and it is also an ideal environment for the reproduction of pathogenic microorganisms (Lomunova and Gershovich, 2023).

The similarity between gene therapy and cystic fibrosis is that gene therapy can be applied to treat the disease's genetic basis. Cystic fibrosis is a result of mutations in a gene coding for the cystic fibrosis transmembrane conductance regulator protein, otherwise known as CFTR (Lomunova and Gershovich, 2023). Traditional treatment for cystic fibrosis using established approaches mainly results in symptomatic control and an improvement in quality of life; however, it does not correct the genetic mutation. This is where gene therapy comes into play; with the discovery of CFTR modulators, it can correct the functioning of the defective protein (Lomunova and Gershovich, 2023). Some of the select CFTR delivery methods include:

Adenoviral (Ad) vectors where normal gene copies are delivered into the airway epithelial cells using Ad aimed at correcting the mutated copy through nasal and endobronchial administration; the adeno-associated viral (AAV) vectors replace the defective gene with a healthy copy of CFTR using administration through the maxillary gland, nostril, or endobronchial administration; the lentiviral (LV) vectors will facilitate the delivery as well as stable expression of the CFTR gene through intranasal administration (perfusion); non-viral gene delivery via liposomes and polymeric nanoparticles that has been seen to slow the decline of pulmonary function in patients suffering from cystic fibrosis and that is administered through aerosol (nebulizer) or intranasal; antisense oligonucleotides (QR-010) are therapeutic molecules used for restoring DNA modifications and for fixing defective DNA in a site-specific manner using intranasal administration. Subsequently, these therapeutic strategies help with correcting the mutated CFTR proteins for enhanced mucus regulation and prevent severe complications associated with cystic fibrosis.

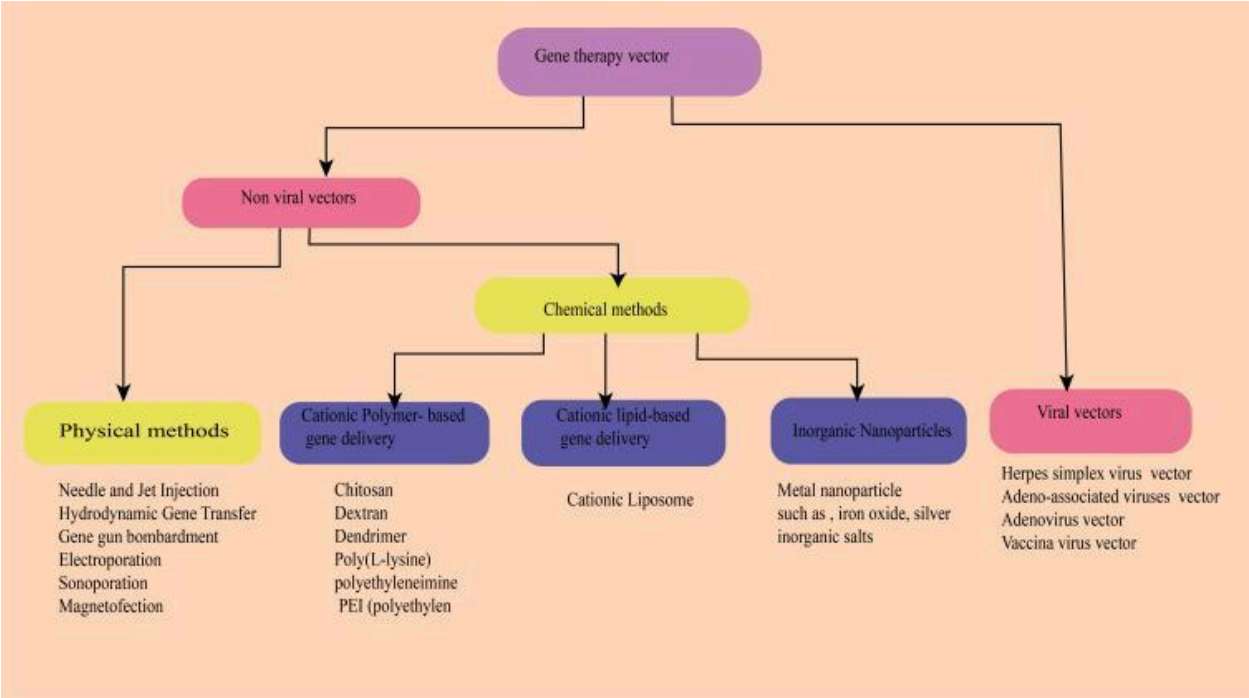

Figure 3 - Overview of the delivery systems utilized in gene therapy (Belete, 2021).

Future Implications and Potential Benefits of Gene Therapy

The future implications and potential benefits of gene therapy are huge and full of uncertainties because of some unexpected circumstances. However, given the ongoing progress with gene therapy, there are implications and definite benefits that can be expected. At least theoretically, gene therapy could provide a cure for life-long or, at best, permanently cure genetic disorders and chronic diseases by correcting underlying genetic mutations. Such treatment would relieve the patient from suffering caused by these ultimately fatal diseases and, in fact, may result

in the complete eradication of the disease. Gene therapy should also be considered regarding the ability to prevent genetically inherited diseases by therapeutic procedures commencing at an early stage, such as embryos or fetuses, which may gradually result in a decrease in the prevalence of genetic disorders around the globe. However, there are, of course, far-reaching issues to consider as gene therapy research progresses at an accelerated pace: ethics, unintended consequences, impact on society, cost, availability, and so forth.

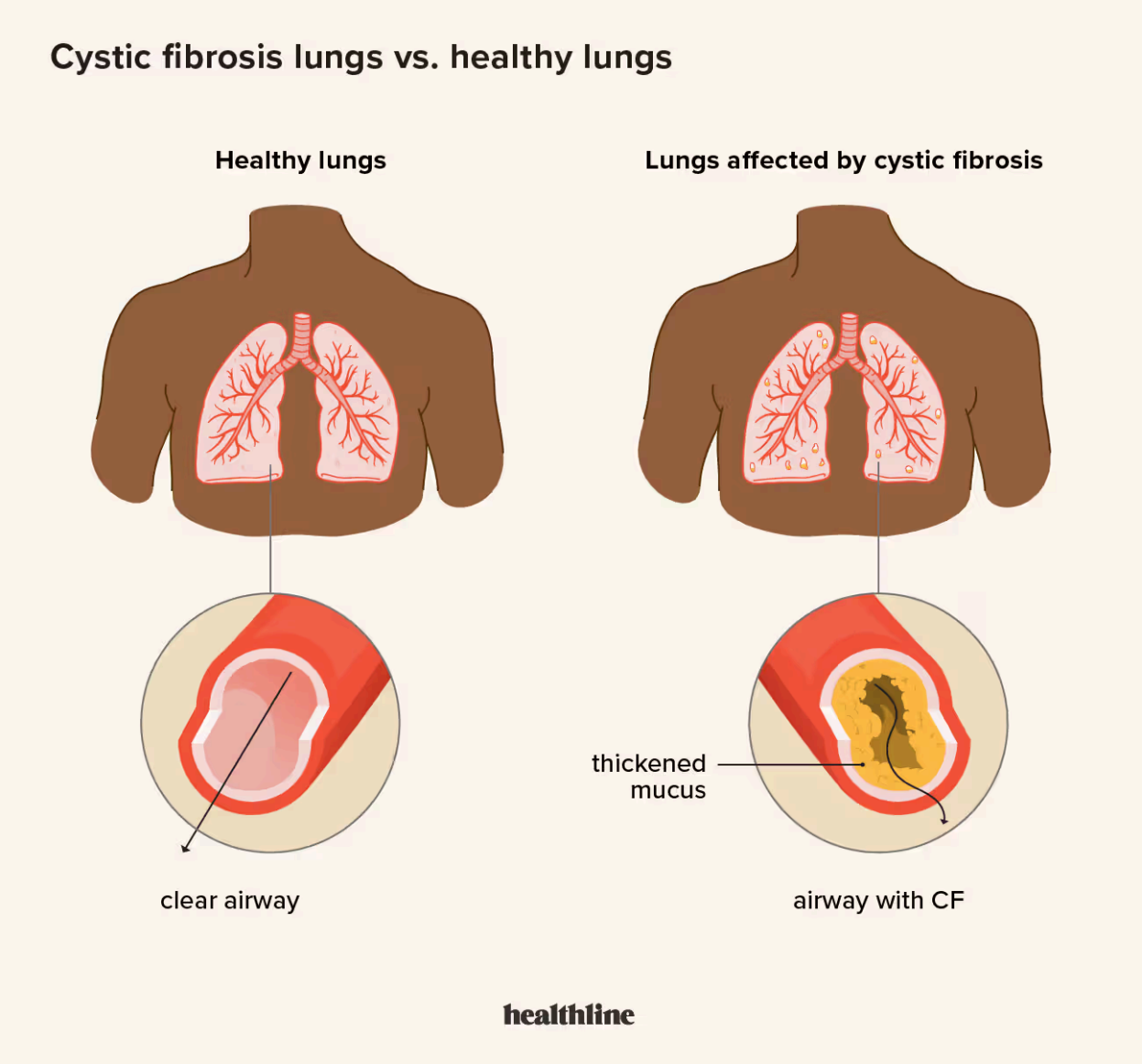

Figure 4 - Visual demonstration of individuals with(out) cystic fibrosis.

Unveiling The High Costs and Financial Burdens of Gene Therapy

With 16 gene therapies authorized thus far in the United States, and 60 more projects on pace to be approved by 2030, the costs ranges from five-figures through to the millions, authors

in Health Affairs wrote: “Such unprecedented high prices have raised concern about the affordability of gene therapy treatments for patients and health care systems.” To give you a better glimpse of the financial challenges associated with these groundbreaking treatments: the FDA has approved 8 oncologic gene therapies at prices ranging from $65,000 to $475,000 and has approved 8 non-oncologic gene therapies at prices from $630,000 to $3.5 million. As evident, the economic effects of gene therapy are profound due to the whopping price tag associated with these cutting-edge treatments. This makes gene therapies cost-prohibitive for low- and middle-income families, leading to health disparities between populations that are already great and thus aggravating existing inequalities. Even in higher-income areas, where insurance may be available to pay for some of the costs, patients and families often face very burdensome financial situations because the insurance plans require very high out-of-pocket payments, specialized treatment centers that offers gene therapy may be far away, and the possible need for many years of follow-up care. The economic challenges, therefore, raise serious concerns for equity regarding gene therapy: not all patients will be able to afford this life-changing treatment, providing for disparities based on socioeconomic status, insurance coverage, and geographical location.

DRUG NAME	MANUFACTURER	INDICATION	COST
Luxturna (voretigene neparvovec-rzyl)	Spark	Inherited retinal disease	$850,000/ for both eyes
Kymriah (tisagenlecleucel)	Novartis	Acute lymphocytic leukemia Diffuse large B-cell lymphoma	$475,000 $373,000
Yescarta (axicabtagene ciloleucel)	Kite	Large B-cell lymphoma and Follicular lymphoma	$373,000
Zolgensma (onasemnogene abeparvovec-xioi)	AveXis	Spinal muscular atrophy	$2.125 million
Tecartus (brexucabtagene autoleucel)	Kite	Mantle cell lymphoma	$373,000
Breyanzi (lisocabtagene maraleucel)	BMS	Large B-cell lymphoma	$410,300
Abecma (idecabtagene vicleucel)	BMS and bluebird bio	Multiple myeloma	$419,500

Figure 5 - Visual representation of the costs associated with a select few of genetic disorders and diseases (Sahli, 2021).

The Biological Side Effects of Gene Therapy

Even though gene therapy offers countless benefits, the delivery technique may also present some unforeseen biological side effects. For instance, there may be unwanted immune system reactions where one's body's immune system may perceive the newly introduced foreign material as an “intruder". Their body rejects it by attacking them, henceforth causing a reaction that may lead to swelling, and organ failure, among other conditions. Complications from inadvertently targeting the wrong cells may arise as well, the foreign material may affect more than one type of cell so it may get into cells beyond those that aren't working properly. There may also be adverse effects associated with inserted genetic material causing unexpected gene expression, in other words: there may be a possibility of causing errors in your genes that may lead to cancer and other unwanted side effects. While the potential of curing genetic disorders is exciting, it cannot come at the expense of a patient's health; these concerns should be addressed carefully to not compromise the safety and health of the patient.

Mitigating The Unintended Effects of Gene Editing

Although gene therapy can present some unforeseen biological side effects, the biomedical field has been actively working on minimizing unintended consequences in gene editing by emphasizing two key points: safety and specificity. Safety improvements can be achieved by the thoughtful design of nucleases and repair templates, the analysis of off-target editing, and the careful utilization of viral vectors (Scharenberg and Lux, 2017). Advancements in understanding the DNA repair mechanisms and the development of new generations of gene editing tools allow for improved targeting of specific sequences whilst minimizing the risk of unintended outcomes (Scharenberg and Lux, 2017). When designing a targeted endonuclease, engineers anticipate potential off-target cleavage sites and select sequences that minimize this potential. This is most commonly carried out in silico using tools such as the PROGNOS tool for zinc fingers, TALENS, and the CRISPR Design tool (Scharenberg and Lux, 2017). Other ways that we can reduce the unintended effects of gene editing is to make use of new technologies, for example, the various CRISPR-Cas9 variants, give better precision to reduce off-target effects in gene editing. Biosensors could also be developed for monitoring changes in gene expression as measures of adverse effects at the cellular level. Tailoring of gene editing strategies to individual patient profiles, which include their unique genetic compositions and how they may respond to treatments could potentially minimize unintended effects of gene editing as well. These provisions will cumulatively lead to the more precise and responsible application of gene editing technologies ensuring gene therapy doesn’t jeopardize a patient’s health and safety.

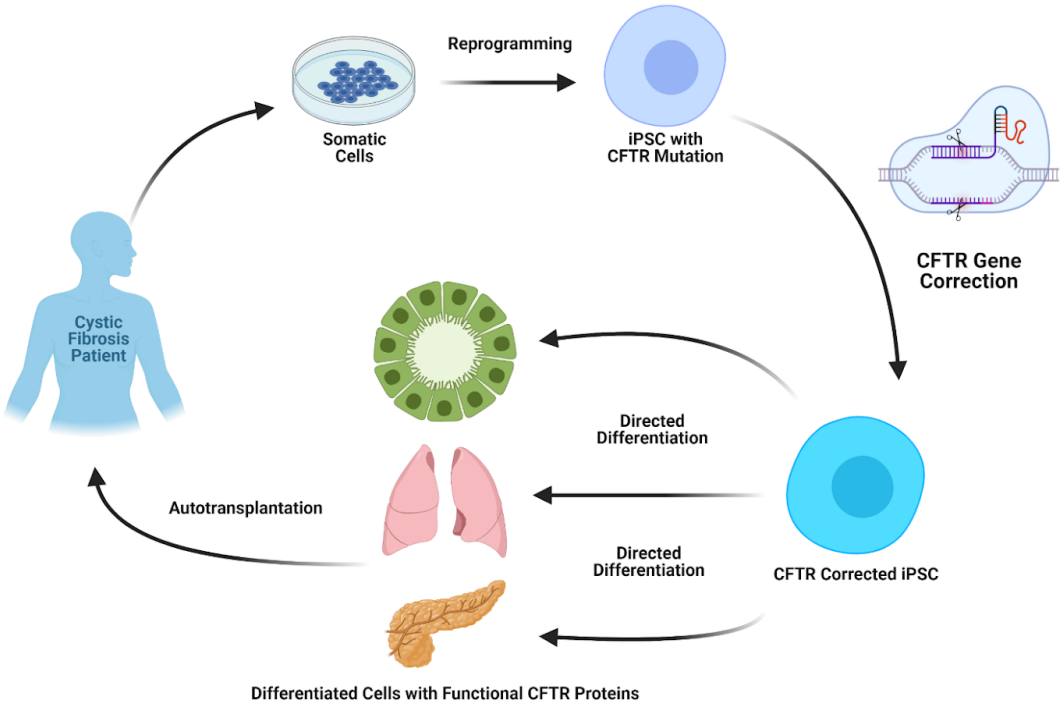

Figure 6 - CFTR Gene Correction in Cystic Fibrosis Induced Pluripotent Stem Cells

Assessing The Efficacy of Gene Editing Technologies

So far only a few handful of patients have been effectively treated. That is not to say, however, that it cannot be done. Although progress with gene therapy has been slow, current prospects for its application appear bright. Many years of research have produced insight into the creation of safe and effective vectors, methods for selective targeting of various cell types, and mechanisms for the modulation of immunological responses in patients. Now, hundreds of clinical trials are being conducted, in which researchers are testing critically to ensure that each gene therapy tested in the clinic is deemed as safe and effective for future usages.

Ethical Considerations in Gene Editing

Gene editing has been researched increasingly to establish if it can eradicate genetic disorders and diseases, including cystic fibrosis, but it has equally been shrouded by an array of ethical dilemmas. The 2018 news of the genetically edited twins from China specifically brought to question the ethics of therapeutic gene editing in human embryos (Normile, 2018). Another main concern is the definition of human nature (Morar, 2014). The use of genetic science in ways that go beyond the prevention and cure of disease, such as trait enhancement and "neo-eugenics," raises troubling ethical concerns as well (Penticuff, 1994). This may cause social pressure and discrimination due to genetic traits. Yet another burning issue is when only wealthy individuals can afford gene-editing technologies, worsening the already existing health

disparities. This emerges as one of the critical ethical dilemmas concerning ensuring equitable access to these treatments. There are also ethical concerns regarding a loss of genetic diversity and the implications such a thing might have in developing "designer" traits. Ethical considerations call for the responsible development of gene-editing technologies to ensure that it's used appropriately taking account of human dignity, rights, and the integrity of future generations.

Conclusion

Using gene therapy for cystic fibrosis and other genetic disorders/diseases offers countless potential, many point in the direction of great hope while others present major challenges. In this regard, gene therapy could provide an avenue where such terrible conditions are taken out from the potential patient, therefore providing a more fulfilling life. However, with the tagged price that comes with these therapies, there has been economic concern and an issue of access given to the privileged few; hence, it only further expands the gap within health disparities. Moreover, while the efficacy of gene therapy is shown in clinical trials, biological side effects and long-term results have to be carefully considered with active monitoring. The ethical implications of gene therapy ensure that this advanced treatment option is used fittingly, it requires that the proper balances are maintained between innovations and the ethical responsibility of making sure that gene therapy benefits people with cystic fibrosis and other genetic disorders.

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The Increasing Relevance of Artificial Intelligence in Cardiology

Hannah Zimmerman

Introduction

Artificial intelligence (AI) is society's newest and upcoming breakthrough, assisting not only corporations and industries but also the average person in their day-to-day tasks. AI aims to build machines that perform typical human-like functions such as rational thinking and adaptive learning. These high-tech machines are developed by teaching the AI tools to adapt to the given information, provide a solution based on its analyses, and, as a result, make further projections [1]. The functionalities and appeal behind AI have attracted various doctors and healthcare professionals, many of whom are incorporating these technologies into their daily practices. The diverse features that AI possesses make it applicable to numerous scientific medical fields.

Cardiology is one of the many medical fields that has benefited significantly from AI. Cardiovascular diseases (CVD) are some of the most complex and life-threatening issues in healthcare, presenting itself as one of the disease categories with the highest morbidity and mortality rates [2]. Therefore, early prediction and intervention for CVDs are critical for improving patient outcomes and potentially saving numerous lives. Cardiovascular devices such as electrocardiogram (ECG) machines, pacemakers, and defibrillators play a crucial role in diagnosing and treating these conditions. However, heterogeneity in CVDs can create obstacles that make diagnosing individuals more difficult and processing data more complex [3]. This is when advanced analytical methods from AI become essential.

The role of AI and machine learning in cardiology is to provide progressive features to improve the outcomes of medical examinations, thereby enhancing the efficiency of cardiologists. With innovative progress being made every day in medicine and cardiology, stronger interpretation methods that go beyond the human mind are necessary. Moreover, the growing demand from patients for personalized care, coupled with the complexity of modern medical treatments, necessitates increased efficiency and expertise from cardiologists. AI has the ability to enhance patient care by analyzing intricate datasets, reducing human error, and, most significantly, accurately predicting disease and diagnoses – all of which promise amplified efficiency, convenience, and reliability in cardiology and healthcare [4].

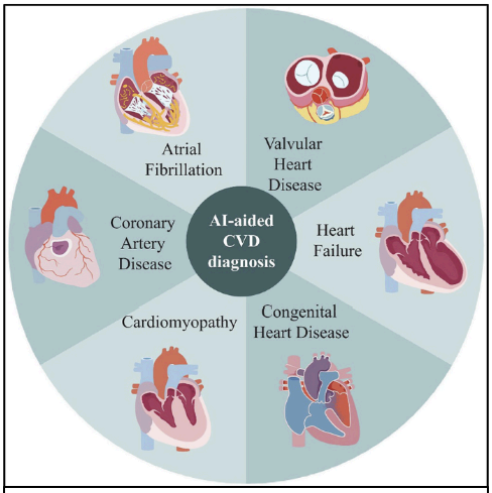

Figure 1: AI applications in aiding CVD diagnosis [7]

Researchers are proposing new ideas and practices involving AI and their applications in managing CVDs. *(Figure 1)*. This paper will address the question of AI's increasing relevance in cardiology, diving into the different

applications of AI in cardiology, evidence of AI taking center stage in cardiology, and the challenges and limitations it presents.

Model of the Heart

To understand the effects of AI in cardiology, it is important to understand the model and structure of the heart. *(Figure 2).* As a vital organ, the heart circulates blood throughout the body, providing oxygen and nutrients to organs and removing carbon dioxide and waste. It also interacts with the nervous and endocrine systems to regulate heart rate and blood pressure.

The heart has three layers: the inner endocardium, the middle myocardium, and the outer epicardium, which is part of the protective pericardium. It consists of four chambers: the right atrium, which collects oxygen-poor blood from the body; the right ventricle, which sends this blood to the lungs; the left atrium, which receives oxygen-rich blood from the lungs; and the left ventricle, which distributes oxygen-rich blood to the body.

Valves within the heart function as gates between these chambers. Atrioventricular (AV) valves manage blood flow between the atria and ventricles, while semilunar (SL) valves control the outflow from the ventricles. Blood travels through arteries (which carry oxygen-rich blood from the heart), veins (which return oxygen-poor blood to the heart), and capillaries (where blood exchanges occur). The coronary arteries nourish the heart with nutrients.

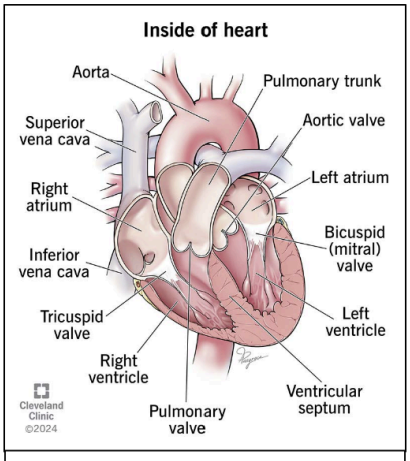

Figure 2: The inside model of the human heart [5]

The heart's rhythm and pace are regulated by its electrical conduction system, which includes the sinoatrial (SA) node, atrioventricular (AV) node, Bundle of His, left and right bundle branches, and Purkinje fibers [5].

Evidence of AI Taking Center Stage

AI is making significant strides in the field of cardiology, offering countless benefits in clinical and patient care. CVDs continue to be a major issue with high mortality rates across the world, and traditional practices in predicting outcomes and guiding treatment decisions have long served their purpose in treating these CVDs [2]. However, as technology advances, these practices begin to have their limitations, such as their reliance on linear relationships and constrained sets of predefined variables, and the benefits of AI begin to outweigh the benefits of traditional treatments [2]. Therefore, medical professionals are beginning to look more into AI tools and technology and its benefits when applied to clinical practice cardiology.

Cardiology is embarking on a new phase of medicine and AI, where clinicians are able to optimize treatment plans and make stronger clinical decision-making choices due to the integration of AI's advanced techniques in detecting critical hidden details and analyzing vast data sets [2]. Its promising uses are constantly being proven effective, which is why medical professionals (and not just cardiologists) are incorporating it more into their clinical usage. The

global market for AI in cardiology is making serious investments into their research and usage, topping $2 billion spent in 2024 and a compound annual growth rate (CAGR) of 39.4%. If growth continues at this rate, the market is expected to reach $40.5 billion in 2033 [6]. *(Figure 3)*. This rate is substantially significant for the future of patients, healthcare, and cardiology.

Applications of AI in Cardiology:
Sports Cardiology

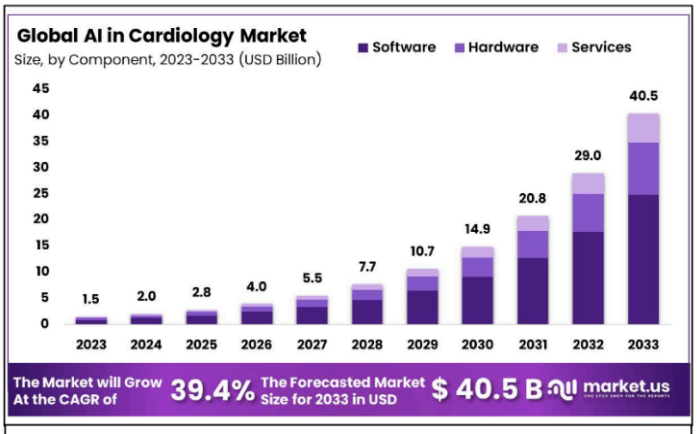

Figure 3: Global AI in Cardiology Market (2023 - 2033) [6]

AI has a significant prevalence in sports cardiology. Sports cardiology is a branch of cardiology that focuses on the hearts of athletes and other active individuals and their associated cardiovascular conditions. The heart undergoes various challenges and risks in response to the demanding activity of athletic sports, including sudden heart attacks, strokes, or the development of arrhythmia [8]. Therefore, it is essential for cardiologists to divert a portion of their research to the athlete's heart in the field of sports cardiology.

Sports cardiology incorporates various aspects of general cardiology, including cardiac imaging, electrophysiology, and electrocardiograms (ECGs). This integration makes the field particularly applicable to AI's benefits, which include improved risk assessment, enhanced diagnostic precision, and athlete monitoring [9]. With these uses of AI in sports cardiology, cardiologists can make comprehensive assessments that are specific and accurate to the complexities of the athlete’s heart [8].

An electrocardiogram is a test used by cardiologists to measure the electrical activity of the heart. It is commonly used to help diagnose heart conditions, including heart attacks and irregular heartbeats [10]. Integrating AI into ECGs (AI-ECGs) offers promising outlooks in interpreting heart abnormalities, monitoring signals from cardiac electronic devices, and connecting ECG data with various cardiac systems [11]. Extreme physical efforts made by athletes during their careers present countless future cardiac conditions, such as heart failure and arrhythmia. AI-ECGs have the ability to detect and predict these issues in their early stages.

AI-ECGs can detect cardiac structural damage, specifically damage in the left ventricular systolic function, which is the heart’s left ventricle’s ability to perform. The heart’s left ventricle is largely responsible for pumping oxygen-rich blood to the body’s various organs, making it essential in keeping the body’s function performing. Failure to do so may result in systolic heart failures such as coronary artery disease and high blood pressure. AI-ECGs have the ability to identify this left ventricular impairment in its subclinical initial phase, where many ECGs do not

have the technologies to identify these issues early on. This feature makes it effectively useful in the emergency room, predicting the need for hospital admission in the early phases of heart failure [12].

In addition to detecting heart failure, AI-ECGs are extremely effective in detecting arrhythmia. Arrhythmia is a condition characterized by an irregular heartbeat, which can vary from harmless to serious. However, if left untreated, it can lead to life-threatening complications such as strokes and cardiac arrests. Detecting arrhythmia at its early stages could help prevent these outcomes. AI usage reports a 98% accuracy rate in the detection and classification of arrhythmia [11]. Additionally, several studies suggest that AI-ECG methods are more efficient than doctors with multiple specializations in detecting these irregular heartbeats [12]. Furthermore, one main condition that AI-ECG focuses on is atrial fibrillation (AF), the most common type of arrhythmia that affects the upper chambers of the heart. AI-ECG's ability to detect the early stages of AF could decrease the number of strokes and mortality rates resulting from AF and similar types of arrhythmia conditions [12].

Beyond detecting the heart conditions associated with a physical athlete's heart, AI-ECG also benefits those who compete sedentarily. eSport athletes are athletes who play online games competitively on a professional level. Although they are seen to be not as physically demanding as regular physical athletes, they pose similar cardiac challenges, such as elevated heart rates and high blood pressure, due to the highly competitive nature of playing against human opponents. Limited current research suggests an increasing occurrence of heart-related issues among eSport athletes. Therefore, it is important to take note of the benefits AI-ECG may have on these athletes. Integrating AI-ECG and other advanced technologies into eSports may improve player cardiovascular health in the long run [12].

AI's integration into sports cardiology offers significant advancements in detecting and predicting cardiovascular issues, enhancing risk assessment, and improving athlete safety. By utilizing these technologies, we can anticipate better outcomes in both traditional sports and emerging fields like eSports, ultimately contributing to a healthier future for all athletes.

Applications of AI in Cardiology: Cardiovascular Imaging

AI has played a significant role in reshaping how we work with CVDs by looking into cardiovascular imaging. Cardiac imaging consists of various methods of capturing images of the heart. Cardiologists use these images to investigate, diagnose, and treat CVDs. AI has magnified the effects of cardiac imaging by enhancing diagnostic accuracy, allowing quicker analysis, and providing detailed insights into the patient's heart and complications [13]. AI is integrated into cardiac imaging through an extensive process involving the complex steps of image acquisition, reconstruction, analysis, interpretation, and ending with a diagnosis, prediction, and treatment plan. (*Figure 4).* These steps combined have marked significant progress toward improving patient treatments overall. Image analysis and cardiac computed tomography (CT) are just a few sectors of cardiac imaging that benefit significantly from AI-based solutions, allowing these techniques to be used effectively in clinical settings for improved patient outcomes [14].

Cardiac image analysis, the process of examining images of the heart to gain better insight into diagnosing and managing CVDs, has been significantly improved by the integration of AI. One of the most beneficial aspects is the option of automated image analysis, a technique that uses specialized software (most typically AI) to examine data from digital images. The automation of cardiac image analysis not only saves time but also increases the accuracy of analyzing these digital images, leading to more accurate diagnoses and treatment planning when investigating cardiac diseases [13].

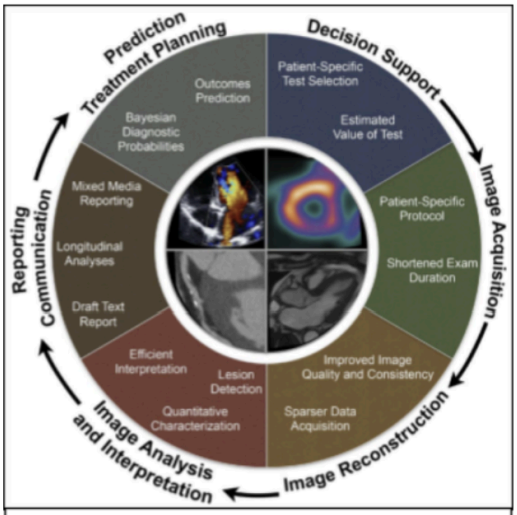

Figure 4: AI's application and primary activities in cardiovascular imaging [18]

An essential part of image analysis involves image classification, and AI has a unique ability to pinpoint specific patterns and characteristics that help categorize certain components of a CVD. As of recent, AI's power to discover precise anatomical landmarks has been tested on about 5,000 3D computed tomography volumes, efficiently identifying landmarks in less than a second with high accuracy [13]. Such rapid and accurate image classification by AI has allowed for timely and precise medical advancements, further improving how medical professionals work with CVDs and similar heart conditions.

In addition to cardiac imaging analysis, AI-based methods have revolutionized the practice of cardiac computed tomography (CT). CT is an imaging procedure that utilizes X-rays and computers to obtain detailed images of the body's internal structures. More detailed than the average X-ray scan, CTs enable doctors to interpret additional data about the diagnosis and condition [15].

However, CTs are susceptible to setbacks such as image deterioration and motion artifacts (an image error due to patient movement) that tamper with the results. Therefore, the use of AI has allowed for a cleaner and more precise processing of the obtained images. Multiple studies show that AI image processing provides higher image quality and a proficient level of accuracy when detecting diseases [16]. One study, in particular, used an AI algorithm to detect coronary artery disease in CT images from 42 patients, resulting in outcomes that achieved 95% accuracy [17]. AI in CT imaging manages to demonstrate its promising potential in studies such as these, and it will continue to enhance diagnostic precision in cardiac imaging as it advances in the medical field.

The integration of AI in cardiovascular imaging provides major advances in identifying and predicting CVDs, strengthening diagnostic accuracy and medical tool utilization. These technologies improve cardiac imaging in clinical settings, resulting in a healthier future for patients and a more optimistic outlook for the field of cardiovascular imaging.

Challenges and Limitations

As discussed, there is an endless amount of evidence showcasing the extensive benefits of AI and its applications. The way this advanced technology works seems generally "simple" in the sense that it is essentially just teaching a machine. However, this process comes with its challenges and limitations, and it is crucial that these limitations be addressed in order for AI to be successfully implemented into clinical practice.

One major, general challenge is the inevitable technology failures. Numerous cases of AI technologies showed initial promise, but as they were tested on broader, real-world terms, they failed to keep up with their performance. Examples of these technology failures include facial recognition errors in diverse populations, historically biased results that unintentionally promote inequity, and poor medical screening tests that are not applicable to various populations [19]. These problems typically arise when unreliable and faulty data sets are used to train the AI algorithms, and this comes as another issue when dealing with the origins and teachings of AI machines [19]. Additionally, another challenge to keep in mind is the heterogeneity of AI models and the need for external validation. The sample size and validation processes of AI-based assessments will vary due to the distinct requirements of these evaluations, but this may come as a challenge when ensuring the reliability of these models because the complicated criteria of these assessments may lead to confusion and human error [2].

As a result, it is important to always be aware of the harmful potentials that defective AI algorithms have in healthcare, cardiology, and patient outcomes. When clinics and medical offices make the choice to implement AI into their practices, it comes with the risk of possibly exacerbating and intensifying the already current healthcare difficulties, and it is essential to acknowledge that vulnerability.

However, despite all of this, there is still immense hope for AI implementation in the future. Numerous studies demonstrate that the overall performance of AI-based models for cardiology applications exceeds 83%, allowing AI applications to be concluded as accurate [20]. Therefore, AI's high accuracy rates exhibit its significant potential as a reliable tool to be used in cardiology and patient care, now and in the future. Integrating AI into cardiology practice should be embraced and accepted, despite the limitations it presents. Due to the increased attentiveness being devoted to implementing AI into cardiology, there's no doubt these limitations will decrease over time.

Conclusion

Cardiology is leading the way in the medical field when it comes to implementing AI. Major achievements that highlight AI's beneficial significance have been made in nearly all areas of cardiology, including some advances in sports cardiology, cardiovascular imaging, ECG analysis, automatic interpretation of imaging, and risk diagnosis prediction [19]. AI has been criticized as a threat that would cause widespread unemployment for doctors and economic upheaval. However, at the same time, technology has been praised as a savior, freeing medical professionals from tedious responsibilities and allowing them to communicate with and

understand their patients' needs, and complete more in-depth projects. As a result, instead of condemning AI as a risk that will replace doctors and nurses, scientists should explore AI research as a tool that will enhance the roles of these medical professionals. AI models are highly valued in cardiology and the medical industry, and they will continue to be utilized for their great potential, discovering and eliminating barriers to health access and patient quality.

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